INTRAMOLECULAR 1,5-HYDROGEN ATOM TRANSFER RADICAL REACTION OF PYRROLIDINE DERIVATIVES*

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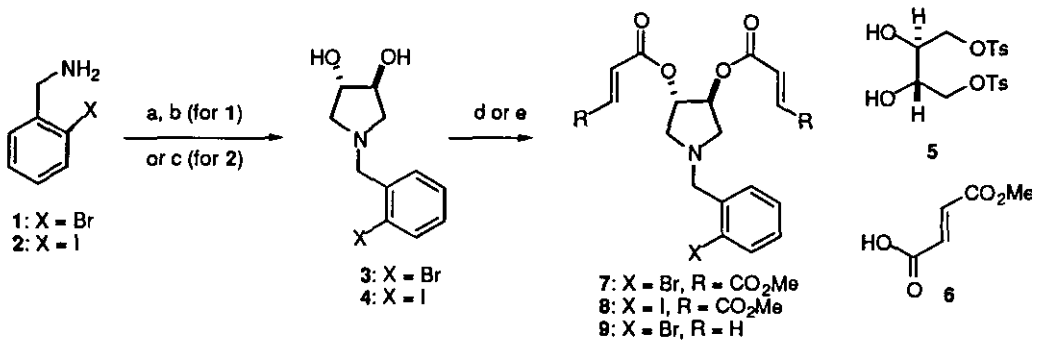
Abstract- Intramolecular 1,5-hydrogen atom transfer radical cyclization reaction of pyrrolidine derivatives was examined. Radical reaction of 3,4-bis(α,β-unsaturated acyloxy)-(**8**, **9**) and 3,4-diacetoxy (**13**) -*N*-[(*o*-halobenzyl)pyrrolidines underwent elimination of two acyloxy groups to give mainly *N*-benzylpyrrole (**11**). On the other hand, the similar reaction of 3,4-diallyloxy-*N*-(*o*-bromobenzyl)pyrrolidine (**16**) gave desired hexahydrofuro[3,2-*b*]pyrroles (**17**, **18**) together with a dimeric hexahydrofuro[3,2-*b*]pyrrole (**19**).

Stereoselective introduction of substituent at C-2 position of pyrrolidine ring[1] was important for the synthesis of many nitrogen containing natural products such as pyrrolizidine and indolizidine alkaloids.[2] In our continuing studies[3] on the synthesis of natural products using radical reaction, we planned synthesis of pyrrolizidine alkaloids using intramolecular 1,5-hydrogen atom transfer radical reaction.[4] In this paper, we wish to describe our results on introduction of substituent at C-2 position of pyrrolidine ring in some optically active *N*-(*o*-halobenzyl)pyrrolidine derivatives,[5] which were derived from L-tartaric acid, by means of the present methodology.

Synthesis of radical precursors is as follows (Scheme 1). Reaction of *o*-bromobenzylamine (**1**)[6] with L-tartaric acid followed by reduction with BH_3 afforded *N*-(*o*-bromobenzyl)-3,4-pyrrolidinediol (**3**) in 87% yield. However, *N*-(*o*-iodobenzyl) congener (**2**) gave in low yield iodo product (**4**) along with its deiodinated product. Therefore, **4** was prepared in 93% yield by coupling of **2** with ditosylate (**5**).[7] Acylation of 3,4-pyrrolidinediols (**3**, **4**) with monomethyl fumarate (**6**)[8] or acryloyl chloride furnished the corresponding acyloxypyrrolidines (**7**-**9**) in 82-85% yield.

With radical precursors (**7**-**9**) in hand, we attempted radical reaction under standard conditions (AIBN/Bu_3SnH/toluene). Contrary to our expectation, reaction of **7** and **8** did not give a desired cyclized product (**12**). Instead, in the case of *N*-(*o*-bromobenzyl) compound (**7**), only 1,4-reduction[9] product (**10**) was

*This paper is dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday.



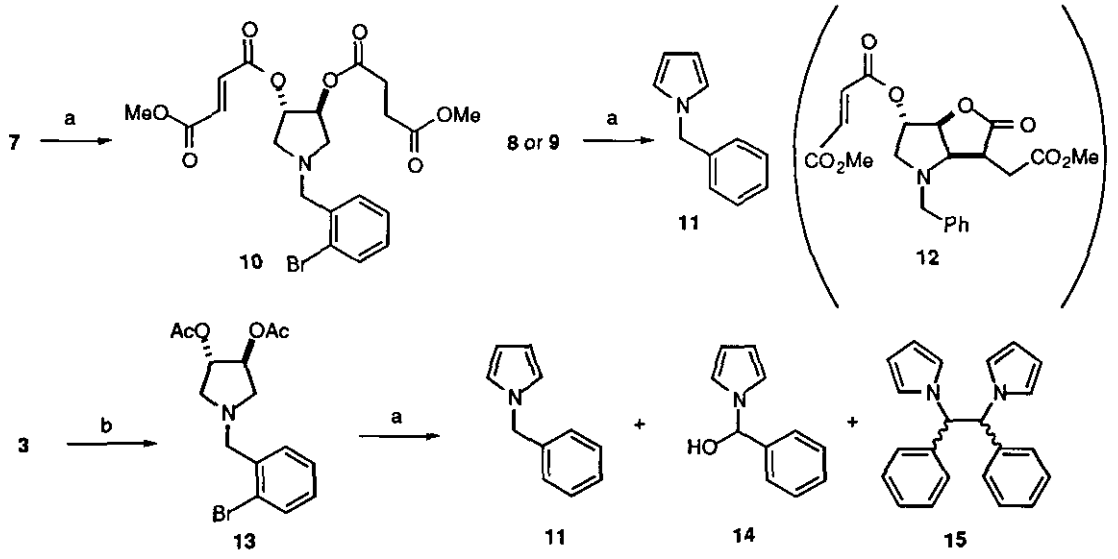
a) L-tartaric acid, *o*-xylene, reflux; b) BH_3, THF; c) **5**, dioxane, reflux; d) **6**, $(COCl)_2$, CH_2Cl_2; **3** or **4**, Et_3N, CH_2Cl_2; e) acryloyl chloride, Et_3N, CH_2Cl_2.

Scheme 1

obtained in low yield. Surprisingly, the reaction of **8** and **9** gave *N*-benzylpyrrole (**11**)[10] in 13 and 60% yield, respectively, by elimination of two acyloxy groups. ^{1}H-NMR spectrum of **11** was identical with that reported in a literature.[10]

Considering the fact that the acyloxy moiety adjacent to radical carbon is not be eliminated,[11] the present results are noteworthy. Although the cyclized product was not formed, formation of **11** suggested intramolecular 1,5-hydrogen atom transfer reaction to take place.

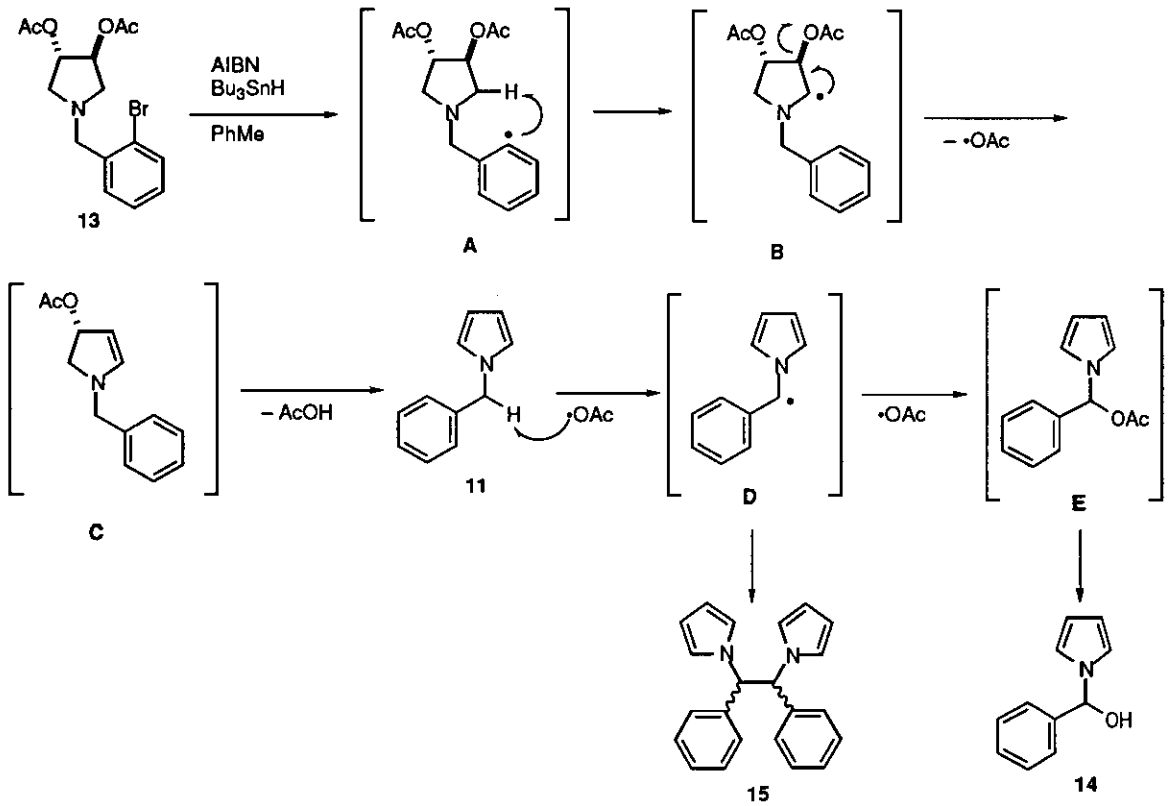
To confirm the effect of acyloxy group in the pyrrolidine ring at C-3 and C-4 positions in the present radical reaction, radical precursor (**13**) was synthesized by the reaction of diol (**3**) with acetyl chloride. Radical



a) AIBN, Bu_3SnH, toluene (0.02 M), reflux; b) acetyl chloride, Et_3N, CH_2Cl_2.

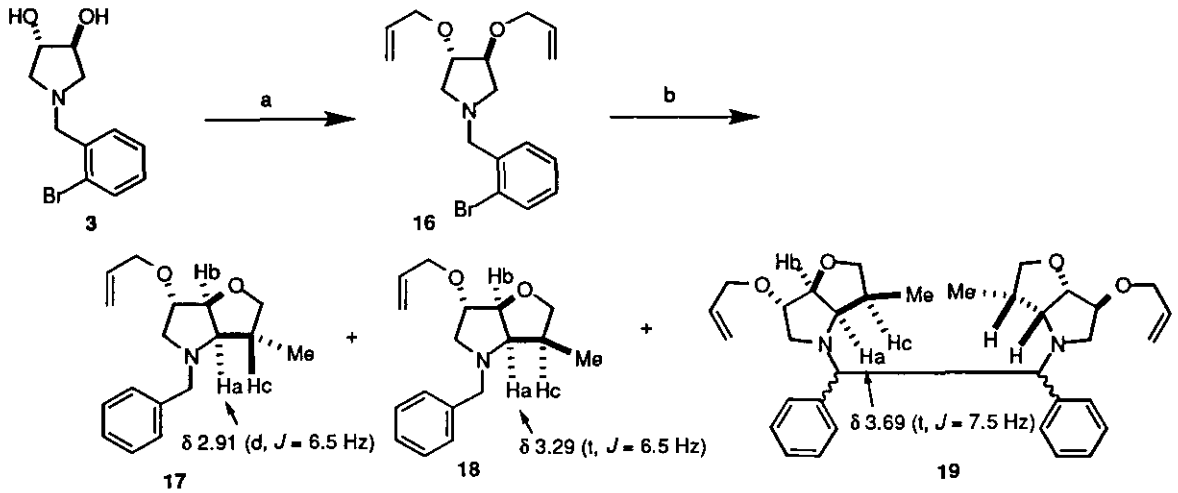
Scheme 2

reaction of 3,4-diacetoxy compound (**13**) furnished pyrroles (**11**, **14**) together with α,α'-bis(*N*-benzylpyrrole) (**15**). Plausible reaction pathway on formation of **11**, **14**, and **15** in the radical reaction of **13** was depicted in Scheme 3. Namely, *N*-benzylpyrrole (**11**) would be formed from **13** *via* 1,5-hydrogen atom transfer reaction of **A**, followed by successive elimination of two acetoxy groups. Abstraction of benzylic hydrogen of **11** by acetoxy radical generates benzylic radical (**D**), which would give a dimeric compound (**15**) by self-condensation and hydroxypyrrole (**14**) by coupling with acetoxy radical followed by hydrolysis.



Scheme 3

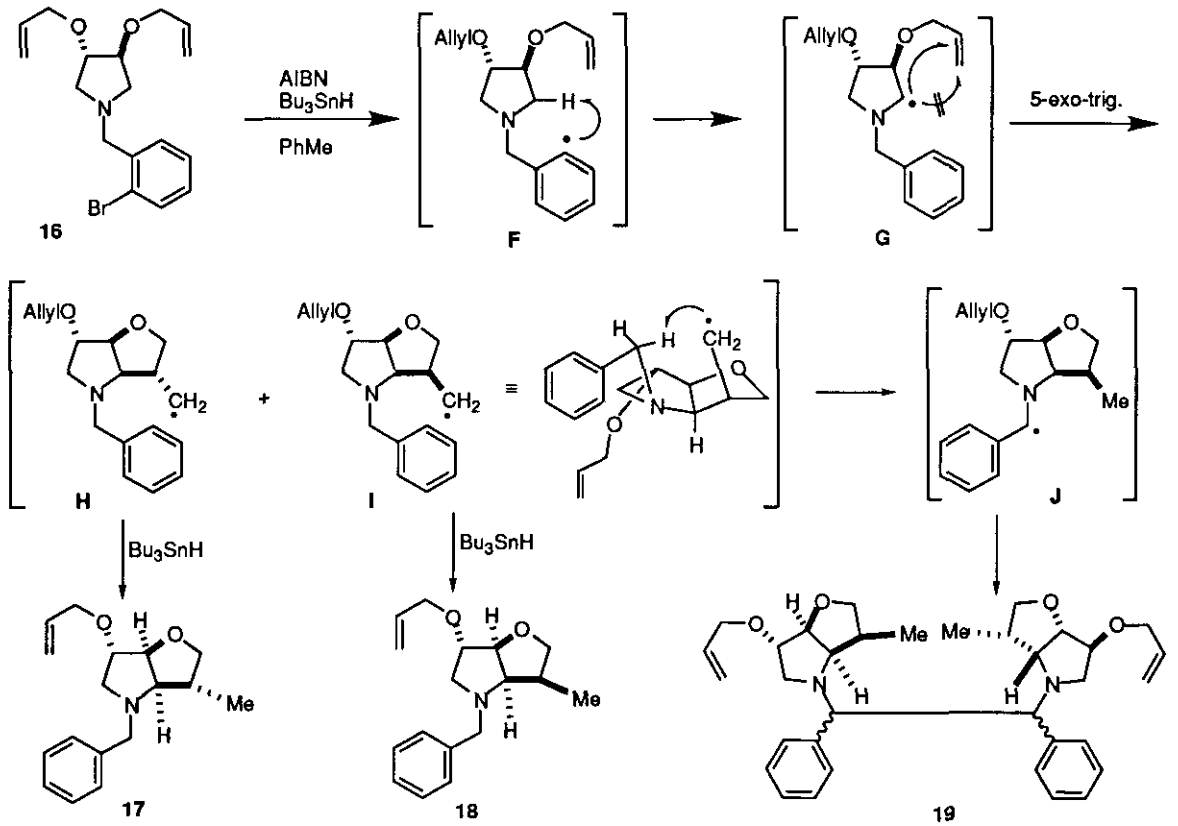
Based on the present findings, we turned our attention to a precursor having ether moiety. Thus, radical precursor (**16**) was synthesized in 40% yield by the reaction of **3** with NaH and allyl bromide in THF (Scheme 4). Intramolecular radical reaction of **16** gave desired cyclized products (**17**, **18**) and dimeric compound (**19**) in 34, 9, and 48% yield, respectively. The stereochemistry of products (**17**, **18**) was determined by ^{1}H-NMR. Namely, in the ^{1}H-NMR (500 MHz), the proton signal due to Ha of compound (**17**) appeared at δ 2.91 as doublet (J = 6.5 Hz), whereas that of **18** was at δ 3.29 as triplet (J = 6.5 Hz). In both compounds (**17**, **18**), coupling constant between Ha and Hb was 6.5 Hz, and in **17** no spin-spin coupling between Ha and Hc was observed. From examination of ^{1}H-NMR coupled with Dreiding



a) NaH, THF; allyl bromide; b) AIBN, Bu_3SnH, toluene (0.02 M), reflux.

Scheme 4

models, **17** was deduced to have an α-methyl substituent. Similarly, stereostructure of dimeric compound (**19**) was estimated by the proton signal (δ 3.69 as triplet, J = 7.5 Hz) due to Ha of compound (**19**) and



Scheme 5

MS spectrum [*m/z* 544 (M^+)], although stereochemistry at benzylic position was uncertain. Moreover, formation of **19** suggested to occur *via* tandem 1,5-hydrogen atom transfer radical reaction as shown in Scheme 5. Thus, 5-exo cyclization of radical (**G**), which could be generated from **F**, would afford two diastereomeric radicals (**H**, **I**). Since β-methylene carbon radical and benzylic hydrogen in **I** could be in close proximity, second 1,5-hydrogen transfer reaction between would occur spontaneously to furnish benzylic radical (**J**), which might be dimerized to give **19**. This assumption could be supported from inspection of Dreiding model.

In conclusion, hydrogen atom transfer radical reaction of pyrrolidine derivatives (**8**, **9**, **13**) having acyloxy moieties at C-3 and C-4 position gave mainly *N*-benzylpyrrole (**11**) by elimination of two diacyloxy groups, whereas diallyloxy derivative (**16**) was successfully cyclized to produce *cis*-fused bicyclic compounds (**17**-**19**). It is noteworthy that in the present reaction, tandem 1,5-hydrogen atom transfer radical reaction took place.

EXPERIMENTAL

General. All melting points were measured on a Büchi melting point apparatus and are uncorrected. IR spectra were performed with a Hitachi 260-10 spectrophotometer in $CHCl_3$ solution, and ^1H NMR spectra were taken with a JEOL JMX-FX100 (100 MHz) or a JEOL GSX-500 (500 MHz) spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal standard. Following abbreviations were used in the NMR data; *s*: singlet, *d*: doublet, *t*: triplet, *m*: multiplet. MS spectra were measured on a Hitachi M-80 or a JEOL JMS D-300 spectrometer. Column chromatography was performed over silica gel (Wako gel C-200 or Merck Kiegelsel 60). Preparative TLCs were run on Merck 5744 or Merck 7730 plates.

(3*S*,4*S*)-*N*-(*o*-Bromobenzyl)pyrrolidine-3,4-diol (3) A mixture of L-tartaric acid (8.0 g, 53.3 mmol) and *o*-bromobenzylamine (**1**, 10.0 g, 53.8 mmol) in *o*-xylene (105 mL) was refluxed for 4 h using a Dean-Stark apparatus. After the mixture had cooled in ice bath, the precipitate was collected by filtration. The crystals were washed with benzene and recrystallized from hot water to give imide (7.49 g, 47%). To the imide (5.0 g, 16.7 mmol) in THF (100 mL) at 0 °C under argon was added 1M BH_3•THF (67 mL, 67 mmol) over a period of 8 min. Then, the mixture was refluxed for 7 h. The reaction was quenched with water and 3 M aqueous HCl. The solvent was evaporated under reduced pressure to give a residue, which was washed with ether, and 3 M aqueous NaOH was added to make alkaline. The aqueous layer was extracted with ether. The extract was washed with brine, dried (K_2CO_3), and evaporated under reduced pressure to give **3** (3.96 g, 87%) as colorless crystals; mp 124-127 °C ($CHCl_3$); $[\alpha]_D^{25}$ +22.9° (c = 0.5, MeOH); ^1H NMR δ 7.44-7.58 (1H, m, arom. H), 6.98-7.42 (3H, m, arom. Hx3), 4.08 (2H, dd, *J* = 4.3, 5.7 Hz, OCHx2), 3.76 (2H, s, ArC$\underline{H}_2$), 3.05 (2H, dd, *J* = 5.7, 10 Hz, H-2, H-5), 2.52 (2H, dd, *J* = 4.3,

10 Hz, H-2, H-5); IR 3445 cm^{-1}; EI MS *m/z* 271 (M^+-1), 273 (M^++1). Anal. Calcd for $C_{11}H_{14}NO_2Br$: C, 48.55; H, 5.19; N, 5.15. Found: C, 48.32; H, 5.18; N, 4.97.

(3*S*,4*S*)-*N*-(*o*-Iodobenzyl)pyrrolidine-3,4-diol (4) To a refluxing solution of ditosylate[7] (**5**, 0.519 g, 1.21 mmol) in dioxane (6 mL) under argon was added a solution of *o*-iodobenzylamine (**2**, 1.14 g, 4.90 mmol) in dioxane (4 mL) over a period of 4 min. The mixture was refluxed for 11 h. After cooling in an ice bath, the precipitate was filtered off. The filtrate was evaporated under reduced pressure to give a residue, to which was added 6 M aqueous NaOH. The aqueous layer was extracted with a mixed solution of ether and THF (1 :1). The extract was washed with brine, dried (K_2CO_3), and evaporated under reduced pressure to afford an oily residue, which was purified by column chromatography ($CHCl_3$: MeOH = 100 : 1) to give **4** (0.359 g, 93%) as colorless oil; ^{1}H NMR δ 7.73-7.87 (1H, m, arom. H), 7.18-7.44 (2H, m, arom. Hx2), 6.84-7.04 (1H, m, arom. H), 4.11 (2H, m, OCHx2), 3.79 (2H, s, ArC$\underline{H}_2$), 3.12 (2H, dd, *J* = 5.7, 10 Hz, H-2, H-5), 2.60 (2H, dd, *J* = 2.9, 10 Hz, H-2, H-5); EI MS *m/z* 319 (M^+).

(3*S*,4*S*)-*N*-(*o*-Bromobenzyl)-3,4-bis[(*E*)-methoxycarbonylethenoyloxy]pyrrolidine (7) A mixture of acid[8] (**6**, 0.146 g, 1.12 mmol), oxalyl chloride (0.11 mL, 1.26 mmol) and DMF (1 drop) in CH_2Cl_2 (2.5 mL) at rt under argon was stirred for 3 h. Evaporation of the solvent *in vacuo* afforded acid chloride as an oil. To the acid chloride in CH_2Cl_2 (2.5 mL) at rt was added a solution of diol (**3**, 0.096 g, 0.35 mmol) in CH_2Cl_2 (7 mL) and Et_3N (0.122 g, 1.2 mmol) in CH_2Cl_2 (4 mL), successively. The mixture was stirred for 17 h. The reaction was quenched with water. The mixture was extracted with $CHCl_3$. The extract was washed with brine, dried (K_2CO_3), and evaporated under reduced pressure to give an oily residue, which was purified by preparative TLC ($CHCl_3$) to afford **7** (0.149 g, 85.3%) as an oil; ^{1}H NMR δ 6.98-7.59 (4H, m, arom. Hx4), 6.85 (4H, s, olefinic Hx4), 5.16-5.34 (2H, m, OCHx2), 3.80 (6H, s, Mex2), 3.76 (2H, s, ArC$\underline{H}_2$), 3.21 (2H, dd, *J* = 5.7, 10.7 Hz, H-2, H-5), 2.68 (2H, dd, *J* = 5.0, 10.7 Hz, H-2, H-5); IR 1725 cm^{-1}; EI MS *m/z* 495 (M^+-1), 497 (M^++1).

(3*S*,4*S*)-*N*-(*o*-Iodobenzyl)-3,4-bis[(*E*)-methoxycarbonylethenoyloxy]pyrrolidine (8) A mixture of acid (**6**, 0.497 g, 3.82 mmol), oxalyl chloride (0.34 mL, 3.90 mmol) and DMF (1 drop) in CH_2Cl_2 (3 mL) at rt under argon was stirred for 3 h. Evaporation of the solvent *in vacuo* afforded acid chloride as an oil. To the acid chloride in CH_2Cl_2 (8 mL) at rt was added a solution of diol (**4**, 0.358 g, 1.12 mmol) in CH_2Cl_2 (4 mL) and Et_3N (0.391 g, 3.87 mmol) in CH_2Cl_2 (3 mL), successively. The mixture was stirred for 15 h. Similar work-up as described above gave an oily residue, which was purified by column chromatography (AcOEt : hexane = 1 : 3) to afford **8** (0.501 g, 82.3%) as an oil; ^{1}H NMR δ 7.80 (1H, d, *J* = 8.6 Hz, arom. H), 7.20-7.40 (2H, m, arom. Hx2), 6.87-7.03 (1H, m, arom. H), 6.85 (4H, s, olefinic Hx4), 5.26 (2H, dd, *J* = 4.3, 7.1 Hz, OCHx2), 3.80 (6H, s, Mex2), 3.70 (2H, s, ArC$\underline{H}_2$), 3.21 (2H, dd, *J* = 7.1, 10.7 Hz, H-2, H-5), 2.68 (2H, dd, *J* = 4.3, 10.7 Hz, H-2, H-5); IR 1725

cm^{-1}; EI MS *m/z* 543 (M^+).

(3*S*,4*S*)-*N*-(*o*-Bromobenzyl)-3,4-diacryloyloxypyrrolidine (9) A mixture of **3** (0.544 g, 2.0 mmol), acryloyl chloride (0.82 mL, 10.1 mmol), and Et_3N (1.02 g, 10.1 mmol) in CH_2Cl_2 (20 mL) at rt under argon was stirred for 3 h. Then, 10% aqueous NaOH was added to the mixture. The mixture was extracted with $CHCl_3$. The extract was washed with water and brine, successively. The extract was dried (K_2CO_3), and evaporated under reduced pressure to give an oily residue, which was purified by column chromatography (AcOEt : hexane = 1 : 50) to afford **9** (0.636 g, 83.7%) as an oil; ^1H NMR δ 6.99-7.58 (4H, m, arom. Hx4), 6.44 (2H, dd, *J* = 2.9, 15.7 Hz, olefinic Hx2), 6.06 (2H, dd, *J* = 10, 15.7 Hz, olefinic Hx2), 5.83 (2H, dd, *J* = 2.9, 10 Hz, olefinic Hx2), 5.16-5.33 (2H, m, H-3, H-4), 3.77 (2H, s, ArC$\underline{H}_2$), 3.22 (2H, dd, *J* = 7.1, 11.4 Hz, H-2, H-5), 2.66 (2H, dd, *J* = 4.3, 11.4 Hz, H-2, H-5); IR 1730 cm^{-1}; EI MS *m/z* 379 (M^+-1), 381 (M^++1).

Radical reaction of 7, 8, and 9. From 7: A mixture of **7** (0.099 g, 0.20 mmol), AIBN (0.004 g, 0.03 mmol), and Bu_3SnH (0.071 g, 0.24 mmol) in toluene (10 mL) was refluxed for 7 h. Then, the solvent was removed *in vacuo* to give an oily residue, which was purified by column chromatography (hexane then $CHCl_3$: MeOH = 10 : 1), followed by preparative TLC (AcOEt : hexane = 1 : 3) to afford **10** (0.021 g, 21.3%) and **7** (0.009 g, 9.0%).

(3*S*,4*S*)-*N*-(*o*-Bromobenzyl)-3-[(*E*)-methoxycarbonylethenoyloxy]-4-(2-methoxycarbonylethoxy)pyrrolidine (10); ^1H NMR δ 6.98-7.57 (4H, m, arom. Hx4), 6.84 (2H, s, olefinic Hx2), 5.11-5.29 (2H, m, H-3, H-4), 3.80 (3H, s, CO_2Me), 3.76 (2H, s, ArC$\underline{H}_2$), 3.67 (3H, s, CO_2Me), 3.18 (2H, dd, *J* = 5.7, 10.7 Hz, H-2, H-5), 2.65-2.76 (2H, m, H-2, H-5), 2.64 (4H, s, $COCH_2$x2); IR 1730 cm^{-1}; EI MS *m/z* 498 (M^+), 500 (M^++2).

From 8: A mixture of **8** (0.166 g, 0.30 mmol), AIBN (0.028 g, 0.17 mmol), and Bu_3SnH (0.117 g, 0.40 mmol) in toluene (15 mL) was refluxed for 9 h. Then, the solvent was removed *in vacuo* to give an oily residue, which was taken up in MeCN. The organic phase was washed with hexane, dried ($MgSO_4$), and evaporated under reduced pressure to give a residue, which was purified by preparative TLC (AcOEt : hexane = 1 : 5) to afford **11** (0.006 g, 12.5%) and **8** (0.010 g, 6.2%), respectively.

***N*-Benzylpyrrole (11)**[10]; ^1H NMR δ 6.88-7.41 (5H, m, arom. Hx5), 6.63 (2H, t, *J* = 1.8 Hz, H-2, H-3), 6.15 (2H, t, *J* = 1.8 Hz, H-3, H-4), 4.95 (2H, s, ArC$\underline{H}_2$); EI MS *m/z* 157 (M^+).

From 9: A mixture of **9** (0.175 g, 0.46 mmol), AIBN (0.041 g, 0.25 mmol), and Bu_3SnH (0.18 mL, 0.67 mmol) in toluene (23 mL) was refluxed for 2 h. Then, the solvent was removed *in vacuo* to give an oily residue, which was taken up in ether. The organic phase was extracted with 3 M aqueous HCl. Then, aqueous extract was made alkaline with 6 M aqueous NaOH and extracted with ether. The extract was washed with brine, dried (K_2CO_3), and evaporated under reduced pressure to give a residue, which was purified by column chromatography (hexane then AcOEt : hexane = 1 : 5) to afford **11** (0.043 g, 59.9%).

(3*S*,4*S*)-*N*-(*o*-Bromobenzyl)-3,4-diacetoxypyrrolidine (13) A mixture of **3** (0.545 g, 2.0 mmol), acetyl chloride (0.72 mL, 10.1 mmol), and Et_3N (1.02 g, 10.1 mmol) in CH_2Cl_2 (20 mL) at rt under argon was stirred for 5 h. Similar work-up as described above gave an oily residue, which was purified by chromatography (AcOEt : hexane = 1 : 10) to afford **13** (0.635 g, 89.2%) as an oil; ^{1}H NMR δ 6.97-7.57 (4H, m, arom. Hx4), 5.12 (2H, dd, *J* = 4.3, 5.7 Hz, OCHx2), 3.74 (2H, s, ArC$\underline{H}_2$), 3.15 (2H, dd, *J* = 5.7, 11.4 Hz, H-2, H-5), 2.60 (2H, dd, *J* = 4.3, 11.4 Hz, H-2, H-5), 2.07 (6H, s, Acx2); IR 1730 cm^{-1}; EI MS *m/z* 355 (M^+-1), 357 (M^++1).

Radical reaction of 3,4-diacetoxypyrrolidine (13). A mixture of **13** (0.197 g, 0.55 mmol), AIBN (0.049 g, 0.30 mmol), and Bu_3SnH (0.22 mL, 0.82 mmol) in toluene (27 mL) was refluxed for 6 h. Then, the solvent was removed *in vacuo* to give an oily residue, which was taken up in MeCN. The organic phase was washed with hexane, dried ($MgSO_4$), and concentrated under reduced pressure to give a residue, which was purified by preparative TLC (AcOEt : hexane = 1 : 10) to afford **11** (0.036 g, 41.0%), **14** (0.007 g, 7.0%), and **15** (0.010 g, 11.4%) as each oil.

***N*-(1-Hydroxy-1-benzyl)pyrrole (14)**; ^{1}H NMR δ 6.95-7.31 (5H, m, arom. Hx5), 6.50 (2H, t, *J* = 2 Hz, H-2, H-5), 5.94 (2H, t, *J* = 2 Hz, H-3, H-4), 5.71 (1H, s, ArC$\underline{H}$); IR 3200-3600 cm^{-1}; EI MS *m/z* 173 (M^+).

α,α'-Bis(*N*-Benzylpyrrole) (15); ^{1}H NMR δ 7.13 (10H, s, arom. Hx10), 6.47 (2H, t, *J* = 2 Hz, H-2x2, H-3x2), 5.98 (4H, t, *J* = 2 Hz, H-3x2, H-4x2), 5.70 (2H, s, ArC$\underline{H}$x2); EI MS *m/z* 312 (M^+).

(3*S*, 4*S*)-3,4-Diallyloxy-*N*-(*o*-bromobenzyl)pyrrolidine (16) A mixture of NaH (0.613 g, 15.3 mmol) and **3** (0.817 g, 3.0 mmol) in THF (21 mL) under argon was refluxed for 1 h. After cooling to rt, allyl bromide (0.65 mL, 7.51 mmol) was added to the mixture and the mixture was stirred at rt for 16 h. The reaction was quenched with water, and the mixture was extracted with $CHCl_3$. The extract was washed with brine, dried (K_2CO_3), and evaporated under reduced pressure to give an oily residue, which was purified by column chromatography (AcOEt : hexane = 1 : 50 to 1 : 25) to afford **16** (0.421 g, 40.1%) as an oil; ^{1}H NMR (100 MHz) δ 6.83-7.59 (4H, m, arom. Hx4), 5.57-6.24 (2H, m, olefinic Hx2), 4.97-5.42 (4H, m, olefinic Hx4), 3.96 (4H, d, *J* = 5 Hz, allylic Hx2), 3.69 (2H, s, ArC$\underline{H}_2$), 2.47-3.16 (4H, m, H-2x2, H-5x2); EI MS *m/z* 351 (M^+-1), 353 (M^++1); high-resolution MS *m/z* calcd for $C_{17}H_{22}NO_2Br$ (M^+-1) 351.0834, found: 351.0834.

Radical reaction of 16 A mixture of **16** (0.111 g, 0.31 mmol), AIBN (0.026 g, 0.16 mmol), and Bu_3SnH (0.13 mL, 0.48 mmol) in toluene (15 mL) under argon was refluxed for 5 h. Removal of the solvent *in vacuo* gave an oily residue, which was taken up in ether. 10% Aqueous KF was added to the ether extract. After being stirred for 15 h, the mixture was filtered through Celite short pad. The filtrate was washed with brine, dried (K_2CO_3), and concentrated under reduced pressure to give an oily residue, which was purified by preparative TLC (AcOEt : hexane = 1 : 5) to afford **17** (0.029 g, 33.9%), **18** (0.008

g, 8.6%), and **19** (0.041 g, 47.6%) as each oil.

17; ^{1}H NMR (500 MHz) δ 7.23-7.33 (5H, m, arom. Hx5), 5.85-5.93 (1H, m, olefinic H), 5.27 (1H, ddd, *J* = 1.5, 3, 17.3 Hz, olefinic H), 5.16 (1H, ddd, *J* = 1.5, 3, 10.5 Hz, olefinic H), 4.42 (1H, dd, *J* = 2.5, 6.5 Hz, H-3), 4.09 (1H, ddt, *J* = 1.5, 5, 12.5 Hz, allylic H), 3.98 (1H, dd, *J* = 5.4, 8.4 Hz, MeCHCHH), 3.95-3.98 (1H, m, allylic H), 3.85-3.89 (1H, m, H-4), 3.84 (1H, d, *J* = 13 Hz, ArCHH), 3.51 (1H, dd, *J* = 2, 8.4 Hz, MeCHCHH), 3.45 (1H, d, *J* = 13 Hz, ArCHH), 3.16 (1H, dd, *J* = 7, 8.5 Hz, H-5), 2.91 (1H, d, *J* = 6.5 Hz, H-2), 2.21 (1H, t, *J* = 8.5 Hz, H-5), 2.03-2.08 (1H, m, MeCH), 0.92 (3H, d, *J* = 7 Hz, Me); EI MS *m/z* 273 (M^+); high-resolution MS *m/z* calcd for $C_{17}H_{23}NO_2$ (M^+) 273.1727, found: 273.1733.

18; ^{1}H NMR (500 MHz) δ 7.23-7.35 (5H, m, arom. Hx5), 5.84-5.92 (1H, m, olefinic H), 5.25 (1H, ddd, *J* = 1.5, 3, 16.5 Hz, olefinic H), 5.15 (1H, ddd, *J* = 1.5, 3, 10.5 Hz, olefinic H), 4.52 (1H, dd, *J* = 4, 6.5 Hz, H-3), 4.07 (1H, ddt, *J* = 1.5, 5, 13 Hz, allylic H), 4.04 (1H, d, *J* = 13 Hz, ArCHH), 3.96 (1H, ddt, *J* = 1.5, 5, 13 Hz, allylic H), 3.82-3.86 (2H, m, H-4, MeCHCHH), 3.43 (1H, dd, *J* = 8.5, 11 Hz, MeCHCHH), 3.29 (1H, t, *J* = 6.5 Hz, H-2), 3.28 (1H, d, *J* = 13 Hz, ArCHH), 3.13 (1H, dd, *J* = 6, 10 Hz, H-5), 2.20 (1H, dd, *J* = 8.5, 10 Hz, H-5), 2.11-2.17 (1H, m, MeCH), 1.14 (3H, d, *J* = 6.5 Hz, Me); EI MS *m/z* 272 (M^+-1).

19; ^{1}H NMR (500 MHz) δ 7.06-7.11 (6H, m, arom. Hx6), 6.86-6.90 (4H, m, arom. Hx4), 5.90-5.98 (2H, m, olefinic Hx2), 5.32 (2H, ddd, *J* = 1.5, 3, 17.3 Hz, olefinic Hx2), 5.19 (2H, ddd, *J* = 1.5, 3, 10.3 Hz, olefinic Hx2), 4.42 (2H, s, PhCHx2), 4.23 (2H, dd, *J* = 5.5, 7.5 Hz, H-3x2), 4.13 (2H, ddt, *J* = 1.5, 5.4, 12.5 Hz, allylic Hx2), 4.05 (2H, ddt, *J* = 1.2, 5.4, 12.5 Hz, allylic Hx2), 3.92 (2H, dd, *J* = 5.5, 7.5 Hz, H-4x2), 3.69 (2H, t, *J* = 7.5 Hz, H-2x2), 3.62 (2H, dd, *J* = 5.5, 9 Hz, MeCHCHHx2), 3.42 (2H, dd, *J* = 4.5, 9 Hz, MeCHCHHx2), 3.31-3.35 (4H, m, H-5x4), 1.70-1.79 (2H, m, MeCHx2), 0.96 (6H, d, *J* = 6.5 Hz, Mex2); EI MS *m/z* 544 (M^+); high-resolution MS *m/z* calcd for $C_{34}H_{44}N_2O_4$ (M^+) 544.3298, found: 544.3287.

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