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Synthesis of *N*-tosyl-3,3,4-trisubstituted pyrrolidine derivatives starting from the Baylis–Hillman adducts via radical cyclization

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Abstract

N-Tosyl-3,3-disubstituted-4-vinylpyrrolidine derivatives **3a–c** were synthesized via radical cyclization from the modified Baylis–Hillman adducts **2**. The required starting materials **2a–c** were prepared in moderate yields from the Baylis–Hillman adducts in three steps: (i) acetylation of the Baylis–Hillman adducts, (ii) S_N2' reaction with tosylamide to prepare **1**, and (iii) alkylation with 1,4-dibromo-2-butene.

Keywords: Pyrrolidines; Baylis–Hillman adducts; Radical cyclization

1. Introduction

The importance of nitrogen heterocycles, especially pyrrolidine and piperidine types as subunits of bioactive molecules, stimulates the development of new synthetic methods. Suitably substituted pyrrolidines constitute key skeleton in many biologically important compounds[1–3] and were used as key intermediates in the synthesis of natural products.[1–3] Consequently, the efficient preparation method of pyrrolidines has received significant attention.[1–3] Metal-catalyzed cyclization of a suitable acyclic precursor,[2a,c,3a,b,e–g] [3+2] cycloaddition of azomethine ylide,[1a,c] and ring-closing metathesis (RCM) reaction[1d,3c] are the most frequently used methods for the synthesis of pyrrolidines.

Recently we were interested in radical cyclizations of modified Baylis–Hillman adducts.[4,5a] We and other research groups also reported the synthesis of various heterocyclic compounds[4,5] including *exo*-methylene dihydrofuran and dihydropyrroles via the radical cyclization reaction as the key step from suitably modified Baylis–Hillman adducts. During the studies we imagined that we could synthesize 3,3-disubstituted-4-vinylpyrrolidine derivatives via the in situ generated allyl radical cyclization protocol[6,7] as in Scheme 1 (vide infra). Although the synthesis of piperidine skeleton via the allyl radical cyclization strategy was reported,[7] to the best of our knowledge, synthesis of pyrrolidine derivatives from the Baylis–Hillman adducts has not been examined.

2. Results and discussion

The starting material **2a** was synthesized from the Baylis–Hillman adduct via the following sequential reactions: (i) acetylation of Baylis–Hillman adduct of methyl acrylate and benzaldehyde, (ii) S_N2' reaction with tosylamide ($TsNH_2$, K_2CO_3, aq THF, 70–80 °C) to produce **1a**,[8] (iii) alkylation with 1,4-dibromo-2-butene (K_2CO_3, DMF, rt). The next radical cyclization of **2a** was examined under the influence of *n*-Bu_3SnH (1.5 equiv)/AIBN (cat) in benzene, and we obtained desired compound **3a** in moderate yield as a diastereomeric mixture (67%). We separated the two isomers in pure form and found that *syn*-**3a** was the major component (57%) by spectroscopic analysis including NOE experiments (vide infra, Fig. 2). The formation of **3a** can be explained as shown in Scheme 1 involving the rearrangement of initially formed allylic radical (**I**) to (**II**), which undergoes 5-*exo-trig* type cyclization. In addition, the reason for the predominant formation of *syn*-**3a** could be explained by the transition state model

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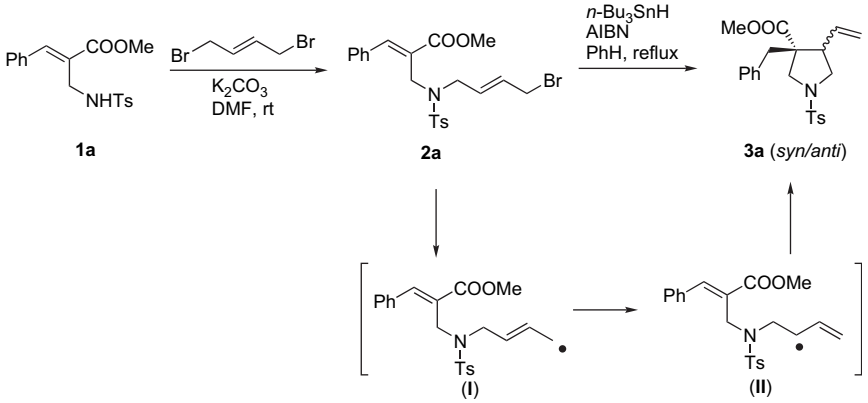


Scheme 1.

(Fig. 1). The compound *syn*-**3a** might be formed via the TS 1 and *anti*-**3a** from TS 2. As shown in Figure 1, appreciable steric crowdedness arose in the transition state TS 2 between the *p*-toluenesulfonyl group and the phenyl moiety, thus made *anti*-**3a** as the minor product.

Encouraged by the successful results we synthesized pyrrolidines **3b** and **3c** as summarized in Table 1. For the ethyl ester **3b** (entry 2), the results were almost same with those of the case of methyl ester **3a**. The nitrile derivative **1c** was prepared as an *E*/*Z* mixture and the separation was very difficult. Thus we used **1c** without further purification. After alkylation with 1,4-dibromo-2-butene, fortunately, we could separate each isomer in pure state albeit in low yields.[9] Either from *E*-**2c** or *Z*-**2c** we obtained similar results as in entries 3 and 4. As a next trial, we examined the synthesis of cyclopentane derivative **3d** by the radical cyclization of **2d** and observed the formation of almost equal amounts of *syn*-**3d** (36%) and *anti*-**3d** (45%). When we used **2e** as substrate (entry 6) we obtained piperidine derivative **3e** (64%) as the sole isolable product.[7] The stereochemistry of products was determined by NOE experiments. Important NOE results of compounds *syn*-**3a**, *anti*-**3a**, *anti*-**3c**, and **3e** are summarized in Figure 2.

As a next trial we examined the synthesis of **2f**, the precursor for the synthesis of tetrahydrofuran derivative **3f**.[10] Initially we made *cis*-**2f** as follows: (i) montmorillonite K10-catalyzed reaction[5c,11] of Baylis–Hillman adduct **1f** and *cis*-1,4-butenediol according to the reported method in a similar case[5c,11] to obtain compound **5** (30%) and (ii) bromination with PBr_3 (50%). However, radical cyclization of *cis*-**2f** gave the desired tetrahydrofuran **3f** in low yield (37%, Scheme 2). From the reaction we isolated compound **4**[12] in 44% yield and the formation of compound **4** could be explained as depicted in Scheme 2 involving the liberation of 2,5-dihydrofuran. Thus, we decided to prepare *trans*-**2f** and examine the radical cyclization. The synthesis of *trans*-**2f** was carried out in two steps: (i) synthesis of compound **6** from **1f** and allyl alcohol (52%) and (ii) cross metathesis reaction between **6** and allyl bromide using second-generation Grubbs catalyst in moderate yield (45%).[13] As expected, the reaction of *trans*-**2f** under the same radical cyclization conditions produced **3f** in higher yield (78%) in a *syn*/*anti*=67:11 ratio and compound **4** was not formed in this case.

In summary, we disclosed the synthesis of some 3,3,4-trisubstituted pyrrolidines and tertahydrofuran starting from rearranged aza-Baylis–Hillman adducts or Baylis–Hillman adduct. Synthetic applications of prepared compounds are actively underway and the results will be published in due course.

3. Experimental

3.1. General procedure

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$. The signal positions are reported in parts per million relative to TMS (δ scale) used as an internal standard. IR spectra are reported in cm^{-1}. Mass spectra were obtained from the Korea Basic Science Institute (Gwangju branch). Melting points are uncorrected. The elemental analyses were carried out at Korea Research Institute of Chemical Technology, Taejeon, Korea. All reagents were purchased from commercial sources and used without further treatment. The separations were carried out by flash column chromatography over silica gel (230–400 mesh ASTM). Organic extracts were dried over anhydrous $MgSO_4$ and the solvents were evaporated on a rotary evaporator under water aspirator pressure.

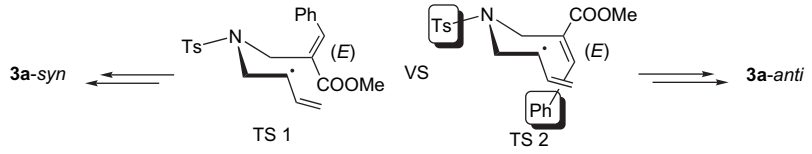
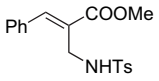
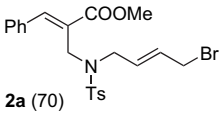
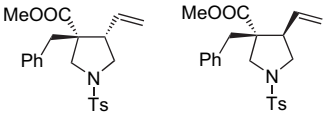
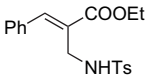
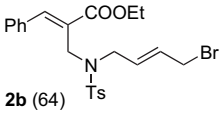
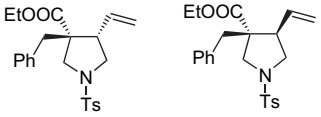
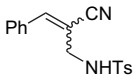
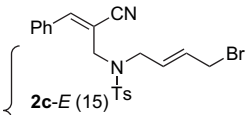
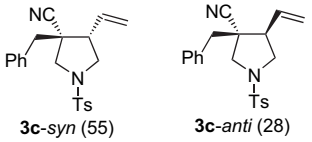
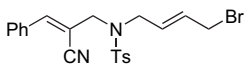
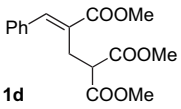
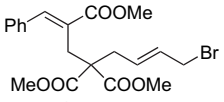
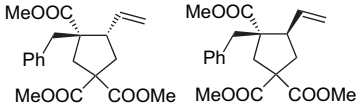
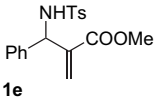
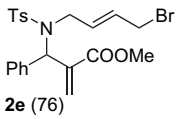
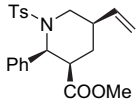


Figure 1. Plausible transition states for the formation of **3a**.

Table 1
Radical cyclization of modified Baylis–Hillman adducts **2a–e**

Entry	Substrate **1**	Substrate **2**[a]	Product **3**[c]
1	 **1a**	 **2a** (70)	 **3a**-*syn* (57) **3a**-*anti* (10)
2	 **1b**	 **2b** (64)	 **3b**-*syn* (55) **3b**-*anti* (10)
3	 **1c** (*E*/*Z* mixture)	 **2c**-*E* (15)	 **3c**-*syn* (55) **3c**-*anti* (28)
4		 **2c**-*Z* (40)	**3c**-*syn* (59) **3c**-*anti* (30)
5	 **1d**	 **2d** (63)[b]	 **3d**-*syn* (36) **3d**-*anti* (45)
6	 **1e**	 **2e** (76)	 **3e** (64)

[a] Conditions for **2a–c** and **2e**: 1,4-dibromo-2-butene (1.5 equiv), K_2CO_3 (2.0 equiv), DMF, rt, 2–3 h.
[b] Conditions for **2d**: 1,4-dibromo-2-butene (1.5 equiv), NaH (2.0 equiv), dry THF, 0 °C, 2 h.
[c] Conditions: *n*-Bu_3SnH (1.5 equiv), AIBN (cat), benzene, reflux, 4–5 h.

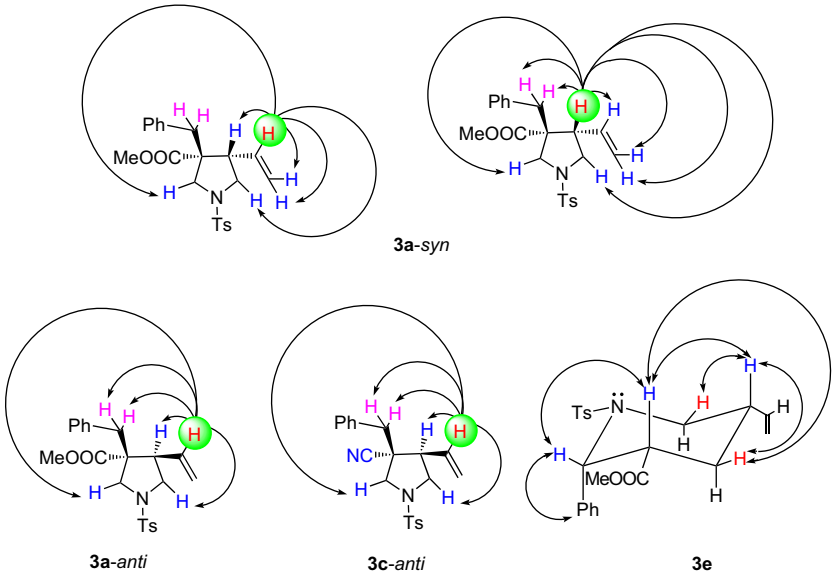
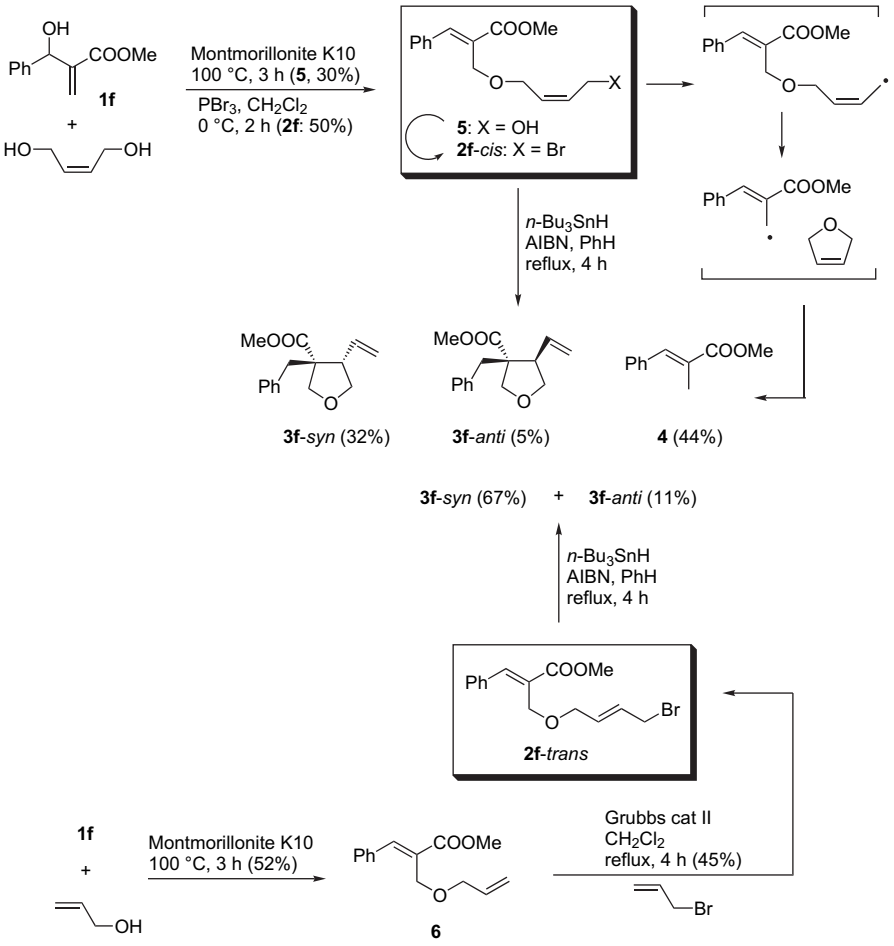


Figure 2. NOE results of *syn*-**3a**, *anti*-**3a**, *anti*-**3c**, **3e** ($CDCl_3$, 500 MHz).



Scheme 2.

3.2. Typical procedure for the synthesis of compound *2a*

Starting materials **1** were synthesized according to the reported methods[8] and the synthesis of compound **2a** was carried out as follows: a solution of **1a** (518 mg, 1.5 mmol), 1,4-dibromo-2-butene (481 mg, 2.25 mmol), and K_2CO_3 (415 mg, 3.0 mmol) in DMF (3 mL) was stirred at room temperature for 2 h. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 3:1) we obtained **2a** (502 mg, 70%) as colorless oil. Other compounds **2b–e** were synthesized analogously and the spectroscopic data are as follows.

3.2.1. Compound *2a*

Yield 70%; colorless oil; IR (CH_2Cl_2) 1715, 1343, 1266, 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3H), 3.66 (d, J=6.3 Hz, 2H), 3.71–3.72 (m, 2H), 3.72 (s, 3H), 4.25 (s, 2H), 5.44–5.49 (m, 2H), 7.25 (d, J=8.1 Hz, 2H), 7.39–7.44 (m, 5H), 7.56 (d, J=8.1 Hz, 2H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.51, 31.43, 43.30, 49.13, 52.19, 127.54, 127.65, 128.68, 129.26, 129.58, 129.68, 129.79, 130.23, 134.33, 136.04, 143.38, 143.88, 167.86; ESIMS *m/z* 478 (M^++1). Anal. Calcd for $C_{22}H_{24}BrNO_4S$: C, 55.23; H, 5.06; N, 2.93. Found: C, 55.14; H, 5.22; N, 2.78.

3.2.2. Compound *2b*

Yield 64%; colorless oil; IR (CH_2Cl_2) 1708, 1342, 1242, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.31 (t, J=7.2 Hz, 3H), 2.41 (s, 3H), 3.66 (d, J=6.3 Hz, 2H), 3.72 (d, J=5.4 Hz, 2H), 4.20 (q, J=7.2 Hz, 2H), 4.26 (s, 2H), 5.38–5.53 (m, 2H), 7.24 (d, J=8.7 Hz, 2H), 7.37–7.44 (m, 5H), 7.56 (d, J=8.7 Hz, 2H), 7.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.18, 21.48, 31.43, 43.36, 49.13, 61.23, 127.48, 127.88, 128.62, 129.15, 129.55, 129.56, 129.74, 130.21, 134.38, 136.00, 143.32, 143.53, 167.37; ESIMS *m/z* 492 (M^++1). Anal. Calcd for $C_{23}H_{26}BrNO_4S$: C, 56.10; H, 5.32; N, 2.84. Found: C, 55.24; H, 5.19; N, 2.71.

3.2.3. Compound *E-2c*

Yield 15%; white solid, mp 100–102 °C; IR (CH_2Cl_2) 2217, 1347, 1160, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 3.67 (d, J=6.3 Hz, 2H), 3.78 (d, J=6.0 Hz, 2H), 4.18 (d, J=1.2 Hz, 2H), 5.47–5.65 (m, 2H), 7.24–7.30 (m, 4H), 7.38 (s, 1H), 7.43–7.45 (m, 3H), 7.68 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.54, 30.76,

43.70, 49.05, 112.32, 118.73, 127.70, 128.65, 128.89, 129.34, 129.78, 130.01, 131.64, 132.88, 135.70, 144.05, 147.28; ESIMS *m/z* 445 (M^++1).

3.2.4. Compound Z-2c

Yield 40%; white solid, mp 96–98 °C; IR (CH_2Cl_2) 2214, 1342, 1159, 1093 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3H), 3.89 (d, J=7.5 Hz, 2H), 3.94 (d, J=6.3 Hz, 2H), 4.12 (s, 2H), 5.61–5.70 (m, 1H), 5.82–5.92 (m, 1H), 7.13 (s, 1H), 7.30 (d, J=8.1 Hz, 2H), 7.42–7.44 (m, 3H), 7.70–7.56 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.53, 30.98, 48.98, 50.38, 105.92, 117.64, 127.44, 128.92, 128.96, 129.06, 129.90, 130.94, 131.85, 132.62, 136.53, 144.02, 146.60; ESIMS *m/z* 445 (M^++1). Anal. Calcd for $C_{21}H_{21}BrN_2O_2S$: C, 56.63; H, 4.75; N, 6.29. Found: C, 56.46; H, 4.91; N, 6.03.

3.2.5. Compound 2d

Yield 63%; colorless oil; IR (CH_2Cl_2) 1734, 1718, 1437, 1264, 1241, 1205 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.41 (d, J=7.5 Hz, 2H), 3.38 (s, 2H), 3.56–3.59 (m, 2H), 3.59 (s, 6H), 3.77 (s, 3H), 4.94–5.04 (m, 1H), 5.42–5.52 (m, 1H), 7.27–7.44 (m, 5H), 7.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.33, 32.27, 35.03, 52.09, 52.32 (2C), 57.59, 128.41, 128.66, 128.72, 128.95, 129.54, 130.21, 135.30, 142.55, 168.33, 170.82 (2C); ESIMS *m/z* 439 (M^++1). Anal. Calcd for $C_{20}H_{23}BrO_6$: C, 54.68; H, 5.28. Found: C, 54.87; H, 5.21.

3.2.6. Compound 2e

Yield 76%; colorless oil; IR (CH_2Cl_2) 1719, 1437, 1340, 1158 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3H), 3.61 (s, 3H), 3.64 (d, J=7.5 Hz, 2H), 3.79 (dd, J=16.5 and 7.2 Hz, 1H), 3.81 (dd, J=16.5 and 7.2 Hz, 1H), 5.12–5.19 (m, 1H), 5.34–5.44 (m, 1H), 5.67 (d, J=1.2 Hz, 1H), 6.12 (s, 1H), 6.43 (d, J=0.9 Hz, 1H), 7.00–7.04 (m, 2H), 7.22–7.26 (m, 3H), 7.28 (d, J=8.1 Hz, 2H), 7.71 (d, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.54, 31.49, 46.86, 52.02, 61.71, 127.54, 127.75, 128.20, 128.53, 128.67, 129.06, 129.54, 131.13, 136.88, 137.61, 139.05, 143.41, 166.21; ESIMS *m/z* 478 (M^++1). Anal. Calcd for $C_{22}H_{24}BrNO_4S$: C, 55.23; H, 5.06; N, 2.93. Found: C, 55.21; H, 4.97; N, 2.61.

3.3. Typical procedure for the synthesis of 3a

To a refluxed solution of **2a** (478 mg, 1.0 mmol) and AIBN (16 mg) in benzene (5 mL) was added *n*-Bu_3SnH (437 mg, 1.5 mmol) slowly and the reaction mixture was heated to reflux for 5 h. After removal of solvent and column chromatographic purification process (hexanes/ether, 4:1) we obtained *syn*-**3a** (228 mg, 57%) and *anti*-**3a** (40 mg, 10%). Other compounds **3b–e** were synthesized analogously and the spectroscopic data are as follows.

3.3.1. Compound syn-3a

Yield 57%; colorless oil; IR (CH_2Cl_2) 1732, 1346, 1165, 1091 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.43 (s, 3H), 2.70 (d, J=13.8 Hz, 1H), 2.78 (dd, J=14.7 and 6.9 Hz, 1H), 3.16 (dd, J=9.9 and 6.9 Hz, 1H), 3.23 (d, J=13.8 Hz, 1H), 3.45 (s, 2H), 3.45 (s, 3H), 3.71 (dd, J=9.9 and 6.9 Hz, 1H), 5.00–5.06 (m, 2H), 5.35–5.47 (m, 1H), 6.97–7.06 (m, 2H), 7.19–7.28 (m, 3H), 7.32 (d, J=8.4 Hz, 2H), 7.71 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.46, 40.72, 50.85, 50.91, 51.22, 51.56, 58.06, 118.38, 126.99, 127.47, 128.43, 129.60, 129.76, 133.91, 134.11, 136.17, 143.39, 171.95; ESIMS *m/z* 400 (M^++1). Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51. Found: C, 66.34; H, 6.29; N, 3.35.

3.3.2. Compound anti-3a

Yield 10%; colorless oil; IR (CH_2Cl_2) 2924, 1731, 1346, 1166, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.44 (s, 3H), 2.62 (d, J=13.5 Hz, 1H), 3.01 (dd, J=14.4 and 7.2 Hz, 1H), 3.05 (d, J=13.5 Hz, 1H), 3.35–3.47 (m, 3H), 3.46 (s, 3H), 3.57 (d, J=10.5 Hz, 1H), 5.12–5.30 (m, 2H), 5.76–5.89 (m, 1H), 6.97–7.00 (m, 2H), 7.20–7.23 (m, 3H), 7.32 (d, J=8.1 Hz, 2H), 7.71 (d, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.69, 37.36, 49.21, 50.69, 51.94, 52.12, 57.32, 118.95, 126.94, 127.57, 128.44, 129.47, 129.66, 133.67, 134.06, 136.61, 143.48, 173.33; ESIMS *m/z* 400 (M^++1). Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51. Found: C, 66.25; H, 6.52; N, 3.43.

3.3.3. Compound syn-3b

Yield 55%; colorless oil; IR (CH_2Cl_2) 1728, 1345, 1163, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02 (t, J=7.2 Hz, 3H), 2.36 (s, 3H), 2.63 (d, J=13.8 Hz, 1H), 2.69 (dd, J=14.4 and 6.6 Hz, 1H), 3.11 (dd, J=10.2 and 6.9 Hz, 1H), 3.16 (d, J=13.8 Hz, 1H), 3.38 (s, 2H), 3.64 (dd, J=10.2 and 6.9 Hz, 1H), 3.83–3.94 (m, 2H), 4.92–4.99 (m, 2H), 5.29–5.42 (m, 1H), 6.94–6.97 (m, 2H), 7.14–7.20 (m, 3H), 7.24 (d, J=8.1 Hz, 2H), 7.64 (d, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.02, 21.46, 40.79, 50.91, 50.96, 51.23, 57.78, 60.81, 118.29, 126.94, 127.44, 128.38, 129.60, 129.81, 133.97, 134.20, 136.25, 143.40, 171.49; ESIMS *m/z* 414 (M^++1). Anal. Calcd for $C_{23}H_{27}NO_4S$: C, 66.80; H, 6.58; N, 3.39. Found: C, 66.63; H, 6.39; N, 3.46.

3.3.4. Compound anti-3b

Yield 10%; colorless oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.06 (t, J=7.2 Hz, 3H), 2.44 (s, 3H), 2.61 (d, J=13.8 Hz, 1H), 3.01 (dd, J=14.7 and 6.6 Hz, 1H), 3.05 (d, J=13.8 Hz, 1H), 3.40–3.46 (m, 3H), 3.59 (d, J=10.2 Hz, 1H), 3.83–4.04 (m, 2H), 5.11–5.25 (m, 2H), 5.79–5.89 (m, 1H), 6.96–7.05 (m, 2H), 7.19–7.26 (m, 3H), 7.32 (d, J=8.1 Hz, 2H), 7.72 (d, J=8.1 Hz, 2H); ESIMS *m/z* 414 (M^++1). Anal. Calcd for $C_{23}H_{27}NO_4S$: C, 66.80; H, 6.58; N, 3.39. Found: C, 66.95; H, 6.26; N, 3.31.

3.3.5. Compound syn-3c

Colorless oil; IR (CH_2Cl_2) 2238, 1348, 1166, 1091 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.42 (s, 3H), 2.70 (d, J=13.8 Hz, 1H), 2.70 (dd, J=18.0 and 8.1 Hz, 1H), 3.02 (d, J=13.8 Hz, 1H), 3.20 (dd, J=10.2 and 7.8 Hz, 1H), 3.45

(d, J=11.1 Hz, 1H), 3.51 (d, J=11.1 Hz, 1H), 3.70 (dd, J=10.2 and 7.8 Hz, 1H), 5.24–5.36 (m, 2H), 5.68–5.81 (m, 1H), 7.18–7.21 (m, 2H), 7.30–7.34 (m, 5H), 7.68 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.53, 40.36, 48.41, 50.83, 51.09, 55.71, 119.24, 121.74, 127.36, 127.87, 128.84, 129.64, 129.91, 131.62, 133.47, 134.12, 144.10; ESIMS *m/z* 367 (M^++1). Anal. Calcd for $C_{21}H_{22}N_2O_2S$: C, 68.82; H, 6.05; N, 7.64. Found: C, 68.97; H, 6.32; N, 7.59.

3.3.6. Compound anti-**3c**

Colorless oil; IR (CH_2Cl_2) 2239, 1350, 1167, 1092 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.45 (s, 3H), 2.65 (d, J=13.5 Hz, 1H), 2.88 (d, J=13.5 Hz, 1H), 3.07 (dd, J=15.6 and 7.8 Hz, 1H), 3.17 (d, J=10.2 Hz, 1H), 3.53 (dd, J=10.2 and 8.1 Hz, 1H), 3.56 (dd, J=10.2 and 8.1 Hz, 1H), 3.59 (d, J=10.2 Hz, 1H), 5.30–5.40 (m, 2H), 5.71–5.83 (m, 1H), 7.20–7.23 (m, 2H), 7.30–7.40 (m, 5H), 7.71 (d, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.56, 36.02, 46.67, 49.80, 50.86, 53.20, 120.43, 121.35, 127.42, 127.77, 128.80, 129.99 (2C), 130.80, 133.53, 134.46, 144.21; ESIMS *m/z* 367 (M^++1). Anal. Calcd for $C_{21}H_{22}N_2O_2S$: C, 68.82; H, 6.05; N, 7.64. Found: C, 68.74; H, 6.22; N, 7.33.

3.3.7. Compound syn-**3d**

Yield 36%; colorless oil; IR (CH_2Cl_2) 1738, 1731, 1454, 1434, 1260, 1198 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.29 (dd, J=13.8 and 6.6 Hz, 1H), 2.42 (d, J=12.0 Hz, 1H), 2.51 (d, J=14.7 Hz, 1H), 2.62–2.69 (m, 1H), 2.66 (d, J=13.5 Hz, 1H), 2.77 (d, J=14.7 Hz, 1H), 3.38 (d, J=13.5 Hz, 1H), 3.60 (s, 3H), 3.70 (s, 3H), 3.72 (s, 3H), 5.11–5.18 (m, 2H), 5.67–5.79 (m, 1H), 7.15–7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 38.18, 41.14, 41.93, 51.38, 52.72, 53.00, 53.49, 57.99, 58.44, 117.12, 126.50, 128.16, 129.92, 135.85, 137.73, 172.08, 173.52, 174.16; ESIMS *m/z* 361 (M^++1). Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.54; H, 6.97.

3.3.8. Compound anti-**3d**

Yield 45%; colorless oil; IR (CH_2Cl_2) 1737, 1731, 1454, 1434, 1259, 1199 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.23 (dd, J=13.8 and 8.7 Hz, 1H), 2.53 (d, J=13.8 Hz, 1H), 2.60 (d, J=15.0 Hz, 1H), 2.66 (dd, J=13.8 and 8.7 Hz, 1H), 2.83 (d, J=15.0 Hz, 1H), 3.03 (dd, J=15.9 and 7.8 Hz, 1H), 3.13 (d, J=13.8 Hz, 1H), 3.61 (s, 3H), 3.70 (s, 3H), 3.75 (s, 3H), 5.11–5.21 (m, 2H), 5.93–6.06 (m, 1H), 7.08–7.11 (m, 2H), 7.15–7.26 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.96, 39.07, 39.23, 51.14, 51.79, 52.85, 52.92, 57.82, 57.83, 117.27, 126.51, 128.17, 129.65, 136.20, 137.66, 172.37, 172.77, 175.42; ESIMS *m/z* 361 (M^++1). Anal. Calcd for $C_{20}H_{24}O_6$: C, 66.65; H, 6.71. Found: C, 66.51; H, 6.89.

3.3.9. Compound **3e**

Yield 64%; colorless oil; IR (CH_2Cl_2) 1734, 1341, 1162 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.84 (dd, J=26.4 and 12.9 Hz, 1H), 2.07 (d, J=14.7 Hz, 1H), 2.14–2.24 (m, 1H), 2.39 (s, 3H), 2.62 (dd, J=13.8 and 12.0 Hz, 1H), 2.88 (ddd, J=12.6, 5.4 and 3.6 Hz, 1H), 3.58 (s, 3H), 3.82 (dd, J=13.8 and 4.2 Hz, 1H), 5.02–5.09 (m, 2H), 5.55–5.65 (m, 1H), 5.67 (d, J=5.4 Hz, 1H), 7.20–7.22 (m, 7H), 7.61 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.43, 26.63, 38.67, 43.61, 45.37, 51.87, 55.77, 115.75, 126.94, 127.54, 128.16, 128.37, 129.63, 136.75, 137.41, 138.18, 143.22, 172.21; ESIMS *m/z* 400 (M^++1). Anal. Calcd for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51. Found: C, 66.23; H, 6.56; N, 3.43.

3.4. Synthesis of compound cis-**2f**

A mixture of Baylis–Hillman adduct **1f** (384 mg, 2.0 mmol), *cis*-1,4-butenediol (1.0 mL), and montmorillonite K10 (1.15 g) was heated to 100 °C for 3 h.[11] After cooling to room temperature, dilution with CH_2Cl_2, passing through a pad of Celite, and column chromatographic purification process (hexanes/ether, 1:1) we obtained alcohol **5** (157 mg, 30%). To a stirred solution of alcohol **5** (131 mg, 0.5 mmol) in CH_2Cl_2 (1.0 mL) was added a solution of PBr_3 (203 mg, 1.5 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C, and stirred further for 2 h. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 6:1) we obtained *cis*-**2f** (82 mg, 50%) as colorless oil.

3.4.1. Compound **5**

Yield 30%; colorless oil; IR (CH_2Cl_2) 3436, 1715, 1436, 1238, 1204, 1117 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.84 (s, 3H), 4.17 (d, J=6.0 Hz, 2H), 4.21 (d, J=6.0 Hz, 2H), 4.31 (s, 2H), 5.66–5.91 (m, 2H), 7.38–7.45 (m, 3H), 7.49–7.54 (m, 2H), 7.93 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.23, 58.58, 64.30, 65.97, 128.09, 128.46, 128.52, 129.43, 129.77, 132.71, 134.56, 144.87, 168.11; ESIMS *m/z* 263 (M^++1).

3.4.2. Compound cis-**2f**

Yield 50%; colorless oil; IR (CH_2Cl_2) 1717, 1436, 1237, 1204, 1116 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.85 (s, 3H), 4.02 (d, J=8.4 Hz, 2H), 4.23 (dd, J=6.3 and 1.2 Hz, 2H), 4.32 (s, 2H), 5.75–5.83 (m, 1H), 5.86–5.96 (m, 1H), 7.38–7.45 (m, 3H), 7.51–7.54 (m, 2H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.35, 52.18, 64.61, 65.46, 128.45, 128.50, 128.52, 129.40, 129.76, 131.03, 134.59, 144.80, 167.94; ESIMS *m/z* 325 (M^++1). Anal. Calcd for $C_{15}H_{17}BrO_3$: C, 55.40; H, 5.27. Found: C, 55.54; H, 5.12.

3.5. Synthesis of compound trans-**2f**

A mixture of Baylis–Hillman adduct **1f** (384 mg, 2.0 mmol), allyl alcohol (0.5 mL), and montmorillonite K10 (1.15 g) was heated to 100 °C for 3 h.[11] After cooling to room temperature, dilution with CH_2Cl_2, passing through a pad of Celite, and column chromatographic purification process (hexanes/ether, 25:1) we obtained alcohol **6** (241 mg, 52%). A mixture of compound **6** (232 mg, 1.0 mmol), allyl bromide (302 mg, 2.5 mmol), and second-generation Grubbs catalyst (42 mg, 5 mol %) in CH_2Cl_2 (50 mL) was heated to reflux for 4 h. After removal of solvent and column

chromatographic purification process (hexanes/ether, 10:1) we obtained *trans*-**2f** (146 mg, 45%) as colorless oil.

3.5.1. Compound *trans*-**2f**

Yield 45%; colorless oil; IR (CH_2Cl_2) 1714, 1435, 1237, 1204, 1115 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.85 (s, 3H), 3.95 (d, J=5.7 Hz, 2H), 4.11 (d, J=4.2 Hz, 2H), 4.31 (s, 2H), 5.86–6.01 (m, 2H), 7.36–7.45 (m, 3H), 7.50–7.54 (m, 2H), 7.94 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.92, 52.20, 64.38, 69.94, 128.54, 128.56, 128.90, 129.41, 129.80, 131.58, 134.67, 144.80, 168.01; ESIMS *m/z* 325 (M^++1). Anal. Calcd for $C_{15}H_{17}BrO_3$: C, 55.40; H, 5.27. Found: C, 55.61; H, 5.23.

3.6. Radical cyclization of compound **2f**

Radical cyclizations of compounds *cis*-**2f** and *trans*-**2f** were carried out similarly to that of compound **3a** and the spectroscopic data of products are as follows.

3.6.1. Compound *syn*-**3f**

Colorless oil; IR (CH_2Cl_2) 1731, 1204 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.80 (s, J=13.5 Hz, 1H), 2.86 (dd, J=15.9 and 6.9 Hz, 1H), 3.34 (d, J=13.5 Hz, 1H), 3.66 (s, 3H), 3.73 (dd, J=9.0 and 6.6 Hz, 1H), 3.85 (d, J=9.3 Hz, 1H), 4.07–4.15 (m, 2H), 5.11–5.18 (m, 2H), 5.64–5.76 (m, 1H), 7.06–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 40.95, 51.53, 53.37, 59.19, 71.85, 71.95, 117.92, 126.76, 128.32, 129.72, 134.89, 137.11, 172.77; ESIMS *m/z* 247 (M^++1). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.02; H, 7.44.

We could not separate *syn*-**3f** and *anti*-**3f** in pure states at this stage, unfortunately. Thus, the ratio of *syn*-**3f**/*anti*-**3f** (ca. 85:15, Scheme 2) and the NMR data were determined from the spectra of mixture.

3.6.2. Compound *anti*-**3f**

^1H NMR ($CDCl_3$, 300 MHz) δ 2.70 (d, J=13.5 Hz, 1H), 3.16 (d, J=13.5 Hz, 1H), 3.20 (dd, J=15.3 and 7.8 Hz, 1H), 3.63 (s. 3H), 3.78–3.82 (m, 2H), 4.03–4.18 (m, 2H), 5.23–5.28 (m, 2H), 5.89–6.01 (m, 1H), 7.06–7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.06, 51.00, 51.88, 58.05, 71.65, 72.78, 118.58, 126.67, 128.30, 129.40, 134.22, 137.44, 174.37.

3.6.3. Compound **4**[12]

Yield 44%; colorless oil; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.12 (d, J=1.5 Hz, 3H), 3.82 (s, 3H), 7.29–7.40 (m, 5H), 7.69 (d, J=1.5 Hz, 1H).

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