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## REGIOSELECTIVE RING-OPENING REACTION OF 2-MONO-SUBSTITUTED AZETIDIN-3-ONES PROMOTED BY THE COMBINED USE OF TITANIUM TETRAIODIDE AND ITS CHLORO OR BROMO COUNTERPART

Shingo Hata, Daisuke Fukuda, Iwao Hachiya, and Makoto Shimizu\*

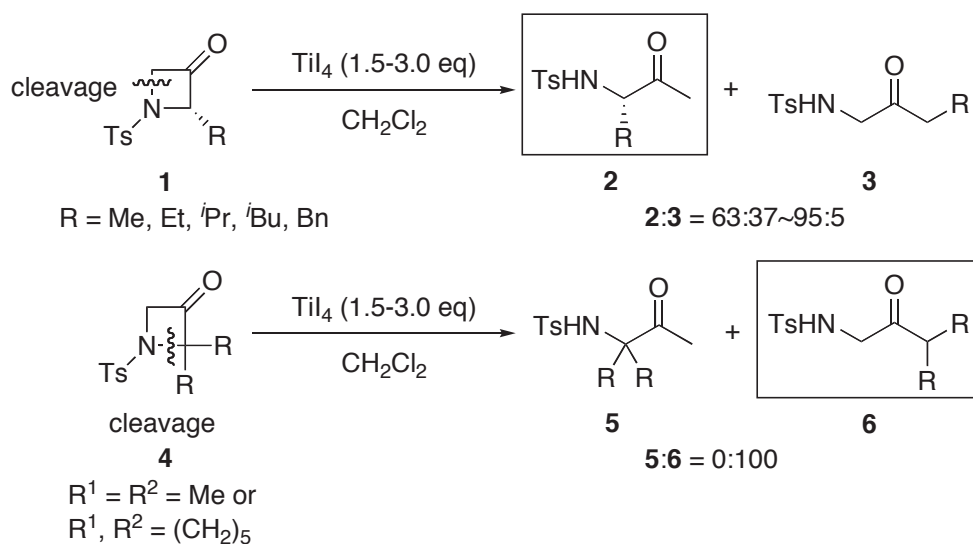
Department of Chemistry for Materials, Graduate School of Engineering, Mie University, Tsu, Mie 514-8507, Japan. E-mail: mshimizu@chem.mie-u.ac.jp

This paper is dedicated to Professor Albert Padwa on the occasion of his 75th birthday.

**Abstract** – The ring-opening reaction of 2-mono-substituted azetidin-3-ones at the more substituted bond occurred with the combined use of  $TiI_4$  and  $TiCl_4$  to give the corresponding ketones in moderate to high yields with high regioselectivity. The reductive aldol reaction of the enolate thus prepared proceeded with chloral in the presence of  $Pd(O_2CCF_3)_2$  to give the *syn*-aldol adduct in moderate yield.

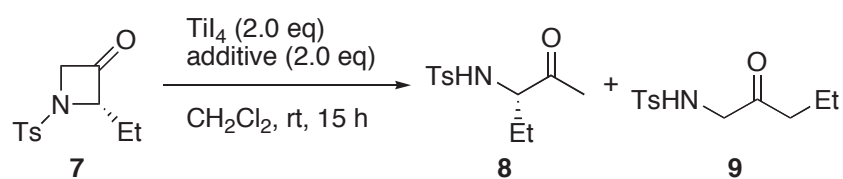
Azetidines are four-membered cycles including one nitrogen atom. Among them, most representative derivatives are azetidin-2-ones such as penicillin, cepharosporin, and thienamycin, etc. On the other hand, azetidin-3-ones have not been well studied because azetidin-3-ones do not exist in nature. However, azetidin-3-ones are proposed as intermediates for the synthesis of natural products or biologically active compounds containing an azetidine ring.<sup>1,2</sup> We have reported titanium tetraiodide promoted aldol and Mannich-type reactions by the reductive generation of enolates *via* ring-opening of aziridines bearing carbonyl groups such as alkoxy-carbonyls or keto carbonyls to give adducts in good to excellent yields.<sup>3</sup> Aza-aldol reaction has also been reported using reductive ring-opening of 2-(1-benzyloxyiminoethyl)-aziridine to afford  $\alpha$ -aminomethyl- $\beta$ -hydroxy ketone *O*-alkyl oximes in good to high yields with *anti*-selectivities.<sup>4</sup> In these reactions, it is crucial that the regioselective ring opening reaction of aziridines followed by reductive enolate formations, which are regarded as  $\beta$ -amino carbonyl compounds synthons. We next examined the reaction of azetidin-3-ones with  $TiI_4$  and found that the enolates were readily

prepared followed by the subsequent aldol or Mannich-type reactions.<sup>5</sup> In the reductive ring-opening reaction of 2-mono-substituted azetidin-3-ones, C-N bond cleavages occurred at the less sterically congested bond to give the ketone **2** preferentially. On the other hand, C-N bond cleavages of 2,2-disubstituted azetidin-3-ones proceeded at the more substituted bond to afford the only ketone **6** (Scheme 1). Regarding the different regioselectivity, we proposed two different pathways including S<sub>N</sub>2-like process by TiI<sub>4</sub> or a one-electron transfer promoted by low-valent titanium species, which were in situ generated *via* the disproportionation of TiI<sub>4</sub>. In order to realize the ring-opening reaction of 2-mono-substituted azetidin-3-ones at the more substituted bond, several conditions were examined. Herein, we describe regioselective ring-opening of 2-mono-substituted azetidin-3-ones with a combined use of TiI<sub>4</sub> and titanium chloride or bromide.



**Scheme 1.** Regioselective Ring-opening of Azetidin-3-ones Using TiI<sub>4</sub>

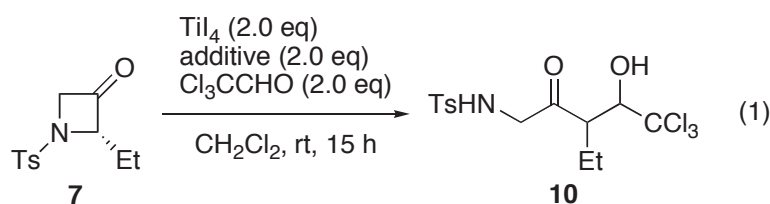
**Table 1.** Effects of Additives



Entry	Additive	Yield (%) <sup>a</sup>	<b>8:9</b> <sup>b</sup>	Entry	Additive	Yield (%) <sup>a</sup>	<b>8:9</b> <sup>b</sup>
1	none	66	83:17	6	AlI <sub>3</sub>	57	74:26
2	Al powder	29	4:96	7	AlBr <sub>3</sub>	60	5:95
3	DIBAL	0	—	8	AlCl <sub>3</sub>	51	5:95
4	LiAlH <sub>4</sub>	31	87:13	9	Et <sub>2</sub> AlCl	45	70:30
5	Zn/Cu	87	85:15	10	EtAlCl <sub>2</sub>	76	14:86

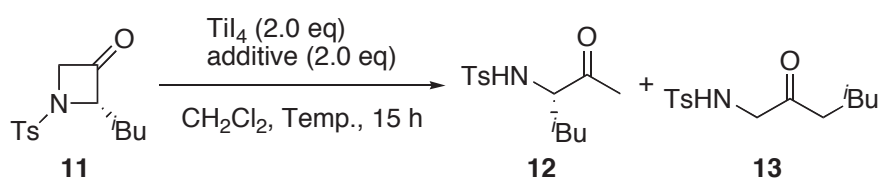
<sup>a</sup>Each regioisomer was not separated. <sup>b</sup>Ratios were determined by <sup>1</sup>H NMR spectra.

First, effects of additives to reduce  $TiI_4$  to low-valent titanium species were examined in the model reaction of 2-mono-substituted azetidin-3-one **7**, which is the most suitable substrate for the reductive aldol reaction.<sup>5</sup> Although among them, Al powder was effective for the regioselectivity, the yield was low (entries 1-5 in Table 1). We next investigated several aluminum reagents. When  $AlBr_3$ ,  $AlCl_3$ , and  $EtAlCl_2$  were used, ketone **9** was obtained in moderate yield with good regioselectivity (entries 6-10).<sup>6</sup> The reductive aldol reaction of azetidin-3-one **7** with chloral was carried out with a combined use of  $TiI_4$  and  $AlBr_3$ ,  $AlCl_3$ , or  $EtAlCl_2$ . No desired aldol adduct **10** was obtained, and instead, those reactions gave ketones **8** and **9** or complex mixtures (Eq. 1).



Effects of other additives were investigated in the reaction of 2-mono-substituted azetidin-3-one **11**. Table 2 summarizes the results. Among additives tested at room temperature,  $TiBr_4$  and  $TiCl_4$  were found to be efficient in both yields and regioselectivities (entries 5 and 6). The ring-opening reaction of **11** with a combined use of  $TiI_4$  and  $TiBr_4$  or  $TiCl_4$  at lower temperatures gave the desired ketone in high yields with good to high selectivities (entries 7 and 8).<sup>7</sup>

**Table 2.** Effects of Additives

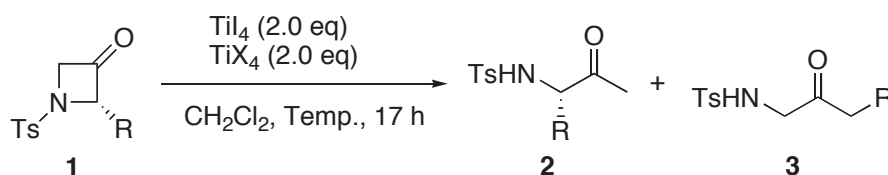


Entry	Additive	Temp.	Yield (%) <sup>a</sup>	<b>12:13</b> <sup>b</sup>
1	none	0 °C to rt	97	63:37
2	<i>i</i> Pr <sub>3</sub> SiOTf	rt	43	17:83
3	Ti(O <i>i</i> Pr) <sub>4</sub>	rt	complex mixture	–
4	Cp <sub>2</sub> TiCl <sub>2</sub>	rt	43	11:89
5	TiBr <sub>4</sub>	rt	72	26:74
6	TiCl <sub>4</sub>	rt	61	9:91
7	TiBr <sub>4</sub>	–20 to 10 °C	90	16:84
8	TiCl <sub>4</sub>	–78 °C to rt	88	0:100

<sup>a</sup>Each regioisomer was not separated. <sup>b</sup>Ratios were determined by <sup>1</sup>H NMR spectra.

The reductive ring-opening reactions of several 2-mono-substituted azetidin-3-ones **1** were examined using  $\text{TiI}_4$ - $\text{TiBr}_4$  or  $\text{TiCl}_4$ . Table 3 summarizes the results. When  $\text{TiBr}_4$  was used as an additive, the reductive ring-opening reaction of several 2-mono-substituted azetidin-3-ones regioselectively proceeded to give ketones in low to moderate yields (entries 1-3). Yields were improved using  $\text{TiCl}_4$  as an additive to give ketones in moderate to high yields with high regioselectivities (entries 4-6).

**Table 3.** Reductive Ring-opening Reaction of Several 2-Mono-substituted Azetidin-3-ones



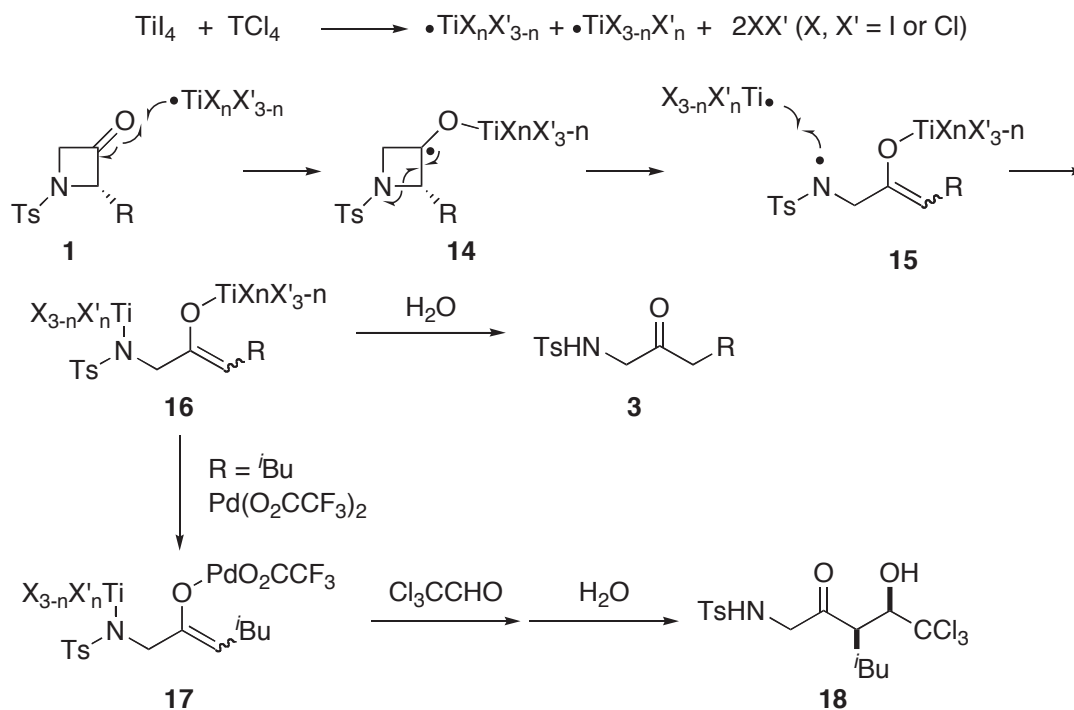
Entry	R	X	Temp.	Yield (%) <sup>a</sup>	2:3 <sup>b</sup>
1	Me	Br	-78 °C to rt	26	25:75
2	Et	Br	-78 °C to rt	30	4:96
3	<sup>i</sup> Pr	Br	-78 °C to rt	56	0:100
4	Me	Cl	0 °C to rt	63	9:91
5	Et	Cl	0 °C to rt	78	4:96
6 <sup>c</sup>	<sup>i</sup> Pr	Cl	-20 to 10 °C	84	0:100

<sup>a</sup>Each regioisomer was not separated. <sup>b</sup>Ratios were determined by <sup>1</sup>H NMR spectra. <sup>c</sup>The reaction was carried out for 21 h.

A plausible reaction mechanism is shown in Scheme 2. The disproportion of titanium tetraiodide and tetrachloride gives low-valent titanium species. A one-electron transfer to 2-mono-substituted azetidin-3-one **1** at the C-3 position gives a radical intermediate **14**. The ring-opening reaction of **14** would proceed by fragmentation at the N-C(2) bond to give the more substituted titanium enolate **16**, which is more stable than the less substituted one, and the subsequent protonation with water to quench the reaction would give the corresponding ketone **3**.

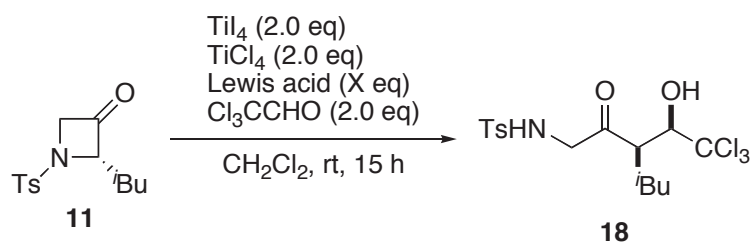
Finally, we examined the reductive aldol reaction of the more substituted titanium enolate generated in situ with an aldehyde. The reaction of 2-mono-substituted azetidin-3-one **11** with chloral was carried out using  $\text{TiI}_4$ - $\text{TiCl}_4$  to give the aldol adduct **18** in 24% yield along with the reduction product **13** in 64% yields (Table 4, entry 1). To improve the yield, several Lewis acids were investigated as an additive (entries 2-7). Among metal salts examined,  $\text{PdCl}_2$  was slightly effective, and therefore, several palladium salts were examined (entries 8-12). As a result,  $\text{Pd}(\text{O}_2\text{CCF}_3)_2$  was found to be the most effective to give the aldol adduct in 66% yield with *syn*-selectivity.<sup>8</sup> Although the role of  $\text{Pd}(\text{O}_2\text{CCF}_3)_2$  is not yet clear, we

presumed that a transmetallation of titanium to palladium would occur to generate the palladium enolate **17**, which would be responsible for the improvement of the yield under the present conditions.



**Scheme 2.** Plausible Reaction Mechanism

**Table 4.** Reductive Aldol Reaction of 2-Mono-substituted Azetidin-3-one **11**



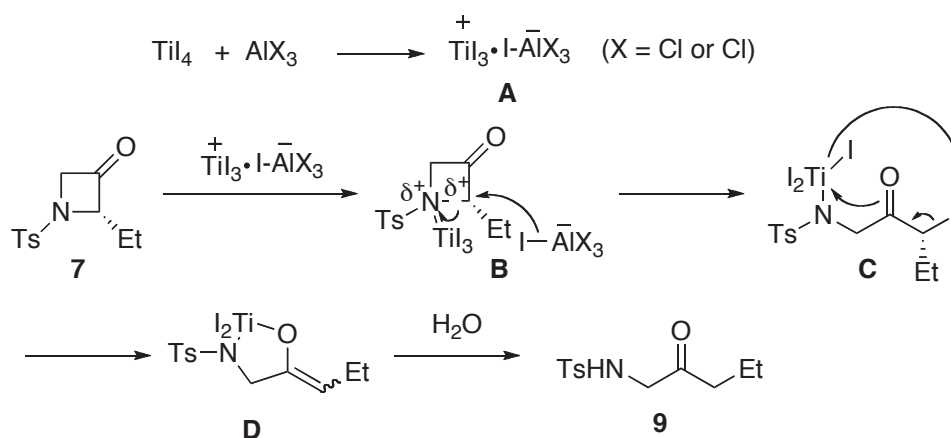
Entry	Lewis acid (eq)	Yield (%) <sup>a</sup>	Entry	Lewis acid (eq)	Yield (%) <sup>a</sup>
1	none	24	7	PdCl <sub>2</sub> (1.0)	27
2	InCl <sub>3</sub> (2.0)	11	8	PdCl <sub>2</sub> (CH <sub>3</sub> CN) <sub>2</sub> (1.0)	16
3	ZnCl <sub>2</sub> (2.0)	13	9	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> (1.0)	27
4	FeCl <sub>3</sub> (2.0)	9	10	Pd(OAc) <sub>2</sub> (1.0)	30
5	ZrCl <sub>4</sub> (2.0)	13	11 <sup>b</sup>	Pd(OAc) <sub>2</sub> (1.0)	47
6	Eu(fod) <sub>3</sub> (2.0)	0	12 <sup>b</sup>	Pd(O <sub>2</sub> CCF <sub>3</sub> ) <sub>2</sub> (1.0)	66 (64) <sup>c</sup>

<sup>a</sup>Isolated yield. <sup>b</sup>The reaction was carried out at 0 °C to room temperature. <sup>c</sup>Pd(O<sub>2</sub>CCF<sub>3</sub>)<sub>2</sub> (0.50 eq) was used.

In conclusion, we found that the ring-opening reaction of 2-mono-substituted azetidin-3-ones occurred at the more substituted bonds using  $\text{TiI}_4$ - $\text{TiCl}_4$  to give the corresponding ketones in moderate to high yields with high regioselectivity and also that the subsequent reductive aldol reaction with chloral proceeded in the presence of  $\text{Pd}(\text{O}_2\text{CCF}_3)_2$  to give the *syn*-aldol adduct in moderate yield.

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- 6.



**Scheme 3.** Plausible Reaction Mechanism

Although the roles of  $\text{AlCl}_3$ ,  $\text{AlBr}_3$ , and  $\text{EtAlCl}_2$  are not yet clear, we presume a mechanism as shown in Scheme 3. First, the reaction of  $\text{TiI}_4$  with aluminum salts may produce a more Lewis acidic titanium species **A**, which in turn activates the tosylamide nitrogen. An  $\text{S}_{\text{N}}2$ -like reaction occurs at the carbon having a partially positive charge to generate the iodo ketone **C** and the subsequent reaction with another iodide anion effects formation of a titanium enolate species **D**, and the protonation with water to quench the reaction would give ketone **9**. On the other hand,  $\text{AlI}_3$  and  $\text{Et}_2\text{AlCl}$  were not effective because they are less Lewis acidic compared to the above aluminum salts

and would not generate any complex like **A**.

7. **Typical procedure (Table 2, entry 8):** To  $\text{TiI}_4$  (222 mg, 0.40 mmol) was added  $\text{TiCl}_4$  (0.04 mL, 0.4 mmol) and  $\text{CH}_2\text{Cl}_2$  (1.0 mL) at room temperature. The mixture was cooled to  $-78\text{ }^\circ\text{C}$  and to it was added a solution of (*S*)-2-isobutyl-*N-p*-tosylazetid-3-one (**11**) (56.2 mg, 0.20 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL) at  $-78\text{ }^\circ\text{C}$ . The resulting mixture was gradually warmed up to room temperature during 15 h and sat. aq.  $\text{NaHCO}_3$ , EtOAc (5.0 mL), and 10% aq.  $\text{NaHSO}_3$  were added to quench the reaction. The mixture was filtrated through a Celite pad. The layers were separated and the aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic extracts were washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo to give a crude product. Purification on silica gel TLC (*n*-hexane/ $\text{CH}_2\text{Cl}_2$ / $\text{Et}_2\text{O}$  = 5/3/2) gave 5-methyl-1-(tosylamino)hexan-2-one (**13**) (24.9 mg, 88%). White solid. Mp  $82\text{-}83\text{ }^\circ\text{C}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.83 (d,  $J$  = 6.4 Hz, 6H), 1.34-1.49 (m, 3H), 2.33 (t,  $J$  = 7.8 Hz, 2H), 2.42 (s, 3H), 3.83 (d,  $J$  = 4.5 Hz, 2H), 5.39 (t,  $J$  = 4.5 Hz, 1H), 7.28-7.31 (m, 2H), 7.72-7.75 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 21.5, 22.1, 27.5, 32.2, 38.1, 51.2, 127.2, 129.7, 136.0, 143.7, 204.0. IR (KBr): 3464, 2953, 2871, 1719, 1495, 1467, 1405, 1370, 1346, 1323, 1159, 1119, 1092, 1064, 1019, 849, 812, 674  $\text{cm}^{-1}$ . HRMS (EI): Calcd for  $\text{C}_{14}\text{H}_{21}\text{NO}_3\text{S}$  (M) $^+$  283.1242, found 283.1246.
8. **Typical procedure (Table 4, entry 12):** To a mixture of  $\text{TiI}_4$  (111 mg, 0.20 mmol),  $\text{TiCl}_4$  (0.02 mL, 0.2 mmol), and  $\text{Pd}(\text{O}_2\text{CCF}_3)_2$  (33.2 mg, 0.10 mmol) was added  $\text{CH}_2\text{Cl}_2$  (1.0 mL) at room temperature. The mixture was cooled to  $0\text{ }^\circ\text{C}$  and to it was added successively a solution of (*S*)-2-isobutyl-*N-p*-tosylazetid-3-one (**11**) (28.1 mg, 0.10 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL) and that of chloral (29.4 mg, 0.20 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL) at  $0\text{ }^\circ\text{C}$ . The resulting mixture was gradually warmed up to room temperature during 15 h and sat. aq.  $\text{NaHCO}_3$ , EtOAc (5.0 mL), and 10% aq.  $\text{NaHSO}_3$  were added successively to quench the reaction. The mixture was filtrated through a Celite pad. The layers were separated and the aqueous layer was extracted with EtOAc (20 mL x 3). The combined organic extracts were washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and concentrated in vacuo to give a crude product. Purification on silica gel TLC (*n*-hexane/ $\text{CH}_2\text{Cl}_2$ / $\text{Et}_2\text{O}$  = 2/3/2, twice) gave (*R* $^*$ )-3-((*R* $^*$ )-2,2,2-trichloro-1-hydroxyethyl)-5-methyl-1-(tosylamino)hexan-2-one (**18**) (28.5 mg, 66%). White solid. Mp  $99\text{-}100\text{ }^\circ\text{C}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 0.88 (d,  $J$  = 6.4 Hz, 3H), 0.92 (d,  $J$  = 6.6 Hz, 3H), 1.31-1.37 (m, 1H), 1.40-1.50 (m, 1H), 1.58-1.65 (m, 1H), 2.43 (s, 3H), 3.31 (ddd,  $J$  = 1.7, 6.3, 8.0 Hz, 1H), 3.98 (dd,  $J$  = 4.4, 20.0 Hz, 1H), 4.04 (dd,  $J$  = 4.4, 20.0 Hz, 1H), 4.11 (dd,  $J$  = 1.7, 9.0 Hz, 1H), 4.79 (d,  $J$  = 9.0 Hz, 1H), 5.28 (t,  $J$  = 4.4, Hz, 1H), 7.29-7.31 (m, 2H), 7.72-7.74 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 21.5, 21.9, 22.5, 25.4, 40.0, 44.8, 52.8, 85.2, 102.4, 127.3, 129.8, 135.9, 144.1, 209.0. IR (KBr): 3478, 3278, 2933, 2870, 1703, 1321, 1166, 1096, 934, 809, 782, 662, 588  $\text{cm}^{-1}$ . HRMS (EI): Calcd for  $\text{C}_{16}\text{H}_{22}\text{Cl}_3\text{NO}_4\text{S}$  (M) $^+$  429.0335, found 429.0346.