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Total Synthesis of the *Myrioneuron* Alkaloid (−)-Schoberine B and Its Enantiomer (+)-Schoberine B

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Dedicated to Professor Miquel A. Pericàs for his leadership and outstanding contributions to organic synthesis and catalysis

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Abstract: A dynamic kinetic asymmetric transformation, involving the generation of four stereogenic centers with a well-defined configuration, occurs in the cyclocondensation of diastereomeric mixtures of 2-oxocyclohexanepropionic acid racemates **6** with (1*S*,2*R*)-*cis*-aminoindanol: two major tetracyclic lactams, **7a** and **7b**, that differ in the configuration of the four stereocenters on the decahydroquinoline moiety were obtained. From the above lactams, the removal of the chiral auxiliary, the introduction of a 2-piperidone ring, and the closure of the diazine ring complete the first enantioselective total synthesis of the *Myrioneuron* alkaloid (−)-schoberine B and its enantiomer (+)-schoberine B.

Keywords: alkaloids; asymmetric synthesis; decahydroquinolines; lactams; total synthesis

Introduction

Myrioneuron alkaloids constitute a group of lysine-based metabolites isolated from plants of the genus *Myrioneuron* (Rubiaceae).[1] Its first members[2] were reported by Bodo *et al.*[3] from the species *Myrioneuron nutans*, a small tree indigenous to North Vietnam. More recently, new complex polycyclic *Myrioneuron* alkaloids have been isolated from *M. faberi*, *M. tonkinesis*, and *M. effusum* by Hao and coworkers[4] in the Southeast of China. The most abundant members of the *Myrioneuron* class of natural products display, as a common structural feature, a *cis*-decahydroquinoline embedded in their structures, which can have an *N*-piperidylmethyl substituent at C-8 or can be fused to 1,3-oxazine or 1,3-diazine rings[5] (Figure 1). *Myrioneuron* alkaloids show interesting biological activities, including antimalarial and antimicrobial properties, KB cell cytotoxicity, and replication inhibition of hepatitis C virus (HCV).[1c] Despite their interesting

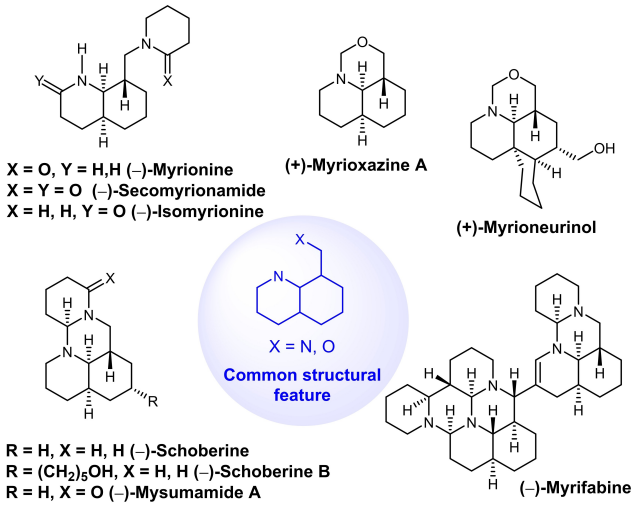


Figure 1. Representative *Myrioneuron* alkaloids.

structures and promising biological activities, the total synthesis of only a limited number of these alkaloids has been described. To date, the enantioselective synthesis of (+)-myroxazines A and B,[3a] as well as (−)-myrionine, (−)-myrionidine, and (−)-schoberine has been reported by Bodo.[3e] More recently, the racemic synthesis of myrioxazine A by Coldham[6] and the more complex alkaloid myrioneurinol by the groups of Weinreb,[7] Smith,[8] and Ma[9] have been described.

In 2016, Hao reported the isolation of the tetracyclic *Myrioneuron* alkaloid (−)-schoberine B[4e] from the aerial parts of *M. faberi* collected in Sichuan Province, People's Republic of China. (−)-Schoberine B shows moderate in vitro activity against HCV. Structurally, it displays the diazatetracyclic system of the well-known alkaloid (−)-schoberine but bears an additional *n*-pentanol lateral chain on the carbocyclic ring, which is assumed to be biosynthetically incorporated from a C-5 unit originating from lysine.

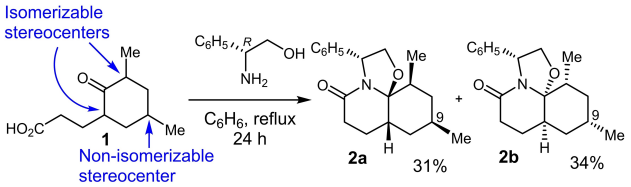
In previous work we have reported synthetic procedures for the preparation of enantiopure *cis*-decahydroquinolines (*cis*-DHQs), with substituents at almost all positions of the carbocyclic ring, from chiral aminoalcohol-derived oxazoloquinolone lactams.[10] The versatility of these enantiopure scaffolds was demonstrated with the enantioselective synthesis of several amphibian,[11] *Lycopodium*,[12] and marine alkaloids.[13] More recently, we have disclosed a methodology for the preparation of both enantiomers of 7,8-, 6,8-, and 5,8-dimethyl-susbstituted *cis*-DHQs from chiral oxazoloquinolone lactams obtained by cyclocondensation of racemic diastereomeric mixtures of dimethylcyclohexanone-based oxo-acids and an enantiopure aminoalcohol through a process involving a dynamic kinetic asymmetric transformation.[14] For instance, reaction of a mixture of racemic diastereomers **1** with (*R*)-phenylglycinol stereoselectively afforded two of the sixteen possible diastereomeric lactams (**2a** and **2b**), which differ in the absolute configuration of the four stereocenters on the decahydroquinoline nucleus (Scheme 1). This reaction can be considered highly stereoselective since the chiral center at the 4-position of the cyclohexanone ring of **1** is not isomerizable; therefore, two series of tricyclic lactams could *a priori* be expected, each one being composed of up to eight diastereomers differing at least in the C-9 stereocenter.

These diastereoconvergent cyclocondensation reactions prompted us to tackle the first total synthesis of (−)-schoberine B by a synthetic strategy based on the use of an aminoalcohol-derived hydroquinolone-lactam (**A**). This enantiopure scaffold possesses the appropriate substitution and the required absolute configuration at the four stereocenters on the DHQ nucleus (Scheme 2). Considering our previous experience in the formal synthesis of myrioxazine A,[10] we envisaged a [dimethyl(phenyl)silyl]methyl substituent as a surrogate of the hydroxymethyl substituent that in subsequent steps would be used to anchor a 2-piperidone moiety (ring D) at the DHQ 8-position. Removal of the chiral auxiliary followed by closure of the central diazine ring (ring C) from intermediate **B** would lead to the target (−)-schoberine B.

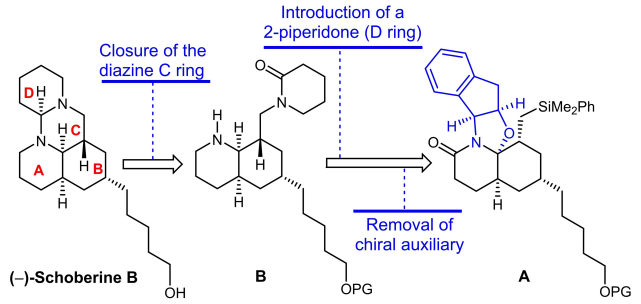
Results and Discussion

The required racemic oxo-acid **6** (mixture of diastereomers) was prepared from the known[15] cyclohexanone **3** by incorporation of the two substituents at the 2- and 6-positions. Treatment of the cyclohexylimine of ketone **3** with (iodomethyl)dimethylphenylsilane under basic conditions afforded **4** in good yield. All attempts to introduce a propionate chain or an allyl substituent at the C-6 position from the regioselectively formed trimethylsilyl enol ether derived from **4** and methyl acrylate or diallyl carbonate resulted in failure. For this reason, a multistep procedure consisting of the regioselective generation of a trimethylsilyl enol ether,[16] followed by treatment with the Böhme salt,[17] afforded the corresponding (dimethylamino)methyl cyclohexanone derivative **5**. Subsequent addition of diethyl malonate under basic conditions,[18] followed by hydrolysis of the resulting diester and thermal decarboxylation, provided the desired oxo-acid **6** (Scheme 3).

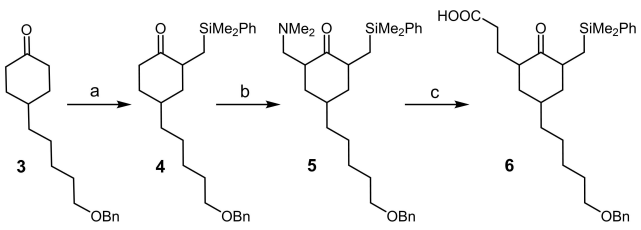
As expected, heating a mixture of oxo-acid **6** and (1*S*,2*R*)-*cis*-aminoindanol in refluxing toluene containing anhydrous $MgSO_4$ stereoselectively afforded lac-



Scheme 1. Previous work: cyclocondensation reaction of racemic mixtures of diastereomeric oxo-acids.

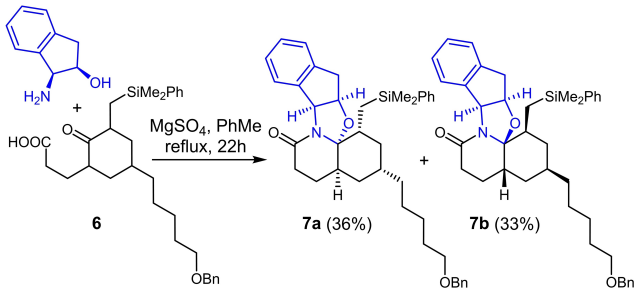


Scheme 2. Synthetic strategy.



Scheme 3. Synthesis of oxo-acid **6**. Reagents: a) i. Cyclohexylamine, PTSA, PhMe; ii. ICH_2SiMe_2Ph, LDA, THF; 76%; b) i. LDA, TMSCl, THF; ii. $CH_2{=}N^+(CH_3)_2Cl^-$, CH_2Cl_2; c) i. Diethyl malonate, NaOH, PhMe; ii. LiOH, THF/H_2O; then PhMe, Δ; 33% from **4**.

tams **7a** (36% yield) and **7b** (33% yield), which differ in the configuration of the four stereocenters on the decahydroquinoline moiety (Scheme 4). Only minor amounts of other two diastereomeric lactams were detected. The use of (*R*)-phenylglycinol instead of

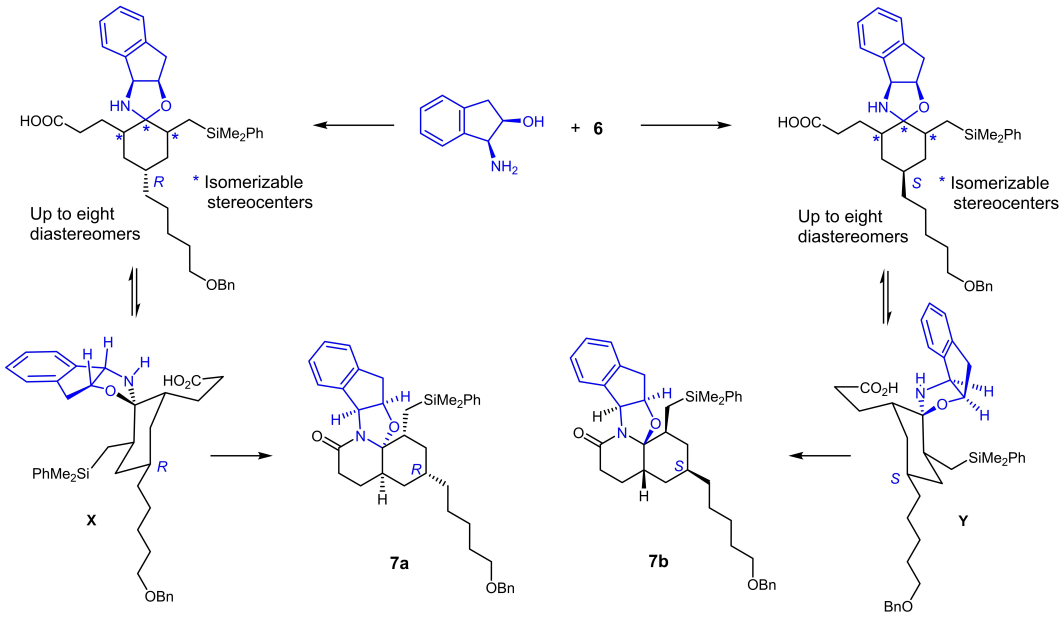


Scheme 4. Cyclocondensation of oxo-acid **6** with (1*S*,2*R*)-*cis*-aminoindanol.

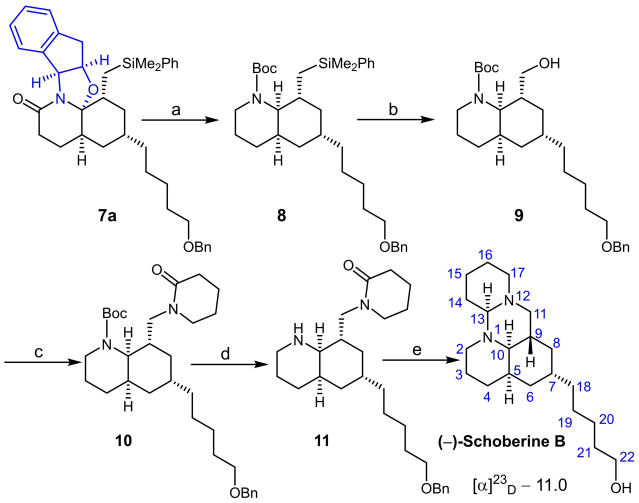
(1*S*,2*R*)-*cis*-aminoindanol as the chiral inductor in the above cyclocondensation was less efficient in terms of chemical yield.

The stereochemical outcome of the above cyclocondensation can be rationalized by considering that the reaction of (1*S*,2*R*)-*cis*-aminoindanol with oxo-acid **6** can afford a mixture of up to sixteen diastereomeric spiro-oxazolidines. The eight oxazolidine intermediates with an *R* configuration at the non-isomerizable stereocenter are in equilibrium through the corresponding imine-enamines arising from the oxazolidine ring opening. The final irreversible lactamization takes place preferentially from oxazolidine **X**, in which the two substituents on the cyclohexane ring are equatorial, leading to lactam **7a** (Scheme 5). The same mechanistic considerations can explain the stereoselective formation of lactam **7b**: of the eight diastereomeric oxazolidines in equilibrium possessing an *S* configuration at the non-isomerizable stereocenter, the lactamization step occurs faster from oxazolidine **Y**.

The removal of the chiral inductor was first carried out from lactam **7a**, which displays the appropriate configuration at the four stereocenters of the decahydroquinoline nucleus for the synthesis of (−)-schoberine B. Treatment of **7a** with $LiAlH_4$ and $AlCl_3$ brought about the lactam carbonyl reduction and the concomitant reductive opening of the oxazolidine ring. Subsequent *N*-debenzylation by catalytic hydrogenation using Pearlman's catalyst in the presence of Boc_2O afforded *cis*-decahydroquinoline **8** as a single isomer in good overall yield (Scheme 6). Attempts to induce the oxidation of the (dimethylphenylsilyl)methyl deriv-



Scheme 5. Stereochemical issues in the lactamization step leading to lactams **7a** and **7b**.

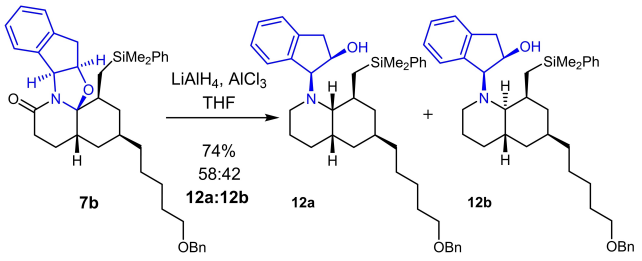


Scheme 6. Synthesis of the *Myrioneuron* alkaloid (−)-schoberine B. Reagents: a) i. $LiAlH_4$, $AlCl_3$, THF; ii. H_2, $Pd(OH)_2$, Boc_2O, MeOH; 75%; b) $PhMe_2COOH$, KH, TBAF, DMF; 80%; c) i. MsCl, Et_3N, CH_2Cl_2; ii. 2-piperidone, KH, DMF; 81%; d) TFA, CH_2Cl_2; 90%; e) i. $POCl_3$, PhMe; then $LiAlH_4$, THF; ii) Na/NH_3, −78 °C, 42%.

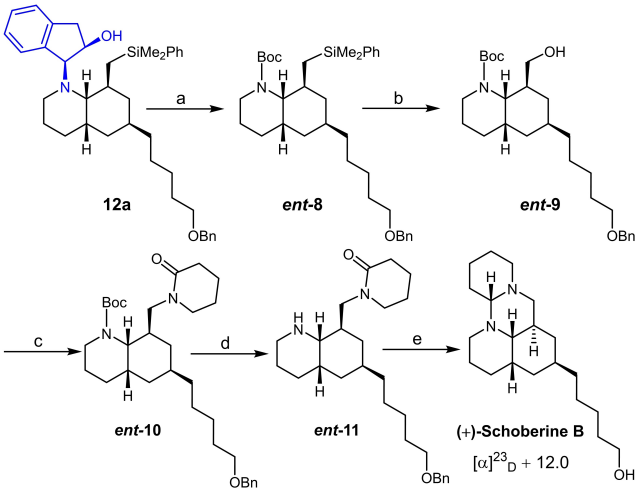
ative **8** to the corresponding primary alcohol **9** under the Tamao-Fleming acidic conditions ($HBF_4 \cdot Et_2O$; *m*-CPBA, KF) provided a complex mixture or low conversion. However, this transformation could be efficiently accomplished following the protocol reported by Woerpel,[19] using cumene hydroperoxide as the oxidant under basic conditions. The late-stage transformations closely follow Bodo's route[3e] to the related natural product schoberine. First, for the introduction of the piperidine D ring the hydroxy substituent was converted to a good leaving group by treatment of **9** with mesyl chloride. Reaction of a DMF solution of the resulting mesylate with 2-piperidone and KH satisfactorily gave **10**. After removal of the *N*-Boc protecting group, the secondary amine **11** was obtained in 73% overall yield. Then, closure of the diazine C-ring was carried out by treatment of **11** with $POCl_3$ under refluxing toluene, and subsequent $LiAlH_4$ reduction of the intermediate iminium salt. Although the reaction with $POCl_3$ caused the partial substitution of the benzyloxy group by a chloride, this byproduct was minimized by shortening the reaction time. Finally, removal of the *O*-benzyl protecting group was accomplished with sodium in liquid ammonia, a procedure that avoids the reductive cleavage of the aminal moiety present in ring C that would occur under catalytic hydrogenation conditions.[20] The NMR data and specific rotation of our synthetic (−)-schoberine B matched those reported in the literature for the natural product, thus confirming the proposed structure of this alkaloid.[4e]

To illustrate the usefulness of the methodology for the preparation of both enantiomers of *cis*-decahydroquinoline derivatives of biological interest, we decided to synthesize (+)-schoberine B, the enantiomer of the natural product. Surprisingly, the reductive opening of the oxazolidine ring of lactam **7b** with $LiAlH_4$ and $AlCl_3$ did not occur with the high *cis*-selectivity observed in related substrates[10,12,14] and afforded *cis*- and *trans*-decahydroquinolines **12a** and **12b** as an almost equimolar mixture (Scheme 7). This stereochemical result could be attributed to the steric hindrance caused by the bulky dimethylphenylsilyl group and dihydroindene moiety of the chiral inductor, which lie over the *Re* face of the intermediate iminium salt, hampering the approach of the reducing aluminium hydride reagent.

The *cis* isomer **12a** was subjected to debenzylation in the presence of Boc_2O to give *ent*-**8**, which was transformed into (+)-schoberine B by using the synthetic sequence described above for the synthesis of (−)-schoberine B (Scheme 8). The NMR data of synthetic (+)-schoberine B coincided with those



Scheme 7. Reduction of lactam **7b**.



Scheme 8. Synthesis of (+)-schoberine B. Reagents: a) i. H_2, $Pd(OH)_2$, Boc_2O, MeOH; 66%; b) $PhMe_2COOH$, KH, TBAF, DMF; 61%; c) i. MsCl, Et_3N, CH_2Cl_2; ii. 2-piperidone, KH, DMF; 55%; d) TFA, CH_2Cl_2; 83%; e) i. $POCl_3$, PhMe; then $LiAlH_4$, THF; ii) Na/NH_3, −78 °C, 45%.

reported in the literature for the natural product. On the other hand, its specific rotation matched the absolute value described for the natural product but with the opposite sign. The absolute configuration of our synthetic (+)-schoberine B was unambiguously confirmed by X-ray crystallographic analysis.

Conclusion

In summary, the first total synthesis of the *Myrioneuron* alkaloid (−)-schoberine B from the chiral (1*S*,2*R*)-*cis*-aminoindanol-derived pentacyclic lactam **7a** has been achieved. This work features, as the most remarkable contribution, the preparation in a single step of an enantiopure scaffold (**7a**) containing the decahydroquinoline core with the appropriate substitution and required absolute configuration for the synthesis of the natural product. Moreover, the synthesis of (+)- and (−)-schoberine B further illustrates the potential of the methodology that allows the generation of disubstituted *cis*-decahydroquinolines in both enantiomeric series from chiral aminoalcohol-derived lactams prepared by cyclocondensation reactions of racemic disubstituted 2-oxocyclohexanepropionic acids.

Experimental Section

(1*R*,3*R*,4a*R*,8a*S*,13a*R*,14a*S*)- and (1*S*,3*S*,4a*S*,8a*S*,13a*R*, 14a*R*)-3-(5-Benzyloxypentyl)-1-[(dimethylphenylsilyl)methyl]-7-oxoperhydroindeno[1',2':4,5]oxazolo[2,3-*j*]quinoline (7a and 7b)

(1*S*,2*R*)-(−)-*cis*-1-Amino-2-indanol (1.09 mg, 7.02 mmol) and anhydrous $MgSO_4$ (1.18 g) were added to a solution of ketoacid **6** (2.32 g, 4.68 mmol) in anhydrous toluene (54 mL). The mixture was heated at reflux for 16 h. After cooling, the solvent was evaporated, and the residue was resuspended in EtOAc and washed with saturated aqueous $NaHCO_3$. The organic phase was dried and concentrated. Flash column chromatography (9:1 to 7:3 hexane/EtOAc) afforded lactams **7a** (1.17 g, 36%) and **7b** (897 mg, 32%) as yellowish oils. Minor amounts of other two diastereomeric lactams were detected.

(4a*R*,6*R*,8*R*,8a*R*)-6-(5-Benzyloxypentyl)-1-(*tert*-butoxycarbonyl)-8-[(dimethylphenylsilyl)methyl]decahydroquinoline (8)

First Step

$LiAlH_4$ (14.00 mL of a 1 M solution in THF, 14.0 mmol) was slowly added to a stirring suspension of $AlCl_3$ (572 mg, 4.29 mmol) in anhydrous THF (20 mL) at 0 °C. After 1 h, the mixture was cooled at −78 °C, and a solution of lactam **7a** (1.30 g, 2.15 mmol) in anhydrous THF (16 mL) was added dropwise. The stirring was continued at −78 °C for 90 min and at rt for 24 h. Cold water was slowly added until no bubbling and the resulting mixture was filtered over Celite®, dried and concentrated.

Second Step

A solution of the above crude and Boc_2O (1.265 g, 5.80 mmol) in MeOH (50 mL) containing 40% $Pd(OH)_2$ (0.52 g) was stirred under hydrogen at rt for 24 h. The catalyst was removed by filtration over Celite®, and the filtrate was concentrated. Flash chromatography (98:2 hexane/Et_2O) afforded decahydroquinoline **8** (900 mg, 75%) as a colorless oil.

(4a*R*,6*R*,8*R*,8a*R*)-6-(5-Benzyloxypentyl)-1-(*tert*-butoxycarbonyl)-8-(hydroxymethyl)decahydroquinoline (9)

Cumene hydroperoxide (1.27 mL, 6.86 mmol) was added dropwise to a stirred suspension of potassium hydride (1.21 mg, 8.57 mmol) in anhydrous DMF (12 mL), and the resulting mixture was stirred for 25 min. Then, a solution of decahydroquinoline **8** (967 mg, 1.71 mmol) in anhydrous DMF (12 mL) and 1.77 mL of a 1 M solution of TBAF in THF were added. After 24 h, saturated aqueous $Na_2S_2O_3$ was added, and the mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried and evaporated. Flash column chromatography (9:1 to 7:3 hexane/EtOAc) afforded decahydroquinoline **9** (611 mg, 80%) as a colorless oil.

(4a*R*,6*R*,8*S*,8a*R*)-6-(5-Benzyloxypentyl)-1-(*tert*-butoxycarbonyl)-8-[(2-oxo-1-piperidyl)methyl]decahydroquinoline (10)

First Step

Triethylamine (39 µL, 0.51 mmol) and MsCl (0.10 mL, 0.71 mmol) were added dropwise under an inert atmosphere at 0 °C to a stirring solution of decahydroquinoline **9** (227 mg, 0.51 mmol) in anhydrous CH_2Cl_2 (2 mL). The mixture was allowed to heat to room temperature and stirred for an additional 3 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered, and evaporated to give a crude mesylate.

Second Step

Freshly distilled 2-piperidone (0.18 mL, 2.04 mmol) was added to a stirred suspension of potassium hydride (293 mg, 2.08 mmol) in DMF (1 mL) at 0 °C and the stirring was continued at this temperature for 10 min. A solution of the above crude mesylate in anhydrous DMF (3 mL) was added dropwise at 0 °C and the mixture was allowed to heat to room temperature and stirred for an additional 48 h. The solution was cooled to 0 °C and ice water was added. The mixture was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, filtered, and evaporated. Flash column chromatography (1:1 hexane/EtOAc to EtOAc) afforded decahydroquinoline **10** (217 mg, 81%) as a colorless oil.

(4a*R*,6*R*,8*S*,8a*R*)-6-(5-Benzyloxypentyl)-8-[(2-oxo-1-piperidyl)methyl]decahydroquinoline (11)

TFA (0.28 mL, 3.77 mmol) was slowly added to a solution of **10** (32 mg, 0.06 mmol) in CH_2Cl_2 (2.8 mL) at 0 °C, and the resulting solution was stirred at room temperature for 1 h. The reaction was quenched by addition of 2 M aqueous solution of KOH and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried, filtered and evaporated to afford decahydroquinoline **11** (23.2 mg, 90%) as a yellowish oil.

(−)-Schoberine B

First Step

$POCl_3$ (16.5 μL, 0.17 mmol) was added to a solution of decahydroquinoline **11** (74.3 mg, 0.17 mmol) in anhydrous toluene (4 mL) and the mixture was heated at reflux for 3 h. The mixture was allowed to cool down to room temperature and the solvent was evaporated. Then, $LiAlH_4$ (0.27 mL of a 1 M solution in THF, 0.27 mmol) was added to a stirring solution of the crude iminium salt in anhydrous THF (2.6 mL) at 0 °C. After 30 min, the mixture was allowed to warm to room temperature and stirred for additional 12 h. Cold water was slowly added until no bubbling and the resulting mixture was dried and concentrated. The residue was purified by flash chromatography (NH–SiO_2, CH_2Cl_2) to afford a crude tetracyclic product.

Second Step

A solution of the above crude in anhydrous THF (3 mL) was added to a solution of liquid ammonia at −78 °C under an argon atmosphere. Sodium was added until a persistent blue color appeared, and the mixture was stirred for 10 min at −78 °C, then saturated aqueous NH_4Cl was added. The mixture was warmed up to room temperature, extracted with CH_2Cl_2, dried, and evaporated. Flash chromatography (NH–SiO_2, CH_2Cl_2 to 9:1 CH_2Cl_2/MeOH) afforded **(−)-schoberine B** (23.5 mg, 42% from **11**) as a colorless gum.

Supporting Information

Complete experimental procedures for the preparation of the oxoacid **6** and the synthesis of (+)-schoberine B, characterization data for all compounds, copies of ^1H and ^{13}C NMR spectra, and X-ray crystallographic data for (+)-schoberine B. CCDC-2294529 contains the supplementary crystallographic data for (+)-schoberine B. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

Acknowledgements

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