Enantiopure 2,6-disubstituted piperidines bearing one alkene- or alkyne-containing substituent: preparation and application to total syntheses of indolizidine-alkaloids†

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A general and efficient procedure for the preparation of 2,6-disubstituted piperidines bearing one alkene- or alkyne-containing substituent was developed by using non-racemic Betti base as a chiral auxiliary. Many chiral benzylamines are excellent auxiliaries, but they were rarely used for this purpose because of the inefficient removal of the *N*-benzyl auxiliary residue under non-hydrogenative conditions. We found that *N*,*N*-disubstituted Betti base derivative has a typical Mannich structure of *o*-naphthol. When it carried out a base-catalyzed formation of *o*-quinone methide, an efficient non-hydrogenative *N*-debenzylation was achieved, and the alkene and alkyne groups survived. To demonstrate the efficiency of the method and the versatility of the products, asymmetric total syntheses of indolizidine-alkaloids (–)-167B, (–)-195H, (–)-209D and (–)-223AB were accomplished.

Introduction

Indolizidines are a class of alkaloids with a nitrogen-bridged bicyclic skeleton. Many chiral 5-substituted and 3,5-disubstituted indolizidines were isolated from ants and amphibians,[1] such as indolizidines (–)-167B (**1**), (–)-195H (**2**), (–)-209D (**3**) and (–)-223AB (**4**) (Fig. 1). Owing to their biological importance and novel structures,[2] they have continuously been challenging targets of total synthesis. In the past decades, a number of routes have been reported for asymmetric total syntheses of alkaloids **1–4**,[3–7] partially because they also served as the excellent test cases for new synthetic methodologies and strategies.

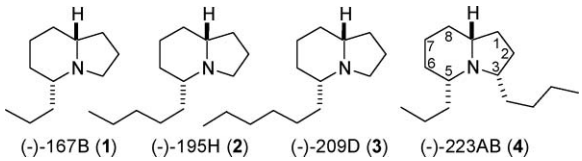
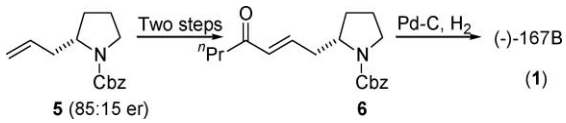


Fig. 1

Many alkene compounds were used as key precursors in the existing synthetic routes. Prominent among these is (*S*)-2-allyl-*N*-Cbz-pyrrolidine (**5**), by which one of the shortest and most efficient synthesis of (–)-167B (**1**) was achieved recently.[3b] It owed its success mainly to a well-established strategy that was originally described by Remuson *et al.* in a racemic synthesis of (±)-167B in 2001.[8] As shown in Scheme 1, (–)-167B (**1**) was obtained in 35% overall yield by a conversion of **5** into α,β-unsaturated ketone **6**

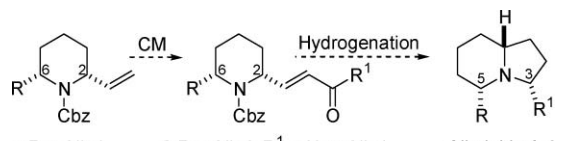


Scheme 1

followed by a catalytic hydrogenation. It is noteworthy that the hydrogenation of **6** was a three-step one-pot reaction including a deprotection of the Cbz group, a reduction of the alkene and an intramolecular reductive amination.

However, this synthetic strategy suffered from tedious preparation of **5** with unsatisfying enantioselectivity. When it was extended to the synthesis of 3,5-disubstituted indolizidines, preparation of the analogues of **5** had become a major obstacle.[9] Since compound **5** and its analogues were prepared already by the best current methods, therefore, it is necessary to find alternatives for them as new precursors to enhance the efficiency of this synthetic strategy.

Herein, we report a general and efficient method for the preparation of enantiopure 2,6-disubstituted piperidines bearing one alkene- or alkyne-containing substituent. As shown in Scheme 2, we propose that (2*R*,6*R*)-2-vinyl-6-alkyl-*N*-Cbz-piperidine (**7**) may be a very suitable precursor for the syntheses of indolizidine-alkaloids. When **7** carries out a cross-metathesis reaction (CM), α,β-unsaturated ketone **8** can be obtained in a singe step. Then, the hydrogenation of **8** offers the corresponding 5-substituted or 3,5-disubstituted indolizidine depending upon the R^1 group. To display the efficiency of our proposed route, the total syntheses of indolizidines **1–4** were demonstrated.



Scheme 2

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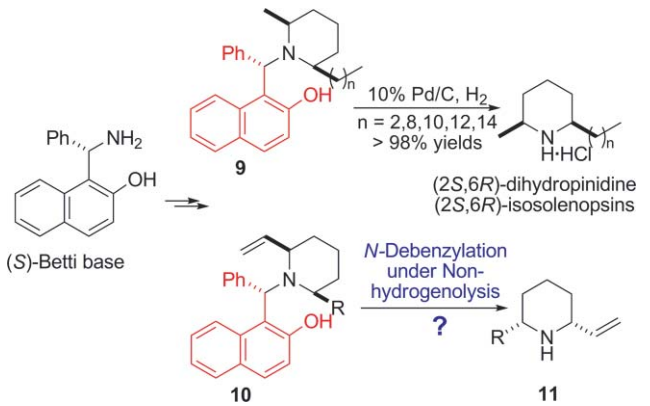
† Electronic supplementary information (ESI) available: Experiments, characterization, and ^{1}H and ^{13}C NMR spectra for **14a–e**, **17**, **7a–r**, **8a–d**, and **1–4**. See DOI: 10.1039/b927007h

Results and discussion

Preparation of enantiopure 2,6-disubstituted piperidines bearing one alkene- or alkyne-containing substituent

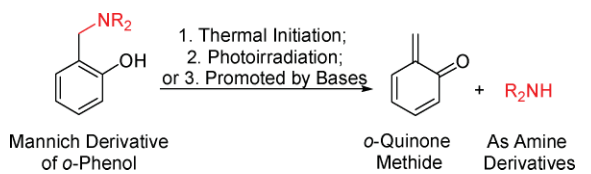
The investigation showed that a number of methods have been reported for the preparation of the title compounds.[3c,d,10,11] Although each of them has some advantages, however, there remains a great need for a highly enantioselective, efficient, convenient and scalable procedure.

In our recent works, Betti base was resolved conveniently to its non-racemic isomers on a kilogram scale by a kinetic resolution.[12a] Then, a highly enantioselective and regioselective strategy was developed for the total syntheses of (2*S*,6*R*)-dihydropinidine and (2*S*,6*R*)-isosolenopsins.[12b] However, this original protocol could not be suitable for the preparation of any alkene-containing chain-substituted piperidines because the auxiliary residue was removed *via* a hydrogenative *N*-debenzylation (Scheme 3). In fact, this was a common problem for most asymmetric syntheses by using chiral benzylamine auxiliaries. For example, non-racemic 2-phenylglycinol is an excellent auxiliary for the preparation of chiral piperidines,[13] but it was rarely used for the preparation of alkene compounds[14] because its auxiliary residue could not be removed efficiently *via* a non-hydrogenative *N*-debenzylation. Since the intermediate **10** can be obtained easily by similar procedures to that of **9**,[12b,15] thus, the key issue for the preparation of 2-vinyl-6-alkyl-piperidines (**11**) is how to develop an efficient non-hydrogenative *N*-debenzylation method.



Scheme 3

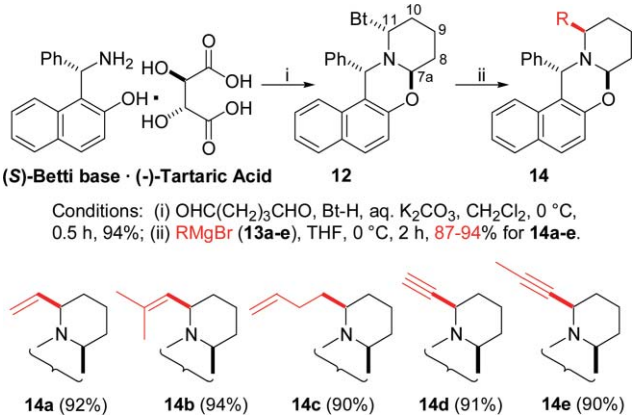
Further investigation showed that Mannich derivatives of *o*-phenol and *o*-naphthol are good precursors for the generation of *o*-quinone methide.[16] As shown in Scheme 4, this transformation is accompanied by a *N*-debenzylation and usually promoted by thermal initiation,[17] photoirradiation[18] or bases.[19] Therefore, when the intermediate **10**, as a typical Mannich derivative of *o*-naphthol, is converted into the corresponding *o*-quinone methide under those



Scheme 4

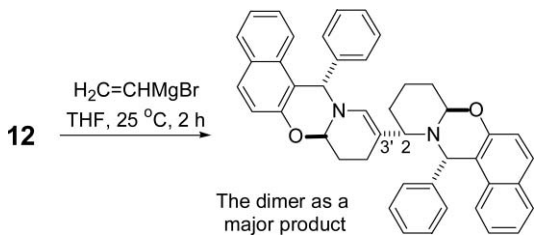
conditions, the expected non-hydrogenative *N*-debenzylation of **10** may be achieved.

Thus, the diastereopure precursor **12** was prepared by a known procedure.[12b] As was expected, when **12** was treated with H_2C=CHMgBr (**13a**) in THF, the alkylation occurred on C11 to give **14a** in 92% yield. As we revealed in our previous study, the regioselectivity of this alkylation was controlled by THF solvent. When Et_2O was used as a solvent, the alkylation occurred on both C7a and C11. As shown in Scheme 5, by using other alkene- or alkyne-containing Grignard reagents **13b–e**, the corresponding **14b–e** were obtained as single diastereoisomers in excellent yields.



Scheme 5

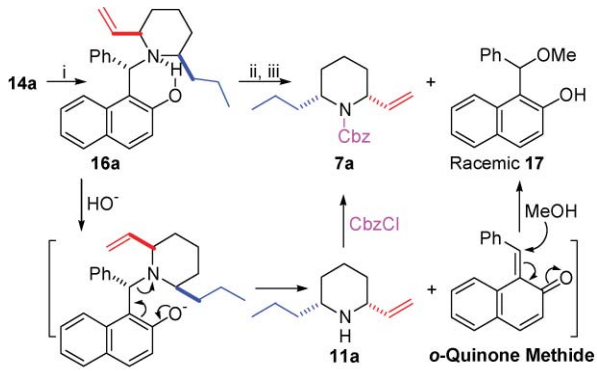
Since diastereopure precursor **12** has three chiral carbons, the diastereomeric purity for products **14a–e** can be easily measured by their ^{1}H and ^{13}C NMR spectra. Therefore, the conversion of **12** to **14a** has been monitored carefully by NMR measurements of the crude product. We found that this conversion was a temperature-controlled reaction. When the reaction proceeded below 0 °C, **14a** was obtained as a single diastereoisomer. However, a complex mixture was obtained when the reaction proceeded above 25 °C, in which a dimer product was isolated as a major product (Scheme 6).



Scheme 6

We proposed that the alkylation of **12** may be a S_N2 reaction at 0 °C because the Bt-group was replaced with complete inversion of configuration. The fact that **14a–e** were obtained as single diastereoisomers may result in the bulky size of Bt-group. While, the dimmer may be obtained by an iminium salt intermediate when the reaction proceeded at higher temperature.

As shown in Scheme 7, when **14a** was treated with ^{n}PrMgBr (**15a**) and quenched with saturated aq. NH_4Cl, the expected **16a** was obtained in almost quantitative yield. Accidentally, when the reaction was quenched with H_2O, an *N*-debenzylated product (2*R*,6*R*)-2-vinyl-6-propylpiperidine (**11a**) was also isolated in 18%



Conditions: i. ^{n}PrMgBr (**15a**), Et_2O, 0 °C, 0.5 h; ii. 6 M aq. NaOH, MeOH, THF, 60 °C, 1 h; iii. Cbz-Cl, K_2CO_3, CH_2Cl_2, rt, 4 h; 84% for three steps.

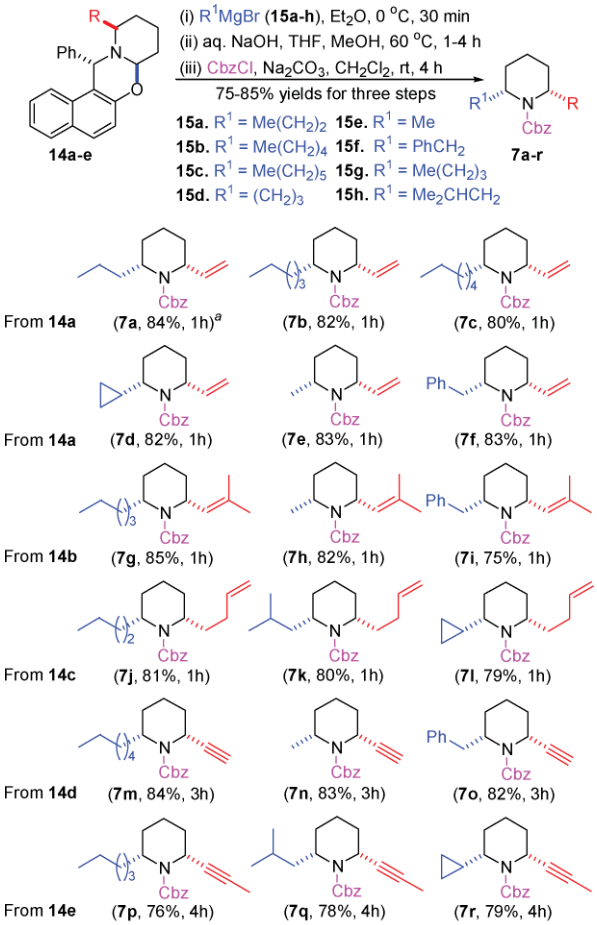
Scheme 7

yield. Realizing that **11a** may be produced by a base-catalyzed *N*-benzylation *via* a generation of *o*-quinone methide mechanism, a group of conditional experiments were tested. We found that the yield of **11a** could be improved by increasing the concentration of aq. NaOH, adding MeOH as a nucleophilic reagent or elevating the reaction temperature. When the mixture of **16a** in 6.0 M aq. NaOH–MeOH–THF (1 : 2 : 2 by v/v) was heated at 60 °C, **16a** was exhausted completely within 1 h. Although the fact that racemic **17** was isolated in 91% yield as a by-product gave strong evidence for our hypothesis, **11a** normally was obtained in less than 40% yield because of its high volatility. However, this problem was resolved easily by treatment of the crude **11a** with CbzCl, by which desired (2*R*,6*R*)-2-vinyl-6-propyl-*N*-Cbz-piperidine (**7a**) was obtained in 84% yield. Since the structural assignments of intermediate **16a** suffered from ambiguous ^{1}H and ^{13}C NMR spectra because of the unusual coalescence phenomenon caused by a strong intramolecular hydrogen bonding,[12b] therefore, it was directly used in the next step without purification and characterization.

For the same reason, the NMR spectra of **16a** could not be used for the measurement of its diastereomeric purity. However, we can use the NMR spectra of compound **7a** (the derivative of **16a**) to measure its diastereomeric purity. Compound **7a** has two chiral carbons that were formed in two separated steps. Theoretically, compound **7a** should be an enantiomeric pure product when its NMR spectra prove that it is a single product. In fact, the NMR spectra of **7a** (see the ESI†) proved that it was a single product. In addition, we also found that the mixture of (2*R*,6*R*)-**7a** and its diastereoisomer (2*R*,6*S*)-**7a** could not be separated under our chromatography conditions (silica gel, EtOAc : PE = 1 : 5). Therefore, these results indirectly proved that the conversion of **14a** to **16a** may be an enantiopure conversion.

As shown in Table 1, the method was quite general and showed high diastereoselectivity. When **14a** was treated with different RMgBr (**15b–f**), the corresponding **7b–f** were obtained in 80–84% yields. The long (**7c**), short (**7e**) or cycloalkyl (**7d**) and benzyl (**7f**) substitutes gave very satisfying results. When **14b–e** were used as substrates, the novel alkene- (**7g–l**) or alkyne-containing (**7m–r**) chain-substituted 2,6-disubstituted piperidines were obtained smoothly. Since the diastereoselectivity of products can be easily monitored by ^{1}H and ^{13}C NMR spectra, all the final products **7a–r** were confirmed to be obtained in enantiopure

Table 1 (2*R*,6*R*)-2,6-Disubstituted piperidines bearing one alkene- or alkyne-containing substituent



a. The time in the parathesis is for the base-catalyzed *N*-debenzylation.

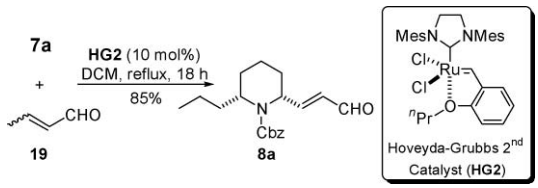
forms. Based on the data of ^{1}H and ^{13}C NMR of **7a–r**, as well as by comparison their rotations with that of known products, we suggested that the alkylation on C7a may go through an iminium salt pathway because the new C–C bond was formed with retention of configuration.

Total syntheses of natural indolizidine-alkaloids

By using our developed method, enantiopure (2*R*,6*R*)-6-propyl- (**7a**), (2*R*,6*R*)-6-pentyl- (**7b**) or (2*R*,6*R*)-6-hexyl-2-vinyl-*N*-Cbz-piperidine (**7c**) was prepared on a gram scale within a few hours.

According to the proposal in Scheme 2, **7a–c** will be converted into the corresponding α,β-unsaturated aldehyde or ketone. In recent years, the conversion of alkene into α,β-unsaturated aldehyde[20,21] or ketone[22] by cross-metathesis reaction (CM) is very popular and it can be influenced by Grubbs 1st (**G1**) and 2nd (**G2**) or Hoveyda–Grubbs (**HG**) catalysts. Although acrolein (**18**)[20] was often used as an aldehyde group donor in the preparation of α,β-unsaturated aldehyde, its CM reaction with **7a** usually gave an unseparated mixture, which may be caused by its higher self-metathesis reactivity. However, when crotonaldehyde (**19**)[21] was used as an alternative, the expected product **8a** was obtained in a variable yield. As shown in Table 2, Grubbs 1st and 2nd catalysts could not offer a satisfying yield of **8a** (entries 1–5). However,

Table 2 Conversion of **7a** into **8a** by CM reaction



Entry	Catalyst (mol%)	Solvent	Temp./°C	Time/h	Yield of **8a** (%)[a]
1	**G1** (5)	CH_2Cl_2	40	20	12
2	**G2** (5)	CH_2Cl_2	40	20	23
3	**G2** (5)	$(CH_2Cl)_2$	80	20	31
4	**G2** (5)	PhMe	110	20	38
5	**G2** (10)	CH_2Cl_2	40	20	47
6	**HG2** (5)	CH_2Cl_2	40	20	72
7	**HG2** (10)	CH_2Cl_2	40	18	85

[a] Isolated yields were obtained.

Hoveyda–Grubbs 2nd catalyst (**HG2**) showed very good catalytic activity for this conversion (entry 6). When 10 mol% of **HG2** was used, **8a** was obtained in 85% yield (entry 7).

By a similar procedure, **8b–c** were prepared in satisfying yields by CM reaction between **7b–c** and **19**. As was expected, CM reaction between **7a** and oct-2-en-4-one (**20**) gave desired α,β-unsaturated ketone **8d** in 92% yield. It was interesting to observed that all *Z*-alkenes were obtained in **8a–d** regardless of *E*/*Z* ratio of the substrates **19** and **20** (Fig. 2).

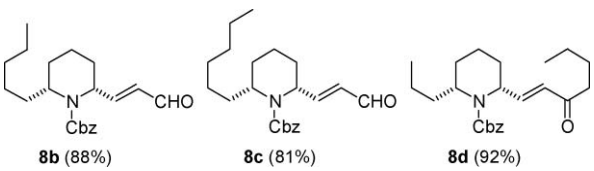
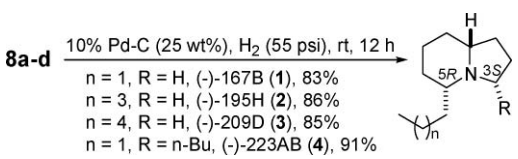


Fig. 2

Finally, the three-step one-pot hydrogenation of **8a–d** proceeded smoothly over Pd–C catalyst to give the target alkaloids **1–4** in high yields (Scheme 8). No surprise, the formation of **4** was accompanied by 9% of (3*R*)-diastereomer. Since alkaloids **1–4** were known products and their stereochemistries have been well established in the literature, therefore, the stereochemistry of **7a–r** and the mechanisms of alkylations in the preparation of **7a–r** were re-confirmed.



Scheme 8

Conclusion

A general and efficient method for the preparation of enantiopure 2,6-disubstituted piperidines bearing one alkene- or alkyne-containing substrate was established by using non-racemic Betti base as a chiral auxiliary. The key step is that the auxiliary residue was removed *via* a base-catalyzed generation of *o*-quinone methide mechanism, by which an efficient non-hydrogenative *N*-debenzylation was achieved and the alkene and alkyne groups were survived. In total, eighteen such novel 2,6-disubstituted piperidines were prepared. By using some of those compounds as versatile building blocks, asymmetric total syntheses of indolizidine-alkaloids (–)-167B, (–)-195H, (–)-209D and (–)-223AB were accomplished, respectively.

Experimental section

General remarks

All melting points were determined on a Yanaco melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 343 polarimeter. IR spectra were recorded on a Nicolet FT-IR 5DX spectrometer with KBr pellets. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL JNM-ECA 300 spectrometer in $CDCl_3$. TMS was used as an internal reference and the *J* values are given in Hz. MS were recorded on a VG-ZAB-MS spectrometer with 70 eV. Elementary analysis data were obtained on a Perkin-Elmer-241C apparatus. PE is petroleum ether (60–90°).

A typical procedure for preparation of (7a*R*,11*R*,13*S*)-11-vinyl-13-phenyl-7a,8,10,11-tetrahydro-9*H*,13*H*-naphtho[1,2-*e*]-pyrido[2,1-*b*][1,3]oxazine (14a). To a cold solution (ice-water bath) of **12** (4.32 g, 10 mmol) in dry THF (70 mL) was added H_2C=CHMgCl (1.6 M in THF, 18.8 mL, 30 mmol) dropwise under N_2. After the reaction was stirred at 0 °C for 0.5 h (monitored by TLC), a saturated aqueous solution of NH_4Cl (30 mL) was added to quench the reaction. Then, the resultant mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with H_2O, brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by chromatography (silica gel, EtOAc : PE = 1 : 15) to give product **14a** (3.14 g, 92%) as a white crystal, mp 137–138 °C (EtOAc–PE), $[\alpha]_D^{25}$ = +173.4° (*c* 0.2, $CHCl_3$). IR: *ν* 3063, 2935, 1628 cm^{-1}; ^{1}H NMR: *δ* 1.43-1.50 (m, 1H), 1.65-1.74 (m, 2H), 1.85-2.07 (m, 3H), 3.62-3.70 (m, 1H), 4.51-4.55 (m, 1H), 4.91-4.97 (m, 2H), 5.17 (s, 1H), 5.92-6.08 (m, 1H), 7.06-7.08 (m, 1H), 7.16-7.31 (m, 8H), 7.65-7.75 (m, 2H); ^{13}C NMR: *δ* 15.2, 29.8, 31.6, 60.2, 63.5, 81.0, 114.4, 115.3, 118.7, 122.8, 123.0, 126.1, 127.0, 128.0 (2C), 128.4, 128.6 (2C), 129.2 (2C), 131.9, 140.6, 143.1, 153.4; MS *m*/*z* (%): 341 (M^+, 6.3), 231 (100). Anal. Calcd. For $C_{24}H_{23}NO$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.20; H, 6.89; N, 4.25.

By using a similar procedure, the intermediates **14b–e** were prepared (see the ESI†).

A typical procedure for preparation of (2*R*,6*R*)-benzyl 2-vinyl-6-propyl-piperidine-1-carboxylate (7a). To a stirred solution of *n*-PrMgBr made from Mg (1.22 g, 50 mmol) and *n*-PrBr (3.69 g, 30 mmol) in dry Et_2O (15 mL) was added a solution of **14a** (3.41 g, 10 mmol) in dry Et_2O (70 mL) within 20 min at 0 °C under N_2. After the resultant mixture was stirred for another 10 min, it was quenched by addition of a saturated aqueous solution of NH_4Cl (40 mL). The organic layer was separated and the aqueous layer was extracted by Et_2O (3 × 30 mL). The combined organic layers were washed with brine (3 × 30 mL) and dried over Na_2SO_4. The solvent was removed to give crude **16a** as an oil residue.

The residue (crude **16a**) was diluted by a solution of THF (10 mL), CH_3OH (10 mL) and aq. NaOH (6.0 M, 5 mL), and was refluxed for 1 h. Then it was cooled to room temperature and quenched by addition of CH_2Cl_2 (50 mL). The resultant mixture was extracted by aq. HCl (6.0 M, 3 × 20 mL) and the combined aqueous layers were neutralized by aq. NaOH (6.0 M). The alkaline solution was extracted with CH_2Cl_2 (3 × 20 mL) again and the combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4.

After Na_2SO_4 was filtered off, the filtrate containing free amine **11a** was treated with CbzCl (3.41 g, 20 mmol) and Na_2CO_3 (5.3 g, 50 mmol). The mixture was stirred for 4 h at room temperature and the solid was filtrated off. Then the solvent was evaporated in vacuum and the residue was purified by chromatography (silica gel, EtOAc : PE = 1 : 30) to give product **7a** (2.45 g, 84%) as a colorless oil, $[\alpha]_D^{25} = +24.7°$ (*c* 1.8, $CHCl_3$). IR: *ν* 2939, 1691, 1408 cm^{-1}; ^1H NMR: *δ* 0.87 (t, *J* = 7.2, 3H), 1.15-1.92 (m, 10H), 4.15-4.30 (m, 1H), 4.75-4.85 (m, 1H), 5.02-5.20 (m, 4H), 5.85-6.05 (m, 1H), 7.25-7.41 (m, 5H); ^{13}C NMR: *δ* 14.0, 14.5, 202, 27.7, 27.8, 36.3, 50.9, 51.7, 66.9, 114.8, 127.8 (3C), 128.4 (2C), 137.0, 139.7, 156.0; MS *m*/*z* (%): 287 (M^+, 4.58), 200 (100). Anal. Calcd. For $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.50; H, 8.72; N, 4.85.

By a similar procedure, the compounds **7a–r** were prepared from **14a–e** and different R^1MgBr (**15a–h**) (see the ESI†).

A typical procedure for the preparation of (2*R*,6*R*,*E*)-benzyl 2-(3-oxoprop-1-enyl)-6-propylpiperidine-1-carboxylate (8a). To a boiling solution of **7a** (500 mg, 1.75 mmol) and crotonaldehyde (**19**, 370 mg, 5.25 mmol) in CH_2Cl_2 was added Hoveyda–Grubbs catalyst [2nd generation (**HG2**), 110 mg, 0.525 mmol] with bubble of N_2 at the bottom of solution. After the reaction system was refluxed for 18 h, the solvent was evaporated in vacuum. The residue was purified by chromatography (silica gel, EtOAc : PE = 1 : 5) to give product **8a** (460 mg, 85%) as a yellowish oil, $[\alpha]_D^{25} = +92.9°$ (*c* 0.4, $CHCl_3$). IR: *ν* 2954, 1686, 1406 cm^{-1}; ^1H NMR: *δ* 0.86 (t, *J* = 7.2, 3H), 1.15-2.05 (m, 10H), 4.15-4.30 (m, 1H), 5.03-5.22 (m, 3H), 6.18 (qd, *J* = 7.6 and 1.8, 1H), 6.83 (dd, *J* = 14.5 and 7.8, 1H), 7.25-7.41 (m, 5H), 9.53 (d, *J* = 7.8, 1H); ^{13}C NMR: *δ* 13.9, 14.5, 20.1, 27.3, 36.1, 50.7, 50.9, 67.4, 128.0 (2C), 128.1 (2C), 128.5 (2C), 131.7, 136.4, 155.8, 158.8, 193.6; MS *m*/*z* (%): 315 (M^+, 1.83), 91 (100). Anal. Calcd. For $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.27; H, 8.05; N, 4.38.

By using a similar procedure, the products **8b–d** were prepared.

(2*R*,6*R*,*E*)-Benzyl 2-(3-oxoprop-1-enyl)-6-pentylpiperidine-1-carboxylate (8b). It is a yellowish oil (88%), $[\alpha]_D^{25} = +88.3°$ (*c* 0.2, $CHCl_3$). IR: *ν* 2933, 1684, 1406 cm^{-1}. ^1H NMR: *δ* 0.84 (t, *J* = 7.2, 3H), 1.15-2.05 (m, 14H), 4.15-4.30 (m, 1H), 5.03-5.22 (m, 3H), 6.17 (dq, *J* = 1.8 and 7.6, 1H), 6.83 (dd, *J* = 14.5 and 7.8, 1H), 7.25-7.45 (m, 5H), 9.53 (d, *J* = 7.8, 1H); ^{13}C NMR: *δ* 14.0, 14.5, 22.5, 26.5, 27.3, 31.5, 33.9, 50.6, 51.1, 67.4, 128.0 (2C), 128.1 (2C), 128.5 (2C), 131.6, 136.4, 155.8, 158.8, 193.5; MS *m*/*z* (%): 343 (M+, 2.84), 91 (100). Anal. Calcd. For $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.05; H, 8.48; N, 4.00.

(2*R*,6*R*,*E*)-Benzyl 2-(3-oxoprop-1-enyl)-6-hexylpiperidine-1-carboxylate (8c). It is a yellowish oil (81%), $[\alpha]_D^{25} = +101.2°$ (*c* 0.5, $CHCl_3$). IR: *ν* 2931, 1686, 1408 cm^{-1}. ^1H NMR: *δ* 0.86 (t, *J* = 7.2, 3H), 1.15-2.05 (m, 16H), 4.15-4.30 (m, 1H), 5.03-5.22 (m, 3H), 6.17 (dq, *J* = 1.8 and 7.6, 1H), 6.83 (dd, *J* = 14.5 and 7.8, 1H), 7.25-7.45 (m, 5H), 9.53 (d, *J* = 7.8, 1H); ^{13}C NMR: *δ* 14.0, 14.5, 22.5, 26.9, 27.3, 27.4, 29.1, 31.7, 33.9, 50.6, 51.1, 67.4, 128.0 (2C), 128.1, 128.5 (2C), 131.6, 136.4, 155.8, 158.8, 193.5; MS *m*/*z* (%): 357 (M+, 2.70), 91 (100). Anal. Calcd. For $C_{22}H_{31}NO_3$: C, 73.91; H, 8.74; N, 3.92. Found: C, 73.87; H, 8.95; N, 4.02.

(2*R*,6*R*,*E*)-Benzyl 2-(3-oxohept-1-enyl)-6-propylpiperidine-1-carboxylate (8d). It is a yellowish oil (92%), $[\alpha]_D^{25} = +67.9°$ (*c* 0.48, $CHCl_3$). IR: *ν* 2936, 1951, 1686, 1408 cm^{-1}; ^1H NMR: *δ* 0.78-0.95 (m, 6H), 1.15-2.00 (m, 13H), 2.50 (t, *J* = 7.2, 3H), 4.15-4.30 (m, 1H), 4.90-5.00 (m, 1H), 5.15 (s, 2H), 6.15 (dd, *J* = 14.5 and 1.8, 1H), 6.81 (dd, *J* = 14.5 and 7.8, 1H), 7.25-7.45 (m, 5H); ^{13}C NMR: *δ* 13.8, 13.9, 14.5, 20.1, 22.3, 26.1, 27.5, 27.7, 36.2, 40.1, 50.4, 50.8, 67.2, 127.9 (2C), 128.0, 128.4 (2C), 129.4, 136.6, 146.7, 155.8, 200.5. MS *m*/*z* (%): 371 (M^+, 13.65), 284 (100). Anal. Calcd. For $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95; N, 3.77. Found: C, 74.45; H, 8.95; N, 3.61.

A typical procedure for the preparation of (–)-(5*R*,9*R*)-indolizidine 167B (1). A suspension of **8a** (420 mg, 1.33 mmol) and 10% Pd–C (105 mg, 25 wt%) in anhydrous MeOH (20 mL) was stirred under hydrogen atmosphere (55 psi) at room temperature for 12 h. After the Pd–C catalyst was filtered off, solvent was removed on a rotary evaporator. The residue was purified by chromatography (silica gel, EtOAc–MeOH = 10 : 1) to give 184 mg (83%) of product **5a** as a yellowish oil, $[\alpha]_D^{25} = -104.4°$ (*c* 0.44, CH_2Cl_2) [lit.[3d] $[\alpha]_D^{22} = -109°$ (*c* 1.32, CH_2Cl_2); lit.[5c] $[\alpha]_D^{20} = -106.9°$ (*c* 1.10, CH_2Cl_2)]. ^1H NMR: *δ* 0.91 (t, *J* = 7.0, 3H), 1.10-2.05 (m, 16H), 2.05 (q, *J* = 8.6, 1H), 3.31 (dt, *J* = 2.1 and 8.6, 1H); ^{13}C NMR: *δ* 14.4, 19.0, 20.2, 24.4, 30.3, 30.4, 30.5, 36.5, 51.2, 63.7, 65.2.

By using a similar procedure, the target products **2–4** were prepared.

(–)-(5*R*,9*R*)-Indolizidine 195H (2)[5a]. It is a yellowish oil (86%), $[\alpha]_D^{25} = -95.6°$ (*c* 1.1, CH_2Cl_2). ^1H NMR: *δ* 0.89 (t, *J* = 6.8, 3H), 1.05-1.95 (m, 20H), 1.97 (q, *J* = 8.8, 1H), 3.25 (dt, *J* = 2.1 and 8.6, 1H); ^{13}C NMR: *δ* 14.0, 20.4, 22.6, 24.7, 25.5, 30.5, 30.8, 31.0, 32.3, 34.6, 51.5, 63.9, 65.0.

(–)-(5*R*,9*R*)-Indolizidine 209D (3). It is a yellowish oil (85%), $[\alpha]_D^{25} = -77.1°$ (*c* 0.34, CH_2Cl_2) [lit.[5c] $[\alpha]_D^{19} = -84.9°$ (*c* 0.98, CH_2Cl_2); lit.[5f] $[\alpha]_D^{25} = -80.4°$ (*c* 1.0, CH_2Cl_2)]. ^1H NMR: *δ* 0.88 (t, *J* = 6.6, 3H), 1.05-1.95 (m, 22H), 1.97 (q, *J* = 8.6, 1H), 3.26 (dt, *J* = 2.1 and 8.6, 1H); ^{13}C NMR: *δ* 14.1, 20.4, 22.6, 24.7, 25.8, 29.7, 30.5, 30.8, 31.0, 31.8, 34.6, 51.5, 63.9, 65.0.

(–)-(3*S*,5*R*,9*R*)-Indolizine 223AB (4). It is a yellowish oil (91%), $[\alpha]_D^{25} = -82.0°$ (*c* 0.8, MeOH), [lit.[3c] $[\alpha]_D^{25} = -11.1°$ (*c* 0.2, MeOH)]. ^1H NMR: *δ* 0.80-0.95 (m, 6H), 1.05-1.50 (m, 16H), 1.50-1.85 (m, 4H), 2.16-2.00 (m, 2H), 2.45-2.57 (m, 1H); ^{13}C NMR: *δ* 14.1, 14.5, 19.3, 22.8, 24.9, 29.3, 29.8, 30.5, 31.0, 31.8, 38.0, 39.9, 62.1, 65.1, 67.4.

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