Tetrahedron 69 (2013) 2745–2752

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

1,4-Elimination/Brønsted acid catalyzed aza-Ferrier reaction sequence as an entry to β-amino-β,γ-unsaturated aldehydes

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ARTICLE INFO

Article history:
Received 26 November 2012
Received in revised form 25 January 2013
Accepted 29 January 2013
Available online 8 February 2013

Keywords:
Elimination
Ferrier reaction
Acyliminium ion
Acetal
Diene

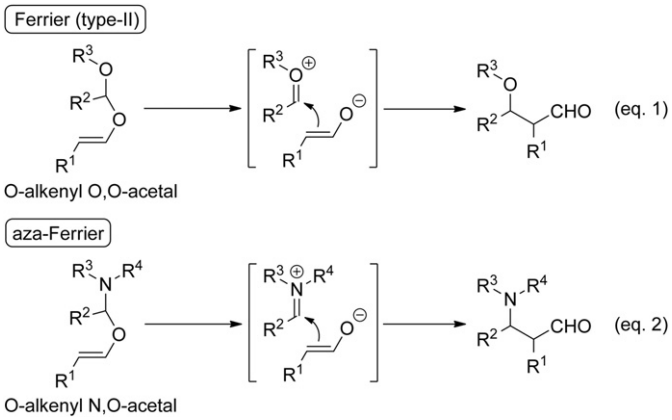
ABSTRACT

The 1,4-elimination reaction of (*Z*)-*N*-Boc-2-(4-methoxy-2-alkenyloxy)amines with Brønsted acids catalyzed aza-Ferrier reaction of the 1,4-eliminated product, thus obtained, afforded various β-amino-β,γ-unsaturated aldehydes. The scope and limitation of this sequential reaction are described.

1. Introduction

The Ferrier (type-II) reaction[1] of *O*-alkenyl *O*,*O*-acetals is a unique synthetic transformation that converts an O–C bond into a new C–C bond; hence, it has found wide application in the synthesis of oxygen-containing heterocycles.[2,3] The reaction proceeds via the formation of an oxocarbenium ion and an enolate (or enol) in the presence of acid catalyst. The subsequent recombination of these species affords various types of β-alkoxy carbonyl compounds (Scheme 1, Eq. 1). The nitrogen version of the reaction, which occurs via the formation of a *N*-acyliminium ion and an enolate generated from *O*-alkenyl *N*,*O*-acetals (aza-Ferrier reaction), is rare (Eq. 2)[4,5] because efficient preparative methods of *O*-alkenyl *N*,*O*-acetals are limited. Transition metal-catalyzed[4] or base-induced[4c,6] isomerization of *O*-allylic *N*,*O*-acetals have been reported; however, these methods are commonly applicable to simple *O*-allyl derivatives that afford *O*-(prop-1-enyl) *N*,*O*-acetals as products.

Previously, we reported the 1,4-elimination of (*Z*)-*N*-Boc-2-(4-methoxy-2-alkenyloxy)pyrrolidine **A** to give *O*-(1,3-dienyl) *N*,*O*-acetal **B** with good 1*E*,3*E*-stereoselectivity (Scheme 2, Eq. 1, step 1).[5] This method enabled us to prepare various *O*-alkenyl *N*,*O*-acetals without the use of special techniques. The Brønsted acid catalyzed aza-Ferrier reaction of **B** provided β-amino-β,γ-unsaturated aldehyde **C** (step 2), which could be a good intermediate for the synthesis of pyrrolidine alkaloids.[7] With this result in hand, we tried to extend this reaction sequence to six-membered, nitrogen-containing heterocyclic (piperidine) and acyclic derivatives, which would afford various β-amino-β,γ-unsaturated aldehydes (Eq. 2).



Scheme 1. Ferrier (type-II) and aza-Ferrier reaction.

2. Results and discussion

We selected piperidine derivatives **1a**–**e** as substrates and performed the reactions to expand the scope of the synthetic protocol

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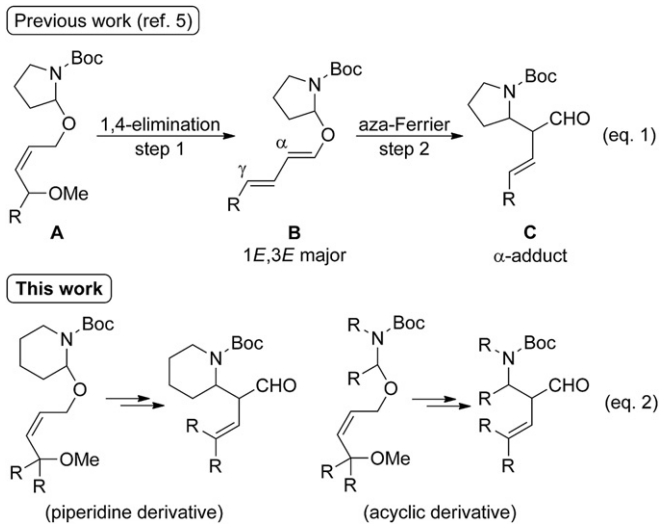
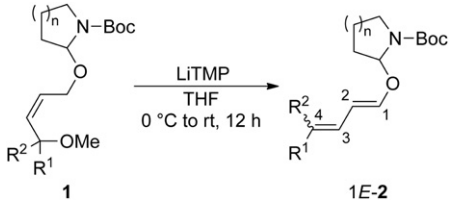
0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.01.088



Scheme 2. 1,4-Elimination and aza-Ferrier reaction.

(Table 1). After the treatment of the 4,4-dimethyl derivative **1a** with lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in THF, the 1,4-elimination proceeded smoothly to afford the 2-(1,3-dienyloxy)piperidine **2a** in a 81% yield as a single regioisomer (entry 1). ^{1}H NMR analysis of **2a** in DMSO-d_6 yielded a clear spectrum, and the C_1–C_2 stereochemistry was assigned as *E* based on the coupling constant of 1-H ($J_{1\text{-H, }2\text{-H}}$=12 Hz). A reaction with the analog **1b** gave the corresponding 1,4-eliminated product **2b** in a similar yield with the same stereoselectivity (entry 2). To investigate the C_3–C_4 stereoselectivity in the 1,4-elimination, we prepared 4-mono-substituted derivatives **1c**–**e** and performed the reactions (entries 3–5). Unfortunately, stereoselectivity at C_3–C_4 was not observed. The corresponding eliminated products, **2c**–**e**, were obtained in similar yields as a mixture of 1*E*,3*E*, 1*E*,3*Z*, and small amounts of 1*Z* isomers. The C_1–C_2 stereochemistries of **2c**–**e** were determined by the coupling constant of 1-H ($J_{1\text{-H, }2\text{-H}}$=11–13 Hz for *E*, 5–7 Hz for *Z*). The C_3–C_4 stereochemistries could not be determined directly by the coupling constant because of multiplet peaks. These stereochemistries were determined after conversion to the cyclic carbamate **5**: the details are described in Scheme 5.

Table 1
1,4-Elimination of cyclic derivatives **1**

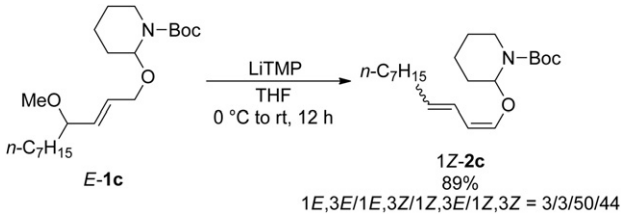


Entry	*n*	R^1	R^2		**2** (%)[a]	1*E*,3*E*/1*E*,3*Z*/1*Z*,3*E*/1*Z*,3*Z*[b]
1	2	Me	Me	**a**	81	1*E* only
2	2	$-(CH_2)_5-$		**b**	88	1*E* only
3	2	*n*-C_7H_{15}	H	**c**	87	60/32/7/1
4	2	*n*-C_4H_9	H	**d**	78	59/33/7/1
5	2	CH_2CH_2Ph	H	**e**	81	58/33/7/2
6	1	Me	Me	**f**	78[c]	1*E* only
7	1	*n*-C_7H_{15}	H	**g**	77[c]	90/10/0/0

[a] Isolated yield.
[b] The ratios were determined by ^{1}H NMR assay of the isolated product.
[c] ^{1}H NMR analysis in DMSO-d_6 showed a mixture of rotamers (**2f**: 55/45, **2g**: 50/50).

To compare the *E*/*Z* selectivity of 1,4-elimination of six- and five-membered nitrogen-containing heterocycles, we re-examined the reaction of pyrrolidine derivatives **1f** and **1g** under the same conditions (Table 1, entries 6, 7).[5] A reaction of 4,4-dimethyl derivative **1f** gave only 1*E*-**2f** (entry 6). The ^{1}H NMR spectrum of **2f** in DMSO-d_6 contained a pair of 1-H peaks with similar coupling constants ($J_{1\text{-H, }2\text{-H}}$=10–11 Hz) that were due to the formation of a mixture of rotamers (55/45) caused by *N*-Boc group.[8] A reaction with 4-*n*-heptyl derivative **1g** gave 1*E*,3*E*-**2g** as a major product (entry 7, 1*E*,3*E*/1*E*,3*Z*=90/10). The ^{1}H NMR spectrum of **2g** had two pairs of 1-H peaks with similar coupling constants ($J_{1\text{-H, }2\text{-H}}$=11–12 Hz) because of the formation of a rotamer mixture (50/50). The C_3–C_4 stereochemistry of **2g** could be determined directly (3*E*/3*Z*=90/10) by the coupling constant of 3-H ($J_{3\text{-H, }4\text{-H}}$=15 Hz for 1*E*,3*E*-**2g**, 12 Hz for 1*E*,3*Z*-**2g**).

To clarify the stereoselectivity of this 1,4-elimination, we examined the reaction with the *E*-isomer of **1c**. The dienyl ether **2c** was obtained as a 1:1 mixture of 1*Z*,3*E* and 1*Z*,3*Z* isomer, with small amounts of 1*E* isomer in a 89% combined yield (Scheme 3). All *E*/*Z*-isomers of **2c** could be identified by ^{1}H NMR analysis.[9] At present, no reasonable explanation can be offered for the 1*Z*-selectivity in 1,4-elimination of *E*-**1c**. Similar 1*E*-to-1*Z* changeover was observed in our previous work.[5,10]



Scheme 3. 1,4-Elimination of *E*-**1c**.

The *E*/*Z* selectivity of 1,4-elimination of *Z*-**1**, though its exact origin is unclear at present, may be rationalized as a result of the precoordination[10] of LiTMP to the oxygen of amide carbonyl to form complex **D** or **E** (Fig. 1). The chelate complex **D** derived from **1c** (Table 1, entry 3, R^1=*n*-C_7H_{15}, R^2=H), which leads to the 1*E*,3*E*-isomer would be preferred to form; however, the non-chelate complex **E** would also be formed to avoid steric repulsion between 4-OMe and 1-H. The complex **E** would afford 1*E*,3*E*- and 1*E*,3*Z*-isomer without selectivity. The formation of the complex **E** derived from 4,4-dialkyl derivatives **1a**, **1b**, and **1f** (Table 1, entries 1, 2, and 6, R^1=R^2=alkyl) may be inhibited because of steric repulsion between 4,4-dialkyl and 1-H. The complex **D** derived from pyrrolidinyl derivatives **1f** and **1g** (Table 1, entries 6 and 7) would be stabilize by its rigid five-membered ring.[11]

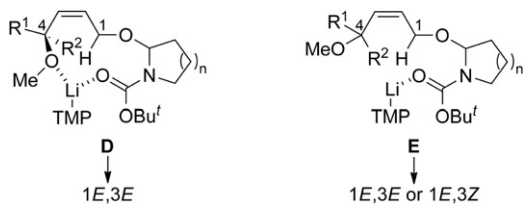
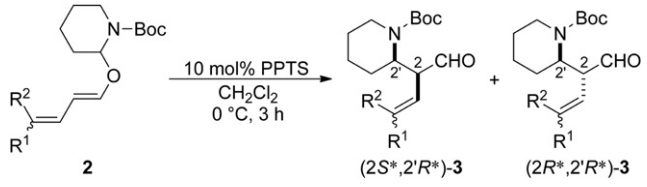


Fig. 1. Proposed transition state of the 1,4-elimination of **1**.

Next, we investigated the aza-Ferrier reaction of *N*-Boc-2-(1,3-dienyloxy)piperidines **2a**–**e** in the presence of pyridinium *p*-toluenesulfonate (PPTS) (Table 2). When a reaction of 4,4-dimethyl derivative **2a** with PPTS was performed at 0 °C for 3 h under an argon atmosphere, the corresponding α-adduct **3a** was obtained in a 89% yield as a mixture of diastereomers [(2*S**,2′*R**)/(2*R**,2′*R**)=75/25]

Table 2
aza-Ferrier reaction of piperidine derivative **2**



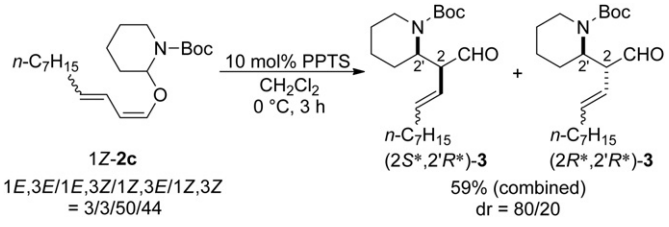
2 (2*S**,2′*R**)-**3** (2*R**,2′*R**)-**3**

Entry	R^1	R^2		**3** (%)[a]	(2*S**,2′*R**)/(2*R**,2′*R**)[b]
1	Me	Me	**a**	89	75/25
2	$-(CH_2)_5-$		**b**	87	75/25
3[c]	n-C_7H_{15}	H	**c**	85	80/20
4[c]	n-C_4H_9	H	**d**	77	80/20
5[c]	CH_2CH_2Ph	H	**e**	77	80/20

[a] Isolated yield.
[b] The ratios were determined by ^{1}H NMR assay of the isolated product.
[c] Mixture of *E*/*Z*-isomers depicted in Table 1.

(entry 1). The reactions of other substrates also proceeded with similar yields and diastereoselectivities (entries 2–5). In all cases, no identifiable amount was obtained of the γ-adducts derived by a vinylogous aza-Ferrier reaction.

To investigate the origin of low selectivity of the relative stereochemistry of **3**, we examined the reaction of 1*Z*-**2c** (Scheme 4). The product **3c** was obtained in a 59% yield with the same ratio of the relative stereoisomers that was obtained in the reaction with 1*E*-**2c**. The 1*E*/1*Z*-geometry of *O*-(1,3-dienyl) moiety, as in substrate **2**, does not affect the relative stereochemistry of product **3**. This result would suggest that the same geometric mixture of the 1,3-dienol is formed from 1*E*- and 1*Z*-**2** under the our reaction conditions and reacts with *N*-acyliminium ion.[12]



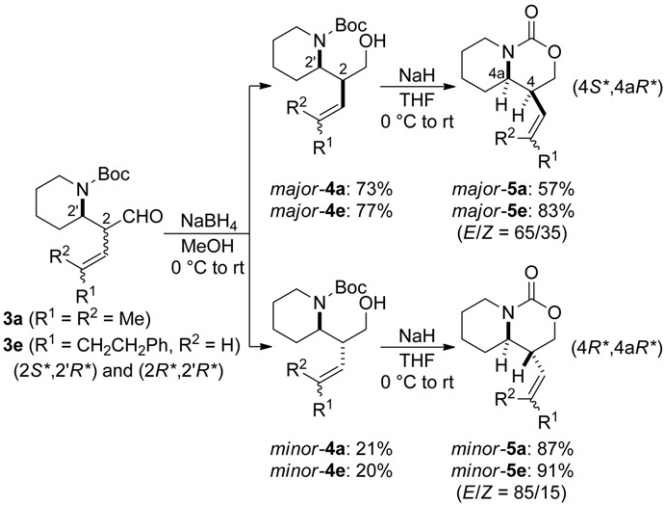
1*Z*-**2c**
1*E*,3*E*/1*E*,3*Z*/1*Z*,3*E*/1*Z*,3*Z* = 3/3/50/44
59% (combined)
dr = 80/20

Scheme 4. aza-Ferrier reaction of 1*Z*-**2c**.

The relative stereochemistry of **3** was determined by NMR analysis after its conversion to the corresponding cyclic carbamate **5** (Scheme 5). The diastereomeric mixture of **3** was reduced with sodium borohydride to give the products *major*-**4** and *minor*-**4**. Chromatographic separation and subsequent cyclization with sodium hydride afforded *major*-**5** and *minor*-**5**. The C_4–C_{4a} relative stereochemistry of **5a** was determined by NOESY (Fig. 2). First, the ^{1}H chemical shifts of 4-H, 4a-H, and alkenyl-H were assigned by COSY. The NOE correlation between 4a-H and alkenyl-H was observed for *minor*-**5a** but not for *major*-**5a**. The relative stereochemistry of *major*-**5a** was assigned as (4*S**,4a*R**), and *minor*-**5a** was assigned as (4*R**,4a*R**). Thus, the major isomer of **3a** was determined to be (2*S**,2′*R**), and the minor isomer of **3a** was determined to be (2*R**,2′*R**). The coupling constants between 4-H and 4a-H for compound **5a** are 6 Hz for (4*S**,4a*R**) and 10 Hz for (4*R**,4a*R**). These data do not contradict our previous assignment.[5]

The ratio of *E*/*Z*-isomer of **5e** was determined by ^{1}H NMR analysis (*major*-**5e**: *E*/*Z*=65/35, *minor*-**5e**: *E*/*Z*=85/15). The major isomer of 1,3-dienyl ether **2e** depicted in Table 1 is 3*E*.

The relative stereochemistry of **5e** was determined after hydrogenation of an *E*/*Z* mixture of *major*-**5e** to **6e** (Scheme 6). The coupling constant between 4-H and 4a-H is 6 Hz. The relative



Scheme 5. Preparation of cyclic carbamates **5**.

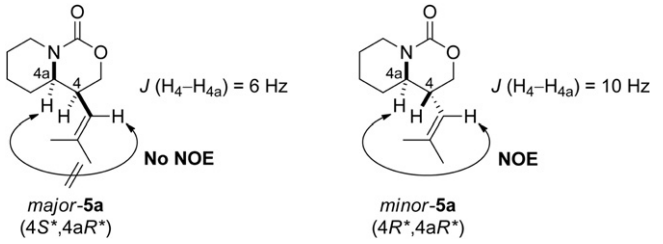
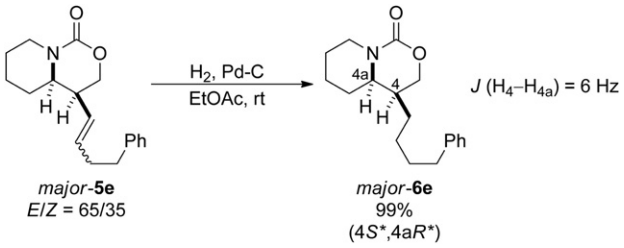


Fig. 2. Determination of relative stereochemistry of **5a**.

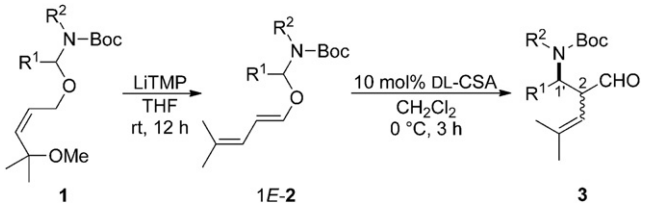


Scheme 6. Hydrogenation of *E*/*Z* mixture of **5e**.

stereochemistry of **6e** was determined to be (4*S**,4a*R**) by comparison to **5a**. Thus, the relative stereochemistry of **3e** and **5e** were also determined. The stereochemistries of **3b**, **3c**, and **3d** depicted in Table 2 were determined by analogy with **3a** and **3e**.

To define the scope and limitation of the 1,4-elimination and aza-Ferrier reaction sequence, we prepared acyclic substrates **1h**–**l** and promoted the reactions to prepare acyclic β-amino-β,γ-unsaturated aldehydes (Table 3). The 1,4-elimination of the *N*-methyl and *N*-ethyl derivatives **1h**–**j** also proceeded (entries 1–3); however, the use of *N*-allyl and *N*-benzyl derivatives **1k** and **1l** lead to the formation of unidentifiable products with the allylic isomerization or recovery of the starting materials (entries 4, 5). Deprotonation of the acidic proton bearing allylic or benzylic methylene, as in **1k** and **1l**, may have caused unfavorable reactions.[13] The aza-Ferrier reaction of **2h** with PPTS resulted in unsuccessful because of lower conversion (**3h**: 50% yield, 31% recovery). The use of more acidic Brønsted acid, such as DL-camphorsulfonic acid (CSA) was effective for acyclic derivatives **2h**–**j**. The desired aldehydes **3** were obtained in 65–91% yields (entries 1–3).

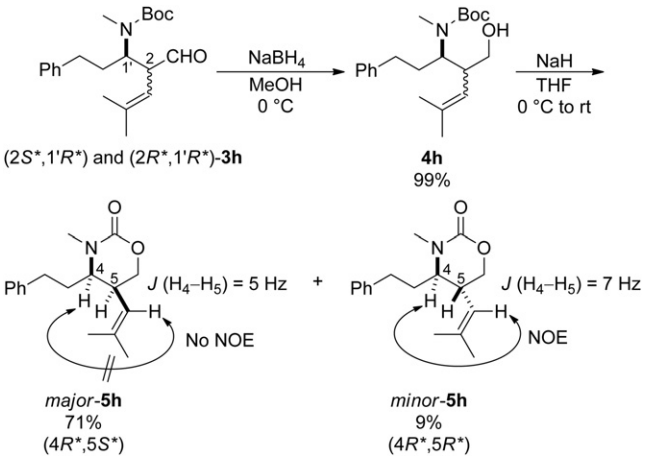
Table 3
1,4-Elimination and aza-Ferrier reaction of acyclic derivative **1**



Entry	R^1	R^2		**2** (%)[a,b]	**3** (%)[a,b]	(2*S**,1′*R**)/(2*R**,1′*R**)[c]
1	CH_2CH_2Ph	Me	**h**	84	91	85/15
2	$CHMe_2$	Me	**i**	91	65	75/25
3	CH_2CH_2Ph	Et	**j**	83	78	80/20
4	CH_2CH_2Ph	$CH_2CH{=}CH_2$	**k**	0[d]	—	—
5	CH_2CH_2Ph	CH_2Ph	**l**	0[e]	—	—

[a] Isolated yield.
[b] ^{1}H NMR analysis in chloroform-*d* showed a mixture of rotamers (**2h**: 50/50, **2i**: 60/40, **2j**: 65/35, **3h**: 50/50, **3i**:55/45, **3j**: 50/50).
[c] The ratios were determined by ^{1}H NMR assay of the isolated product.
[d] The corresponding enamide was obtained in ca. 28% by allylic isomerization.
[e] Recovery of **1l**: 57%.

The relative stereochemistry of the acyclic compound **3h** was determined by the same procedures described in Scheme 5 and Fig. 2 (Scheme 7). The *major*-**3h** was assigned as (2*S**,1′*R**) and the *minor*-**3h** was assigned as (2*R**,1′*R**) by NMR analysis of the corresponding cyclic carbamates **5h**. The stereochemistries of **3i** and **3j** were also tentatively determined by analogy with **3h**.



Scheme 7. Determination of relative stereochemistry of **5h**.

In conclusion, we have demonstrated that 1,4-elimination of (*Z*)-*N*-Boc-2-(4-methoxy-2-alkenyloxy)amines (**1**) with LiTMP followed by a Brønsted acids catalyzed aza-Ferrier reaction of the 1,4-eliminated products (**2**) afforded the corresponding β-amino-β,γ-unsaturated aldehydes (**3**). The products may act as interesting building blocks for several classes of alkaloids. Our method expands the synthetic scope of the Ferrier reaction.

3. Experimental

3.1. General

Infrared spectra were recorded on a Perkin Elmer Spectrum GX FT-IR spectrometer or a HITACHI Infrared 270–30 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Varian 400 MHz spectrometer (^{1}H: 400 MHz, ^{13}C: 100 MHz) and a 700 MHz spectrometer (^{1}H: 700 MHz, ^{13}C: 175 MHz). The splitting patterns are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad peak. High-resolution mass spectra were measured on a Thermo Fisher Scientific LC/FT-MS spectrometer. Reactions involving air- or moisture-sensitive compounds were conducted in appropriate round-bottomed flasks with a magnetic stirring bar under an argon atmosphere. Tetrahydrofuran (THF) was purchased from KANTO Chemical Co., Inc., Japan as an anhydrous solvent. Dichloromethane was distilled from calcium hydride prior to use. Merck thin layer chromatography (TLC) plates (silica gel 60 F_{254}) were used for analysis. The products were purified by preparative column chromatography on silica gel (silica gel 60N, spherical neutral, KANTO Chemical Co., Inc., Japan). The ^{13}C NMR analysis of *N*-*tert*-butoxycarbonyl derivatives was not performed because of the low sensitivity of the rotamers, the products mainly obtained as a mixture of isomers, and the lack of reliability of the data. The spectra were not improved under higher temperature (50 °C, DMSO-d_6).

3.2. Representative procedure of 1,4-elimination of 1

A solution of 2,2,6,6-tetramethylpiperidine (100 μL, 0.59 mmol) in THF (0.7 mL) was treated with a 1.6 M hexane solution of *n*-butyllithium (0.34 mL, 0.54 mmol) at 0 °C under an argon atmosphere and the solution was stirred for 30 min at room temperature. The solution was cooled at 0 °C and a solution of **1a** (112.1 mg, 0.358 mmol) in THF (0.7 mL) was added. The mixture was allowed to warm to room temperature and stirred for 12 h. The resulting mixture was quenched with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and then concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate=20/1 as the eluent) to obtain **2a** (81.1 mg, 81% yield) as a colorless oil.

*3.2.1. (E)-N-tert-Butoxycarbonyl-2-(4′-methylpenta-1′,3′-dien-1′-yloxy)piperidine [(1E)-**2a**].* Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.40 (1H, d, J=12.0 Hz, 1′-H), 5.84–5.56 (1H, br, 2-H), 5.79 (1H, dd, J=12.0, 11.2 Hz, 2′-H), 5.60 (1H, d, J=11.2 Hz, 3′-H), 3.76 (1H, br, 6-H), 2.95–2.67 (1H, br, 6-H), 1.84 (1H, d, J=12.0 Hz, CH_2), 1.75–1.29 (5H, m, CH_2), 1.69 (3H, s, $C(CH_3)_2$), 1.62 (3H, s, $C(CH_3)_2$), 1.42 (9H, s, *t*-Bu); IR (film) 2912, 1682, 1616, 1362, 1335, 1244, 1140, 1106, 1035, 985, 916, 890, 866, 810, 765 cm^{-1}; HRMS–ESI (*m*/*z*): [M+Na]$^+$ calcd for $C_{16}H_{27}NO_3Na$: 304.1883. Found: 304.1879.

*3.2.2. (E)-N-tert-Butoxycarbonyl-2-(3′-cyclohexylideneprop-1′-en-1′-yloxy)piperidine [(1E)-**2b**].* Colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.43 (1H, d, J=12.4 Hz, 1′-H), 5.83 (1H, dd, J=12.4, 11.2 Hz, 2′-H), 5.78–5.60 (1H, br, 2-H), 5.55 (1H, d, J=11.2 Hz, 3′-H), 3.74 (1H, br, 6-H), 2.94–2.66 (1H, br, 6-H), 2.13 (2H, t, J=5.0 Hz, CH_2), 2.05 (2H, t, J=5.2 Hz, CH_2), 1.83 (1H, d, J=12.4 Hz, CH_2), 1.70–1.22 (11H, m, CH_2), 1.41 (9H, s, *t*-Bu); IR (film) 2848, 1656, 1612, 1362, 1236, 1108, 1030, 920, 864, 810, 758 cm^{-1}; HRMS–ESI (*m*/*z*): [M+Na]$^+$ calcd for $C_{19}H_{31}NO_3Na$: 344.2196. Found: 344.2193.

*3.2.3. (1E)-N-tert-Butoxycarbonyl-2-(undeca-1′,3′-dien-1′-yloxy)piperidine [(1E)-**2c**].* Colorless oil. (1*E*,3*E*)/(1*E*,3*Z*)/(1*Z*,3*E*)/(1*Z*,3*Z*)=60/32/7/1 mixture. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.52 (0.32H, d, J=11.2 Hz, 1′-H), 6.43 (0.60H, d, J=12.8 Hz, 1′-H), 6.26 (0.08H, dd, J=14.6, 11.4 Hz, 3′-H), 6.16 (0.01H, d, J=5.2 Hz, 1′-H), 6.01 (0.07H, d, J=6.0 Hz, 1′-H), 5.90–5.33 and 5.20–5.05 (3.40H, m), 5.61 (0.60H, dd, J=11.6, 11.6 Hz, 2-H), 3.74 (1H, br), 2.78 (1H, br), 2.08–1.93 (2H, m, 5′-H), 1.90–1.77 (1H, br), 1.72–1.45 (4H, m), 1.45–1.15 (11H, m), 1.41 (9H, s, *t*-Bu), 0.85 (3H, t, J=6.8 Hz, 11′-H); IR (film) 2912, 2848, 1684, 1654, 1364, 1335, 1246, 1120, 1090, 1040, 946, 864, 815,

760 cm^{-1}; HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{21}H_{37}NO_3Na$: 374.2666. Found: 374.2664.

*3.2.4. (1E)-N-tert-Butoxycarbonyl-2-(octa-1′,3′-dien-1′-yloxy)piperidine [(1E)-**2d**].* Colorless oil. (1*E*,3*E*)/(1*E*,3*Z*)/(1*Z*,3*E*)/(1*Z*,3*Z*)=59/33/7/1 mixture. ^1H NMR (400 MHz, DMSO-d_6) δ 6.52 (0.33H, d, J=11.6 Hz, 1′-H), 6.43 (0.59H, d, J=12.4 Hz, 1′-H), 6.27 (0.08H, dd, J=15.0, 11.0 Hz, 3′-H), 6.16 (0.01H, d, J=5.2 Hz, 1′-H), 6.01 (0.07H, d, J=6.0 Hz, 1′-H), 5.91–5.34 and 5.20–5.04 (3.41H, m), 5.61 (0.59H, dd, J=11.6, 11.6 Hz, 2-H), 3.74 (1H, br), 2.95–2.65 (1H, br), 2.10–1.94 (2H, m, 5′-H), 1.91–1.77 (1H, br), 1.74–1.46 (4H, m), 1.41 (9H, s, *t*-Bu), 1.35–1.20 (5H, m), 0.90–0.81 (3H, m, 8′-H); IR (film) 2908, 2860, 1680, 1654, 1615, 1362, 1335, 1236, 1120, 1080, 1030, 946, 864, 810, 760 cm^{-1}; HRMS–ESI (m/z): $[M+H]^+$ calcd for $C_{18}H_{32}NO_3$: 310.2377. Found: 310.2375.

*3.2.5. (1E)-N-tert-Butoxycarbonyl-2-(6′-phenylhexa-1′,3′-dien-1′-yloxy)piperidine [(1E)-**2e**].* Colorless oil. (1*E*,3*E*)/(1*E*,3*Z*)/(1*Z*,3*E*)/(1*Z*,3*Z*)=58/33/7/2 mixture. ^1H NMR (400 MHz, DMSO-d_6) δ 7.30–7.13 (5H, m, Ph), 6.53 (0.33H, d, J=11.2 Hz, 1′-H), 6.44 (0.58H, d, J=12.0 Hz, 1′-H), 6.35–6.25 (0.09H, m, 3′-H), 6.16 (0.02H, d, J=6.0 Hz, 1′-H), 6.03 (0.07H, d, J=6.4 Hz, 1′-H), 5.95–5.38 and 5.23–5.03 (3.33H, m), 5.61 (0.58H, dd, J=11.6, 11.6 Hz, 2-H), 3.76 (1H, br), 2.95–2.70 (1H, br), 2.69–2.56 (2H, m), 2.42–2.25 (2H, m), 1.90–1.75 (1H, br), 1.75–1.15 (15H, m, CH_2 and *t*-Bu); IR (film) 2920, 1684, 1654, 1364, 1335, 1242, 1116, 946, 885, 865, 735 cm^{-1}; HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{22}H_{31}NO_3Na$: 380.2196. Found: 380.2190.

*3.2.6. (E)-N-tert-Butoxycarbonyl-2-(4′-methylpenta-1′,3′-dien-1′-yloxy)pyrrolidine [(1E)-**2f**].* Colorless oil. ^1H NMR (400 MHz, DMSO-d_6, 55/45 mixture of rotamers) δ 6.63 (0.45H, d, J=10.4 Hz, 1′-H), 6.57 (0.55H, d, J=10.8 Hz, 1′-H), 5.70–5.56 (2H, m, 2′- and 3′-H), 5.49 (0.45H, s, 2-H), 5.41 (0.55H, d, J=2.4 Hz, 2-H), 3.40–3.30 (1H, m, 5-H), 3.27–3.14 (1H, m, 5-H), 1.96–1.80 (4H, m, CH_2), 1.69 (3H, s, $C(CH_3)_2$), 1.60 (3H, s, $C(CH_3)_2$), 1.41 (9H, s, *t*-Bu); IR (film) 2975, 2919, 1705, 1663, 1625, 1477, 1455, 1390, 1326, 1286, 1256, 1160, 1128, 1090, 1043, 980, 944, 917, 883, 855, 772 cm^{-1}; HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{15}H_{25}NO_3Na$: 290.1727. Found: 290.1728.

*3.2.7. (1E)-N-tert-Butoxycarbonyl-2-(undeca-1′,3′-dien-1′-yloxy)pyrrolidine [(1E)-**2g**].* Colorless oil. (1*E*,3*E*)/(1*E*,3*Z*)/(1*Z*,3*E*)/(1*Z*,3*Z*)=90/10/0/0 mixture. ^1H NMR (400 MHz, DMSO-d_6, 50/50 mixture of rotamers) δ 6.74 (0.05H, d, J=10.8 Hz, 1′-H), 6.71–6.54 (0.05H, m, 1′-H), 6.65 (0.45H, d, J=12.2 Hz, 1′-H), 6.59 (0.45H, d, J=12.2 Hz, 1′-H), 5.84 (0.9H, dd, J=15.2, 10.8 Hz, 3′-H), 5.70 (0.1H, dd, J=11.6, 11.6 Hz, 3′-H), 5.55–5.30 (2.9H, m, 2-, 2′-, and 4′-H), 5.16–5.06 (0.1H, m), 3.40–3.30 (1H, m, NCH_2), 3.26–3.12 (1H, m, NCH_2), 2.07–1.78 (6H, m, CH_2), 1.40 (9H, s, *t*-Bu), 1.35–1.16 (10H, m, CH_2), 0.85 (3H, t, J=6.8 Hz, 11′-H); IR (film) 2957, 2925, 2854, 1705, 1660, 1625, 1456, 1389, 1325, 1286, 1254, 1168, 1148, 1116, 1089, 1032, 971, 943, 915, 884, 854, 772 cm^{-1}; HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{20}H_{35}NO_3Na$: 360.2509. Found: 360.2509.

*3.2.8. (1Z)-N-tert-Butoxycarbonyl-2-(undeca-1′,3′-dien-1′-yloxy)piperidine [(1Z)-**2c**].* Colorless oil. (1*E*,3*E*)/(1*E*,3*Z*)/(1*Z*,3*E*)/(1*Z*,3*Z*)=3/3/50/44 mixture. ^1H NMR (400 MHz, DMSO-d_6) δ 6.52 (0.03H, d, J=10.8 Hz, 1′-H), 6.43 (0.03H, d, J=12.4 Hz, 1′-H), 6.31–6.21 (0.06H, m, 3′-H), 6.26 (0.94H, dd, J=12.0, 12.0 Hz, 3′-H), 6.15 (0.44H, d, J=6.0 Hz, 1′-H), 6.02 (0.50H, d, J=6.4 Hz, 1′-H), 5.90–5.59 (0.94H, br), 5.90–5.00 (0.18H, m), 5.52 (0.50H, dt, J=15.6, 6.8 Hz, 4′-H), 5.34 (0.44H, br), 5.26 (0.44H, dt, J=10.8, 8.0 Hz, 4′-H), 5.09 (0.50H, br), 3.84–3.67 (1H, br), 2.95–2.66 (1H, br), 2.11–1.93 (2H, m), 1.93–1.80 (1H, m), 1.76–1.46 (4H, m), 1.46–0.96 (11H, m), 1.40 (9H, s, *t*-Bu), 0.85 (3H, t, J=6.4 Hz, 11′-H); IR (film) 2926, 2854, 1701, 1656, 1616, 1603, 1454, 1404, 1365, 1338, 1318, 1272, 1255, 1238, 1162, 1088, 1050, 1030, 992, 971, 958, 930, 890, 868, 815, 770 cm^{-1}; HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{21}H_{37}NO_3Na$: 374.2666. Found: 374.2668.

*3.2.9. (E)-N-tert-Butoxycarbonyl-N-methyl-1-(4′-methylpenta-1′,3′-dien-1′-yloxy)-3-phenylpropan-1-amine [(E)-**2h**].* Colorless oil. ^1H NMR (400 MHz, $CDCl_3$, 50/50 mixture of rotamers) δ 7.33–7.25 (2H, m, Ph), 7.23–7.16 (3H, m, Ph), 6.38 (0.5H, d, J=11.6 Hz, 1′-H), 6.27 (0.5H, d, J=12.2 Hz, 1′-H), 5.91 (0.5H, dd, J=11.6, 11.6 Hz, 2′-H), 5.85 (0.5H, dd, J=12.2 Hz, 11.6 Hz, 2′-H), 5.75 (0.5H, dd, J=6.8, 6.8 Hz, 1-H), 5.64 (0.5H, d, J=11.6 Hz, 3′-H), 5.60 (0.5H, d, J=11.6 Hz, 3′-H), 5.46 (0.5H, dd, J=6.6, 6.6 Hz, 1-H), 2.79–2.52 (2H, m, 3-H), 2.74 (1.5H, s, NCH_3), 2.67 (1.5H, s, NCH_3), 2.17–2.02 (1H, m, 2-H), 1.97–1.83 (1H, m, 2-H), 1.74 (3H, s, $C(CH_3)_2$), 1.68 (3H, s, $C(CH_3)_2$), 1.48 (4.5H, s, *t*-Bu), 1.42 (4.5H, s, *t*-Bu); IR (film) 2904, 1682, 1612, 1430, 1326, 1246, 1118, 1016, 975, 912, 875, 738 cm^{-1}; HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{21}H_{31}NO_3Na$: 368.2196. Found: 368.2199.

*3.2.10. (E)-N-tert-Butoxycarbonyl-N,2-dimethyl-1-(4′-methylpenta-1′,3′-dien-1-yloxy)propan-1-amine [(E)-**2i**].* Colorless oil. ^1H NMR (400 MHz, $CDCl_3$, 60/40 mixture of rotamers) δ 6.37 (0.6H, d, J=12.4 Hz, 1′-H), 6.29 (0.4H, d, J=12.0 Hz, 1′-H), 5.88 (0.6H, dd, J=11.4, 11.4 Hz, 2′-H), 5.85 (0.4H, dd, J=10.4, 10.4 Hz, 2′-H), 5.65 (0.6H, d, J=11.4 Hz, 3′-H), 5.62 (0.4H, d, J=10.4 Hz, 3′-H), 5.28 (0.6H, d, J=9.6 Hz, 1-H), 5.03 (0.4H, d, J=9.6 Hz, 1-H), 2.69 (1.2H, s, NCH_3), 2.65 (1.8H, s, NCH_3), 2.01–1.88 (1H, m, C*H*$(CH_3)_2$), 1.74 (1.2H, s, C=$C(CH_3)_2$), 1.73 (1.8H, s, C=$C(CH_3)_2$), 1.68 (3H, s, C=$C(CH_3)_2$), 1.49 (3.6H, s, *t*-Bu), 1.47 (5.4H, s, *t*-Bu), 1.024 (1.8H, d, J=6.4 Hz, $CH(CH_3)_2$), 1.015 (1.2H, d, J=6.4 Hz, $CH(CH_3)_2$), 0.82 (3H, d, J=7.2 Hz, $CH(CH_3)_2$); IR (film) 2968, 2925, 2876, 1699, 1664, 1620, 1473, 1442, 1388, 1368, 1334, 1257, 1203, 1165, 1140, 1106, 1044, 995, 941, 921, 879, 855, 771, 736, 711 cm^{-1}; HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{16}H_{29}NO_3Na$: 306.2040. Found: 306.2034.

*3.2.11. (E)-N-tert-Butoxycarbonyl-N-ethyl-1-(4′-methylpenta-1′,3′-dien-1′-yloxy)-3-phenylpropan-1-amine [(E)-**2j**].* Colorless oil. ^1H NMR (400 MHz, $CDCl_3$, 65/35 mixture of rotamers) δ 7.32–7.25 (2H, m, Ph), 7.24–7.16 (3H, m, Ph), 6.38 (0.65H, d, J=11.6 Hz, 1′-H), 6.28 (0.35H, d, J=11.6 Hz, 1′-H), 5.87 (1H, dd, J=11.6, 10.0 Hz, 2′-H), 5.75 (0.65H, br, 1-H), 5.63 (1H, d, J=10.0 Hz, 3′-H), 5.46 (0.35H, br, 1-H), 3.33–3.05 (2H, br, NCH_2), 2.80–2.53 (2H, m, 3-H), 2.20–2.01 (1H, m, 2-H), 1.99–1.82 (1H, m, 2-H), 1.74 (3H, s, $C(CH_3)_2$), 1.68 (3H, s, $C(CH_3)_2$), 1.48 (5.85H, s, *t*-Bu), 1.43 (3.15H, s, *t*-Bu), 1.20–1.06 (3H, br, NCH_2CH_3); IR (film) 3027, 2973, 2929, 2872, 1695, 1622, 1453, 1409, 1368, 1336, 1293, 1254, 1223, 1202, 1165, 1141, 1124, 1091, 1044, 971, 919, 862, 795, 774, 751 cm^{-1}; HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{22}H_{33}NO_3Na$: 382.2353. Found: 382.2351.

3.3. Representative procedure of aza-Ferrier reaction of 2

A solution of **2a** (112.6 mg, 0.400 mmol) and pyridinium *p*-toluenesulfonate (10.1 mg, 0.040 mmol) in dichloromethane (2 mL) was stirred for 3 h at 0 °C under an argon atmosphere. The resulting mixture was quenched with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and then concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate=5/1 as the eluent) to obtain **3a** (100.7 mg, 89% yield) as a colorless oil.

*3.3.1. N-tert-Butoxycarbonyl-4-methyl-2-(piperidin-2′-yl)pent-3-enal (**3a**).* Colorless oil. (2*S**,2′*R**)/(2*R**,2′*R**)=75/25 mixture. ^1H NMR (400 MHz, $CDCl_3$) δ 9.39 (0.75H, d, J=4.0 Hz, CHO), 9.36–9.30 (0.25H, br, CHO), 5.06 (1H, br), 4.80–4.40 (1H, br), 3.99 (1H, br), 3.80–3.50 (1H, br), 2.95–2.75 (0.25H, br, 6′-H), 2.52 (0.75H, t, J=13.0 Hz, 6′-H), 1.79 (0.75H, s, $C(CH_3)_2$), 1.75 (2.25H, s, $C(CH_3)_2$), 1.70 (2.25H, s, $C(CH_3)_2$), 1.67 (0.75H, s, $C(CH_3)_2$), 1.66–1.51 (6H, m,

CH_2), 1.47 (6.75H, s, *t*-Bu), 1.43 (2.25H, s, *t*-Bu); IR (film) 2912, 2856, 2700, 1672, 1405, 1390, 1362, 1305, 1242, 1142, 1050, 990, 915, 830, 758 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{28}NO_3$: 282.2064. Found: 282.2059.

*3.3.2. N-tert-Butoxycarbonyl-3-cyclohexylidene-2-(piperidin-2′-yl) propanal (**3b**).* Colorless oil. (2*S**,2′*R**)/(2*R**,2′*R**)=75/25 mixture. ^1H NMR (400 MHz, $CDCl_3$) δ 9.41 (0.75H, d, *J*=3.6 Hz, CHO), 9.36 (0.25H, br, CHO), 4.99 (1H, br), 4.85–4.37 (1H, br), 4.20–3.60 (2H, br), 2.95–2.75 (0.25H, br, 6′-H), 2.52 (0.75H, t, *J*=13.2 Hz, 6′-H), 2.23–2.05 (4H, m, CH_2), 1.75–1.23 (12H, m, CH_2), 1.46 (9H, s, *t*-Bu); IR (film) 2908, 2848, 2696, 1670, 1385, 1360, 1306, 1242, 1138, 1070, 1025, 985, 915, 840, 758 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{19}H_{31}NO_3Na$: 344.2196. Found: 344.2194.

*3.3.3. N-tert-Butoxycarbonyl-2-(piperidin-2′-yl)undec-3-enal (**3c**).* Colorless oil. (2*S**,2′*R**,*E*)/(2*S**,2′*R**,*Z*)/(2*R**,2′*R**,*E*)/(2*R**,2′*R**,*Z*)= 50/30/15/5 mixture. ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (0.50H, d, *J*=3.6 Hz, CHO), 9.43 (0.30H, d, *J*=3.6 Hz, CHO), 9.42 (0.15H, br, CHO), 9.38 (0.05H, br, CHO), 5.78–5.61 (0.20H, m, 4-H), 5.71 (0.30H, dt, *J*=10.8, 8.0 Hz, 4-H), 5.66 (0.50H, dt, *J*=15.2, 7.2 Hz, 4-H), 5.30 (1H, br), 4.85–4.40 (1H, br), 4.20–3.65 and 3.65–3.30 (2H, br), 2.95–2.70 and 2.70–2.45 (1H, br), 2.13–1.97 (2H, m, CH_2), 1.78–1.20 (25H, m, CH_2 and *t*-Bu), 0.91–0.85 (3H, m, 11-H); IR (film) 2912, 2848, 2696, 1672, 1390, 1362, 1306, 1242, 1140, 1030, 968, 862, 750 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{37}NO_3Na$: 374.2666. Found: 374.2653.

*3.3.4. N-tert-Butoxycarbonyl-2-(piperidin-2′-yl)oct-3-enal (**3d**).* Colorless oil. (2*S**,2′*R**,*E*)/(2*S**,2′*R**,*Z*)/(2*R**,2′*R**,*E*)/(2*R**,2′*R**,*Z*)= 50/30/15/5 mixture. ^1H NMR (700 MHz, $CDCl_3$) δ 9.51 (0.50H, s, CHO), 9.43 (0.30H, s, CHO), 9.42 (0.15H, br, CHO), 9.37 (0.05H, br, CHO), 5.77–5.61 (1H, m, 4-H), 5.45–5.15 (1H, br), 4.85–4.40 (1H, br), 4.20–3.65 and 3.60–3.30 (2H, br), 2.95–2.45 (1H, br), 2.14–1.98 (2H, m, 5-H), 1.77–1.24 (19H, m, CH_2 and *t*-Bu), 0.93–0.85 (3H, m, 8-H); IR (film) 2912, 2852, 2700, 1672, 1390, 1362, 1308, 1246, 1140, 1030, 970, 862, 752 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{31}NO_3Na$: 332.2196. Found: 332.2184.

*3.3.5. N-tert-Butoxycarbonyl-6-phenyl-2-(piperidin-2′-yl)hex-3-enal (**3e**).* Colorless oil. (2*S**,2′*R**,*E*)/(2*S**,2′*R**,*Z*)/(2*R**,2′*R**,*E*)/(2*R**,2′*R**,*Z*)= 50/30/15/5 mixture. ^1H NMR (400 MHz, $CDCl_3$) δ 9.48 (0.50H, d, *J*=2.8 Hz, CHO), 9.38 (0.15H, br, CHO), 9.34 (0.05H, d, *J*=5.2 Hz, CHO), 9.26 (0.30H, br, CHO), 7.32–7.24 (2H, m, Ph), 7.22–7.12 (3H, m, Ph), 5.81–5.62 (0.20H, m, 4-H), 5.74 (0.30H, dt, *J*=10.8, 7.6 Hz, 4-H), 5.68 (0.50H, dt, *J*=15.6, 6.8 Hz, 4-H), 5.33 (1H, br), 4.85–4.35 (1H, br), 4.15–3.80 (1H, br), 3.80–3.25 (1H, br), 2.90–2.49 (3H, m), 2.48–2.26 (2H, m), 1.69–1.32 (15H, m, CH_2 and *t*-Bu); IR (film) 2920, 2848, 2704, 1670, 1390, 1358, 1306, 1244, 1142, 1030, 970, 862, 725 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{31}NO_3Na$: 380.2196. Found: 380.2188.

*3.3.6. N-tert-Butoxycarbonyl-4-methyl-2-(1′-(methylamino)-3′-phenylpropyl)pent-3-enal (**3h**).* Colorless oil. (2*S**,1′*R**)/(2*R**,1′*R**)=85/15 mixture. ^1H NMR (400 MHz, $CDCl_3$, 50/50 mixture of rotamers) δ 9.37 (0.425H, d, *J*=3.2 Hz, CHO), 9.36 (0.425H, d, *J*=4.0 Hz, CHO), 9.32–9.26 (0.075H, br, CHO), 9.28 (0.075H, d, *J*=5.2 Hz, CHO), 7.32–7.23 (2H, m, Ph), 7.22–7.13 (3H, m, Ph), 5.06–4.87 (0.15H, m, 3-H), 5.03 (0.425H, d, *J*=10.0 Hz, 3-H), 4.91 (0.425H, d, *J*=10.0 Hz, 3-H), 4.65–4.30 (0.575H, br, 1′-H), 4.60 (0.425H, ddd, *J*=10.0, 10.0, 3.2 Hz, 2-H), 3.42–3.20 (0.575H, br, 1′-H), 3.31 (0.425H, ddd, *J*=10.0, 10.0, 4.0 Hz, 2-H), 2.83–2.45 (5H, m, 3′-H and NCH_3), 1.91–1.54 (8H, m, 2′-H and $C(CH_3)_2$), 1.51–1.40 (9H, m, *t*-Bu); IR (film) 2908, 2700, 1672, 1426, 1380, 1332, 1246, 1128, 826, 738 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{21}H_{32}NO_3$: 346.2377. Found: 346.2376.

*3.3.7. N-tert-Butoxycarbonyl-4-methyl-2-(2′-methyl-1′-(methylamino)propyl)pent-3-enal (**3i**).* Colorless oil. (2*S**,1′*R**)/(2*R**,1′*R**)= 75/25 mixture. ^1H NMR (400 MHz, $CDCl_3$, 55/45 mixture of rotamers) δ 9.43 (0.41H, d, *J*=4.0 Hz, CHO), 9.41 (0.34H, d, *J*=3.6 Hz, CHO), 9.34 (0.11H, d, *J*=3.2 Hz, CHO), 9.26 (0.14H, d, *J*=4.8 Hz, CHO), 5.15–5.06 (0.25H, m, 3-H), 4.97 (0.41H, dqq, *J*=9.6, 1.4, 1.4 Hz, 3-H), 4.88 (0.34H, dqq, *J*=9.6, 1.4, 1.4 Hz, 3-H), 4.42–4.09 (1H, m), 3.53–3.38 (1H, m), 2.69 (0.33H, br, NCH_3), 2.66 (0.42H, s, NCH_3), 2.64 (1.02H, s, NCH_3), 2.60 (1.23H, s, NCH_3), 2.00–1.65 (7H, m, C=C(CH_3)$_2$ and $CH(CH_3)_2$), 1.48 (3.06H, s, *t*-Bu), 1.47 (0.99H, s, *t*-Bu), 1.45 (3.69H, s, *t*-Bu), 1.44 (1.26H, s, *t*-Bu), 0.96 (0.66H, d, *J*=6.8 Hz, $CH(CH_3)_2$), 0.95 (0.84H, d, *J*=6.8 Hz, $CH(CH_3)_2$), 0.91 (2.46H, d, *J*=6.4 Hz, $CH(CH_3)_2$), 0.88 (2.04H, d, *J*=6.8 Hz, $CH(CH_3)_2$); IR (film) 2970, 2925, 2876, 2812, 2708, 1718, 1692, 1473, 1444, 1388, 1366, 1338, 1305, 1255, 1147, 1049, 982, 939, 877, 835, 771, 704 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{29}NO_3Na$: 306.2040. Found: 306.2037.

*3.3.8. N-tert-Butoxycarbonyl-2-(1′-(ethylamino)-3′-phenylpropyl)-4-methylpent-3-enal (**3j**).* White solid. (2*S**,1′*R**)/(2*R**,1′*R**)=80/20 mixture. ^1H NMR (400 MHz, $CDCl_3$, 50/50 mixture of rotamers) δ 9.40 (0.1H, s, CHO), 9.35 (0.8H, d, *J*=4.0 Hz, CHO), 9.31 (0.1H, d, *J*=4.8 Hz, CHO), 7.33–7.23 (2H, m, Ph), 7.23–7.13 (3H, m, Ph), 5.03–4.88 (0.2H, m, 3-H), 5.00 (0.4H, d, *J*=9.6 Hz, 3-H), 4.91 (0.4H, d, *J*=9.2 Hz, 3-H), 4.50–4.33 (0.5H, m), 3.53–3.38 (0.5H, m), 3.27–2.76 (2H, m), 2.76–2.50 (2H, m), 2.00–1.55 (9H, m), 1.51–1.43 (9H, m, *t*-Bu), 1.17 (1.5H, t, *J*=7.0 Hz, NCH_2CH_3), 1.12 (1.5H, t, *J*=7.0 Hz, NCH_2CH_3); IR (KBr) 3059, 3025, 2973, 2933, 2862, 2734, 1722, 1677, 1601, 1475, 1453, 1413, 1366, 1334, 1284, 1243, 1212, 1175, 1149, 1093, 1044, 991, 943, 910, 862, 833, 798, 777, 753, 701 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{33}NO_3Na$: 382.2353. Found: 382.2346.

3.4. Representative procedure of the reduction of 3 with sodium borohydride

Sodium borohydride (0.20 g, 0.53 mmol) was added to a solution of **3a** (145.3 mg, 0.516 mmol) in methanol (2.6 mL) at 0 °C, and the mixture was stirred for 3 h at room temperature. The resulting mixture was diluted with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate=2/1 as the eluent) to obtain *major*-**4a** (106.8 mg, 73% yield) as a colorless oil and *minor*-**4a** (30.4 mg, 21% yield) as a white solid.

3.4.1. (2S,2′R*)-N-tert-Butoxycarbonyl-4-methyl-2-(piperidin-2′-yl) pent-3-en-1-ol (major-**4a**).* Colorless oil. ^1H NMR (700 MHz, $CDCl_3$) δ 4.96 (1H, d, *J*=10.5 Hz, 3-H), 4.16 (1H, br), 3.93 (1H, br), 3.56 (1H, br), 3.32 (1H, dd, *J*=10.9, 8.1 Hz), 2.94 (1H, br), 2.65 (1H, br), 1.74 (3H, d, *J*=0.7 Hz, $C(CH_3)_2$), 1.69 (3H, d, *J*=1.4 Hz, $C(CH_3)_2$), 1.68–1.53 (6H, m), 1.49–1.38 (1H, m), 1.45 (9H, s, *t*-Bu); IR (film) 3446, 2973, 2932, 2865, 1688, 1664, 1475, 1421, 1366, 1316, 1272, 1252, 1163, 1066, 1014, 993, 919, 870, 845, 815, 766, 736 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{30}NO_3$: 284.2220. Found: 284.2218.

3.4.2. (2R,2′R*)-N-tert-Butoxycarbonyl-4-methyl-2-(piperidin-2′-yl) pent-3-en-1-ol (minor-**4a**).* White solid. ^1H NMR (700 MHz, $CDCl_3$) δ 5.22 (1H, d, *J*=8.4 Hz, 3-H), 4.17 (1H, br), 3.99 (1H, d, *J*=11.2 Hz), 3.53–3.36 (2H, br), 2.79–2.68 (1H, m), 2.72 (1H, ddd, *J*=13.0, 13.0, 2.8 Hz), 1.76 (3H, s, $C(CH_3)_2$), 1.72–1.54 (4H, m), 1.67 (3H, s, $C(CH_3)_2$), 1.54–1.36 (3H, m), 1.47 (9H, s, *t*-Bu); IR (film) 3444, 2933, 2861, 1684, 1658, 1424, 1366, 1343, 1316, 1275, 1252, 1160, 1074, 1032, 996, 977, 919, 866, 843, 813, 771 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{16}H_{29}NO_3Na$: 306.2040. Found: 306.2037.

3.4.3. (2S,2′R*)-N-tert-Butoxycarbonyl-6-phenyl-2-(piperidin-2′-yl) hex-3-en-1-ol (major-**4e**).* Colorless oil. *E*/*Z*=65/35 mixture. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.25 (2H, m, Ph), 7.22–7.13 (3H, m, Ph), 5.64 (0.35H, dt, *J*=11.2, 7.4 Hz, 4-H), 5.56 (0.65H, dt, *J*=14.8,

6.8 Hz, 4-H), 5.27–5.14 (1H, m, 3-H), 4.13 (1H, br), 3.89 (1H, br), 3.49 (1H, br), 3.32–3.20 (1H, m), 2.80–2.50 (4H, m), 2.50–2.25 (2H, m), 1.64–1.49 (6H, br), 1.45 (5.85H, s, *t*-Bu), 1.44 (3.15H, s, *t*-Bu), 1.34–1.23 (1H, m); IR (film) 3449, 3062, 2933, 2863, 1687, 1661, 1604, 1470, 1449, 1421, 1366, 1314, 1272, 1163, 1063, 975, 914, 869, 813, 745, 700 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{33}NO_3Na$: 382.2353. Found: 382.2349.

3.4.4. (2R,2′R*)-N-tert-Butoxycarbonyl-6-phenyl-2-(piperidin-2′-yl) hex-3-en-1-ol (minor-**4e**).* Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.24 (2H, m, Ph), 7.22–7.13 (3H, m, Ph), 5.53 (2H, br, 3-H and 4-H), 4.15 (1H, br), 3.96 (1H, br), 3.55–3.20 (2H, br), 2.85–2.60 (3H, m), 2.55–2.30 (3H, m), 1.75–1.20 (7H, m), 1.46 (9H, s, *t*-Bu); IR (film) 3440, 3062, 2933, 2859, 1687, 1656, 1476, 1423, 1366, 1317, 1275, 1252, 1161, 1075, 1033, 996, 974, 918, 867, 812, 746 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{22}H_{33}NO_3Na$: 382.2353. Found: 382.2349.

*3.4.5. N-tert-Butoxycarbonyl-4-methyl-2-(1′-(methylamino)-3′-phenylpropyl)pent-3-en-1-ol (**4h**).* Colorless oil. (2*S**,1′*R**)/(2*R**,1′*R**)= 85/15 mixture. ^1H NMR (400 MHz, $CDCl_3$, 80/20 mixture of rotamers) δ 7.32–7.25 (2H, m, Ph), 7.22–7.13 (3H, m, Ph), 5.19 (0.12H, d, *J*=10.4 Hz, 3-H), 4.98 (0.03H, d, *J*=10.4 Hz, 3-H), 4.89 (0.17H, d, *J*=10.4 Hz, 3-H), 4.79 (0.68H, d, *J*=10.8 Hz, 3-H), 4.35 (0.68H, br, 1′-H), 4.20–3.85 (0.32H, br, 1′-H), 3.60 (0.17H, dd, *J*=11.0, 5.4 Hz), 3.48 (0.12H, dd, *J*=11.4, 4.2 Hz), 3.43–3.27 (1.71H, m), 2.80–2.42 (1.64H, m), 2.71 (3H, s, NCH_3), 2.57 (1.36H, t, *J*=8.0 Hz, 3′-H), 1.94–1.57 (4.92H, m), 1.71 (2.04H, s, $C(CH_3)_2$), 1.64 (2.04H, s, $C(CH_3)_2$), 1.49 (7.2H, s, *t*-Bu), 1.45 (1.8H, s, *t*-Bu); IR (film) 3440, 3061, 3026, 2972, 2928, 2866, 1689, 1666, 1603, 1480, 1452, 1394, 1365, 1346, 1254, 1153, 1057, 980, 874, 770, 749, 700 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{21}H_{33}NO_3Na$: 370.2353. Found: 370.2346.

3.5. Representative procedure of the cyclization of 4

Sodium hydride (60 wt % in oil, 17 mg, 0.43 mmol) in THF (1.8 mL) was added to a solution of *major*-**4a** (101.7 mg, 0.359 mmol) at 0 °C. After stirring for 2 h at 0 °C and 15 h at room temperature, the resulting mixture was quenched with saturated aqueous ammonium chloride at 0 °C. Extractive workup and purification of the residue by chromatography on silica gel (ethyl acetate as the eluent) afforded *major*-**5a** (42.7 mg, 57% yield) as a white solid.

3.5.1. (4S,4aR*)-4-(2′-Methylprop-1′-enyl)hexahydropyrido[1,2-c] [1,3]oxazin-1(3H)-one (major-**5a**).* White solid. ^1H NMR (700 MHz, $CDCl_3$) δ 4.99 (1H, dqq, *J*=9.8, 1.4, 1.4 Hz, 1′-H), 4.45–4.41 (1H, m, 8-H), 4.08 (1H, dd, *J*=10.7, 9.3 Hz, 3-H), 4.02 (1H, dd, *J*=10.7, 3.7 Hz, 3-H), 3.30 (1H, ddd, *J*=12.3, 5.6, 2.5 Hz, 4a-H), 3.05 (1H, dddd, *J*=9.8, 9.3, 5.6, 3.7 Hz, 4-H), 2.68 (1H, ddd, *J*=12.8, 12.8, 3.2 Hz, 8-H), 1.95–1.90 (1H, m, 6-H), 1.75 (3H, d, *J*=1.4 Hz, $C(CH_3)_2$), 1.70–1.62 (2H, m, 5-H and 6-H), 1.69 (3H, d, *J*=1.4 Hz, $C(CH_3)_2$), 1.52–1.40 (2H, m, 7-H), 1.36 (1H, ddd, *J*=12.3, 12.3, 3.9 Hz, 5-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 137.0, 117.4, 67.5, 57.9, 46.3, 35.2, 27.7, 25.9, 25.4, 24.2, 18.3; IR (KBr) 2948, 2859, 1705, 1691, 1479, 1448, 1383, 1355, 1339, 1302, 1258, 1223, 1198, 1175, 1157, 1133, 1092, 1049, 1016, 953, 922, 858, 831, 745 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{20}NO_2$: 210.1489. Found: 210.1488.

3.5.2. (4R,4aR*)-4-(2′-Methylprop-1′-enyl)hexahydropyrido[1,2-c] [1,3]oxazin-1(3H)-one (minor-**5a**).* White solid. ^1H NMR (700 MHz, $CDCl_3$) δ 4.81 (1H, dqq, *J*=9.5, 1.4, 1.4 Hz, 1′-H), 4.49–4.44 (1H, m, 8-H), 3.97 (1H, dd, *J*=10.9, 4.6 Hz, 3-H), 3.84 (1H, dd, *J*=10.9, 10.9 Hz, 3-H), 2.95 (1H, ddd, *J*=11.6, 9.5, 2.5 Hz, 4a-H), 2.68 (1H, dddd, *J*=10.9, 9.5, 9.5, 4.6 Hz, 4-H), 2.66 (1H, ddd, *J*=13.2, 13.2, 2.8 Hz, 8-H), 1.88–1.81 (2H, m, 5-H and 7-H), 1.74 (3H, d, *J*=1.4 Hz, $C(CH_3)_2$), 1.71–1.66 (1H, m, 6-H), 1.70 (3H, d, *J*=1.4 Hz, $C(CH_3)_2$), 1.47 (1H, ddddd, *J*=13.0, 13.0, 13.0, 4.2, 4.2 Hz, 7-H), 1.35 (1H, ddddd, *J*=13.0, 13.0, 13.0, 4.2, 4.2 Hz, 6-H), 1.12 (1H, dddd, *J*=13.0, 13.0, 11.6, 4.2 Hz, 5-H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 153.4, 138.0, 119.4, 67.7, 59.9, 45.1, 39.7, 31.8, 25.9, 25.0, 23.7, 18.5; IR (KBr) 2932, 2857, 1676, 1478, 1443, 1390, 1364, 1347, 1320, 1304, 1262, 1229, 1177, 1137, 1104, 1049, 1010, 967, 951, 923, 853, 756 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{20}NO_2$: 210.1489. Found: 210.1486.

3.5.3. (4S,4aR*)-4-(4′-Phenylbut-1′-enyl)hexahydropyrido[1,2-c] [1,3]oxazin-1(3H)-one (major-**5e**).* Yellow oil. *E*/*Z*=65/35 mixture. ^1H NMR (700 MHz, $CDCl_3$) δ 7.30–7.25 (2H, m, Ph), 7.22–7.13 (3H, m, Ph), 5.66 (0.35H, dt, *J*=10.5, 7.7 Hz, 2′-H), 5.59 (0.65H, dt, *J*=15.4, 7.0 Hz, 2′-H), 5.27 (0.65H, dd, *J*=15.4, 8.4 Hz, 1′-H), 5.20 (0.35H, dt, *J*=10.5, 1.4 Hz, 1′-H), 4.42–4.34 (1H, m, 8-H), 4.09–4.05 (1.3H, m, 3-H), 3.90 (0.35H, dd, *J*=10.7, 8.8 Hz, 3-H), 3.79 (0.35H, dd, *J*=10.7, 3.5 Hz, 3-H), 3.24 (0.65H, ddd, *J*=12.1, 6.2, 2.3 Hz, 4a-H), 2.96–2.90 (0.35H, m), 2.88 (0.35H, ddd, *J*=11.6, 6.0, 2.5 Hz, 4a-H), 2.78–2.65 (2.65H, m), 2.65 (0.65H, ddd, *J*=12.6, 12.6, 2.8 Hz), 2.58 (0.35H, ddd, *J*=13.0, 13.0, 2.8 Hz), 2.46–2.32 (2H, m), 1.89–1.81 (1H, m), 1.67–1.59 (1H, m), 1.47–1.21 (3.35H, m), 1.15 (0.65H, dddd, *J*=12.5, 12.5, 12.5, 3.5 Hz); ^{13}C NMR (175 MHz, $CDCl_3$) δ 153.0, 152.9, 141.2, 141.1, 134.0, 133.3, 128.6, 128.4, 128.22, 128.16, 126.0, 125.7, 124.5, 123.3, 67.4, 67.0, 57.9, 57.5, 46.11, 46.09, 39.5, 35.32, 35.26, 34.22, 34.19, 29.7, 27.9, 27.5, 25.2, 25.1, 24.04, 23.98; IR (film) 3059, 3024, 2936, 2855, 1693, 1602, 1475, 1430, 1371, 1316, 1296, 1247, 1176, 1142, 1112, 1084, 1015, 974, 910, 855, 833, 819, 752, 700 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{18}H_{24}NO_2$: 286.1802. Found: 286.1796.

3.5.4. (4R,4aR*)-4-(4′-Phenylbut-1′-enyl)hexahydropyrido[1,2-c] [1,3]oxazin-1(3H)-one (minor-**5e**).* Colorless oil. *E*/*Z*=85/15 mixture. ^1H NMR (700 MHz, $CDCl_3$) δ 7.30–7.26 (2H, m, Ph), 7.21–7.13 (3H, m, Ph), 5.70–5.64 (0.15H, m, 2′-H), 5.67 (0.85H, dt, *J*=15.6, 7.2 Hz, 2′-H), 5.11 (0.85H, dd, *J*=15.6, 8.8 Hz, 1′-H), 5.05 (0.15H, ddt, *J*=10.2, 10.2, 1.4 Hz, 1′-H), 4.47–4.41 (1H, m, 8-H), 4.00 (0.85H, dd, *J*=11.0, 4.2 Hz, 3-H), 3.86 (0.85H, dd, *J*=11.0, 11.0 Hz, 3-H), 3.73 (0.15H, dd, *J*=10.9, 10.9 Hz, 3-H), 3.63 (0.15H, dd, *J*=10.9, 4.6 Hz, 3-H), 2.90 (0.85H, ddd, *J*=11.6, 9.1, 2.5 Hz, 4a-H), 2.87 (0.15H, ddd, *J*=11.2, 8.8, 2.8 Hz, 4a-H), 2.75–2.58 (2.15H, m), 2.63 (0.85H, ddd, *J*=13.0, 13.0, 2.8 Hz), 2.46–2.33 (3H, m), 1.84–1.75 (2H, m), 1.70–1.63 (1H, m), 1.49–1.38 (0.15H, m), 1.45 (0.85H, ddddd, *J*=13.2, 13.2, 13.2, 3.7, 3.7 Hz), 1.35–1.24 (0.15H, m), 1.31 (0.85H, ddddd, *J*=13.2, 13.2, 13.2, 3.7, 3.7 Hz), 1.06 (0.85H, dddd, *J*=13.2, 13.2, 11.8, 3.7 Hz), 0.97 (0.15H, dddd, *J*=13.2, 13.2, 11.8, 3.7 Hz); ^{13}C NMR (175 MHz, $CDCl_3$) δ 153.3, 153.2, 141.2, 141.0, 134.9, 134.4, 128.5, 128.4, 128.3, 128.2, 126.1, 125.9, 125.7, 125.0, 67.9, 67.4, 59.4, 59.1, 45.2, 45.0, 43.6, 38.8, 35.5, 35.4, 34.3, 31.6, 29.9, 24.91, 24.88, 23.63, 23.59; IR (film) 3059, 3025, 2935, 2855, 1694, 1602, 1474, 1432, 1388, 1368, 1343, 1313, 1293, 1251, 1225, 1169, 1124, 1095, 1050, 1008, 971, 907, 849, 758, 700 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{18}H_{23}NO_2Na$: 308.1621. Found: 308.1617.

3.5.5. (4R,5S*)-3-Methyl-5-(2′-methylprop-1′-enyl)-4-phenethyl-1,3-oxazinan-2-one (major-**5h**).* Colorless oil. ^1H NMR (700 MHz, $CDCl_3$) δ 7.31 (2H, dd, *J*=7.7, 7.7 Hz, Ph), 7.22 (1H, t, *J*=7.4 Hz, Ph), 7.16 (2H, d, *J*=7.4 Hz, Ph), 4.94–4.90 (1H, m, 1′-H), 4.15 (1H, dd, *J*=10.9, 10.2 Hz, 6-H), 4.10 (1H, ddq, *J*=10.9, 4.9, 1.1 Hz, 6-H), 3.24 (1H, td, *J*=5.8, 4.9 Hz, 4-H), 3.12 (1H, dddd, *J*=10.2, 10.2, 4.9, 4.9 Hz, 5-H), 2.97 (3H, s, NCH_3), 2.68 (2H, t, *J*=8.4 Hz, CH_2Ph), 1.97–1.85 (2H, m, CH_2CH_2Ph), 1.77 (3H, s, $C(CH_3)_2$), 1.71 (3H, d, *J*=1.4 Hz, $C(CH_3)_2$); ^{13}C NMR (175 MHz, $CDCl_3$) δ 153.2, 140.8, 137.8, 128.5, 128.1, 126.2, 117.4, 67.7, 59.5, 36.8, 35.5, 33.4, 32.3, 25.9, 18.3; IR (film) 3060, 3025, 2929, 1709, 1684, 1602, 1482, 1452, 1406, 1385, 1318, 1243, 1226, 1177, 1145, 1080, 1040, 1033, 1002, 983, 930, 909, 841, 755, 701 cm^{-1}; HRMS–ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{17}H_{23}NO_2Na$: 296.1621. Found: 296.1618.

3.5.6. (4R,5R*)-3-Methyl-5-(2′-methylprop-1′-enyl)-4-phenethyl-1,3-oxazinan-2-one (minor-**5h**).* Pale yellow solid. ^1H NMR

(700 MHz, $CDCl_3$) δ 7.30 (2H, dd, J=7.6, 7.6 Hz, Ph), 7.22 (1H, t, J=7.6 Hz, Ph), 7.16 (2H, d, J=7.6 Hz, Ph), 5.03–5.00 (1H, m, 1′-H), 4.16 (1H, dd, J=10.9, 4.2 Hz, 6-H), 3.91 (1H, dd, J=10.9, 7.7 Hz, 6-H), 3.15 (1H, ddd, J=7.0, 7.0, 2.8 Hz, 4-H), 2.96 (3H, s, NCH_3), 2.87 (1H, dddd, J=8.4, 7.7, 7.0, 4.2 Hz, 5-H), 2.61 (2H, t, J=8.4 Hz, CH_2Ph), 1.99 (1H, dtd, J=15.1, 8.4, 2.8 Hz, CH_2CH_2Ph), 1.90 (1H, ddt, J=15.1, 8.4, 7.0 Hz, CH_2CH_2Ph), 1.75 (3H, d, J=1.4 Hz, $C(CH_3)_2$), 1.71 (3H, d, J=0.7 Hz, $C(CH_3)_2$); ^{13}C NMR (175 MHz, $CDCl_3$) δ 154.6, 140.8, 136.8, 128.6, 128.1, 126.2, 120.7, 67.4, 61.9, 35.2, 34.7, 33.1, 30.3, 25.8, 18.3; IR (KBr) 3061, 3028, 2975, 2933, 2872, 1695, 1664, 1487, 1454, 1429, 1403, 1385, 1349, 1324, 1291, 1272, 1240, 1226, 1190, 1145, 1097, 1073, 1037, 846, 761, 701 cm^{-1}; HRMS–ESI (m/z): $[M+Na]^+$ calcd for $C_{17}H_{23}NO_2Na$: 296.1621. Found: 296.1618.

3.6. Hydrogenation of *major*-5e

A mixture of *major*-**5e** (35.0 mg, 0.123 mmol) and palladium on activated carbon (loading: 10 wt %, 2 mg) in ethyl acetate (1.5 mL) was stirred for 3 h at room temperature under a hydrogen atmosphere. The resulting mixture was filtered through a pad of Celite, and the filtrate was concentrated to obtain *major*-**6e** (34.9 mg, 99% yield) as a colorless oil.

3.6.1. (4S,4aR*)-4-(4′-Phenylbutyl)hexahydropyrido[1,2-c][1,3]oxazin-1(3H)-one (major-**6e**).* Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.25 (2H, m, Ph), 7.22–7.14 (3H, m, Ph), 4.45–4.38 (1H, m, 8-H), 4.03–3.96 (2H, m, 3-H), 3.25 (1H, ddd, J=12.4, 5.9, 2.3 Hz, 4a-H), 2.67 (1H, ddd, J=12.4, 12.4, 2.8 Hz, 8-H), 2.62 (2H, t, J=7.8 Hz, 4′-H), 2.24–2.13 (1H, m, 4-H), 2.02–1.88 (1H, m), 1.70–1.20 (11H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 142.0, 128.2, 125.7, 66.8, 57.7, 46.8, 35.5, 35.1, 31.3, 26.4, 26.3, 25.7, 25.4, 24.4; IR (film) 3059, 3024, 2931, 2856, 1688, 1602, 1477, 1431, 1361, 1314, 1296, 1241, 1177, 1150, 1105, 1085, 1012, 950, 917, 855, 834, 821, 754, 700 cm^{-1}; HRMS–ESI (m/z): $[M+H]^+$ calcd for $C_{18}H_{26}NO_2$: 288.1958. Found: 288.1954.

Acknowledgements

This work was supported by MEXT KAKENHI Grant Number 18037021 (Grant-in-Aid for Scientific Research on Priority Areas 'Advanced Molecular Transformations of Carbon Resources').

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.01.088.

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8. ^1H NMR analysis of the oxygen analog, 2-(1,3-dienyloxy) tetrahydrofuran does not form a mixture of rotamers. See, Ref. 3b and its Supplementary data (Copies of NMR spectrum).
9. A representative copy of ^1H NMR spectrum of **2c**: see, Supplementary data.
10. Our previous studies on the 1,4-elimination of *E*-isomer and precoordination transition state: (a) Tayama, E.; Sugai, S. *Tetrahedron Lett.* **2007**, *48*, 6163–6166; (b) Tayama, E.; Sugai, S. *Synlett* **2006**, 849–852 See, also Ref. 3a.
11. When we examined the 1,4-elimination of 4-mono-substituted acyclic derivatives **1**, similar *E*/*Z*-selectivity with the piperidinyl derivatives **1c**–**e** were obtained.
12. Similar results were obtained in the previous studies on aza-Ferrier reaction (Refs. 4a, 4c, and 4d). However, Terada and Toda reported regiospecific reaction. The reaction of the geometry pure (1*E* or 1*Z*) of *O*-alkenyl *N*,*O*-acetals catalyzed chiral phosphonic acid proceeds with high regiospecifically to give the almost single relative stereoisomer (Ref. 4b).
13. The unidentifiable products were observed by TLC analysis.