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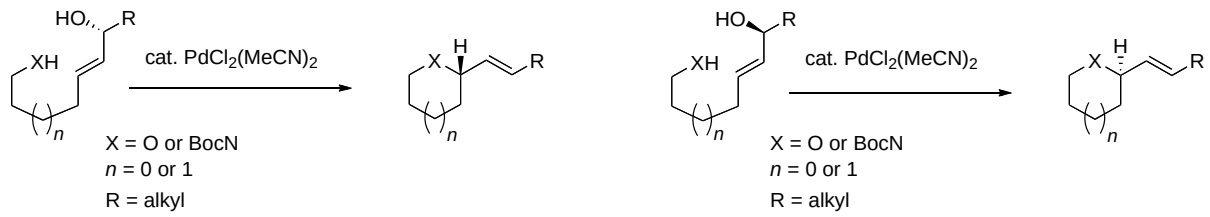
# A SHORT ACCESS TO CHIRAL NON-RACEMIC OXA- AND AZAHETEROCYCLES BY CROSS-METATHESIS AND PD-CATALYZED CYCLIZATION SEQUENCE

**Jun'ichi Uenishi* and Yogesh S. Vikhe**

Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607-8412, Japan.
E-mail: juenishi@mb.kyoto-phu.ac.jp

**Abstract** – A concise synthesis of chiral non-racemic 2-(3-benzoyloxyprop-1-enyl)tetrahydrofuran (**5a**), tetrahydropyran (**5b**), and piperidine (**8**) is described. Cross-metathesis of optically pure (*S*)-1-*O*-benzoyl-3-butene-1,2-diol (**2**) with protected 4-pentenol, 5-hexenol, and 5-hexenylamine gave the corresponding allyl alcohols (**3a**), (**3b**), and (**7**) in one step, respectively. $PdCl_2(MeCN)_2$ catalyzed cyclization of **4a**, **4b**, and **7** afforded **5a**, **5b**, and **8** in excellent yields with high enantiomeric purity.

$Pd^{II}$-catalyzed reactions are valuable in stereoselective organic synthesis.[1] We have recently reported that the $Pd^{II}$-catalyzed reaction of chiral non-racemic ζ–, ε–hydroxy, and ζ-*N*-Boc-amino allyl alcohol occurs to give substituted tetrahydrofurans, tetrahydropyrans and piperidines with high stereoselectivity through the 1,3-chirality transfer process.[2] The *syn* oxy- and azapalladations occur predominantly in intra- and intermolecular reactions,[3,2d] and we have achieved the stereocontrolled synthesis of natural products, such as (-)-aspergillide B,[4a] (-)-diospongin B,[4b] (-)-laulimalide,[4c] and (+)-coniine,[2d] using this reaction.




**Scheme 1**

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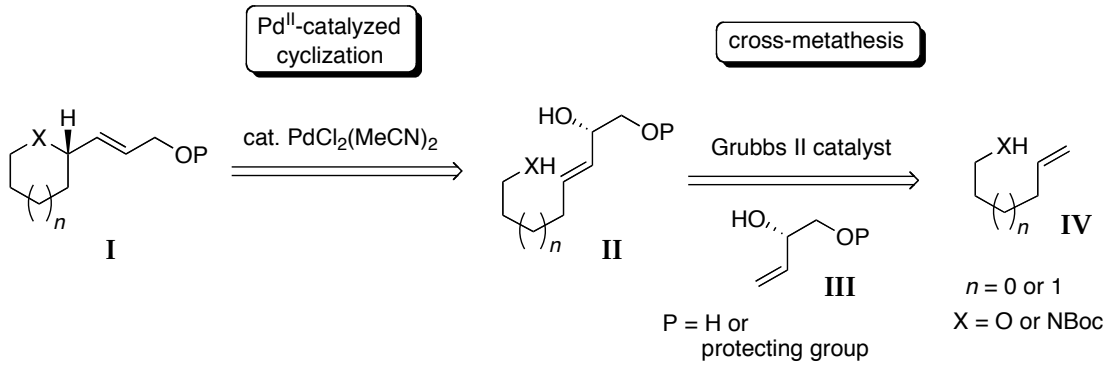
This paper is dedicated to Professor Akira Suzuki on the occasion of his 80th birthday.

However, there were a few drawback using this synthesis. First, the substituent R group has been limited to alkyl groups so far. Second, chiral secondary allyl alcohol has to be prepared for every substrate. Therefore, flexible syntheses for various chiral non-racemic allyl alcohols are highly desired for the synthesis of chiral heterocycles.[5] For this reason, we designed a new synthetic approach for the preparation of chiral non-racemic heterocylic compound **I**, as shown in Scheme 2. A cross-metathesis of terminal alkene **IV** that has heteroatom functionality at γ- or δ-position, with chiral non-racemic but-3-en-1,2-diol **III**, would provide chiral non-racemic allyl alcohol **II** in one step. This allyl alcohol could be transformed quite easily with $PdCl_2(MeCN)_2$ catalyst into **I** *via* an intramolecular SN2' reaction. The resulting heterocyclic compound **I** possesses a protected allyl alcohol unit, which is able to transform into other functional groups to extend its carbon chain.

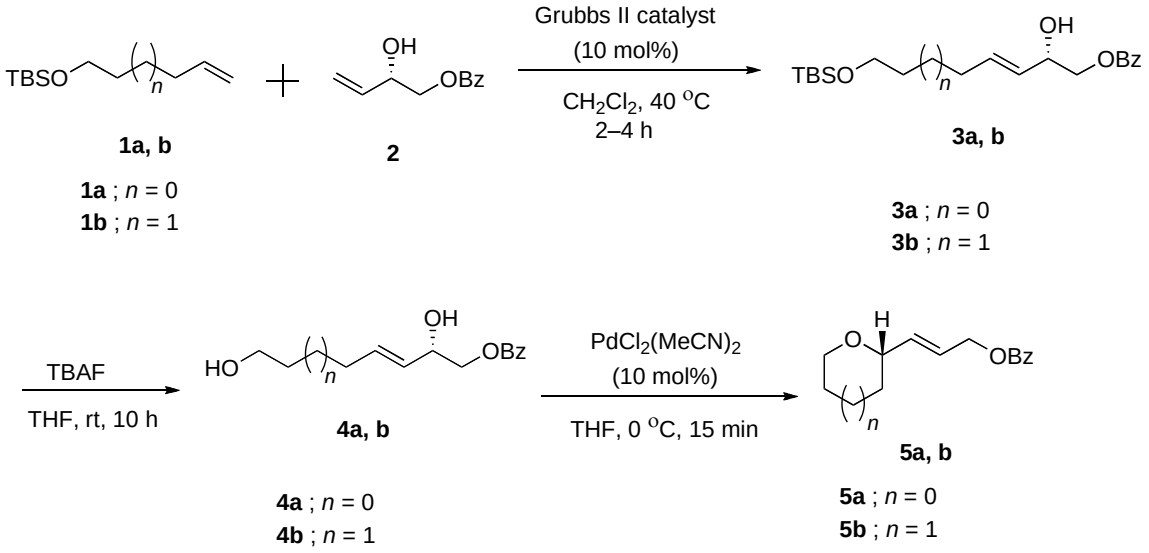



**Scheme 2** A synthetic plan of chiral non-racemic heterocycles

In this note, we report a short and convenient synthetic route for the 2-(3-benzoyloxyprop-1-enyl) substituted chiral non-racemic tetrahydrofuran (**5a**), tetrahydropyran (**5b**), and piperidine (**8**) by cross-metathesis and consecutive $Pd^{II}$-catalyzed cyclization reaction.

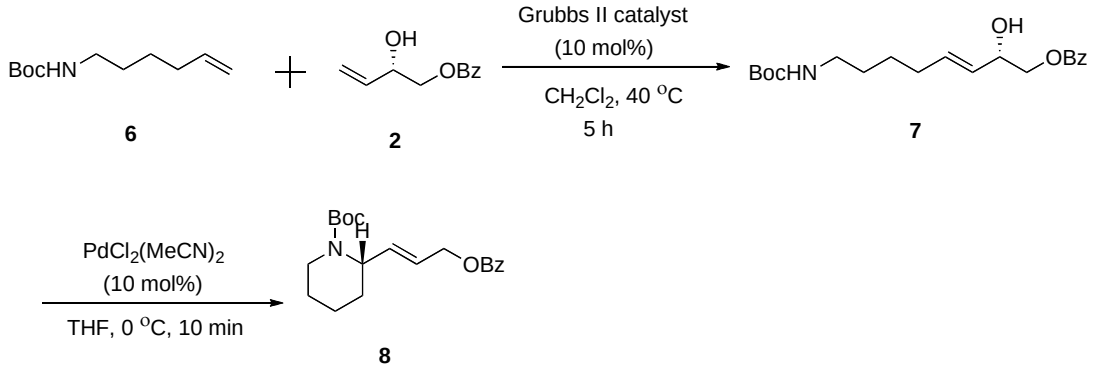
The synthesis of oxa-heterocycles is shown in Scheme 3. A mixture of alkene **1a** and optically pure allyl alcohol (**2**) (>98% ee)[6] was heated in $CH_2Cl_2$ at 40 °C in the presence of 10 mol% of Grubbs II catalyst[7] to give **3a** in 60% yield along with two alkenes derived from the homo-metathesis reactions of each **1a** and **2**. Similarly, the reaction of **1b** with **2** gave **3b** in 61% yield. Deprotection of the TBS group of **3a** and **3b** with TBAF in THF at rt for 10 h afforded the precursors for the cyclization, **4a** and **4b**, in 91% and 84% yields, respectively. The cyclization of **4a** and **4b** were conducted in the presence of 10 mol% $PdCl_2(MeCN)_2$ at 0 °C for 15 min in THF. Compound **5a** was obtained in 87% yield from **4a**. The enantiomeric ratio was determined to be 97.5:2.5 by chiral HPLC analysis, while cyclization of **4b** afforded **5b** in 92% yield with a 99:1 ratio of enantiomers. We have also examined a cross-metathesis

reaction of **1** with (*S*)-3-butene-1,2-diol, though the chemical yield of the cross-metathesis product was unsatisfactory. The stereochemistry of the products were assumed to have an (*S*)-configuration based on the previous results that we have reported in this series.[2-4] In fact, ozonolysis and Kraus oxidation of **5a** afforded (–)-tetrahydrofuran-2-carboxylic acid, of which the chiral center was identified to be *S*.[8]




**Scheme 3** Synthesis of **5a** and **5b**

The synthesis of **8** is performed by the same reaction sequence described for **5** using *N*-Boc protected 5-hexenylamine (**6**)[9] as a partner of cross-metathesis instead of **1**. The cross-metathesis of **6** and **2** was carried out in $CH_2Cl_2$ at 40 °C in the presence of 10 mol% of Grubbs II catalyst for 5 h to give **7** in 56% yield. Then, the precursor **7** was subjected to a $Pd^{II}$-catalyzed cyclization in THF at rt for 10 min to give piperidine (**8**) in 97% yield. Although the chemical yield was excellent, the enantiomeric ratio was found to be slightly lower (93:7) than that of **5**. This trend is consistent with the previous results,[2d] in which the reaction of an *N*-protected nitrogen nucleophiles was less stereoselective than that of a hydroxy nucleophiles.




**Scheme 4**

We have demonstrated a short synthetic method for the optically pure oxa- and azaheterocycles by cross-metathesis and $Pd^{II}$-catalyzed cyclization reactions. An allyl alcohol unit of the resulting heterocycles can be functionalized for the further carbon extension reaction. The formation of (*R*)-enantiomers of **5** and **8** would be expected, if an (*R*)-enantiomer of **5** is used for the metathesis reaction. Thus, this method would be useful for the synthesis of natural products containing chiral THF, THP and piperidine rings in the molecules.

## EXPERIMENTAL

**General.** Column chromatography was performed on E. Merck silica gel (230–400 mesh). The plate used for TLC is E. Merck precoated silica gel 60 $F_{254}$ (0.25–mm thick). Optical rotations were measured on a JASCO P–2200 polarimeter. Infrared (IR) spectra were recorded on a JASCO FT/IR–410 spectrometer. NMR spectra were recorded on a JEOL–AL300 (300 MHz for $^1$H NMR and 75 MHz for $^{13}$C NMR) in $CDCl_3$, and chemical shifts are reported relative to TMS as internal standard or solvent ($CDCl_3$, 7.26 ppm). Low-resolution and high-resolution mass spectra (Exact FAB–MS) were obtained with a JEOL JMS–SX 102. Non-aqueous reactions were carried out in flame-dried glassware under an Ar atmosphere. THF were dried over sodium benzophenone ketyl. $CH_2Cl_2$ was dried over $P_4O_{10}$. These solvents were distilled freshly before use.

**Cross-metathesis reaction; Synthesis of 3a and 3b.** A mixture of (*S*)-2-hydroxybut-3-enyl benzoate (**2**) (100 mg, 0.52 mmol) and terminal alkene **1a** or **1b (**0.78 mmol) in $CH_2Cl_2$ (10 mL) was heated at 40 $^o$C for 2-4 h in the presence of Grubbs II catalyst (44 mg, 0.052 mmol). Solvent was removed and the residue was purified by flash chromatography on silica gel eluted with 25% EtOAc in hexane to give **3a** in 60% yield or **3b** in 61% yield. **(2*S*,3*E*)-7-(*tert*-Butyldimethylsilyloxy)-2-hydroxyhept-3-enyl benzoate** (**3a**); Colorless oil; $[\alpha]_D^{20}$ +3.8 (*c* 0.8, $CHCl_3$); $R_f$ = 0.27 (20% EtOAc in hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.07–8.03 (m, 2H), 7.59–7.53 (m, 1H), 7.46–7.41 (m, 2H), 5.83 (dtd, *J* = 15.4, 6.7, 1.1 Hz, 1H), 5.58 (ddt, *J* = 15.4, 6.4, 1.2 Hz, 1H), 4.47 (m, 1H), 4.36 (dd, *J* = 11.3, 3.6 Hz, 1H), 4.27 (dd, *J* = 11.3, 7.3 Hz, 1H), 3.60 (t, *J* = 6.2 Hz, 2H), 2.5–2.2 (br, 1H), 2.12 (q, *J* = 6.9 Hz, 2H), 1.64–1.55 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 166.6, 134.1, 133.1, 129.9, 129.7, 128.4, 128.0, 70.9, 68.6, 62.3, 32.0, 28.6, 25.9, 18.3, –5.30, –5.32; IR (film, $cm^{-1}$) 3434, 2929, 1723, 1602, 1452, 1274, 1177, 1100, 970, 836, 776, 711; MS (CI) *m/z* 365 ($M^+$+1); HRMS calcd for $C_{20}H_{33}O_4Si$ ($M^+$+1) 365.2148; Found: *m/z* 365.2150. **(2*S*,3*E*)-8-(*tert*-Butyldimethylsilyloxy)-2-hydroxy-oct-3-enyl benzoate (3b)**; Colorless oil; $[\alpha]_D^{20}$ +5.7 (*c* 1.01, $CHCl_3$); $R_f$ = 0.53 (20% EtOAc in hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.07–8.04 (m, 2H), 7.60–7.54 (m, 1H), 7.47–7.41 (m, 2H), 5.82 (dtd, *J* = 15.4, 6.6, 0.7 Hz, 1H), 5.56 (ddt, *J* = 15.4, 6.6, 1.4 Hz, 1H), 4.48 (m, 1H), 4.37 (dd, *J* = 11.3, 3.6 Hz, 1H), 4.27 (dd, *J* = 11.3, 7.3 Hz,

1H), 3.59 (t, *J* = 5.8 Hz, 2H), 2.17 (d, *J* = 3.8 Hz, 1H), 2.08 (q, *J* = 6.6 Hz, 2H), 1.56–1.37 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 166.6, 134.5, 133.1, 129.9, 129.7, 128.4, 127.9, 71.0, 68.6, 62.9, 32.2, 32.0, 25.9, 25.2, 18.4, –5.28, –5.3; IR (film, cm$^{-1}$) 3431, 2930, 2857, 1723, 1602, 1452, 1386, 1274, 1177, 1101, 1026, 971, 835, 776, 771; MS (CI) *m/z* 379 ($M^+$+1); HRMS calcd for $C_{21}H_{35}O_4Si$ ($M^+$+1) 379.2304; Found: *m/z* 379.2313.

**Preparation of 4a and 4b.** To a solution of **3a** or **3b** (0.12 mmol) in THF (1 mL) was added TBAF (182 μL, 0.18 mmol, 1 M in THF) and the mixture was stirred for 10-12 h at rt. The mixture was diluted with EtOAc and washed with water. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified on flash silica gel column chromatography eluted with 80% EtOAc in hexane to give **4a** in 91% yield or **4b** in 84% yield. **(2*S*,3*E*)-2,7-Dihydroxyhept-3-enyl benzoate (4a)**; Colorless oil; $[\alpha]_D^{20}$ –1.6 (*c* 0.63, $CHCl_3$); $R_f$ = 0.23 (60% EtOAc in hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.06–8.03 (m, 2H), 7.60–7.53 (m, 1H), 7.46–7.40 (m, 2H), 5.82 (dtd, *J* = 15.4, 6.8, 1.1 Hz, 1H), 5.59 (ddt, *J* = 15.4, 6.4, 1.2 Hz, 1H), 4.46 (m, 1H), 4.35 (dd, *J* = 11.2, 3.8 Hz, 1H), 4.27 (dd, *J* = 11.2, 7.3 Hz, 1H), 3.62 (t, *J* = 6.4 Hz, 2H), 2.22 (br s, 2H), 2.15 (q, *J* = 6.9 Hz, 2H), 1.64 (quin, *J* = 6.6 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 166.7, 133.6, 133.1, 129.8, 129.6, 128.4, 128.3, 70.8, 68.5, 62.1, 31.7, 28.5; IR (film, cm$^{-1}$) 3389, 2938, 1716, 1601, 1451, 1277, 1119, 971, 712; MS (CI) *m/z* 251 ($M^+$+1); HRMS calcd for $C_{14}H_{19}O_4$ ($M^+$+1) 251.1283; Found: *m/z* 251.1277. **(2*S*,3*E*)-2,8-Dihydroxyoct-3-enyl benzoate (4b)**; Colorless oil; $[\alpha]_D^{20}$ –9.9 (*c* 0.55, $CHCl_3$); $R_f$ = 0.1 (40% EtOAc in hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.07–8.03 (m, 2H), 7.6–7.54 (m, 1H), 7.47–7.41 (m, 2H), 5.81 (dtd, *J* = 15.4, 6.7, 1.1 Hz, 1H), 5.57 (ddt, *J* = 15.5, 6.6, 1.1 Hz, 1H), 4.46 (m, 1H), 4.36 (dd, *J* = 11.3, 3.6 Hz, 1H), 4.27 (dd, *J* = 11.3, 7.3 Hz, 1H), 3.61 (t, *J* = 6.4 Hz, 2H), 2.1 (q, *J* = 6.6 Hz, 2H), 1.75–1.40 (m, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 166.6, 134.1, 133.1, 129.8, 129.6, 128.4, 128.2, 70.9, 68.5, 62.6, 32.0, 31.9, 25.0; IR (film, cm$^{-1}$) 3392, 2935, 1714, 1602, 1452, 1275, 1116, 1070, 971, 755, 713; MS (CI) *m/z* 265 ($M^+$+1); HRMS calcd for $C_{15}H_{21}O_4$ ($M^+$+1) 265.1440; Found: *m/z* 265.1437.

**Pd-Catalyzed cyclyzation of 4a and 4b.** A mixture of **4a** or **4b** (0.1 mmol) and $PdCl_2(MeCN)_2$ (2.6 mg, 0.01 mmol) in THF (3 mL) was stirred at 0 $^o$C for 15 min. Then, the mixture was diluted with hexane (2 mL) and purified directly by flash column chromatography on silica gel eluted with 10% EtOAc in hexane to give **5a** in 87% yield or **5b** in 92% yield. **(*S*,*E*)-2-(3-Benzoyloxyprop-1-enyl)-tetrahydrofuran (5a)** Colorless oil; $[\alpha]_D^{20}$ –5.4 (*c* 1.1, $CHCl_3$); $R_f$ = 0.43 (10% EtOAc in hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.07–8.04 (m, 2H), 7.58–7.52 (m, 1H), 7.46–7.41 (m, 2H), 5.96–5.82 (m, 2H), 4.82 (d, *J* = 4.4 Hz, 2H), 4.38–4.32 (m, 1H), 3.95–3.88 (m, 1H), 3.83–3.76 (m, 1H), 2.13–2.03 (m, 1H), 1.98–1.86 (m, 2H), 1.70–1.59 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 166.3, 135.3, 133.0, 130.1, 129.6,

128.3, 124.9, 78.7, 68.1, 64.7, 32.0, 25.8; IR (film, $cm^{-1}$) 2972, 1720, 1601, 1451, 1271, 1112; MS (EI) *m/z* 232 ($M^+$), 110 (base), 105; HRMS calcd for $C_{14}H_{16}O_3$ ($M^+$) 232.1099; Found: *m/z* 232.1102. The enantiomeric ratio was determined to be 97.5:2.5 by chiral HPLC analysis using the following conditions; column, Chiralcel OD-H; detector, 254 nm; solvent, 2–propanol/hexane (1/99); flow rate, 0.8 mL/min. Retention time; $t_r$=15.6 min (major isomer) and $t_r$=16.5 min (minor isomer). **(*S,E*)-2-(3-Benzoyloxyprop-1-enyl)tetrahydro-2*H*-pyran (5b)** Colorless oil; $[\alpha]_D^{20}$ –4.7 (*c* 0.97, $CHCl_3$); $R_f$ = 0.4 (10% EtOAc in hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.07–8.03 (m, 2H), 7.58–7.52 (m, 1H), 7.46–7.40 (m, 2H), 5.96–5.82 (m, 2H), 4.82 (dd, *J* = 4.4, 0.9 Hz, 2H), 4.06–4.0 (m, 1H), 3.88–3.82 (m, 1H), 3.49 (td, *J* =11.0, 2.5 Hz, 1H), 1.89–1.82 (m, 1H), 1.71–1.34 (m, 5H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 166.3, 135.5, 132.9, 130.1, 129.6, 128.3, 124.2, 77.1, 68.4, 64.9, 31.8, 25.8, 23.3; IR (film, $cm^{-1}$) 2864, 1717, 1601, 1452, 1268, 1084, 971, 711; MS (EI) *m/z* 246 ($M^+$), 124 (base), 105; HRMS calcd for $C_{15}H_{18}O_3$ ($M^+$) 246.1256; Found: *m/z* 246.1258. The enantiomeric ratio was determined to be 99:1 by chiral HPLC analysis using the following conditions; column, Chiralcel OF; detector, 254 nm; solvent, 2–propanol/hexane (1/99); flow rate, 1 mL/min. Retention time; $t_r$=27.1 min (minor isomer) and $t_r$=35.4 min (major isomer).

**(2*S*,3*E*)-8-(*tert*-Butoxycarbonylamino)-2-hydroxyoct-3-enyl benzoate (7)**. The compound was obtained in 56% yield by the same manner described for the synthesis of **3**. Colorless oil; $[\alpha]_D^{20}$ +8.1 (*c* 0.66, $CHCl_3$); $R_f$ = 0.28 (30% EtOAc in hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.06–8.03 (m, 2H), 7.59–7.53 (m, 1H), 7.46–7.41 (m, 2H), 5.78 (dtd, *J* = 15.4, 6.6, 0.9 Hz, 1H), 5.56 (ddt, *J* = 15.4, 6.4, 1.2 Hz, 1H), 4.52 (br s, 1H), 4.46 (m, 1H), 4.36 (dd, *J* = 11.2, 3.6 Hz, 1H), 4.28 (dd, *J* = 11.3, 7.1 Hz, 1H), 3.07 (q, *J* = 6.2 Hz, 2H), 2.50 (br s, 1H), 2.07 (q, *J* = 6.4 Hz, 2H), 1.56–1.33 (m, 13H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 166.6, 155.9, 133.8, 133.1, 129.8, 129.6, 128.4, 128.3, 79.1, 70.9, 68.5, 40.3, 31.8, 29.3, 28.4, 25.9; IR (film, $cm^{-1}$) 3389, 2928, 1695, 1452, 1276, 756, 711; MS (CI) *m/z* 364 ($M^+$+1); HRMS calcd for $C_{20}H_{30}NO_5$ ($M^+$+1) 364.2124; Found: *m/z* 264.2129.

**(*S,E*)-*N*-*tert*-Butoxycarbonyl-2-(3-benzoyloxyprop-1-enyl)piperidine (8).** The compound was obtained in 97% yield by the same manner described for the synthesis of **5**. Colorless oil; $[\alpha]_D^{20}$ –18.4 (*c* 0.84, $CHCl_3$); $R_f$ = 0.44 (20% EtOAc in hexane); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.06–8.03 (m, 2H), 7.59–7.53 (m, 1H), 7.46–7.41 (m, 2H), 5.79 (dd, *J* = 15.7, 4.0 Hz, 1H), 5.73 (dtd, *J* = 15.7, 5.6, 1.1 Hz, 1H), 4.83–4.81 (m, 3H), 3.95 (d, *J* = 13.3 Hz, 1H), 2.83 (td, *J* = 13.0, 2.5 Hz, 1H), 1.74–1.38 (m, 15H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 166.3, 155.3, 133.8, 133.0, 130.2, 129.6, 128.3, 125.2, 79.5, 65.1, 51.5, 39.8, 29.0, 28.4, 25.4, 19.5; IR (film, $cm^{-1}$) 2937, 1722, 1692, 1452, 1409, 1271, 1163, 1114, 1025, 973, 869, 713; MS (EI) *m/z* 345 ($M^+$), 289, 272, 167 (base); HRMS calcd for $C_{20}H_{27}NO_4$ ($M^+$) 345.1940; Found: *m/z*

345.1935. The enantiomeric ratio was determined to be 93:7 by chiral HPLC analysis using the following conditions; column, Chiralcel AS-H; detector, 254 nm; solvent, 2–propanol/hexane (1/99); flow rate, 1 mL/min. Retention time; $t_r$=7.7 min (major isomer) and $t_r$=8.4 min (minor isomer).

## ACKNOWLEDGEMENTS

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