Concise Asymmetric Synthesis of (+)-Febrifugine Utilizing *trans*-Selective Intramolecular Conjugate Addition

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Abstract: Intramolecular conjugate addition of γ-substituted (*E*)-α,β-unsaturated ketones with a Lewis acid (BF_3·OEt_2) selectively afforded *trans*-2,3-disubstituted piperidine derivatives. Chiral substrates were synthesized by Sharpless asymmetric dihydroxylation of the enamine; the antimalarial compound febrifugine was synthesized from the major product of the conjugate addition reaction.

Key words: Lewis acid, intramolecular conjugate addition, febrifugine, asymmetric synthesis

The piperidine ring is a basic structural element of many natural products. Examples of natural products that contain a 2,3-disubstituted piperidine ring are (+)-febrifugine (**1**), which has antimalarial activity,[1,2] (–)-swainsonine, which has anticancer activity,[3] and (–)-7-*epi*-deoxynupharidine, which has insecticidal activity (Figure 1).[4]

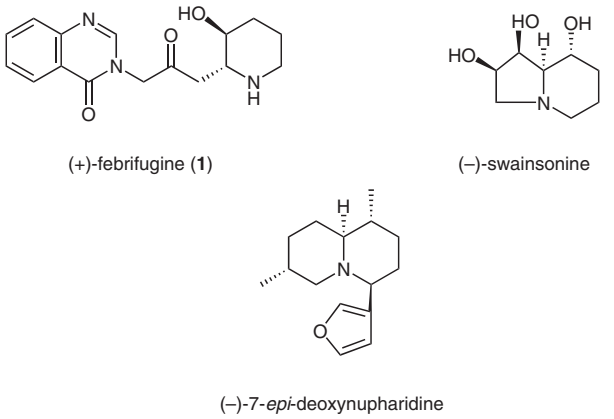
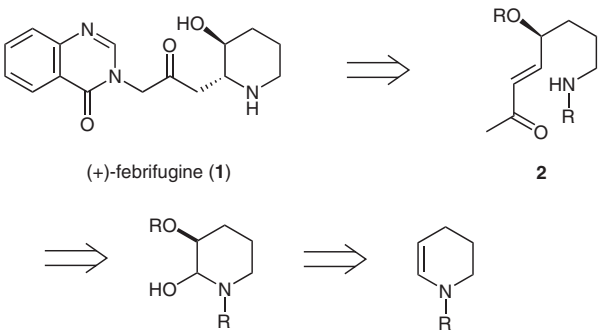


Figure 1 2,3-Disubstituted piperidine derivatives

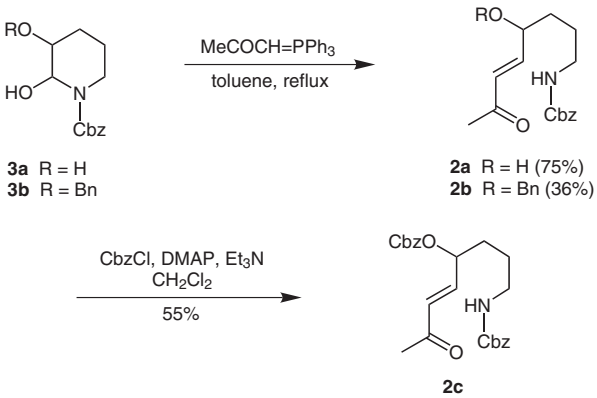
It is well known that 2,3-disubstituted piperidine rings can be formed by intramolecular conjugate addition in the presence of a base, and many studies have focused on this reaction.[5] However, only a few studies have been conducted on acid-catalyzed conjugate addition. In our previous study, we successfully carried out conjugate addition with a Lewis acid.[6] Here we report the stereoselectivity of the acid-catalyzed intramolecular conjugate addition of γ-substituted α,β-unsaturated ketones **2** and the asymmetric synthesis of (+)-febrifugine[7] by stereoselective conjugate addition (Scheme 1). Although febrifugine is an antimalarial compound, it is precluded from use as a clinical drug due to its liver toxicity.[8] Therefore, derivatives of febrifugine that may become valuable leads for novel drugs have been synthesized and, as a result, many methods for its synthesis have been developed.



Scheme 1

Racemic γ-substituted α,β-unsaturated ketones **2a** and **2b** were prepared from 2-hydroxypiperidines **3a**[9] and **3b**[7i] by Wittig reactions, and **2c** was synthesized by protecting **2a** (Scheme 2).

The results of the intramolecular conjugate addition of the γ-substituted α,β-unsaturated ketones **2** with a base (K_2CO_3) or an acid (BF_3·OEt_2) are shown in Table 1. The



Scheme 2

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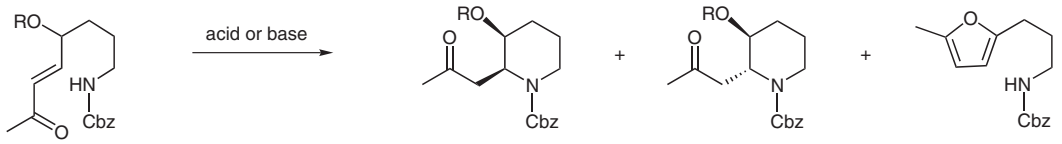
Table 1 Conjugate Addition Reactions



2 *cis*-**4** *trans*-**4** **5**

Entry	Substrates **2**	R	Acid or base (mol%)	Conditions	Yield (%)		
					cis-**4**	*trans*-**4**	**5**
1	**2a**	H	K_2CO_3 (250)	DMF, r.t., 16 h	*cis*-**4a**, 5	*trans*-**4a**, 76	–
2	**2b**	Bn	K_2CO_3 (250)	DMF, 80 °C, 24 h	*cis*-**4b**, 74	*trans*-**4b**, 7	–
3	**2c**	Cbz	K_2CO_3 (250)	DMF, r.t., 16 h	*cis*-**4c**, 76	*trans*-**4c**, 5	–
4	**2a**	H	$BF_3{\cdot}OEt_2$ (50)	MeCN, 0 °C, 15 min	–	*trans*-**4a**, 77	7
5	**2b**	Bn	$BF_3{\cdot}OEt_2$ (50)	MeCN, 0 °C, 15 min	*cis*-**4b**, 7	*trans*-**4b**, 74	–
6	**2c**	Cbz	$BF_3{\cdot}OEt_2$ (50)	MeCN, 0 °C, 15 min	*cis*-**4c**, 16	*trans*-**4c**, 82	–

reactions of **2**, which are Baldwin-favored 6-*exo*-trig cyclizations, afforded *cis* or *trans* adducts in good yields. The reaction of **2a**, in which the hydroxy group was not protected, with the base (entry 1), preferentially gave the *trans* adduct (*trans*-**4a**) over the *cis* adduct (*cis*-**4a**[10]). In contrast, the reactions of **2b** and **2c**, in which the hydroxy group was protected, with the base, afforded the *cis* adducts (*cis*-**4b** and *cis*-**4c**) with high selectivity (entries 2 and 3). It is noteworthy that the conjugate additions of **2a–c** with the Lewis acid, selectivity afforded the *trans* adducts (*trans*-**4a–c**) (entries 4–6).[11] The reaction of **2a** with the Lewis acid did not afford *cis*-**4a** but instead gave **5** as a minor product (entry 4). It is known that *cis*-**4a** can be transformed into **5**.[10]

In order to explain the selectivities of the above reactions, we considered the following transition states. Generally, the intramolecular conjugate addition of a γ-substituted (*E*)-α,β-unsaturated compound with a base, yields *cis* adducts.[5] According to Hirama et al.,[5a] A1 and A2, in which the allylic alkoxy group (electron-withdrawing group) is antiperiplanar to the nitrogen nucleophile, are the transition states in the reactions of **2b** and **2c** with the base (Figure 2). However, steric repulsions between methyl ketone and the N-protecting group indicate that A1, which produces *cis*-**4b** and *cis*-**4c**, is more likely to be the transition state in these reactions than A2. With regard to **2a**, we postulate that B1 and B2, in which the allylic oxygen anions (electron-donating groups) are not antiperiplanar to the nitrogen anion nucleophile,[12] are the transition states in its reaction. However, B2 is assumed to be the preferred transition state, which produces *trans*-**4a**. Since electrons in the *p*-orbital of the nitrogen atom attack the double bond under acidic conditions, the conformation of the Cbz group under these conditions differs from that adopted under basic conditions. In such a case, the plane of the carbamate group is parallel to that of the enone group, and these planes do not repel each other strongly. Thus, we as-

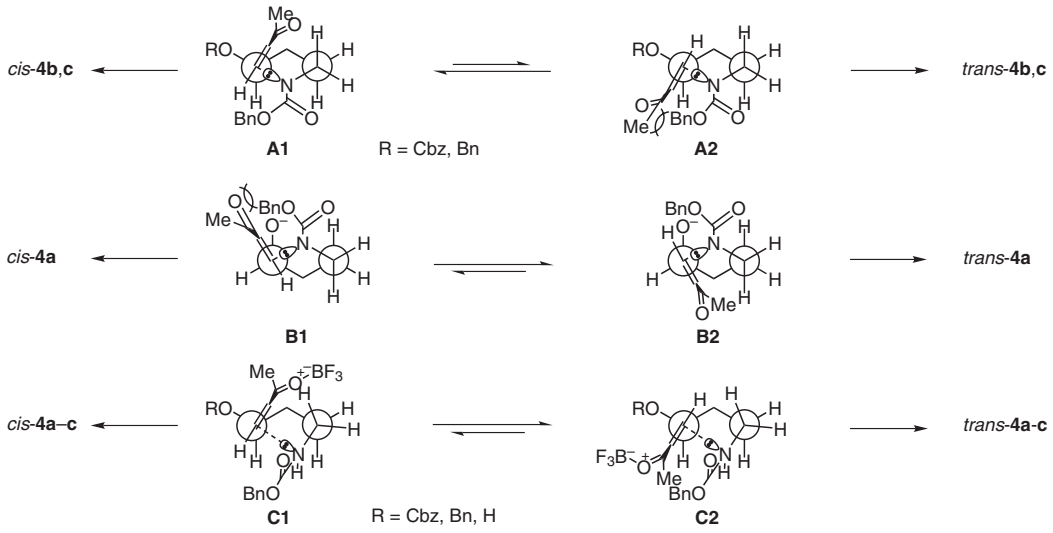
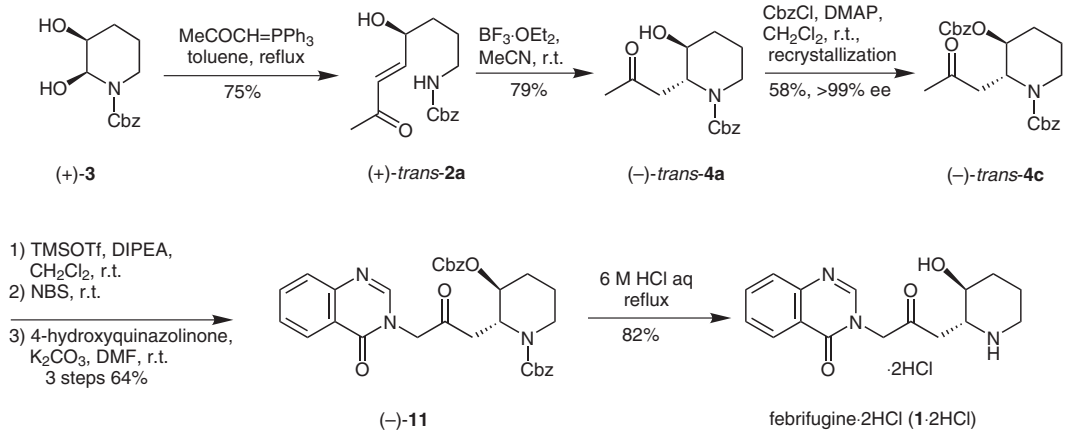


Figure 2



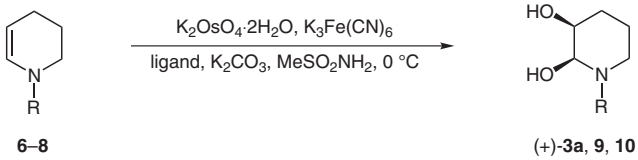
Scheme 3

sume that C1 and C2, in which steric repulsions between methyl ketone and the N-protecting group are negligible, constitute the transition states formed under acidic conditions. Although transition states C1 and C2 are similar, Felkin–Anh modeling studies[13] predict that the C2 conformation is preferred.

We synthesized (+)-febrifugine by *trans*-selective conjugate addition as shown in Scheme 3. Chiral 2-hydroxypiperidine was produced by asymmetric dihydroxylation[14] in good yield (62–96%) and moderate enantioselectivity (40–77% ee) (Table 2). High enantioselectivity was not obtained irrespective of the ligand [$(DHQ)_2PYR$, entry 2; $(DHQ)_2PHAL$, entry 3], the solvent (*t*-BuOH–H_2O, entry 2; acetone–H_2O, entry 3; MeCN–H_2O, entry 4), the presence of $MeSO_2NH_2$ (entries 4 and 5), or the protecting group used (Cbz, entry 5; PhOCO, entry 6; *t*-Boc, entry 7). The best result was 94% yield and 74% ee (entry 5). The *trans* product, (–)-*trans*-**4a**, was obtained by the Wittig reaction of (+)-**3a**, followed by *trans*-selective conjugate addition with $BF_3·OEt_2$. Enhanced optical activity (99% ee) was achieved by recrystallizing (–)-*trans*-**4c**, which was synthesized after protecting the hydroxy group of (–)-*trans*-**4a** with CbzCl. Protected febrifugine (–)-**11** was successfully obtained by the silylation of (–)-*trans*-**4c**, bromination, and a coupling reaction with 4-hydroxyquinazolinone. Deprotection of (–)-**11** with 6 N hydrochloric acid afforded febrifugine dihydrochloride (**1**·2HCl; Scheme 3).

In summary, we have found that the major product of the intramolecular conjugate addition of γ-substituted (*E*)-α,β-unsaturated ketones with a Lewis acid ($BF_3·OEt_2$) differed from that obtained using a base. This will be useful in the synthesis of other compounds. Thus, we have dem-

Table 2 Asymmetric Dihydroxylation



Entry	Substrate	R	Ligand[a]	Solvent	$MeSO_2NH_2$ (mol%)	Time (h)	Product	Yield (%)	ee (%)[b]	*cis*/*trans*[b]
1	**6**	Cbz	$(DHQ)_2PYR$	*t*-BuOH–H_2O	100	2.0	(+)-**3a**	80	59	95:5
2	**6**	Cbz	$(DHQ)_2PHAL$	*t*-BuOH–H_2O	100	4.0	(+)-**3a**	96	56	99:1
3	**6**	Cbz	$(DHQ)_2PHAL$	acetone–H_2O	100	2.0	(+)-**3a**	70	60	100:0
4	**6**	Cbz	$(DHQ)_2PHAL$	MeCN–H_2O	100	48.0	(+)-**3a**	83	77	100:0
5	**6**	Cbz	$(DHQ)_2PHAL$	MeCN–H_2O	–	48.0	(+)-**3a**	94	74	100:0
6	**7**	PhOCO	$(DHQ)_2PHAL$	MeCN–H_2O	–	72.0	(+)-**9**[c]	80	72	85:5
7	**8**	Boc	$(DHQ)_2PHAL$	MeCN–H_2O	–	48.0	(+)-**10**[c]	62	40[d]	100:0[e]

[a] DHQ: dihydroquinine; PYR: diphenylpyrimidine; PHAL: phthalazine.
[b] Determined by chiral HPLC analysis.
[c] The absolute configuration was not determined.
[d] Determined by chiral HPLC analysis as *tert*-butyl *N*-[(*E*)-4-hydroxy-7-oxo-5-octenyl]carbamate via reaction with $MeCOCH=PPh_3$.
[e] Determined by ^1H NMR analysis.

onstrated the asymmetric synthesis of febrifugine in good yield in the smallest number of reaction steps.

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR 350 spectrometer. Mass spectra (MS) were recorded on an AutoSpec spectrometer. ^{1}H NMR and ^{13}C NMR spectra were run on a Varian Mercury 300, a Varian VXR500 or a Varian Unity INOVA AS600 spectrometer. Optical rotations were measured on a JASCO DIP-1000 spectrometer. Merck silica gel 60 (230–400 mesh) and Wako activated alumina (300 mesh) were employed for column chromatography.

_N_-Benzyloxycarbonyl-1,2,3,4-tetrahydropyridine (6)
Prepared according to the literature.[7i]

_N_-Phenoxycarbonyl-1,2,3,4-tetrahydropyridine (7)[15]
Prepared by extending a method described in the literature[7i] as follows: To a solution of oxalyl chloride (1.00 mL, 11.1 mmol) in CH_2Cl_2 (16 mL) was added DMSO (1.57 mL, 22.1 mmol) at –78 °C and the mixture was stirred for 2 min. A solution of 5-amino-*N*-phenoxycarbonylpentanol[16] (1.90 g, 8.5 mmol) in CH_2Cl_2 (16 mL) was added dropwise below –60 °C, and the reaction mixture was stirred at –78 °C for 1 h. The reaction was quenched with Et_3N (6.28 mL, 45.1 mmol) at the same temperature and the mixture was warmed to 0 °C for 1 h. Aqueous HCl (3 M, 25 mL) was added and the suspension was warmed to r.t. and stirred vigorously for 14 h at the same temperature. The mixture was extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic layers were washed with H_2O (30 mL), sat. aq $NaHCO_3$ (30 mL), and brine (30 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was subjected to column chromatography (SiO_2; EtOAc–hexane, 1:6) to give **7** as colorless solid (1.22 g, 71%). The structure was confirmed by comparison of its spectral data with those of an authentic sample.[15]

_N_-(*tert*-Butoxycarbonyl)-1,2,3,4-tetrahydropyridine (8)[17]
Prepared according to the method described for compound **7**, starting from 5-amino-*N*-*tert*-butoxycarbonylpentanol[18] in 81% yield as a colorless oil. The structure was confirmed by comparison of its spectral data with those of an authentic sample.[17]

Benzyl (*E*)-4-Hydroxy-7-oxooct-5-enylcarbamate (2a)
A solution of **3a** (7.6 g, 30 mmol) and acetyl methylenetriphenylphosphorane (14.3 g, 45 mmol) in toluene (120 mL), was stirred at reflux for 2 h. After removal of the solvent, the residue was subjected to column chromatography (SiO_2; EtOAc–hexane, 1:1 then *i*-PrOH–hexane, 1:7) to give **2a**.

Yield: 6.6 g (75%); colorless oil.

IR (neat): 3340, 1695, 1680 cm^{-1}.

^{1}H NMR (600 MHz, acetone-d_6): δ = 1.50–1.70 (m, 4 H), 2.21 (s, 3 H), 3.18 (q, *J* = 6.0 Hz, 2 H), 4.24 (d, *J* = 4.8 Hz, 1 H), 4.31–4.36 (m, 1 H), 5.05 (s, 2 H), 6.21 (dd, *J* = 16.2, 1.2 Hz, 1 H), 6.36 (br s, 1 H), 6.84 (dd, *J* = 16.2, 4.8 Hz, 1 H), 7.28–7.38 (m, 5 H).

^{13}C NMR (150 MHz, acetone-d_6): δ = 26.6, 27.1, 34.5, 41.4, 66.4, 70.7, 128.5, 128.6, 129.1, 129.5, 138.4, 150.9, 157.3, 198.5.

Anal. Calcd for $C_{16}H_{22}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.83; H, 7.08; N, 4.85.

(+)-2a
Colorless oil; $[\alpha]_D^{19}$ +12.3 (*c* 1.00, EtOH).

Benzyl (*E*)-4-Benzyloxy-7-oxooct-5-enylcarbamate (2b)
A solution of **3b** (3.41 g, 10 mmol) and acetyl methylenetriphenylphosphorane (6.36 g, 20 mmol) in toluene (30 mL), was stirred at reflux for 20 h. After removal of the solvent, the residue was subjected to column chromatography (SiO_2; EtOAc–hexane, 1:1) to give **2b**.

Yield: 1.37 g (36%); colorless oil.

IR (neat): 3340, 1720, 1680 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 1.51–1.74 (m, 4 H), 2.24 (s, 3 H), 3.16 (q, *J* = 6.0 Hz, 2 H), 4.05–4.16 (m, 1 H), 4.45 and 4.58 (AB q, *J* = 12.0 Hz, 2 H), 5.05 (s, 2 H), 6.22 (d, *J* = 16.2 Hz, 1 H), 6.34 (br s, 1 H), 6.75 (dd, *J* = 16.2, 6.6 Hz, 1 H), 7.24–7.40 (m, 10 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 26.5, 27.1, 32.8, 41.3, 66.4, 71.5, 78.9, 128.3, 128.6, 129.1, 131.9, 138.5, 139.7, 147.7, 157.2, 198.1.

HRMS-FAB: *m/z* [M + H]$^+$ calcd for $C_{23}H_{28}NO_4$: 382.2018; found: 382.2007.

Benzyl (*E*)-4-Benzyloxycarbonyloxy-7-oxooct-5-enylcarbamate (2c)
To a solution of **2a** (582 mg, 2.0 mmol) in CH_2Cl_2 (10 mL) was added DMAP (489 mg, 4.0 mmol) and CbzCl (571 μL, 4.0 mmol). The mixture was stirred at r.t. for 2 h, then the mixture was poured into H_2O (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was subjected to column chromatography (SiO_2; EtOAc–hexane, 1:3) to give **2c**.

Yield: 522 mg (66%); colorless oil.

IR (neat): 3340, 1745, 1720, 1700, 1680 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 1.51–1.66 (m, 2 H), 1.72–1.87 (m, 2 H), 2.23 (s, 3 H), 3.18 (q, *J* = 6.6 Hz, 2 H), 5.05 (s, 2 H), 5.19 (s, 2 H), 5.35 (q, *J* = 5.7 Hz, 1 H), 6.17 (d, *J* = 16.2 Hz, 1 H), 6.38 (br s, 1 H), 6.79 (dd, *J* = 16.2, 5.7 Hz, 1 H), 7.25–7.45 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.6, 27.8, 31.1, 40.5, 66.8, 70.1, 76.3, 128.2, 128.5, 128.6, 128.8, 128.8, 130.7, 135.0, 136.6, 142.7, 154.4, 156.5, 197.8.

Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.68; H, 6.21; N, 3.34.

Synthesis of 4 and 5
Base-Mediated Conjugate Addition; General Procedure
To a solution of **2** (0.20 mmol) in DMF (4 mL) was added K_2CO_3 (69 mg, 0.50 mmol). The mixture was stirred at r.t. (or 80 °C) for 16–24 h then poured into H_2O (20 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was subjected to column chromatography (SiO_2; EtOAc–hexane) to give the desired compounds.

Lewis Acid Mediated Conjugate Addition; General Procedure
To a solution of **2** (0.20 mmol) in MeCN (2 mL) was added $BF_3{\cdot}OEt_2$ (12 μL, 0.10 mmol) at 0 °C. The mixture was stirred at the same temperature for 10 min then poured into sat. aq $KHCO_3$ (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was subjected to column chromatography (SiO_2; EtOAc–hexane) to give the desired compounds.

(2*R,3*R**)-1-Benzyloxycarbonyl-3-hydroxy-2-(2-oxopropyl)piperidine (*cis*-4a)[10]**
Colorless oil.

IR (neat): 3420, 1700, 1680 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.22–1.48 (m, 2 H), 1.53–1.68 (m, 2 H), 2.03 and 2.09 (2 × br s, total 3 H), 2.75 (dd, *J* = 14.7, 3.9

Hz, 2 H), 3.48–3.60 (m, 1 H), 3.72–3.84 (m, 1 H), 4.70 (br s, 1 H), 4.95–5.11 (m, 3 H), 7.22–7.43 (m, 5 H).

(2*R,3*S**)-1-Benzyloxycarbonyl-3-hydroxy-2-(2-oxopropyl)piperidine (*trans*-4a)**
Colorless needles; mp 74–75 °C.

IR (neat): 3440, 1695 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.40 and 1.45 (2 × br s, total 1 H), 1.58–1.98 (m, 3 H), 2.14 (br s, 3 H), 2.65 (d, *J* = 7.5 Hz, 2 H), 2.87 (t, *J* = 12.3 Hz, 1 H), 3.82 (br s, 1 H), 4.07 (d, *J* = 11.7 Hz, 1 H), 4.67–4.80 (br s, 1 H), 5.13 (s, 2 H), 7.27–7.37 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 25.9, 30.0, 39.5, 43.7, 54.0, 66.8, 67.3, 127.7, 127.8, 128.3, 136.4, 156.0, 205.8.

Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.67; H, 7.06; N, 4.90.

(2*R,3*R**)-3-Benzyloxy-1-benzyloxycarbonyl-2-(2-oxopropyl)piperidine (*cis*-4b)**
Colorless oil.

IR (neat): 1700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.37–1.79 (m, 3 H), 1.86–1.97 (m, 1 H), 2.06 and 2.17 (2 × br s, total 3 H), 2.42–2.58 (m, 1 H), 2.69–2.97 (m, 2 H), 3.53 (br s, 1 H), 3.98 (br s, 1 H), 4.44–4.74 (m, 2 H), 5.03–5.28 (m, 3 H), 7.24–7.41 (m, 10 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ (rotamers) = 23.8, 24.2, 25.6, 29.9, 30.5, 38.7, 39.8, 50.4, 67.4, 70.9, 75.3, 127.7, 127.8, 127.9, 128.1, 128.5, 128.6, 136.7, 138.2, 155.2, 155.4, 206.3, 207.1.

HRMS-FAB: *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{28}NO_4$: 382.2018; found: 382.2060.

(2*R,3*S**)-3-Benzyloxy-1-benzyloxycarbonyl-2-(2-oxopropyl)piperidine (*trans*-4b)[7k,m]**
Colorless oil.

IR (neat): 1700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.32–1.46 (m, 1 H), 1.55–1.69 (m, 1 H), 1.78–2.01 (m, 2 H), 2.12 (br s, 3 H), 2.56–2.73 (m, 2 H), 2.75–2.94 (m, 1 H), 3.44 (br s, 1 H), 4.11 (br s, 1 H), 4.42–4.80 (m, 2 H), 4.90–5.18 (m, 3 H), 7.24–7.39 (m, 10 H).

(2*R,3*R**)-1-Benzyloxycarbonyl-3-benzyloxycarbonyloxy-2-(2-oxopropyl)piperidine (*cis*-4c)**
Colorless needles; mp 76–78 °C.

IR (neat): 1750, 1700 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.46–2.02 (m, 4 H), 2.07 and 2.17 (2 × br s, total 3 H), 2.59 (br s, 1 H), 2.78 (dd, *J* = 15.0, 5.5 Hz, 2 H), 4.05 (br s, 1 H), 4.72–4.79 (m, 1 H), 5.07–5.19 (m, 5 H), 7.29–7.41 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 24.6, 29.9, 38.4, 39.9, 49.5, 67.4, 69.8, 73.5, 127.9, 128.0, 128.3, 128.4, 128.5, 128.6, 135.0, 136.4, 153.8, 155.1, 205.3.

Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.89; H, 6.49; N, 3.35.

(2*R,3*S**)-1-Benzyloxycarbonyl-3-benzyloxycarbonyloxy-2-(2-oxopropyl)piperidine (*trans*-4c)**
Colorless needles; mp 74–76 °C.

IR (neat): 1745, 1695 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.41–1.98 (m, 4 H), 2.11 and 2.24 (2 × br s, total 3 H), 2.58–2.75 (m, 2 H), 2.88 (br s, 1 H), 4.14 (br s, 1 H), 4.68 (br s, 1 H), 4.95–5.20 (m, 5 H), 7.23–7.44 (m, 10 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ (rotamers) = 19.1, 23.5, 29.6, 38.6, 38.9, 43.2, 50.6, 67.1, 69.5, 73.0, 127.4, 127.5, 127.8, 128.2, 128.3, 128.4, 128.4, 134.9, 136.4, 154.2, 155.3, 155.6, 204.7, 205.5.

Anal. Calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.87; H, 6.40; N, 3.41.

Benzyl 3-(5-Methylfuran-2-yl)propylcarbamate (5)[10]
Colorless oil.

IR (neat): 3334, 1696 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.84 (tt, *J* = 7.2, 7.2 Hz, 2 H), 2.23 (s, 3 H), 2.62 (t, *J* = 7.5 Hz, 2 H), 3.25 (q, *J* = 6.3 Hz, 2 H), 4.80 (br s, 1 H), 5.10 (s, 2 H), 5.81–5.89 (m, 2 H), 7.26–7.40 (m, 5 H).

Asymmetric Dihydroxylation; General Procedure
To a solution of AD-mix-α (1.4 g per 1 mmol of olefin) [or $K_2OsO_4{\cdot}2H_2O$ (10 mol%), $K_3Fe(CN)_6$ (300 mol%), $(DHQ)_2PYR$ (25 mol%), and K_2CO_3 (300 mol%)] and $MeSO_2NH_2$ in *t*-BuOH–H_2O (1:1) at 0 °C was added enamine **6**–**8**. The mixture was stirred for 1.5–72 h then quenched with sodium sulfite (600 mol%). The mixture was poured into H_2O (8 mL/mmol of enamine) and extracted with EtOAc (2 × 8 mL/mmol of enamine). The combined organic layers were washed with brine (1 × 8 mL/mmol of enamine), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was subjected to column chromatography (SiO_2; EtOAc–hexane) to give the desired compounds.

(2*S*,3*S*)-*N*-Benzyloxycarbonyl-2,3-dihydroxypiperidine [(+)-3a][7i]
Colorless oil; 74% ee [HPLC (CHIRALCEL OD, *i*-PrOH–hexane, 1:6, flow rate: 1.0 mL/min, UV = 254 nm); t_R = 10.4 (minor), 13.7 min (major)]; $[\alpha]_D^{20}$ +22.1 (*c* 1.00, EtOH).

IR (neat): 3400, 1680 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.40–1.87 (m, 4 H), 2.41 (br s, 1 H), 3.04 (td, *J* = 12.6, 3.0 Hz, 1 H), 3.52–3.66 (m, 1 H), 3.84 (d, *J* = 12.0 Hz, 1 H), 5.14 (s, 2 H), 5.74 (t, *J* = 3.6 Hz, 1 H), 7.28–7.38 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 26.5, 38.1, 67.6, 69.2, 76.6, 128.0, 128.2, 128.6, 136.3, 156.0.

HRMS-FAB: *m*/*z* $[M + H - H_2O]^+$ calcd for $C_{13}H_{16}NO_3$: 234.1130; found: 234.1141.

(–)-*trans*-3a
Colorless oil; $[\alpha]_D^{20}$ –19.3 (*c* 1.00, EtOH).

***N*-Phenoxycarbonyl-2,3-dihydroxypiperidine [(+)-9]**
Colorless needles; ratio *cis*/*trans* = 84:16; 72% ee [HPLC (CHIRALPAK AD, *i*-PrOH–hexane, 1:6, flow rate: 1.0 mL/min, UV = 254 nm); t_R = 8.9 (*trans*, major), 9.5 (*trans*, minor), 11.4 (*cis*, major), 12.9 min (*cis*, minor)]; mp 98–100 °C; $[\alpha]_D^{23}$ +25.1 (*c* 1.00, EtOH).

IR (neat): 3420, 1720, 1700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.46–2.03 (m, 4 H), 2.44–2.54 (m, 1 H), 2.98–3.39 (m, 1 H), 3.48–3.79 (m, 1 H), 3.85–4.06 (m, 1 H), 5.62 (br s, 0.14 H), 5.79 (br s, 0.86 H), 7.05–7.46 (m, 5 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 23.2, 23.5, 24.6, 26.2, 38.0, 38.6, 66.8, 68.9, 76.5, 78.1, 121.6, 121.7, 125.5, 129.2, 129.2, 150.9, 153.7, 154.6.

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.73; H, 6.36; N, 5.88.

***cis*-*N*-*tert*-Butoxycarbonyl-2,3-dihydroxypiperidine [(+)-10]**
Colorless needles; 40% ee; mp 98–100 °C; $[\alpha]_D^{23}$ +14.6 (*c* 1.00, EtOH).

IR (nujol): 3410, 3210, 1690 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.34–1.89 (m, 4 H), 1.47 (s, 9 H), 2.29 (br s, 1 H), 2.96 (td, *J* = 12.6, 2.7 Hz, 1 H), 3.51–3.66 (m, 1 H), 3.74 (d, *J* = 11.7 Hz, 1 H), 5.67 (br s, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 23.5, 26.7, 28.3, 38.2, 69.1, 76.0, 80.5, 155.3.

Anal. Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.81; N, 6.45. Found: C, 55.38; H, 8.66; N, 6.50.

(2*R*,3*S*)-*N*-Benzyloxycarbonyl-3-benzyloxycarbonyloxy-2-(2-oxopropyl)piperidine [(–)-*trans*-4c]

To a solution of (–)-*trans*-**4a** (291 mg, 1.0 mmol) in CH_2Cl_2 (4 mL) was added DMAP (146 mg, 1.2 mmol) and CbzCl (171 μL, 1.2 mmol). The mixture was stirred at r.t. for 1.5 h then DMAP (146 mg, 1.2 mmol) and CbzCl (171 L, 1.2 mmol) were added. The mixture was stirred at r.t. for 1.5 h then poured into H_2O (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous MgSO4, filtered, and concentrated. The residue was subjected to column chromatography (SiO_2; EtOAc–hexane, 1:3) and recrystallized (EtOAc–hexane, 1:2) to give (–)-*trans*-**4c**.

Yield: 245 mg (58%); colorless needles; 99% ee [HPLC (CHIRALPAK AD, *i*-PrOH–hexane, 1:4, flow rate: 1.0 mL/min, UV = 254 nm); t_R = 13.4 (minor), 14.9 min (major)]; mp 80–82 °C; $[\alpha]_D^{24}$ –39.0 (c 1.0, EtOH).

(2*R*,3*S*)-1-Benzyloxycarbonyl-3-benzyloxycarbonyloxy-2-{2-oxo-3-[4-oxoquinazolin-3(4*H*)-yl]propyl}piperidine [(–)-11]

To a solution of (–)-*trans*-**4c** (213 mg, 0.50 mmol) in CH_2Cl_2 (3 mL) was added DIPEA (139 μL, 0.80 mmol) and TMSOTf (136 μL, 0.80 mmol). The mixture was stirred at r.t. for 0.5 h then NBS (124 mg, 0.70 mmol) was added. The mixture was stirred at r.t. for 0.5 h then poured into aq $Na_2S_2O_3$ (10%, 10 mL) and extracted with EtOAc (2 × 15 mL). The combined organic layers were washed with sat. aq $KHCO_3$ (15 mL) and brine (15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. A solution of the residue, 4-hydroxyquinazolinone (110 mg, 0.75 mmol), and K_2CO_3 (110 mg, 0.80 mmol) was stirred for 7 h, then the mixture was poured into H_2O (30 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was subjected to column chromatography (Al_2O_3; EtOAc–hexane, 1:1) to give (–)-**11**.

Yield: 183 mg (64%); colorless oil; $[\alpha]_D^{19}$ –28.3 (*c* 1.00, EtOH).

IR (neat): 1740, 1700, 1685, 1675 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.42–2.03 (m, 4 H), 2.72–2.93 (m, 2 H), 3.01 (br s, 1 H), 4.07 (br s, 1 H), 4.51–4.84 (m, 2 H), 4.88–5.27 (m, 6 H), 7.21–7.43 (m, 10 H), 7.50 (t, *J* = 6.9 Hz, 1 H), 7.69–7.82 (m, 2 H), 7.99 (s, 1 H), 8.27 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ (rotamers) = 19.1, 23.6, 38.9, 40.4, 50.4, 51.3, 53.6, 67.5, 69.9, 73.1, 121.7, 126.6, 127.1, 127.5, 127.7, 128.0, 128.4, 128.4, 128.5, 134.3, 134.8, 136.1, 146.1, 146.7, 148.2, 154.4, 156.3, 160.9, 199.4.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{32}H_{32}N_3O_7$: 570.2240; found: 570.2351.

Febrifugine Dihydrochloride (1·2HCl)

A solution of (–)-**11** (114 mg, 0.20 mmol) in HCl (6 M, 6 mL), was stirred at reflux for 2 h. The solvent was removed through azeotropic treatment and recrystallization of the residue from EtOH to give the dihydrochloride of **1**.

Yield: 61 mg (82%); colorless powder; mp 217–219 °C (dec.) [Lit.[19] 223–225 °C (dec.)]; $[\alpha]_D^{28}$ +13.3 (*c* 1.00, H_2O) [Lit.[19] +12.8 (*c* 0.85, H_2O)].

Febrifugine (1)

Mp 138–140 °C (Lit.[2a] 139–140 °C); $[\alpha]_D^{21}$ +15.9 (*c* 0.65, MeOH) [Lit.[20] +13.0 (*c* 0.65, MeOH)].

Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94. Found: C, 63.58; H, 6.28; N, 13.84.

The spectral data were in agreement with those of the natural compound.[20]

***tert*-Butyl *N*-[(*E*)-4-Hydroxy-7-oxo-5-octenyl]carbamate**

Prepared according to the method described for compound **2b** starting from (+)-**10**.

Yield: 82%; colorless oil; 40% ee [HPLC (CHIRALCEL OD, *i*-PrOH–hexane, 1:12, flow rate: 1.0 mL/min, UV = 254 nm); t_R = 15.6 (major), 17.5 min (minor)]; $[\alpha]_D^{23}$ +9.3 (*c* 1.00, EtOH).

IR (neat): 3360, 1684 cm^{-1}.

^1H NMR (300 MHz, acetone-d_6): δ = 1.39 (s, 9 H), 1.49–1.70 (m, 4 H), 2.21 (s, 3 H), 3.02–3.15 (m, 2 H), 4.23 (d, *J* = 5.1 Hz, 1 H), 4.29–4.38 (m, 2 H), 5.96 (br s, 1 H), 6.21 (dd, *J* = 16.2, 1.8 Hz, 1 H), 6.84 (dd, *J* = 16.2, 4.8 Hz, 1 H).

^{13}C NMR (150 MHz, acetone-d_6): δ = 26.7, 27.1, 28.7, 34.5, 40.8, 70.7, 78.5, 129.5, 151.0, 156.8, 198.5.

HRMS-FAB: *m/z* $[M + H]^+$ calcd for $C_{13}H_{24}NO_4$: 258.1705; found: 258.1705.

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