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Diastereoselective α-Iodination Reaction of 4-Alkenylamide Having a β-Chiral Center

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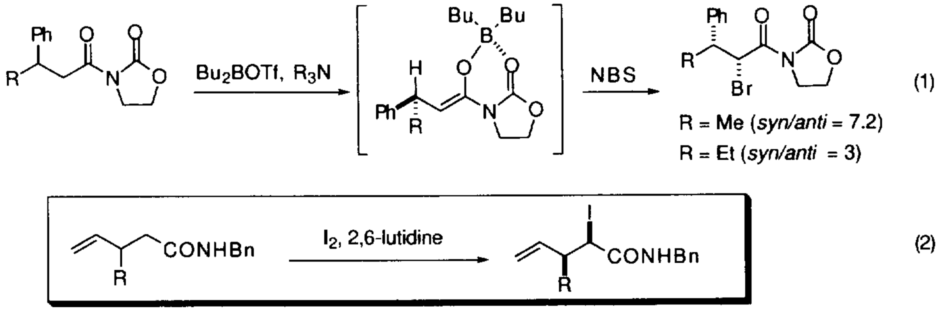
Abstract: α-Iodination reaction of 4-alkenylamide with a β-chiral center proceeds with high diastereoselectivity to give *syn* α-iodoalkenamide through the formation of cyclic ketene *N,O*-acetal and subsequent α-iodination from the opposite side of a β-substituent. © 1997 Elsevier Science Ltd.

In contrast to the cyclic enolate,[1,2] stereocontrol in the reaction of the acyclic enolate having a β-chiral center with an electrophile should be generally difficult due to the flexibility of a single bond between the α- and β-carbons.[2] There are only a few methods for the highly diastereoselective reaction of acyclic enolates with a β-chiral center. In the reaction of β-hydroxy enolate, a high level of diastereoselectivity has been achieved through the construction of a cyclic enolate structure by metal chelation.[3] It was also reported that the reaction of the enolate having a sterically hindered group at the β-position proceeds with high diastereoselectivity due to conformational restriction by the 1,3-allylic strain.[4] The stereocontrol by this allylic strain concept was applicable to the bromination of *N*-(3'-arylbutanoyl) or *N*-(3'-arylpentanoyl)oxazolidinone, in which moderate diastereoselectivity was achieved through the formation of 1,3-allylic-strained boron enolates (Scheme 1, Eq. 1).[5] In this paper, we report the results of diastereoselective α-iodination reactions of 4-alkenylamides with a β-chiral center through an iodine-mediated activating process which was previously disclosed by our group (Scheme 1, Eq. 2).[6a] The highly *syn*-selective α-iodination in the present reaction arises from the formation of

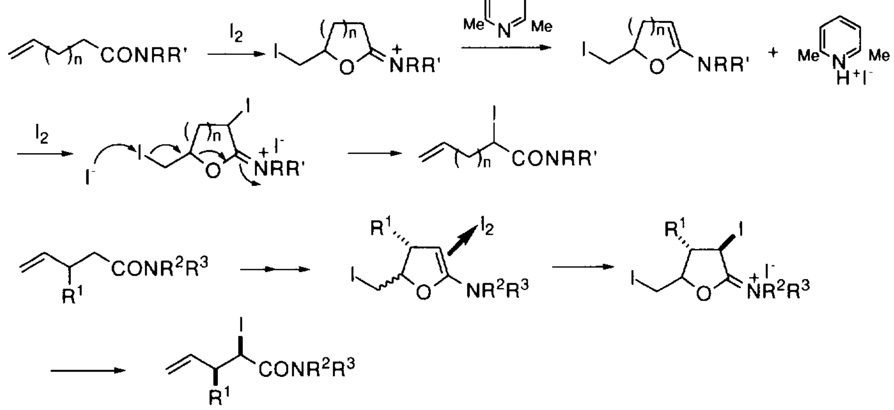
Scheme 1

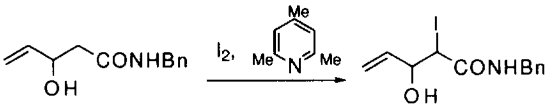


a cyclic intermediate by an iodocyclization reaction, so that it should be difficult to achieve such stereocontrol by using enolate chemistry.

We have recently reported that the α-iodination reaction of unsaturated carboxamide proceeds in a good yield in the presence of iodine and 2,6-lutidine or *s*-collidine (Scheme 2).[6] In the reaction pathway, deprotonation occurs even by a weak base through the formation of a cationic halocyclization intermediate which brings about remarkable increase in the acidity of amide α-hydrogen. Subsequent α-iodination of cyclic ketene *N,O*-acetal followed by the ring opening of the α-iodoiminium intermediate gives rise to the corresponding α-iodoamides. According to this reaction mechanism, it was expected that the reaction of 4-alkenamide with a β-chiral center might proceed with high diastereoselectivity to give *syn* α-iodoalkenamide through the α-iodination from the opposite side of a β-substituent in the cyclic ketene *N,O*-acetal intermediate (Scheme 2).

Scheme 2





1a **2a**

Table 1. α-Iodination of *N*-Benzyl-3-hydroxy-4-pentenamide **1a**

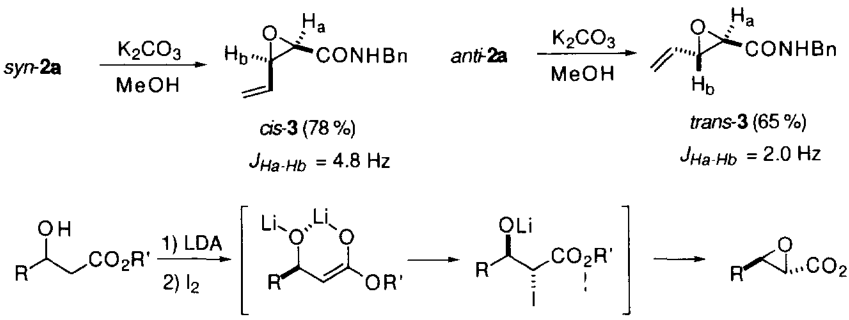
Entry	Conditions	Solvent	Temp.	Time (h)	Yield (%)[a]	*syn* : *anti*[b]
1	A[c]	CH_2Cl_2	rt	24.5	31	10 : 1
2	A[c]	CH_2Cl_2	40 °C	22	45	6 : 1
3	B[d]	CH_2Cl_2	40 °C	16.5	50	8 : 1
4	B[d]	THF	40 °C	16	74	8.9 : 1
5	B[d]	CH_3CN	40 °C	14.5	71	7.9 : 1
6	B[d]	DMF	40 °C	14	67	15 : 1

[a] Isolated yield. [b] Determined by 400 MHz ^{1}H-NMR. [c] Conditions A: **1a** (0.5 mmol), I_2 and *s*-collidine (0.75 mmol), solvent (4 ml). [d] Conditions B: **1a** (0.5 mmol), I_2 and *s*-collidine (1.5 mmol), solvent (7 ml).

On the basis of this assumption, α-iodination reaction of *N*-benzyl-β-hydroxy-4-pentenamide **1a** was examined under various conditions (Table 1). Under the conditions reported previously (Conditions A: 1.5 eq of I_2 and *s*-collidine , CH_2Cl_2, rt),[6a] the reaction of **1a** gave *syn*-α-iodoamide **2a** in a ratio of *syn*/*anti*=10, but in low yield (Entry 1). Higher reaction temperature (Entry 2) or increase in the molar ratio of reagents (Conditions B: 3 eq of I_2 and *s*-collidine, Entry 3) resulted in a slight increase in the chemical yields. The use of polar solvents such as THF, CH_3CN or DMF under Conditions B gave good yield of **2a** (Entries 4-6); especially, DMF was the most effective from the viewpoint of both chemical yield and the diastereoselectivity (Entry 6). The substituent on an amide nitrogen atom considerably affected on the stability of the product, for example, the α-iodination product of *N*,*N*-dialkylamide such as *N*,*N*-diethyl-β-hydroxy-4-pentenamide could not be isolated as a pure compound due to its unstability.

The stereochemistries of *syn*- and *anti*-**2a** were determined by these coupling constants after conversion to the corresponding epoxides, *cis*- and *trans*-**3**, respectively (Scheme 3). It should be noted that the formation of *cis*-epoxide **3** through the present *syn*-selective reaction is significant, while the *trans*-epoxide is major through *anti*-selective α–iodination of lithium enolate of β-hydroxy ester (Scheme 3).[7]

Scheme 3



α-Iodination reactions of 4-pentenamides having a β-alkyl substituent were further examined (Tables 2, 3). Under the above Conditions A in CH_2Cl_2, the reaction of *N*-benzyl-3-methyl-4-pentenamide **1b** preferentially gave *syn*-**2b** in a ratio of *syn*/*anti* = 10.3 and in 41 % yield (Table 2, Entry 1). Longer reaction time or higher reaction temperature resulted in an increase in the chemical yield, but a marked drop in the diastereoselectivity (Entries 2, 3). In contrast to the case of **1a**, the use of DMF was not effective (Entry 4). The drop in the diastereoselectivity in Entries 2-4 may be due to epimerization of labile *syn*-**2b** in solution because pure *syn*-**2b** in $CDCl_3$ gradually converted to a mixture of *syn*- and *anti*-**2b** after standing overnight at room temperature.[8]

As shown in Table 3, the reaction of 3-phenyl-4-pentenamide **1c** in DMF at 50 °C proceeded in a highly *syn*-selective manner (*syn*/*anti* = 13) to give **2c** in moderate yield (43 %, Entry 1). When the reaction of **1c** was carried out at room temperature, **2c** was obtained in a similar diastereomer ratio (*syn*/*anti* =13.5) and in lower yield (34 %). The present reaction was found quite effective with amides **1d** or **1e** having a cyclic olefinic moiety such as cyclohexenyl or cyclopentenyl; that is, the reaction of **1d** and **1e** proceeded with excellent diastereoselectivity (*syn*/*anti* = 40-50) to give iodoamides *syn*-**2d** and *syn*-**2e** as the major isomers in good yields, respectively (Entries 2, 3).

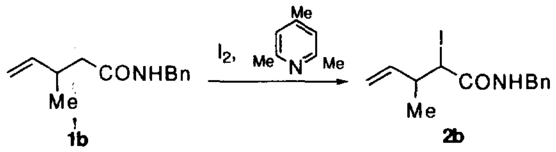


Table 2. α-Iodination of *N*-Benzyl-3-methyl-4-pentenamide **1b**[a]

Entry	Solvent	Temp.	Time (h)	Yield (%)[b]	*syn* : *anti*[c]
1	CH_2Cl_2	rt	14	41	10.3 : 1
2	CH_2Cl_2	0 °C - rt	40	52	6.1 : 1
3	CH_2Cl_2	45 °C	20	76	2.8 : 1
4	DMF	rt	60	55	2.5 : 1

[a] **1b** (1 mmol), I_2 and *s*-collidine (1.5 mmol), solvent (6-7 ml).
[b] Isolated yield. [c] Determined by 400 MHz ^{1}H-NMR.

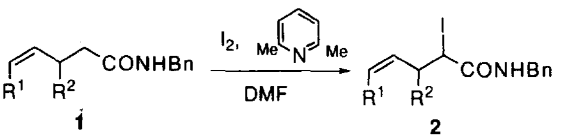


Table 3. α-Iodination of Substituted 4-Pentenamides **1**[a]

Entry	Amide **1**		Temp.	Time (h)	**2**	Yield (%)[b]	*syn* : *anti*[c]
1	R^1=H, R^2= Ph	**1c**	50 °C	36	**2c**	43	13 : 1
2	R^1, R^2=-$(CH_2)_3$-	**1d**	rt	22	**2d**	65	45 : 1
3	R^1, R^2=-$(CH_2)_2$-	**1e**	rt	24	**2e**	84	44 : 1

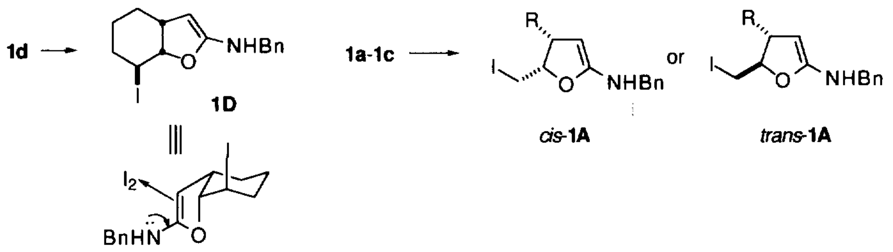
[a] **1** (0.5 mmol), I_2 (1 mmol), lutidine (1.2 mmol) and DMF (3 ml).
[b] Isolated yield. [c] Determined by 400 MHz ^{1}H-NMR.

In the cases of cycloalkenyl derivatives **1d** and **1e**, a single reactive intermediate such as **1D** should be formed, while in the cases of acyclic amides **1a** and **1c**, the formation of two kinds of intermediate such as *cis*- or *trans*-**1A** on the basis of the newly formed chiral center would be possible (Scheme 4).[9] The attack of I_2 to a single intermediate **1D** would be restricted to one side because of the rigid *cis*-fused bicyclic structure of **1D**. Therefore, the reaction of **1d** and **1e** having a cyclic olefin may proceed with excellent diastereoselectivity to give *syn*-**2d** and *syn*-**2e**. In the reaction of **1a** and **1c**, the formation of *trans*-**1A** as an intermediate may lead to the decrease in *syn*-selectivity, because the attack of I_2 from the opposite side of β-substituent R in *trans*-**1A** results in steric repulsion with an iodomethyl group.

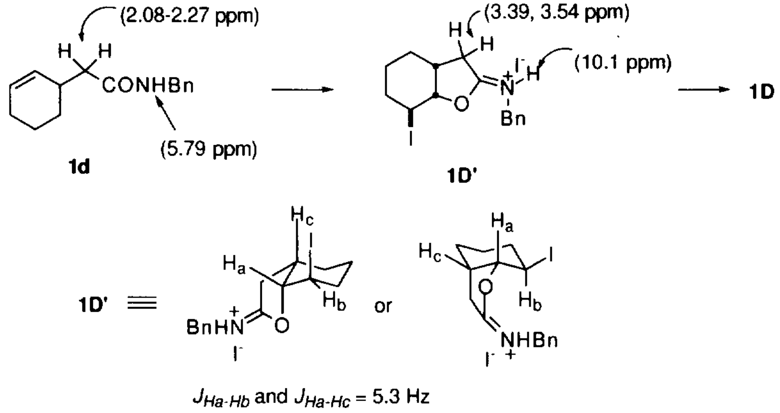
Imidate **1D'**, precursor of **1D**, can be easily observed by ^{1}H- and ^{13}C-NMR. The NMR spectra of **1D'** indicate the formation of a single stereoisomer (probably *cis*-fused bicyclic structure) with remarkable increase in acidity of the α-hydrogen in **1D'** from the downfield shift (1.3 ppm) as compared with amide **1d** (Scheme 5).

However, conformational details of **1D'** could not be determined by the coupling constants between H_a and vicinal protons H_b, H_c ($J_{Ha\text{-}Hb} = J_{Ha\text{-}Hc} = 5.3$ Hz).

Scheme 4

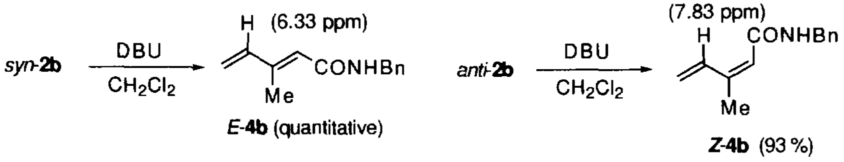


Scheme 5

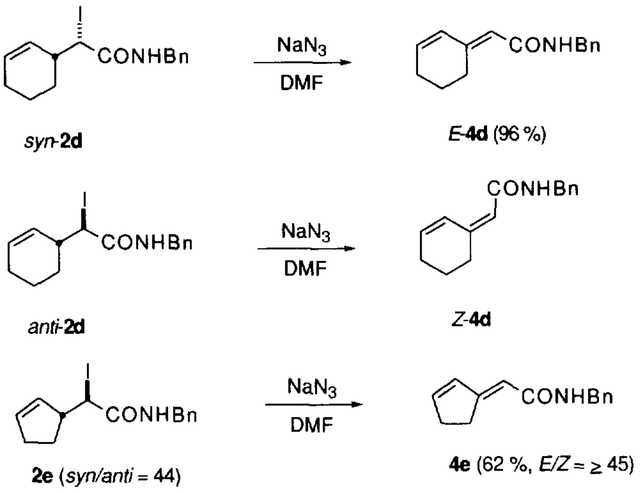


The stereochemistries of **2b-2e** were determined on the basis of the chemical shift of γ-hydrogen after conversion to dienamides **4b-4e**. For example, after separation of major- and minor-**2b** by MPLC, each was treated with DBU to give dienamides *E*-**4b** and *Z*-**4b** as a single isomer through complete *E*2-reaction, respectively (Scheme 6). The γ-hydrogen (7.82 ppm) of *Z*-**4b** obtained from minor-**2b** (*anti*-**2b**) was found in a remarkable downfield area owing to anisotropic effect of the carbonyl group as compared with that (6.34 ppm) of *E*-**4b** from major-**2b** (*syn*-**2b**). Similar to **2b**, the stereochemistry of major-**2c** was determined as *syn*-**2c** after conversion to diene. In the cases of **2d** and **2e**, *exo*-dienes *E*-**4d** and *E*-**4e** were obtained in a completely stereospecific manner by using NaN_3 as a base (Scheme 7),[10] while in the use of DBU, *syn*-**2d** gave a mixture of *E*- and *Z*-**4d** in a ratio of *E* : *Z* = 15 : 1. The formation of *Z*-**4d** as a side-product from pure *syn*-**2d** may arise from *E*2-elimination of *anti*-**2d** produced by the epimerization of *syn*-**2d**.

Scheme 6



Scheme 7



The stereoselective synthesis of *exo*-dienes such as **4d** or **4e** should be generally difficult; for example, it has been reported that by the Wittig or Horner-Emmons reaction with cyclohexenone, dienoates are obtained in poor chemical yields and stereoselectivities (E/Z = 2-1/5).[11] Therefore, the present diastereoselective α-iodination and subsequent $E2$ reaction should provide a new means for the stereoselective construction of *exo*-diene.

In conclusion, we have succeeded in the development of a *syn*-selective α-iodination reaction of 4-alkenamides with a β-chiral center. The present reaction could be applied to the stereoselective construction of *cis*-2,3-epoxy amide and 2*E*-conjugated dienamides.

Experimental Section

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a 400- or 300-MHz spectrometer. In ^1H and ^{13}C NMR spectra, chemical shifts were expressed in δ (ppm) downfield from $CHCl_3$ (7.26 ppm) and $CDCl_3$ (77.0 ppm), respectively. Mass spectra were recorded by electron impact or chemical ionization. Column chromatography was performed on silica gel, Wakogel C-200 (75-150 μm). Preparative TLC was performed on precoated plates (1 mm thickness, 20 x 20 cm). Medium-pressure liquid chromatography (MPLC) was performed on a 30 X 4 cm i. d. prepacked column (silica gel, 50 μm) with a UV detector.

General Procedure for α-Iodination Reactions. To a solution of the amide **1** (0.5 mmol) in dry DMF were added 2,4,6-collidine (0.2 ml) and I_2 (380 mg, 1.5 mmol), and then the reaction mixture was stirred at the indicated temperature and for the indicated period (see Tables 1 - 3). The mixture was poured into 5% HCl and extracted with ether. The ether extracts were washed with aqueous $Na_2S_2O_3$ solution, dried over $MgSO_4$, and evaporated to dryness. The residue was purified by column chromatography.

(2*R,3*S**) and (2*S**,3*S**)-*N*-Benzyl-3-hydroxy-2-iodo-4-pentenamide (*syn*- and *anti*-2a).** Compounds *syn*- and *anti*-**2a** were prepared from **1a** (102 mg, 0.5 mmol). Purification by column chromatography (hexane/AcOEt = 2) and then MPLC (hexane/AcOEt = 2.3) gave *syn*-**2a** (less polar, 105 mg, 63 %) and *anti*-**2a** (more polar, 5 mg, 3 %). ***syn*-2a**: white crystals; mp 125 °C; IR ($CHCl_3$) 3425, 2935, 1670 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.56 (d, *J* = 4.9 Hz, 1H), 3.89 (m, 1H), 4.42 (d, *J* = 2.5 Hz, 1H), 4.45 (dd, *J* = 5.7, 14.8 Hz, 1H), 4.48 (dd, *J* = 5.7, 14.8 Hz, 1H), 5.31(td, *J* = 1.3, 10.5 Hz, 1H), 5.40 (td, *J* = 1.3, 17.1 Hz, 1H), 5.76 (ddd, *J* = 4.9, 10.5, 17.1 Hz, 1H), 6.71 (brs, 1H), 7.25-7.38 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 33.9, 43.9, 71.4, 117.9, 127.6, 127.7, 128.8, 137.4, 170.0; MS (EI) *m/z* 331 (M$^+$), 314; Anal. Calcd for $C_{12}H_{14}INO_2$: C, 43.52; H, 4.26; N, 4.23. Found: C, 43.64; H, 4.28; N, 4.28. ***anti*-2a**: white crystals; mp 133 °C; IR ($CHCl_3$) 3420, 2920, 1670 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ 3.58 (brd, *J* = 5.7 Hz, 1H), 4.33 (d, *J* = 5.5 Hz, 1H), 4.42-4.53 (m, 3H), 5.39 (ddd, *J* = 1.2, 2.4, 10.5 Hz, 1H), 5.42(ddd, *J* = 1.3, 2.4, 17.1 Hz, 1H), 5.95 (ddd, *J* = 5.9, 10.5, 17.1 Hz, 1H), 6.46 (brs, 1H), 7.27-7.38 (5H, m); MS (EI) *m/z* 331 (M$^+$), 314; HRMS *m/z* Calcd for $C_{12}H_{13}INO$ (M$^+$-OH), 314.0042. Found: 314.0049. Anal. Calcd for $C_{12}H_{14}INO_2$: C, 43.52; H, 4.26; N, 4.23. Found: C, 43.16; H, 4.19; N, 4.21.

(2*R,3*S**) and (2*S**,3*S**)-*N*-Benzyl-2-iodo-3-methyl-4-pentenamide (*syn*-2b and *anti*-2b).** Compounds *syn*- and *anti*-**2b** were prepared from **1b** (102 mg, 0.5 mmol). Purification by column chromatography (hexane/AcOEt = 5) and then MPLC (hexane/AcOEt = 10) gave *syn*-**2b** (less polar, 68 mg, 41 %) and *anti*-**2b** (more polar, 23 mg, 14 %). ***syn*-2b**: white crystals; mp 90-91.5 °C; IR ($CHCl_3$) 3455, 2925, 1668 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.18 (d, *J* = 6.6 Hz, 3H), 2.67 (qdd, *J* = 6.6, 7.0, 7.1 Hz, 1H), 4.27 (d, *J* = 7.1Hz, 1H), 4.44 (s, 1H), 4.46 (s, 1H), 5.10 (brd *J* = 10.4 Hz, 1H), 5.14 (brd, *J* = 17.2 Hz, 1H), 5.74 (ddd, *J* = 7.0, 10.4, 17.2 Hz, 1H), 6.28 (brs, 1H), 7.22-7.40 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 19.7, 36.1, 41.5, 44.1, 116.5, 127.5, 127.7, 128.6, 137.6, 138.8, 169.0; MS (EI) *m/z* 329 (M$^+$), 314; Anal. Calcd for $C_{13}H_{16}INO$: C, 47.43; H, 4.90; N, 4.26. Found: C, 47.55; H, 4.83; N, 4.24. ***anti*-2b**: white crystals; mp 109-111 °C; IR (KBr) 3460, 3012, 1668 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.14 (d, *J* = 6.6 Hz, 3H), 2.61 (qdd, *J* = 6.6, 6.7, 7.8 Hz, 1H), 4.24 (d, *J* = 6.7 Hz, 1H), 4.44 (dd, *J* = 6.0, 15.0 Hz, 1H), 4.48 (dd, *J* = 5.5, 15.0 Hz, 1H), 5.07-5.15 (m, 2H), 5.65-5.77 (m, 1H), 6.32 (brs, 1H), 7.25-7.40 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 19.2, 36.0, 41.9, 44.1, 116.5, 127.5, 127.6, 128.7, 137.6, 140.8, 169.2; MS (EI) *m/z* 329 (M$^+$), 314; HRMS *m/z* Calcd for $C_{13}H_{16}INO$ (M$^+$), 329.0277. Found: 329.0260.

(2*R,3*R**)-*N*-Benzyl-2-iodo-3-phenyl-4-pentenamide (*syn*-2c).** Compound *syn*-**2c** was prepared from **1c** (133 mg, 0.5 mmol). Purification by column chromatography (hexane/AcOEt = 5) and then MPLC (hexane/AcOEt = 8) gave the mixture of *syn*-**2c** and *anti*-**2c** in a ratio of *syn*/*anti* = 13 (85 mg, 43 %). ***syn*-2c**: white crystals; IR (KBr) 3452, 3004, 1676 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.99 (dd, *J* = 7.8, 10.0 Hz, 1H), 4.45 (dd, *J* = 5.7, 11.0 Hz, 1H), 4.47 (dd, *J* = 5.7, 11.0 Hz, 1H), 4.49 (d, *J* = 10.0 Hz, 1H), 5.10-5.18 (m, 2H), 6.02 (ddd, *J* = 7.8, 10.1, 17.7 Hz, 1H), 6.03 (brs, 1H) 7.18-7.32 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ 31.9, 44.0, 54.4, 118.0, 127.4, 127.6, 127.8, 128.0, 128.6, 128.7, 136.6, 137.6, 141.3, 169.2; MS (EI) *m/z* 391 (M$^+$), 264; Anal. Calcd for $C_{18}H_{18}INO$: C, 55.25; H, 4.64; N, 3.58. Found: C, 55.12; H, 4.71; N, 3.68.

(2*S,1'*R**) and (2*R**,1'*R**)-*N*-Benzyl-2'-cyclohexenyl-iodoacetamide (*syn*-2d and *anti*-2d).** Compounds *syn*- and *anti*-**2d** were prepared from **1d** (92 mg, 0.4 mmol). Purification by column chromatography (hexane/AcOEt = 5) and then MPLC (hexane/AcOEt = 7) gave *syn*-**2d** (less polar, 93 mg, 65 %) and *anti*-**2d** (more polar, trace). ***syn*-2d**: white crystals; mp 103-109 °C; IR (KBr) 3444, 3028, 1670 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.40-1.52 (m, 1H), 1.52-1.65 (m, 1H), 1.65-1.76 (m, 1H), 1.84-2.06 (m, 3H), 2.61-2.72 (m, 1H), 4.25 (d, *J* = 8.1 Hz, 1H), 4.45 (dd, *J* = 5.6, 14.8 Hz, 1H), 4.51 (dd, *J* = 5.8, 14.8 Hz, 1H), 5.56 (brd, *J* = 10.1 Hz, 1H), 5.85 (m, 1H), 6.25 (brs, 1H) 7.24-7.40 (m, 5H); ^{13}C-NMR (CDCl$_3$) δ 20.8, 25.2, 28.8, 35.5, 39.4, 44.2, 127.1, 127.6, 127.7, 128.7, 130.8, 137.7, 169.1; MS (EI) *m/z* 355 (M$^+$), 228; Anal. Calcd for $C_{15}H_{18}INO$: C, 50.72; H, 5.11; N, 3.94. Found: C, 50.96; H, 5.13; N, 4.05. ***anti*-2d**: white crystals; mp 100-103 °C; ^{1}H-NMR (CDCl$_3$) δ 1.35 (m, 1H), 1.50-1.65 (m, 1H), 1.69-1.78 (m, 1H), 1.83-1.94 (m, 1H), 1.94-2.02 (m, 2H), 2.65 (m, 1H), 4.16 (d, *J* = 7.8 Hz, 1H), 4.48 (s, 1H), 4.50 (s, 1H), 5.73 (brd, *J* = 10.2 Hz, 1H), 5.84 (m, 1H), 6.18 (brs, 1H), 7.23-7.41 (m, 5H); MS (EI) *m/z* 355 (M$^+$), 228.

(2*S,1'*R**)-*N*-Benzyl-2'-cyclopentenyl-iodoacetamide (*syn*-2e).** Compound *syn*-**2e** was prepared from **1e** (86 mg, 0.4 mmol). Purification by column chromatography (hexane/AcOEt = 5) gave *syn*-**2e** (114 mg, 84 %) including *anti*-**2e** in a ratio of *syn*/*anti* = 44. ***syn*-2e**: white crystals; mp 118-120 °C; IR (KBr) 3288, 2928, 1642 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 1.66 (m, 1H), 2.18 (m, 1H), 2.24-2.41 (m, 2H), 3.32 (m, 1H), 4.26 (d, *J* = 8.1 Hz, 1H), 4.45 (dd, *J* = 5.6, 14.8 Hz, 1H), 4.51 (dd, *J* = 5.9, 14.8 Hz, 1H), 5.58 (m, 1H), 5.99 (td, *J* = 2.3, 7.9 Hz, 1H), 6.12 (brs, 1H), 7.20-7.40 (m, 5H); ^{13}C-NMR (CDCl$_3$) δ 30.2, 31.7, 34.3, 44.1, 50.8, 127.6, 127.7, 128.7, 131.0, 134.3, 137.8, 169.5; MS (EI) *m/z* 341 (M$^+$), 275; Anal. Calcd for $C_{14}H_{16}INO$: C, 49.28; H, 4.73; N, 4.11. Found: C, 49.28; H, 4.96; N, 4.18.

Cyclic Imidate Intermediate (1D'). To a solution of the amide **1d** (57 mg, 0.25 mmol) in CDCl$_3$ (10 ml) was added I$_2$ (191 mg, 0.75 mmol). After stirring for 1 h at rt, the ^{1}H- and ^{13}C-NMR spectra of the reaction mixture were measured. **1D'**: ^{1}H-NMR (CDCl$_3$) δ 1.44-1.55 (m, 1H), 1.59-1.83 (m, 2H), 1.83-2.10 (m, 3H), 3.18 (m, 1H), 3.39 (dd, *J* = 5.4, 18.3 Hz, 1H), 3.54 (dd, *J* = 7.1, 18.3 Hz, 1H), 4.56 (ddd, *J* = 4.0, 5.3, 6.0 Hz, 1H), 4.84 (s, 2H), 5.47 (t, *J* = 5.3 Hz, 1H), 7.40-7.55 (5H, m), 10.15 (brs, 1H); ^{13}C-NMR (CDCl$_3$) δ 20.6, 22.6, 26.0, 31.8, 34.3, 38.7, 49.7, 95.8, 129.1, 129.7, 129.7, 131.8, 180.8.

(2*S,3*S**)-*N*-Benzyl-2,3-epoxy-4-pentenamide (*cis*-3).** To a solution of the iodide *syn*-**2a** (30 mg, 0.09 mmol) in CH$_3$OH (4 ml) was added K$_2$CO$_3$ (19 mg, 0.14 mmol) and then the reaction mixture was stirred for 5 h at rt. The mixture was poured into water and extracted with ether. The ether extracts were dried over MgSO$_4$, and evaporated to dryness. Purification of the residue by preparative TLC (hexane/AcOEt = 1) gave *cis*-**3** (14 mg, 78 %). *cis*-**3**: white crystals; mp 90 °C; IR (CHCl$_3$) 3425, 2935, 1670 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 3.65 (m, 1H), 3.72 (d, *J* = 4.8 Hz, 1H), 4.47 (d, *J* = 5.9 Hz, 1H), 4.48 (d, *J* = 5.9 Hz, 1H), 5.42 (m, 1H), 5.55-5.62 (m, 2H), 6.49 (brs, 1H), 7.20-7.40 (m, 5H); ^{13}C-NMR (CDCl$_3$) δ 43.0, 56.3, 58.6, 123.6, 127.7, 127.9, 128.7, 130.0, 137.4, 166.5; MS (CI) *m/z* 204 (M$^+$+H$^+$), 186; HRMS *m/z* Calcd for $C_{12}H_{13}NO_2$ (M$^+$), 203.0969. Found: 203.0946.

(2*R,3*S**)-*N*-Benzyl-2,3-epoxy-4-pentenamide (*trans*-3).** *trans*-**3** was prepared from *anti*-**2a** (12 mg, 0.036 mmol) in accordance with the procedure for the preparation of *cis*-**3**. Purification by preparative TLC gave *trans*-**3** (5 mg, 65 %). *trans*-**3**: white crystals; mp 68.5 °C; IR (CHCl$_3$) 3425, 2925, 1680 cm^{-1}; ^{1}H-NMR (CDCl$_3$) δ 3.39 (m, 1H), 3.43 (d, *J* = 2.0 Hz, 1H), 4.42 (s, 1H), 4.44 (s, 1H), 5.40 (m, 1H), 5.55-5.58 (m, 2H), 6.43 (brs, 1H), 7.20-7.40 (m, 5H); MS (EI) *m/z* 203 (M$^+$), 186.

(2*E*)-*N*-Benzyl-3-methyl-2,4-pentadienamide (*E*-4b). To a solution of the iodide *syn*-**2b** (56 mg, 0.17 mmol) in CH_2Cl_2 (3 ml) was added 2 drops of DBU and then the reaction mixture was stirred for 16 h at rt. The mixture was poured into 2 % HCl and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by preparative TLC (hexane/AcOEt = 2) gave *E*-**4b** (34 mg, quantitative). *E*-**4b**: white crystals; mp 53-56 °C; IR ($CHCl_3$) 3475, 2935, 1660, 1630, 1610 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 2.28 (d, *J* = 1.1 Hz, 3H), 4.46 (s, 1H), 4.47 (s, 1H), 5.31 (d, *J* = 10.6 Hz, 1H), 5.53 (d, *J* = 17.3 Hz, 1H), 5.71 (s, 1H), 5.99 (brs, 1H), 6.33 (dd, *J* = 10.6, 17.3 Hz, 1H), 7.20-7.36 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 12.9, 43.4, 118.1, 122.4, 127.4, 127.8, 128.6, 138.3, 140.3, 148.0, 166.7; MS (EI) *m/z* 201 (M^+), 186; HRMS *m/z* Calcd for $C_{13}H_{15}NO$ (M^+), 201.1160. Found: 201.1154.

(2*Z*)-*N*-Benzyl-3-methyl-2,4-pentadienamide (*Z*-4b). *Z*-**4b** was prepared from *anti*-**2b** (18 mg, 0.055 mmol) in accordance with the procedure for the preparation of *E*-**4b**. Purification by column chromatography (hexane/AcOEt = 2) gave Z-**4b** (10 mg, 93 %). *Z*-**4b**: white crystals; mp 46-49 °C; IR ($CHCl_3$) 3470, 3010, 1660 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.95 (d, *J* = 1.2 Hz, 3H), 4.47 (s, 1H), 4.49 (s, 1H), 5.38 (brd, *J* = 10.8 Hz, 1H), 5.51 (brd, *J* = 17.6 Hz, 1H), 5.65 (s, 1H), 5.81 (brs, 1H), 7.22-7.39 (m, 5H), 7.83 (dd, *J* = 10.8, 17.6 Hz, 1H); MS (EI) *m/z* 201 (M^+), 186; HRMS *m/z* Calcd for $C_{13}H_{15}NO$ (M^+), 201.1160. Found: 201.1153.

(*E*)-*N*-Benzyl-(2-cyclohexen-1-ylidene)acetamide (*E*-4d). To a solution of the iodide *syn*-**2d** (25 mg, 0.073 mmol) in DMF (1 ml) was added NaN_3 (13 mg, 0.2 mmol) and then the reaction mixture was stirred for 18 h at rt. The mixture was poured into 2 % HCl and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 4) gave *E*-**4d** (16 mg, 96 %). *E*-**4d**: white crystals; mp 119-121 °C; IR ($CHCl_3$) 3456, 2928, 1650, 1610 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.72 (tt, *J* = 6.0, 6.5 Hz, 2H), 2.18 (m, 2H), 3.04 (dt, *J* = 1.9, 6.5 Hz, 2H), 4.47(s, 1H), 4.48 (s, 1H), 5.47 (s, 1H), 5.76 (brs, 1H), 6.05 (td, *J* = 1.9, 9.9 Hz, 1H), 6.14 (td, *J* = 4.1, 9.9 Hz, 1H), 7.20-7.36 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 21.9, 25.5, 26.1, 43.2, 117.2, 127.2, 127.7, 128.5, 130.2, 136.4, 138.5, 150.0, 166.9; MS (EI) *m/z* 227 (M^+); Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.11; H, 7.53; N, 6.24.

(*Z*)-*N*-Benzyl-(2-cyclohexen-1-ylidene)acetamide (*Z*-4d). *Z*-**4d** was prepared from *anti*-**2d** (4 mg, 0.011 mmol) in accordance with the procedure for the preparation of *E*-**4d**. Purification by preparative TLC (hexane/AcOEt = 2) gave Z-**4d** (trace). *Z*-**4d**: colorless oil; ^1H-NMR ($CDCl_3$) δ 1.77 (quint, *J* = 6.3 Hz, 2H), 2.21 (m, 2H), 2.35 (dt, *J* = 1.6, 6.3 Hz, 2H), 4.48(s, 1H), 4.50 (s, 1H), 5.38 (s, 1H), 5.68 (brs, 1H), 6.16 (dtd, *J* = 1.5, 4.1, 10.2 Hz, 1H), 7.20-7.36 (m, 5H), 7.55 (td, *J* = 2.2, 10.2 Hz, 1H).

(*E*)-*N*-Benzyl-(2-cyclopenten-1-ylidene)acetamide (*E*-4e). *E*-**4e** was prepared from *syn*-**2e** (18 mg, 0.053 mmol) in accordance with the procedure for the preparation of *E*-**4d**. Purification by preparative TLC (hexane/AcOEt = 3) gave *E*-**4e** (7 mg, 62 %). *E*-**4e**: white crystals; mp 105-109 °C; IR ($CHCl_3$) 3300, 2916, 1644, 1618 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 2.61 (tt, *J* = 2.2, 2.5 Hz, 2H), 3.11 (sept, *J* = 2.5 Hz, 2H), 4.48(s, 1H), 4.50 (s, 1H), 5.69 (s, 1H), 5.72 (brs, 1H), 6.24 (td, *J* = 2.3, 5.5 Hz, 1H), 6.54 (td, *J* = 2.7, 5.5 Hz, 1H), 7.20-7.36 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 29.4, 33.4, 43.4, 110.6, 127.3, 127.8, 128.7, 134.6, 138.8, 146.5, 164.1, 167.3; MS (EI) *m/z* 213 (M^+); HRMS *m/z* Calcd for $C_{14}H_{15}NO$ (M^+), 213.1153. Found: 213.1166.

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