Organocatalytically Enantioselective Approach to Polysubstituted Tetrahydropyridines and Piperidines

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A convenient and highly enantioselective method for assembly of functionalized 1,2,3,4,5-pentasubstituted tetrahydropyridines and piperidines was developed. This method relies on preparing the required enantiopure cyclic semi-acetals via an organocatalyzed Michael addition/cyclization cascade reaction of aldehydes and *α*-keto-*α*,*β*-unsaturated esters, and subsequent reductive amination/condensation with primary amines.

Keywords organocatalysis, Michael addition, reductive amination, substituted piperidine, tetrahydropyridine

Introduction

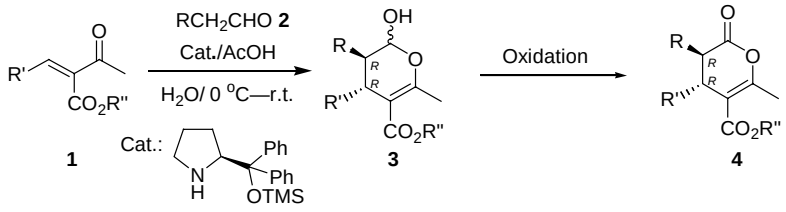
Polysubstituted piperidines are common subunits in natural products and biologically relevant molecules.[1] The classical approaches for constructing these compounds include aza-Prins cyclizations,[2] hetero-Diels-Alder reactions,[3] intramolecular Michael reactions,[4] and [3+3] annulations of aziridines with allenoates.[5] Recently, some novel methods for enantioselective synthesis of polysubstituted piperidines and related compounds have been disclosed. For example, Davies and coworkers discovered that tetrasubstituted piperidin-2-ones could be synthesized via a homochiral lithium amide-controlled process;[6] while Chen group reported that pentasubstituted piperidin-2-ones could be elaborated through highly diasteroselective nitro-Mannich reaction.[7]

During the investigations on the enamine-based Michael addition reactions,[8] we found that polysubstituted dihydropyrones **4** could be prepared from semi-actals **3** that was produced via a *O*-TMS protected diphenylprolinol catalyzed domino Michael addition/cyclization process (Scheme 1, Eq. 1).[8b] Obviously, condensation of **3** with primary amines followed by reductive amination would give polysubstituted tetrahydropyridines **6**, which could be converted into polysubstituted piperidine **7** by further reduction (Scheme 1, Eq. 2).

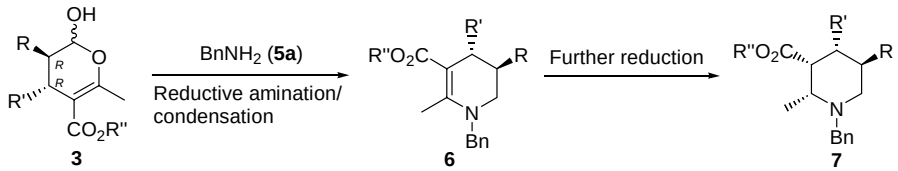
Results and discussion

With this idea in hand, we started our attempt to construct polysubstituted tetrahydropyridines. Under our optimized reaction conditions,[8b] the reaction of 1-*tert*-butyl 4-ethyl 2-acetylmaleate (**1a**) and *n*-butanal worked well to afford cyclic semi-acetal **3a**. As expected, reductive amination of **3a** with benzylamine under the action of $NaBH(OAc)_3$ proceeded smoothly, affording the desired tetrahydropyridine **6a** in 47%

Scheme 1



(1)



(2)

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yield, together with piperidine **7a** in 20% yield and 1,4-dihydropyridine **8a** in 12% yield (Scheme 2). Similar results were observed when two other semi-acetals were used.

The direct formation of piperidines **7** in the above process prompted us to study the reaction conditions for reductive amination in order to improve the yields of **7**. After some experimentations, we found that we could reach this goal by adding HOAc to adjust pH to 6—7, and increasing the amount of amine and $NaBH(OAc)_3$. Under these conditions, 1,2,3,4,5-pentasubstituted piperidine **7d** was isolated in 81% yield and 97% *ee* (Table 1, Entry 1). Further studies indicated that changing amines and semi-acetals was possible, thereby giving 1,2,3,4,5-pentasubstituted piperidines with good diversity. For examples, PMB and cyclopropanyl groups could be introduced at the 1-position using suitable amines; some functional groups could be added at the 4- and 5-positions. Noteworthy is that reduction of **7g**—**7j** with LAH was necessary because the resultant alcohol could be used for enantiopurity determination.

Based on our previous studies, the configuration at the 4 and 5 position in **7** should be *R,R*. To determine the relative stereochemistry in the two newly generated stereocenters, we carried out NOESY study to piperidine **7f** and found that substituents at 2, 3 and 4 positions were *cis* to each other (Figure 1). Strong NOE between 2-H/6-Ha, 2-H/4-H, 4-H/6-Ha and 4-H/2-H shows that 2-H, 4-H and 6-Ha are on the same face in the molecule. The coupling constants of 4-H and 6-Ha (11.6, 10.8 Hz) indicate that 4-H, 5-H and 6-Ha should occupy the axial (ax) positions, hence the other substituents at position 4, 5, 6 must be equatorial (eq) and 2-H must be axial (ax). The significant NOE between 4-H and 3-H shows that they are *cis* to each other and 3-H should be equatorial (eq). The coupling constant of 3-H (4.8 Hz) confirms its equatorial position. The coupling constants of 6-Hb (4.0, 11.2 Hz) also confirm its equatorial position. It is reasonable because during the second reductive amination, the borohydride anion might attack the iminium **10** from *Si* face to get favored conformation **B**, thereby giving the present product.

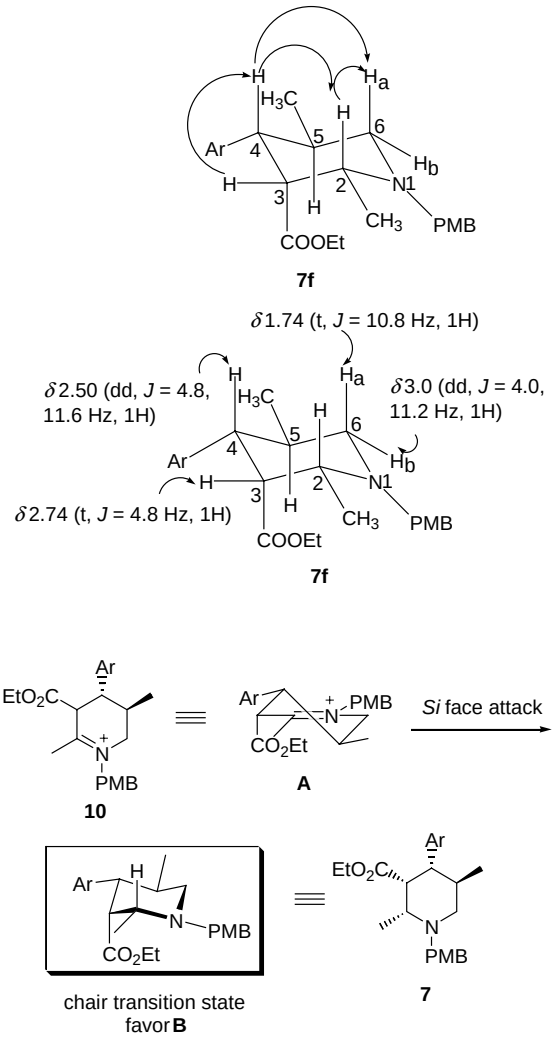

Figure 1 Determination of relative stereochemistry of **7**.

Conclusion

In conclusion, we have developed a convenient and highly enantioselective method for the assembly of functionalized pentasubstituted piperidines. This method may find special usages in synthesis of bioactive compounds.

Experimental

General information

For thin-layer chromatography (TLC), silica gel plates GF254 were used and compounds were visualized by irradiation with UV light, I_2, or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. Optical rotations were measured by using a Perkin-Elmer 241MC polarimeter in the solvent indicated. ^1H and ^{13}C NMR spectra were recorded on MERCURY300, Bruker DRX-400, and Bruker AV-500

Scheme 2 Synthesis of tetrahydropyridines

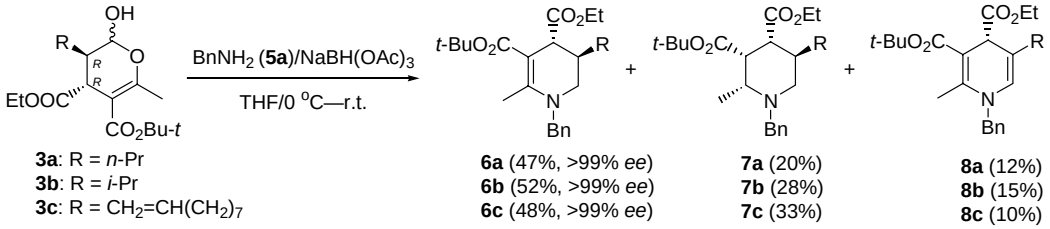

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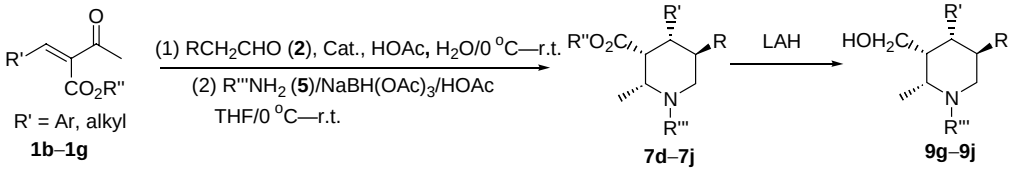
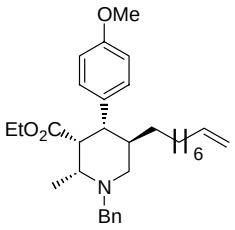
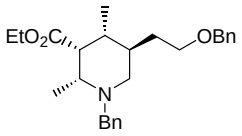
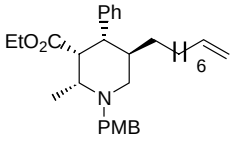
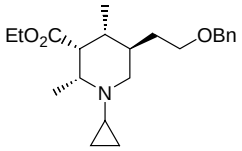
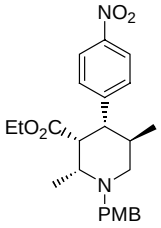
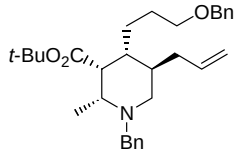
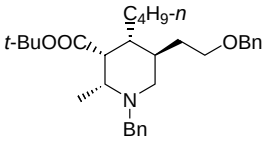
Table 1 Synthesis of polysubstituted piperidine **7**[a]



Entry	Product	Yield[b]/% ($1^{st}/2^{nd}$ step)	*ee*[c]/%	Entry	Product	Yield[b]/% ($1^{st}/2^{nd}$ step)	*ee*[c]/%
1	 **7d**	70/81	97	5	 **7h**	80/70	97[d]
2	 **7e**	79/60	98	6	 **7i**	80/69	97[d]
3	 **7f**	80/69	97	7	 **7j**	77/87	97[d]
4	 **7g**	78/87	97[d]				

[a] Reaction conditions for first step: **1** (0.25 mmol), cat. (0.025 mmol), aldehyde **2** (0.5 mmol), HOAc (0.125 mmol), water (0.25 mL), 0 ℃ for 1 h, then r.t. for the indicated time. For second step: amine (4.5 equiv., based on semi-acetal **3**), $NaBH(OAc)_3$ (7.0 equiv., based on semi-acetal **3**), r.t., 16 h. [b] Isolated yield. [c] Determined by chiral-phase HPLC analysis. [d] The *ee* value of **9** was determined.

spectrometers with TMS as the internal standard. HRMS were recorded by using either FTMS-7 or Ion-Spec 4.7 spectrometers. HPLC was carried out using a Water 515 pump, a Waters 2487 UV detector, a Millennium workstation, and a Daicel Chiralpak HPLC column. Yields refer to pure compounds, unless otherwise indicated.

General procedure for synthesis of cyclic semi-acetal 3 via the Michael addition/aldol addition process

To a suspension of (*S*)-*α*,*α*-diphenylprolinol O-TMS ether (10 mol%) and acetic acid (50 mol%) and *α*-keto-*α*,*β*-unsaturated ester **1** (0.5 mmol) in H_2O (0.2 mL) was added aldehyde **2** (1.0 mmol) at 0 ℃. The reaction mixture was stirred for 1 h at the same temperature and then allowed to warm to r.t. The stirring was continued until **1** was consumed (monitored by TLC). Ethyl acetate and saturated NaCl were added. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product. Purification of the residue by flash column chromatography (silica gel) eluting with 10∶1 petroleum ether/ethyl acetate afforded the cyclic hemiacetal **3**.

General procedure for sythesis of 6a—6c, 7a—7c, and 8a—8c

The cyclic hemiacetal **3a**—**3c** (0.2 mmol) was dissolved in dry THF (1 mL). $NaBH(OAc)_3$ (0.4 mmol, 4 equiv.) and $BnNH_2$ (0.24 mmol) were added to the solution at 0 ℃. After 10 min, the solution was allowed to warm up to r.t. After 16 h , ethyl acetate and 2 mL saturated $NaHCO_3$ were added. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4, then concentrated *in vacuo*. Purification of the residue by flash column chromatography eluting with 10∶1 petroleum ether/ethyl acetate afforded the corresponding piperidine derivatives **6**, **7** and **8**. The enantiomeric excess (*ee*) value of **6a**—**6c** was determined by analysis of the piperidine derivative using HPLC on a chiral phase.

(4*R*,5*R*)-3-*tert*-Butyl-4-ethyl-1-benzyl-2-methyl-5-propyl-1,4,5,6-tetrahydropyridine-3,4-dicarboxylate (6a) 80% yield for Michael addition/aldol addition, 47% yield for reductive amination; $[\alpha]_D^{25}$ +78.67 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.18—7.36 (m, 5H), 4.52 (d, J=17.2 Hz, 1H), 4.44 (d, J=17.2 Hz, 1H), 4.12 (q, J=6.8 Hz, 2H), 3.31—3.35 (m, 2H), 2.82 (dt, J=2.0, 13.2 Hz, 1H), 2.49 (s, 3H), 1.88—1.92 (m, 1H), 1.42 (s, 9H), 1.17—1.37 (m, 7H), 0.85 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 176.52, 168.75, 154.52, 137.98, 128.81 (2C), 127.35, 126.57 (2C), 92.66, 78.44, 60.43, 54.73, 49.47, 45.86, 34.39, 33.48, 28.60 (3C), 20.38, 16.48, 14.46, 14.09; ESI-MS *m*/*z*: 402.3 $(M+H)^+$; ESI-HRMS calcd for $C_{24}H_{35}NO_4$ $(M+H)^+$ 402.2652, found 402.2639; HPLC (Chiralpak OD-H, hexane/*i*-PrOH=98∶2, flow rate 0.5 mL/min, λ=214 nm), t_R=19.08 (major), 20.28 (minor) min; *ee*>99%.

(2*R*,3*R*,4*R*,5*R*)-3-*tert*-Butyl-4-ethyl-1-benzyl-2-methyl-5-propylpiperidine-3,4-dicarboxylate (7a) 80% yield for Michael addition/aldol addition, 20% yield for reductive amination; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.21—7.35 (m, 5H), 4.06—4.19 (m, 2H), 3.93 (d, J=14.1 Hz, 1H), 3.22 (d, J=14.1 Hz, 1H), 2.93 (dd, J=3.9, 15.6 Hz, 1H), 2.83—2.86 (m, 1H), 2.61—2.69 (m, 1H), 2.42—2.53 (m, 1H), 2.28—2.33 (m, 1H), 1.63—1.72 (m, 1H), 1.47 (s, 9H), 1.22—1.27 (m, 10H), 0.79 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.04, 170.45, 140.04, 128.35 (2C), 128.08 (2C), 126.56, 80.38, 60.27, 57.84, 57.34, 56.24, 49.62, 49.17, 34.80, 32.69, 28.13 (3C), 25.35, 19.89, 16.68, 14.21; ESI-MS *m*/*z*: 404.3 $(M+H)^+$; ESI-HRMS calcd for $C_{24}H_{38}NO_4$ $(M+H)^+$ 404.2807, found 404.2794.

(*R*)-3-*tert*-Butyl-4-ethyl-1-benzyl-2-methyl-5-propyl-1,4-dihydropyridine-3,4-dicarboxylat (8a) 80% yield for Michael addition/aldol addition, 12% yield for reductive amination; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.21—7.36 (m, 5H), 5.77 (s, 1H), 4.66 (d, J=16.4 Hz, 1H), 4.51 (d, J=16.4 Hz, 1H), 4.09—4.22 (m, 2H), 4.16 (s, 1H), 2.35 (s, 3H), 2.05—2.13 (m, 1H), 1.89—1.93 (m, 1H), 1.54—1.56 (m, 2H), 1.44 (s, 9H), 1.26 (t, J=7.2 Hz, 3H), 0.89 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 174.14, 168.03, 149.49, 138.27, 128.97 (2C), 127.68, 127.37, 125.94 (2C), 114.18, 96.65, 79.44, 60.54, 53.72, 45.63, 34.73, 28.50 (3C), 20.15, 15.47, 14.51, 13.88; ESI-MS *m*/*z*: 400.3 $(M+H)^+$; ESI-HRMS calcd for $C_{24}H_{33}N_1NaO_4$ $(M+Na)^+$ 422.2319, found 422.2301.

(4*R*,5*R*)-3-*tert*-Butyl-4-ethyl-1-benzyl-5-isopropyl-2-methyl-1,4,5,6-tetrahydropyridine-3,4-dicarboxylate (6b) 65% yield for Michael addition/aldol addition, 52% yield for reductive amination; $[\alpha]_D^{25}$ +58.03 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.18—7.35 (m, 5H), 4.57 (d, J=16.4 Hz, 1H), 4.38 (d, J=16.4 Hz, 1H), 4.12 (q, J=6.8 Hz, 2H), 3.63 (s, 1H), 3.27 (dd, J=3.2, 13.2 Hz, 1H), 2.98 (dt, J=2.4, 13.2 Hz, 1H), 2.48 (s, 3H), 1.55—1.61 (m, 2H), 1.44 (s, 9H), 1.25 (t, J=7.2 Hz, 3H), 0.96 (d, J=6.4 Hz, 3H), 0.79 (d, J=6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 176.65, 168.70, 154.90, 137.99, 128.86 (2C), 127.37, 126.60 (2C), 93.06, 78.40, 60.42, 54.81, 47.81, 43.49, 40.61, 28.64 (3C), 27.50, 21.17, 20.32, 16.49, 14.48; ESI-MS *m*/*z*: 402.1 $(M+H)^+$; ESI-HRMS calcd for $C_{24}H_{35}NO_4$ $(M+H)^+$ 402.2643, found 402.2639; HPLC (Chiralpak OD-H, hexane/*i*-PrOH=98∶2, flow rate 0.5 mL/min, λ=214 nm), t_R=14.37 (major), 15.90 (minor) min; *ee*>99%.

(2*R*,3*R*,4*R*,5*R*)-3-*tert*-butyl-4-ethyl-1-benzyl-5-isopropyl-2-methylpiperidine-3,4-dicarboxylate (7b) 65% yield for Michael addition/aldol addition, 28% yield for reductive amination; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.21—7.36 (m, 5H), 4.06—4.18 (m, 2H), 3.85 (d, J=13.5 Hz, 1H), 3.29 (d, J=13.8 Hz, 1H), 2.62—2.84 (m, 4H), 2.32—2.42 (m, 1H), 1.86—1.93 (m, 2H), 1.48 (s, 9H), 1.25 (t, J=7.2 Hz, 3H), 1.21 (t, J=5.4 Hz, 3H), 0.84 (d, J=6.6 Hz, 3H), 0.70 (d, J=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.45, 170.74, 140.11, 128.60 (2C), 128.22 (2C), 126.74, 80.44, 60.46, 57.88, 57.37, 50.18, 49.05, 46.28, 38.53, 28.29 (3C), 27.42, 21.10, 17.50, 15.55, 14.36; ESI-MS *m*/*z*: 404.1 $(M+H)^+$; ESI-HRMS calcd for $C_{24}H_{38}NO_4$ $(M+H)^+$ 404.2785, found 404.2795.

(*R*)-3-*tert*-Butyl-4-ethyl-1-benzyl-5-isopropyl-2-methyl-1,4-dihydropyridine-3,4-dicarboxylate (8b) 65% yield for Michael addition/aldol addition, 15% yield for reductive amination; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.22—7.36 (m, 5H), 5.80 (s, 1H), 4.71 (d, J=17.2 Hz, 1H), 4.52 (d, J=17.2 Hz, 1H), 4.27 (s, 1H), 4.09—4.19 (m, 2H), 2.30—2.42 (m, 1H), 2.33 (s, 3H), 1.45 (s, 9H), 1.25 (t, J=7.2 Hz , 3H), 1.06 (d, J=6.8 Hz, 3H), 1.01 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 174.52, 168.02, 149.44, 138.30, 128.94 (2C), 127.34, 126.45, 125.95 (2C), 120.42, 96.74, 79.42, 60.51, 53.97, 44.27, 30.31, 28.54 (3C), 21.96, 20.76, 15.54, 14.46; ESI-MS *m*/*z*: 400.1 $(M+H)^+$; ESI-HRMS calcd for $C_{24}H_{33}N_1NaO_4$ $(M+Na)^+$ 422.2311, found 422.2302.

(4*R*,5*R*)-3-*tert*-Butyl-4-ethyl-1-benzyl-2-methyl-5-(non-8-enyl)-1,4,5,6-tetrahydropyridine-3,4-dicarboxylate (6c) 75% yield for Michael addition/aldol addition, 48% yield for reductive amination; $[\alpha]_D^{25}$

+128.27 (*c* 1.10, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.18—7.36 (m, 5H), 5.76—5.86 (m, 1H), 4.92—5.01 (m, 2H), 4.50 (d, J=16.4 Hz, 1H), 4.45 (d, J=16.4 Hz, 1H), 4.12 (q, J=6.8 Hz, 2H), 3.30—3.34 (m, 2H), 2.83 (dt, J=2.4, 12.8 Hz, 1H), 2.49 (s, 3H), 2.03 (q, J=7.2 Hz, 2H), 1.86—1.88 (m, 1H), 1.44 (s, 9H), 1.31—1.39 (m, 2H), 1.16—1.27 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 176.55, 168.87, 154.55, 139.32, 138.02, 128.85 (2C), 127.40, 126.63 (2C), 114.29, 92.61,78.48, 60.46, 54.74, 49.42, 46.00, 33.92, 33.81, 32.24, 29.64, 29.50, 29.19, 29.02, 28.62 (3C), 27.31, 16.53, 14.50; ESI-MS *m*/*z*: 484.3 $(M+H)^+$; ESI-HRMS calcd for $C_{30}H_{45}NO_4$ $(M+H)^+$ 484.3432, found 484.3421; HPLC (Chiralpak AD-H, hexane/*i*-PrOH=98∶2, flow rate 0.5 mL/min, λ=214 nm), t_R=18.62 (major), 22.43 (minor) min; *ee* >99%.

(2*R*,3*R*,4*R*,5*R*)-3-*tert*-Butyl-4-ethyl-1-benzyl-2-methyl-5-(non-8-en-1-yl)piperidine-3,4-dicarboxylate (7c) 75% yield for Michael addition/aldol addition, 33% yield for reductive amination; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.20—7.35 (m, 5H), 5.74—5.84 (m, 1H), 4.90—4.99 (m, 2H), 4.06—4.20 (m, 2H), 3.91 (d, J=14.0 Hz, 1H), 3.23 (d, J=14.0 Hz, 1H), 2.92 (dd, J=4.0, 11.6 Hz, 1H), 2.85 (t, J=4.0 Hz, 1H), 2.63—2.68 (m, 1H), 2.42—2.50 (m, 1H), 2.29—2.32 (m, 1H), 2.01 (q, J=7.2 Hz, 2H), 1.66—1.72 (m, 1H), 1.47 (s, 9H), 1.04—1.41 (m, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.23, 170.64, 140.21, 139.40, 128.50 (2C), 128.23 (2C), 126.72, 114.22, 80.52, 60.45, 57.92, 57.49, 49.67, 49.24, 33.93, 33.02, 32.64, 29.86 (2C), 29.47, 29.21, 29.03, 28.27 (3C), 26.84, 16.72, 14.38; ESI-MS *m*/*z*: 486.3 $(M+H)^+$; ESI-HRMS calcd for $C_{30}H_{48}NO_4$ $(M+H)^+$ 486.3599, found 486.3577.

(*R*)-3-*tert*-Butyl-4-ethyl-1-benzyl-2-methyl-5-(non-8-en-1-yl)-1,4-dihydropyridine-3,4-dicarboxylate (8c) 75% yield for Michael addition/aldol addition, 10% yield for reductive amination; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.20—7.38 (m, 5H), 5.76—5.85 (m, 1H), 5.76 (s, 1H), 4.90—5.0 (m, 2H), 4.65 (d, J=17.6 Hz, 1H), 4.51 (d, J=17.2 Hz, 1H), 4.09—4.21 (m, 2H), 4.18 (s, 1H), 2.34 (s, 3H), 1.91—2.11 (m, 2H), 1.56 (m, 2H), 1.44 (s, 9H), 1.25—1.37 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 174.15, 168.04, 149.47, 139.35, 138.27, 128.97 (2C), 127.55, 127.38, 125.93 (2C), 114.41, 114.29, 96.63, 79.44, 60.54, 53.73, 45.67, 33.95, 32.60, 29.43, 29.35, 29.25, 29.06, 28.51 (3C), 26.97, 15.47, 14.52; ESI-MS *m*/*z*: 482.3 $(M+H)^+$; ESI-HRMS calcd for $C_{24}H_{35}N_1NaO_4$ $(M+Na)^+$ 504.3105, found 504.3084.

General procedure for sythesis of 7d—7f

The cyclic hemiacetal **3d**—**3f** (0.2 mmol) was dissolved in dry THF (2 mL). $NaBH(OAc)_3$ (1.0 mmol, 5 equiv.) and amine (0.3 mmol) was added to the solution at 0 ℃. HOAc was added to reduce the reaction pH to 6—7. After 10 min, the solution was allowed to warm up to r.t. (25—30 ℃). After 12 h, another potion of $NaBH(OAc)_3$ (0.4 mmol, 2 equiv.) and amine (0.6 mmol) was added. After 24 h, ethyl acetate and 2 mL saturated $NaHCO_3$ were added. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4, then concentrated *in vacuo*. Purification of the residue by column chromatography eluting with 150∶1—80∶1 DCM/MeOH afforded the corresponding piperidine derivative **7d**—**7f**.

(2*R*,3*R*,4*R*,5*R*)-Ethyl-1-benzyl-4-(4-methoxyphenyl)-2-methyl-5-(non-8-enyl)piperidine-3-carboxylate (7d) 70% yield for Michael addition/aldol addition, 81% yield for reductive amination; $[\alpha]_D^{25}$ +25.00 (*c* 2.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.25—7.42 (m, 5H), 7.06 (d, J=8.4 Hz, 2H), 6.79 (d, J=8.6 Hz, 2H), 5.72—5.82 (m, 1H), 4.89—4.98 (m, 2H), 4.06 (d, J=14.0 Hz, 1H), 3.86—3.92 (m, 2H), 3.77 (s, 3H), 3.30 (d, J=14.0 Hz, 1H), 3.14 (dd, J=4.4, 11.2 Hz, 1H), 2.64—2.77 (m, 3H), 2.42 (dd, J=4.4, 11.6 Hz, 1H), 1.97 (q, J=7.2 Hz, 2H), 1.74 (t, J=10.8 Hz, 1H), 1.21—1.31 (m, 3H), 1.01—1.21 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.84, 158.21, 139.98, 139.39, 133.90, 129.46 (2C), 128.68 (2C), 128.26 (2C), 126.66, 114.19, 113.73 (2C), 59.54, 59.33, 58.61, 57.27, 55.90, 55.31, 50.62, 33.89, 33.69, 31.67, 29.75, 29.40, 29.12, 28.99, 26.53, 18.86, 14.33; ESI-MS *m*/*z*: 492.4 $(M+H)^+$; ESI-HRMS calcd for $C_{32}H_{45}NO_3$ $(M+H)^+$ 492.3464, found 492.3472; HPLC (Chiralpak AD-H, hexane/*i*-PrOH=95∶5, flow rate 0.7 mL/min, λ=214 nm), t_R=5.97 (minor), 8.22 (major) min; *ee*=97%.

(2*R*,3*R*,4*R*,5*R*)-Ethyl-1-(4-methoxybenzyl)-2-methyl-5-(non-8-enyl)-4-phenylpiperidine-3-carboxylate (7e) 79% yield for Michael addition/aldol addition, 60% yield for reductive amination; $[\alpha]_D^{25}$ +37.2 (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.14—7.33 (m, 7H), 6.87 (d, J=8.4 Hz, 2H), 5.73—5.83 (m, 1H), 4.90—4.99 (m, 2H), 4.01 (d, J=13.6 Hz, 1H), 3.86—3.94 (m, 2H), 3.82 (s, 3H), 3.31 (d, J=12.8 Hz, 1H), 3.16 (d, J=8.4 Hz, 1H), 2.72—2.82 (m, 2H), 2.64 (m, 1H), 2.48 (m, 1H), 1.98 (q, J=6.8 Hz, 2H), 1.69—1.75 (m, 1H), 1.05—1.33 (m, 15H), 0.98 (t, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.72, 158.51, 141.77, 139.38, 131.53, 129.89 (2C), 128.57 (2C), 128.35 (2C), 126.51, 114.19 (2C), 113.65, 59.51, 58.98, 58.34, 56.53, 55.72, 55.38, 51.49, 33.89, 33.41, 31.70, 29.75, 29.39, 29.12, 28.99, 26.54, 18.79, 14.23; ESI-MS *m*/*z*: 492.5 $(M+H)^+$; ESI-HRMS calcd for $C_{32}H_{45}NO_3(M+H)^+$ 492.3469, found 492.3472; HPLC (Chiralpak AD-H, hexane/*i*-PrOH=95∶5, flow rate 0.7 mL/min, λ=214 nm), t_R=6.51 (minor), 8.88 (major) min; *ee*=98%.

(2*R*,3*R*,4*R*,5*R*)-Ethyl-1-(4-methoxybenzyl)-2,5-dimethyl-4-(4-nitrophenyl)piperidine-3-carboxylate (7f) 80% yield for Michael addition/aldol addition, 69% yield for reductive amination; $[\alpha]_D^{25}$ +77.88 (*c* 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.13 (d, J=8.8 Hz, 2H), 7.35 (d, J=8.4 Hz, 2H), 7.30 (d, J=8.8 Hz, 2H), 6.87 (d, J=8.4 Hz, 2H), 4.02 (d, J=13.6 Hz, 1H), 3.85—3.98 (m, 2H), 3.79 (s, 3H), 3.16 (d, J=13.6 Hz, 1H), 3.0 (dd, J=4.0, 11.2 Hz, 1H), 2.89—2.96 (m, 1H),

2.73 (t, J=4.8 Hz,, 1H), 2.66—2.68 (m, 1H), 2.51 (dd, J=4.8, 11.6 Hz, 1H), 1.74 (t, J=10.8 Hz, 1H), 1.24 (d, J=6.4 Hz, 3H), 1.02 (t, J=6.8 Hz, 3H), 0.60 (d, J=6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.06, 158.66, 149.70, 146.87, 131.47, 129.87 (2C), 129.51 (2C), 123.64 (2C), 113.76 (2C), 60.87, 59.90, 58.83, 56.38, 55.40, 55.06, 52.82, 28.89, 18.76, 17.40, 14.34; ESI-MS *m*/*z*: 427.1 $(M+H)^+$; ESI-HRMS calcd for $C_{24}H_{30}N_2O_5$ $(M+H)^+$ 427.2227, found 427.2227; HPLC (Chiralpak IA, hexane/*i*-PrOH=90∶10, flow rate 0.7 mL/min, λ=214 nm), t_R=13.39 (major), 20.21 (minor) min; *ee*=97%.

General procedure for sythesis of 9

The cyclic hemiacetal **3g**—**3i** (0.2 mmol) was dissolved in dry THF (2 mL). $NaBH(OAc)_3$ (1.0 mmol, 5 equiv.) and amine (0.3 mmol) were added to the solution at 0 ℃. HOAc was added to reduce the reaction pH to 6—7. After 10 min, the solution was allowed to warm up to r.t. (25—30 ℃). After 12 h, another potion of $NaBH(OAc)_3$ (0.4 mmol, 2 equiv.) and amine (0.6 mmol) was added. After 12 h, ethyl acetate and 2 mL saturated $NaHCO_3$ were added. The organic phase was separated and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with saturated NaCl and dried over Na_2SO_4, then concentrated *in vacuo*. Purification of the residue by column chromatography eluting with 150∶1—60∶1 DCM/MeOH afforded the corresponding piperidine derivative **7g**—**7j**.

To a stirred suspension of $LiAlH_4$ (12 mg, 0.3 mmol) in dry THF (0.5 mL) was added a solution of the piperidine ester **7g**—**7j** in THF (1 mL) at 0 ℃. After being stirred overnight, water (10 μL) and 15% NaOH (10 μL) were carefully added, filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography (DCM/MeOH 100∶1) gave the corresponding alcohol **9g**—**9j** as a colorless oil.

((2*R*,3*R*,4*R*,5*R*)-1-Benzyl-5-(2-(benzyloxy)ethyl)-4-butyl-2-methylpiperidin-3-yl)methanol (9g) 78% yield for Michael addition/aldol addition, 87% yield for reductive amination/91% yield for reduction of the piperidine ester; $[\alpha]_D^{25}$ −17.86 (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.20—7.35 (m, 10H), 4.32 (s, 2H), 4.17 (d, J=13.2 Hz, 1H), 4.07 (dd, J=3.3, 11.7 Hz, 1H), 3.81 (d, J=11.4 Hz, 1H), 3.26—3.32 (m, 2H), 2.86—2.91 (m, 2H), 2.59—2.62 (m, 1H), 1.94—2.0 (m, 1H), 1.76—1.90 (m, 1H), 1.60—1.68 (m, 2H), 1.38—1.45 (m, 3H), 1.10—1.25 (m, 9H), 0.88 (t, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.54 (2C), 129.05, 128.62 (2C), 128.44 (2C), 127.73 (2C), 127.60 (2C), 127.32, 73.08, 68.74, 62.80, 59.24, 58.93, 58.14, 44.99, 41.66, 36.54, 32.16, 29.27, 28.94, 23.04, 18.72, 14.25; ESI-MS *m*/*z*: 410.3 $(M+H)^+$; ESI-HRMS calcd for $C_{27}H_{39}NO_2$ $(M+H)^+$ 410.3059, found 410.3053; HPLC (Chiralpak OD, hexane/*i*-PrOH=80∶20, flow rate 0.7 mL/min, λ=214 nm), t_R=9.05 (major), 11.36 (minor) min; *ee*=97%.

((2*R*,3*R*,4*R*,5*R*)-1-Benzyl-5-(2-(benzyloxy)ethyl)-2,4-dimethylpiperidin-3-yl)methanol (9h) 80% yield for Michael addition/aldol addition, 70% yield for reductive amination/91% yield for reduction of the piperidine ester; $[\alpha]_D^{25}$ −37.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.19—7.32 (m, 10 H), 6.06 (brs, 1H), 4.32 (s, 2H), 4.17 (d, J=12.8 Hz, 1H), 4.07 (dd, J=3.2, 12.0 Hz, 1H), 3.89 (d, J=11.2 Hz, 1H), 3.28—3.33 (m, 2H), 2.88—2.94 (m, 2H), 2.65—2.67 (m, 1H), 1.94—1.97 (m, 1H), 1.75—1.84 (m, 1H), 1.62—1.68 (m, 1H), 1.43—1.49 (m, 4H), 1.18—1.26 (m, 2H), 1.05 (d, J=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.57 (2C), 128.94, 128.60 (2C), 128.45 (2C), 127.74 (2C), 127.58 (2C), 127.21, 73.07, 68.76, 62.63, 59.17, 59.04, 58.10, 46.50, 40.27, 37.72, 32.39, 18.62, 17.15; ESI-MS *m*/*z*: 368.2 $(M+H)^+$; ESI-HRMS calcd for $C_{24}H_{33}NO_2$ $(M+H)^+$ 368.2589, found 368.2584; HPLC (Chiralpak OD, hexane/*i*-PrOH=95∶5, flow rate 0.5 mL/min, λ=214 nm), t_R=19.92 (major), 22.67 (minor) min; *ee*=97%.

((2*R*,3*R*,4*R*,5*R*)-5-(2-(Benzyloxy)ethyl)-1-cyclopropyl-2,4-dimethylpiperidin-3-yl)methanol (9i) 80% yield for Michael addition/aldol addition, 80% yield for reductive amination/90% yield for reduction of the piperidine ester; $[\alpha]_D^{25}$ −30.89 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26—7.35 (m, 5H), 4.49 (dd, J=7.6, 16.4 Hz, 2H), 3.96 (dd, J=4.0, 15.2 Hz, 1H), 3.80 (d, J=15.2 Hz, 1H), 3.49 (t, J=10.0 Hz, 2H), 3.14 (d, J=10.0 Hz, 1H), 2.60—2.67 (m, 1H), 1.84—2.0 (m, 3H), 1.38—1.41 (m, 6H), 1.23—1.29 (m, 2H), 1.05 (d, J=6.9 Hz, 3H), 0.60—0.67 (m, 2H), 0.38—0.47 (m, 1H), 0.18—0.27 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.65, 128.52 (2C), 127.79 (2C), 127.67, 73.14, 68.90, 64.60, 61.48, 58.97, 45.93, 39.98, 37.87, 36.97, 32.52, 18.24, 17.09, 10.12, 4.51; ESI-MS *m*/*z*: 318.1 $(M+H)^+$; ESI-HRMS calcd for $C_{20}H_{31}NO_2$ $(M+H)^+$ 318.2423, found 318.2427; HPLC (Chiralpak OD, hexane/*i*-PrOH=100∶1, flow rate 0.7 mL/min, λ=214 nm), t_R=15.63 (minor), 17.02 (major) min; *ee*=97%.

((2*R*,3*R*,4*R*,5*R*)-5-Allyl-1-benzyl-4-(2-(benzyloxy)-ethyl)-2-methylpiperidin-3-yl)methanol (9j) 77% yield for Michael addition/aldol addition, 87% yield for reductive amination/92% yield for reduction of the piperidine ester; $[\alpha]_D^{25}$ −58.06 (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.22—7.36 (m, 10H), 5.53—5.64 (m, 1H), 4.86—4.91 (m, 2H), 4.49 (s, 2H), 4.16 (d, J=12.0 Hz, 1H), 4.07 (dd, J=3.2, 11.6 Hz, 1H), 3.82 (d, J=11.6 Hz, 1H), 3.46 (t, J=6 Hz, 2H), 2.81—2.90 (m, 2H), 2.57—2.59 (m, 1H), 2.17—2.21 (m, 1H), 2.01 (m, 1H), 1.73—1.80 (m, 2H), 1.59—1.64 (m, 2H), 1.32—1.44 (m, 3H), 1.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.60 (2C), 135.18, 129.74 (2C), 128.95 (2C), 128.51 (2C), 127.78 (2C), 127.72 (2C), 117.09, 73.13, 70.47, 63.51, 62.95, 58.12, 57.86, 43.47, 41.36, 36.80, 35.92, 27.12, 25.51, 17.97; ESI-MS *m*/*z*: 408.2 $(M+H)^+$; ESI-HRMS calcd for $C_{27}H_{38}NO_2$ $(M+H)^+$ 408.2888, found 408.2897; HPLC (Chiralpak OD-H, hexane/*i*-PrOH=70∶30, flow rate 0.7 mL/min, λ=214 nm),

t_R=6.14 (major), 9.12 (minor) min; *ee*=97%.

References

1 (a) Gogfraid, T.; Miller, R.; Wibo, M. *Pharmacol*. *Rev*. **1986**, *38*, 321.
(b) Watson, P. S.; Jiang, B.; Scott, B. *Org*. *Lett*. **2000**, *2*, 3679.
2 (a) Murty, M. S. R.; Ram, R.; Yadav, J. S. *Tetrahedron Lett*. **2008**, *49*, 1141.
(b) Carballo, R. M.; Ramirez, M. A.; Rodriguez, M. L.; Martin, V. S.; Padron, J. I. *Org*. *Lett*. **2006**, *8*, 3837.
(c) Dobbs, A. P.; Guesne, S. J. J. *Synlett* **2005**, 2101.
3 (a) Zhu, W.; Mena, M.; Jnoff, E.; Sun, N.; Pasau, P.; Ghosez, L. *Angew*. *Chem*., *Int*. *Ed*. **2009**, *48*, 5880.
(b) Xiao, D.; Wang, L.; Feng, X. *Synlett* **2005**, *10*, 1531.
(c) Sarkar, N.; Banerjee, A.; Nelson, S. G. *J*. *Am*. *Chem*. *Soc*. **2008**, *130*, 9222.
4 (a) Fustero, S.; Jimenez, D.; Moscardo, J.; Catalan, S.; del Pozo, C. *Org*. *Lett*. **2007**, *9*, 5283.
(b) Clarke, P. A.; Zaytsev, A. V.; Morgan, T. W.; Whitwood, A. C.; Wilson, C. *Org*. *Lett*. **2008**, *10*, 2877.
5 Guo, H.; Xu, Q.; Kwon, O. *J*. *Am*. *Chem*. *Soc*. **2009**, *131*, 6318.
6 Davies, S. G.; Smith, A. D.; Cowley, A. R. *Synlett* **2004**, *11*, 1957.
7 Han, B.; Xiao, Y.-C.; He, Z.-Q.; Chen, Y.-C. *Org*. *Lett*. **2009**, *11*, 4660.
8 (a) Zhu, S.; Yu, S.; Ma, D. *Angew*. *Chem*., *Int*. *Ed*. **2008**, *47*, 545.
(b) Wang, J.; Yu, F.; Zhang, X.; Ma, D. *Org*. *Lett*. **2008**, *10*, 2561.
(c) Wang, J.; Ma, A.; Ma, D. *Org*. *Lett*. **2008**, *10*, 5425.
(d) Zhu, S.; Wang, Y.; Ma, D. *Adv*. *Synth*. *Catal*. **2009**, *351*, 2563.
(e) Ma, A.; Ma, D. *Org*. *Lett*. **2010**, *12*, 3634.
(f) Xu, D.; Zhang, Y.; Ma, D. *Tetrahedron Lett*. **2010**, *51*, 3827.

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