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## **$\beta$ -TRICHLOROACETYLATION OF CYCLIC AMINES: APPLICATION TO SYNTHESIS OF CHIRAL AZABICYCLO-*N*-OXYLS**

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**Abstract** –  $\beta$ -Trichloroacetylation of cyclic amines was developed under mild reaction conditions, and the desired trichloroacetylated products were obtained in good yields. This method was applied to the preparation of optically active azabicyclo compounds, which were converted to chiral azabicyclo-*N*-oxyls.

### **INTRODUCTION**

Trichloroacetyl moiety is known as a key structure in biologically active agents and a useful acyl chloride surrogate due to its balanced features in reactivity and stability.<sup>1,2</sup> In spite of its wide application possibility,<sup>2</sup> the introduction method of trichloroacetyl group has been still developing,<sup>3</sup> in which inert or harsh reaction conditions were required in most cases. Recently, Lee and co-workers reported metal-free synthesis of 2,2,2-trichloroacetophenone derivatives under mild conditions.<sup>3d</sup> While trichloroacetyl group has been successfully introduced to heteroaryl compounds,<sup>4</sup> *C*-trichloroacetylation of cyclic amines is particularly quite rare although cyclic amines are one of highly important structures in synthetic organic chemistry.<sup>5,6</sup> On the other hand, azabicyclo frameworks are also key substructures and intermediates of bioactive compounds and chiral *N*-oxyl catalysts.<sup>7,8</sup> Herein, we report  $\beta$ -trichloroacetylation of cyclic amines and its application to synthesis of chiral azabicyclo-*N*-oxyls.

### **RESULTS AND DISCUSSION**

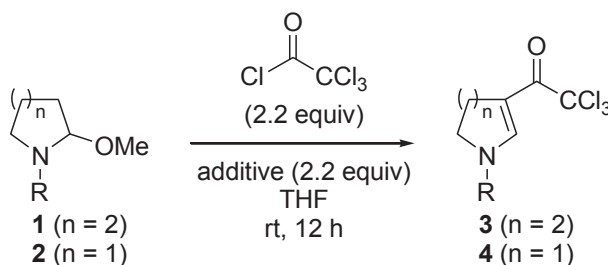
At the outset, protective groups were examined in the  $\beta$ -trichloroacetylation of 2-methoxypiperidine derivatives with trichloroacetyl chloride at room temperature (Table 1), in which enamides or enecarbamates would be produced, leading to acylation at the  $\beta$ -position.<sup>5a</sup> *N*-Methoxycarbonyl-2-methoxypiperidine (**1a**) was converted into trichloroacetylated product **3a** in 53% yield without Lewis acids or

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Dedicated with respect to Dr. Tohru Fukuyama on the occasion of his 70th birthday

additives (entry 1). Increase in amount of trichloroacetyl chloride gave the desired product in 70% yield (entry 2). The use of *tert*-butoxycarbonyl group as a protective unit led to 81% yield, but 5 equivalents of trichloroacetyl chloride afforded a lower yield (entries 3 and 4). In the trichloroacetylation reaction with 2-methyl-2-butene as a proton scavenger, the desired product was obtained in 88% yield (entry 5). Substrates protected with benzyloxycarbonyl or benzoyl group provided significant decreases in yield (entries 6 and 7). Then, *N*-methoxycarbonyl-2-methoxypyrrolidine (**2a**) was examined, giving product **4a** in 36% yield (entry 8). While 2-methoxypyrrolidine bearing *tert*-butoxycarbonyl group led to 41% yield (entry 9), the introduction of trichloroacetyl group with 2-methyl-2-butene afforded 61% yield (entry 10).

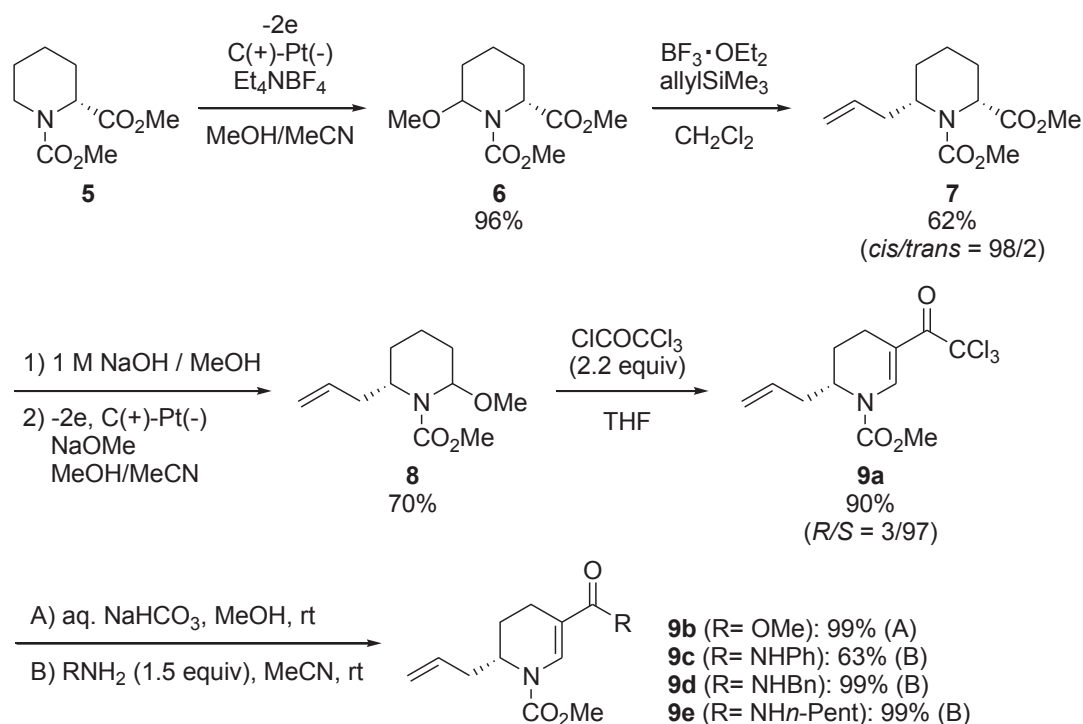
**Table 1.**  $\beta$ -Trichloroacetylation of cyclic amines with trichloroacetyl chloride



entry	n	R	additive	yield (%)
1	2	CO <sub>2</sub> Me	( <b>1a</b> )	53 ( <b>3a</b> )
2 <sup>a</sup>	2	CO <sub>2</sub> Me	( <b>1a</b> )	70 ( <b>3a</b> )
3	2	Boc	( <b>1b</b> )	81 ( <b>3b</b> )
4 <sup>a</sup>	2	Boc	( <b>1b</b> )	76 ( <b>3b</b> )
5	2	Boc	( <b>1b</b> ) 2-Me-2-butene	88 ( <b>3b</b> )
6	2	Cbz	( <b>1c</b> )	33 ( <b>3c</b> )
7	2	COPh	( <b>1d</b> )	30 ( <b>3d</b> )
8	1	CO <sub>2</sub> Me	( <b>2a</b> )	36 ( <b>4a</b> )
9	1	Boc	( <b>2b</b> )	41 ( <b>4b</b> )
10	1	Boc	( <b>2b</b> ) 2-Me-2-butene	61 ( <b>4b</b> )

<sup>a</sup> ClCOCCl<sub>3</sub> (5 equiv).

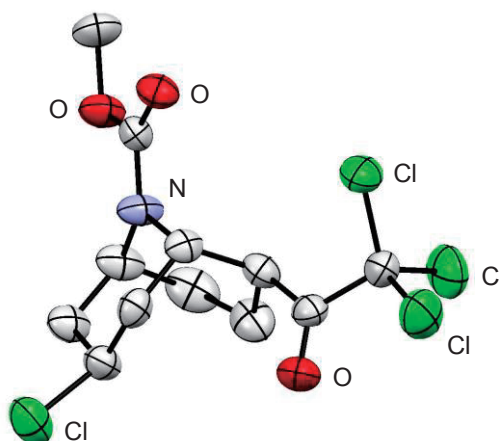
Subsequently, key intermediates for synthesis of azabicyclo frameworks were steadily prepared shown in Scheme 1. After electrochemical methoxylation of D-pipecolic acid derivative **5** was conducted efficiently, 6-methoxypipecolate **6** was converted into 6-allylated pipecolate **7** in 62% yield with high diastereoselectivity. In hydrolysis of an ester moiety followed by electrochemical methoxylation, the desired product **8** was obtained in 70% yield. Then,  $\beta$ -trichloroacetylation reaction was successfully carried out to give key intermediate **9a** in high yield. Trichloroacetyl group in **9a** was readily transformed into an ester moiety or a few kinds of amide group in good to high yields.

Scheme 1. Synthesis of intermediates **9**

Lewis acid-mediated cyclization with chiral piperidine derivatives **9a-e** were examined to construct azabicyclo frameworks (Table 2).<sup>8c</sup> The transformation of trichloroacetylated substrate **9a** smoothly proceeded, providing desired product **10a** in 58% yield (entry 1). The molecular structure of **10a** was confirmed with X-ray crystallography (Figure 1).<sup>9</sup> Substrates with a few kinds of amide group as well as an ester group proved to be suitable for this cyclization reaction to give high yields (entries 2-5).

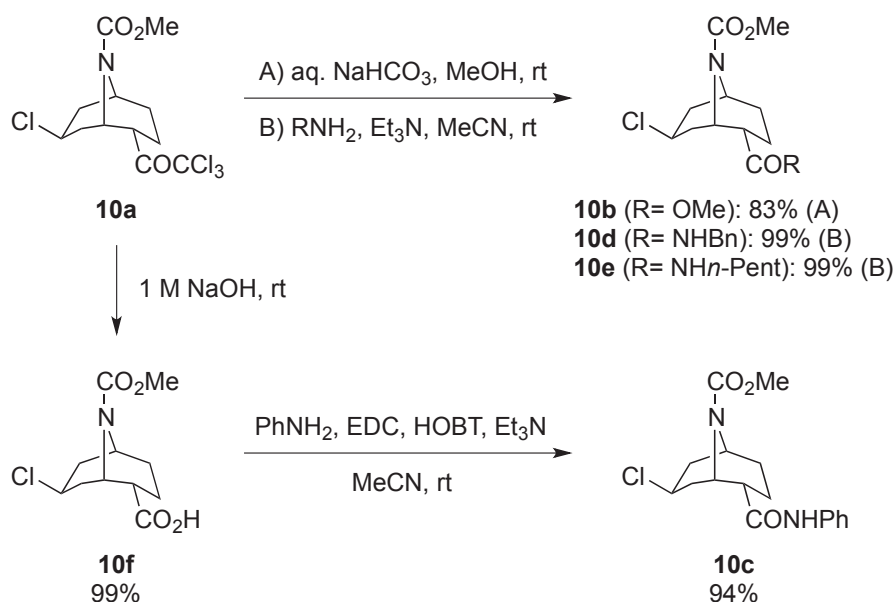
Table 2. Synthesis of azabicyclo frameworks **10** via Lewis acid-mediated cyclization

entry	R	yield (%)
1	CCl <sub>3</sub> ( <b>9a</b> )	58 ( <b>10a</b> )
2	OMe ( <b>9b</b> )	81 ( <b>10b</b> )
3	NHPPh ( <b>9c</b> )	74 ( <b>10c</b> )
4	NHBn ( <b>9d</b> )	86 ( <b>10d</b> )
5	NH <i>n</i> -Pent ( <b>9e</b> )	71 ( <b>10e</b> )



**Figure 1.** ORTEP drawing of **10a**

Transformation of trichloroacetyl group in azabicyclo compound **10a** was examined (Scheme 2). Esterification was readily achieved to give desired product **10b** in high yield. In addition, amide formation smoothly proceeded without problems (**10d-e**). Two-step transformation was also applicable. After trichloroacetyl group of **10a** was hydrolyzed with a quantitative yield of **10f**, condensation of carboxylic acid **10f** and aniline was conducted to give desired product **10c** in 94% yield.



**Scheme 2.** Transformation of trichloroacetyl group in azabicyclo compound **10a**

Chiral azabicyclo-*N*-oxyls were synthesized through deprotection of methoxycarbonyl group with iodotrimethylsilane followed by *m*-CPBA oxidation (Table 3). This transformation with azabicyclo compound **10a** was carried out to afford desired *N*-oxyl **11a** in 90% yield (entry 1). In the presence of an ester group,

no significant decrease in yield was observed (entry 2). Substrates with amide groups (**10c-e**) were converted into azabicyclo-*N*-oxyls **11c-e** in good to high yields (entries 3-5).

**Table 3.** Synthesis of chiral azabicyclo-*N*-oxyls **11** from **10**<sup>a</sup>

entry	R	yield (%)	
1	CCl <sub>3</sub>	<b>(10a)</b>	90 <b>(11a)</b>
2	OMe	<b>(10b)</b>	71 <b>(11b)</b>
3	NHPh	<b>(10c)</b>	62 <b>(11c)</b>
4	NHBn	<b>(10d)</b>	79 <b>(11d)</b>
5	NH <i>n</i> -Pent	<b>(10e)</b>	75 <b>(11e)</b>

<sup>a</sup> Reaction conditions: TMS-I (3 equiv), *m*-CPBA (1.2 equiv).

In summary, trichloroacetyl group was successfully introduced into the  $\beta$ -position of cyclic amines under mild reaction conditions. This trichloroacetylation reaction was applied to synthesis of key intermediates for chiral azabicyclo compounds. After cyclization with a Lewis acid to form azabicyclo frameworks, chiral azabicyclo-*N*-oxyls were smoothly prepared under oxidation conditions. Trichloroacetyl groups in chiral intermediate **9a** and azabicyclo molecule **10a** were readily converted into ester and amide groups.

## EXPERIMENTAL

**General.** All melting points are not corrected. IR spectra were expressed in cm<sup>-1</sup>. <sup>1</sup>H NMR spectra were measured at 300 MHz, and <sup>13</sup>C NMR spectra were taken at 100 MHz. Chemical shift values are expressed in ppm relative to internal or external TMS. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded using electron ionization (EI) mass spectrometry or fast atom bombardment (FAB) mass spectrometry. The products were isolated by silica gel column chromatography. Compounds **5-8** were prepared on the basis of previous reports.<sup>8,10</sup> All reagents and solvents were used as received without further purification.

**Typical procedure for  $\beta$ -trichloroacetylation of cyclic amines.** To *tert*-butyl 2-methoxypiperidine-1-carboxylate (**1b**) (215 mg, 1 mmol) and 2-methyl-2-butene (0.233 mL, 2.2 mmol) in THF (5 mL)

was added trichloroacetyl chloride (0.240 mL, 2.2 mmol), and the reaction mixture was stirred at room temperature for 12 h. Then, saturated aqueous NaHCO<sub>3</sub> solution was added, and the resulting mixture was extracted with Et<sub>2</sub>O. The combined organic layers were dried over MgSO<sub>4</sub>. Concentration and purification through silica gel column chromatography gave desired product **3b**.

**Methyl 5-(2,2,2-trichloroacetyl)-3,4-dihydropyridine-1(2H)-carboxylate (3a).** White solids of mp 61-64 °C. IR (neat): 2960, 1730, 1670 cm<sup>-1</sup>. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 8.71 (s, 1H), 3.89 (s, 3H), 3.68 (t, *J* = 6.0 Hz, 2H), 2.48 (t, *J* = 6.0 Hz, 2H), 1.96-1.89 (m, 2H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ: 180.1, 153.3, 141.9, 107.7, 95.8, 54.1, 42.5, 21.5, 20.3. HRMS (EI): *m/z* calcd for C<sub>9</sub>H<sub>10</sub><sup>35</sup>Cl<sub>3</sub>NO<sub>3</sub> [M<sup>+</sup>] 284.9726, found 284.9714.

**tert-Butyl 5-(2,2,2-trichloroacetyl)-3,4-dihydropyridine-1(2H)-carboxylate (3b).** Yellow solids of mp 82-84 °C. IR (neat): 2980, 1730, 1680 cm<sup>-1</sup>. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 8.75 (s, 1H), 3.62 (t, *J* = 6.0 Hz, 2H), 2.45 (t, *J* = 6.0 Hz, 2H), 1.94-1.86 (m, 2H), 1.54 (s, 9H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ: 180.0, 142.7, 96.0, 83.3, 42.1, 27.9, 21.3, 20.3. HRMS (EI): *m/z* calcd for C<sub>12</sub>H<sub>16</sub><sup>35</sup>Cl<sub>3</sub>NO<sub>3</sub> [M<sup>+</sup>] 327.0196, found 327.0171.

**Benzyl 5-(2,2,2-trichloroacetyl)-3,4-dihydropyridine-1(2H)-carboxylate (3c).** Yellow oil. IR (neat): 2950, 2850, 1730, 1670 cm<sup>-1</sup>. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 8.77 (s, 1H), 7.40-7.33 (m, 5H), 5.28 (s, 2H), 3.69 (t, *J* = 6.0 Hz, 2H), 2.46 (t, *J* = 6.0 Hz, 2H), 1.91-1.87 (m, 2H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ: 180.2, 153.6, 142.0, 135.0, 128.7-128.2 (5C), 108.1, 95.9, 68.9, 42.6, 21.5, 20.3. HRMS (EI): *m/z* calcd for C<sub>15</sub>H<sub>14</sub><sup>35</sup>Cl<sub>3</sub>NO<sub>3</sub> [M<sup>+</sup>] 361.0039, found 361.0034.

**1-(1-Benzoyl-1,4,5,6-tetrahydropyridin-3-yl)-2,2,2-trichloroethanone (3d).** White solids of mp 58-62 °C. IR (neat): 2940, 2850, 1690 cm<sup>-1</sup>. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 8.46 (s, 1H), 8.12 (d, *J* = 9.3 Hz, 2H), 7.66-7.45 (m, 3H), 3.85 (t, *J* = 6.3 Hz, 2H), 2.54 (t, *J* = 6.3 Hz, 2H), 2.04-2.00 (m, 2H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ: 180.1, 171.5, 143.4, 133.7-128.3 (7C), 108.4, 42.2, 22.1, 20.4. HRMS (EI): *m/z* calcd for C<sub>14</sub>H<sub>12</sub><sup>35</sup>Cl<sub>3</sub>NO<sub>2</sub> [M<sup>+</sup>] 330.9934, found 330.9987.

**Methyl 4-(2,2,2-trichloroacetyl)-2,3-dihydropyrrole-1-carboxylate (4a).** Colorless oil. IR (neat): 2960, 2360, 1730, 1630 cm<sup>-1</sup>. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 7.98 (s, 1H), 3.95 (t, *J* = 9.6 Hz, 2H), 3.86 (s, 3H), 3.05 (t, *J* = 9.6 Hz, 2H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ: 178.1, 145.2 and 144.7 (1C), 112.1, 95.6, 53.8, 46.4, 29.1 and 28.1 (1C). HRMS (FAB): *m/z* calcd for C<sub>8</sub>H<sub>8</sub><sup>35</sup>Cl<sub>3</sub>NO<sub>3</sub> [M<sup>+</sup>] 270.9570, found 271.9578.

**tert-Butyl 4-(2,2,2-trichloroacetyl)-2,3-dihydropyrrole-1-carboxylate (4b).** Colorless oil. IR (neat): 2980, 1720, 1660 cm<sup>-1</sup>. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ: 8.01 (brs, 1H), 3.90 (t, *J* = 9.6 Hz, 2H), 3.03 (t, *J* = 9.6 Hz, 2H), 1.53 (s, 9H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ: 178.1, 145.8, 95.7, 83.0, 46.4, 28.5, 27.9, 19.7. HRMS (EI): *m/z* calcd for C<sub>11</sub>H<sub>14</sub><sup>35</sup>Cl<sub>3</sub>NO<sub>3</sub> [M<sup>+</sup>] 313.0039, found 313.0021.

**(S)-Methyl 2-allyl-5-(2,2,2-trichloroacetyl)-3,4-dihydropyridine-1(2H)-carboxylate (9a).** Trichloroacetyl chloride (2.2 equiv) was used. White solids of mp 70-72 °C. IR (neat): 2920, 1730, 1670, 1590

$\text{cm}^{-1}$ .  $[\alpha]_{\text{D}}^{23} -99.6$  ( $c$  1.00,  $\text{CHCl}_3$ ). IR (neat): 2920, 1730, 1670, 1590  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.69 (s, 1H), 5.82-5.69 (m, 1H), 5.12-5.07 (m, 2H), 4.38 (brs, 1H), 3.89 (s, 3H), 2.63 (dd,  $J = 3.8, 13.8$  Hz, 1H), 2.41-2.02 (m, 3H), 1.75-1.60 (m, 2H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 180.0, 152.8, 140.7, 133.1, 118.1, 107.0, 95.7, 54.0, 50.3, 35.9, 22.2, 17.3. HRMS (EI):  $m/z$  calcd for  $\text{C}_{12}\text{H}_{14}^{35}\text{Cl}_3\text{NO}_3$  [ $\text{M}^+$ ] 325.0039, found 325.0016. HPLC: CHIRALPAK AD, Hexane/EtOH = 100/1, wavelength 254 nm, flowrate 0.3 mL/min, retention time 18.0 min [(*S*)-isomer], 20.9 min [(*R*)-isomer].

**(*S*)-Dimethyl 6-allyl-5,6-dihydropyridine-1,3(4*H*)-dicarboxylate (9b).** To **9a** (326 mg, 1 mmol) in MeOH (5 mL) was added saturated aqueous  $\text{NaHCO}_3$  solution (1 mL), and the reaction mixture was stirred at room temperature for 6 h. After MeOH was removed under reduced pressure, the resulting mixture was extracted with AcOEt. The combined organic layers were dried over  $\text{MgSO}_4$ , and concentration gave desired product **9b** (237 mg, 99%) as colorless oil.  $[\alpha]_{\text{D}}^{23} -88.3$  ( $c$  1.00,  $\text{CHCl}_3$ ). IR (neat): 2950, 2860, 1720, 1700, 1630  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.01 (s, 1H), 5.82-5.69 (m, 1H), 5.09-5.05 (m, 2H), 4.33 (brs, 1H), 3.83 (s, 3H), 3.75 (s, 3H), 2.46-1.94 (m, 4H), 1.68-1.65 (m, 2H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 167.8, 153.3, 134.3, 133.7, 117.8, 107.6, 53.4, 51.2, 50.2, 35.7, 22.5, 16.7. HRMS (EI):  $m/z$  calcd for  $\text{C}_{12}\text{H}_{17}\text{NO}_4$  [ $\text{M}^+$ ] 239.1158, found 239.1140.

**Typical procedure for amidation of trichloroacetylated cyclic amines.** To **9a** (791 mg, 2.4 mmol) in MeCN (12 mL) was added benzylamine (0.397 mL, 3.6 mmol), and the reaction mixture was stirred at room temperature for 6 h. After MeCN was removed under reduced pressure and aqueous 3% HCl solution was added, the resulting mixture was extracted with  $\text{CHCl}_3$ . The combined organic layers were dried over  $\text{MgSO}_4$ . Concentration and purification through silica gel column chromatography gave the desired product.

**(*S*)-Methyl 2-allyl-5-(phenylcarbamoyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (9c).** Colorless oil.  $[\alpha]_{\text{D}}^{15} -103.9$  ( $c$  1.00,  $\text{CHCl}_3$ ). IR (neat): 2950, 2930, 2860, 1720, 1660  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 8.14 (brs, 1H), 8.00 (s, 1H), 7.57 (d,  $J = 5.7$  Hz, 2H), 7.37-7.35 (m, 2H), 7.20-7.10 (m, 1H), 5.85-5.78 (m, 1H), 5.14-5.10 (m, 2H), 4.42 (brs, 1H), 3.85 (s, 3H), 2.35-2.06 (m, 5H), 1.79-1.70 (m, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 172.7, 153.1, 138.1, 136.3, 133.6, 128.9, 124.0, 120.1, 118.0, 53.7, 50.3, 35.8, 22.4, 16.4. HRMS (EI):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_3$  [ $\text{M}^+$ ] 300.1474, found 300.1467.

**(*S*)-Methyl 2-allyl-5-(benzylcarbamoyl)-3,4-dihydropyridine-1(2*H*)-carboxylate (9d).** Colorless oil.  $[\alpha]_{\text{D}}^{20} -65.4$  ( $c$  1.00,  $\text{CHCl}_3$ ). IR (neat): 3320, 2950, 2930, 1720  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.90 (s, 1H), 7.38-7.24 (m, 5H), 5.85-5.68 (m, 2H), 5.08-5.04 (m, 2H), 4.54 (t,  $J = 5.1$  Hz, 2H), 4.35 (brs, 1H), 3.79 (s, 3H), 2.35-1.98 (m, 4H), 1.72-1.61 (m, 2H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 167.0, 153.2,

138.6, 133.7, 128.5 (2C), 127.7 (3C), 127.2, 117.7, 53.2, 49.6, 43.5, 35.3, 22.5, 16.9. HRMS (EI):  $m/z$  calcd for  $C_{18}H_{22}N_2O_3$  [ $M^+$ ] 314.1630, found 314.1618.

**(S)-Methyl 2-allyl-5-(pentylcarbamoyl)-3,4-dihydropyridine-1(2H)-carboxylate (9e).** Colorless oil.  $[\alpha]_D^{20} -73.9$  ( $c$  1.00,  $CHCl_3$ ). IR (neat): 3310, 2950, 2930, 2860, 1720, 1660  $cm^{-1}$ .  $^1H$ -NMR (300 MHz,  $CDCl_3$ )  $\delta$ : 7.87 (s, 1H), 5.78-5.62 (m, 2H), 5.08 (d,  $J = 9.7$  Hz 2H), 4.39 (brs, 1H), 3.83 (s, 3H), 3.38-3.32 (m, 2H), 2.32-2.01 (m, 5H), 1.74-1.65 (m, 1H), 1.61-1.54 (m, 2H), 1.40-1.30 (m, 4H), 0.95-0.92 (t,  $J = 5.3$  Hz, 3H).  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$ : 167.1, 153.3, 133.8, 130.4, 117.7, 109.6, 53.3, 49.6, 39.6, 35.3, 29.3, 29.0, 22.6, 22.3, 16.9, 13.8. HRMS (EI):  $m/z$  calcd for  $C_{16}H_{26}N_2O_3$  [ $M^+$ ] 294.1943, found 294.1946.

**Typical procedure for synthesis of azabicyclo derivatives (10).** To **9a** (326 mg, 1 mmol) in  $CH_2Cl_2$  (10 mL) was added  $TiCl_4$  (0.124 mL, 1.1 mmol) over 10 min at  $-78$  °C. The reaction mixture was warmed slowly to room temperature and stirred for 12 h. After saturated aqueous  $NaHCO_3$  solution was added, the resulting mixture was extracted with  $CHCl_3$ . The combined organic layers were dried over  $MgSO_4$ . Concentration and purification through silica gel column chromatography gave the desired product.

**(1S,2S,5S,7S)-7-Chloro-9-(methoxycarbonyl)-2-(trichloroacetyl)-9-azabicyclo[3.3.1]nonane (10a).** White solids of mp 116-118 °C.  $[\alpha]_D^{25} +89.8$  ( $c$  1.00,  $CHCl_3$ ). IR (neat): 2950, 1730  $cm^{-1}$ .  $^1H$ -NMR (300 MHz,  $CDCl_3$ )  $\delta$ : 4.96-4.87 (m, 1H), 4.82 and 4.69 (brs, 1H), 4.56 and 4.45 (brs, 1H), 3.87-3.77 (m, 4H), 2.50 (dd,  $J = 3.8, 6.6$  Hz, 1H), 2.35-2.32 (m, 1H), 2.25-2.11 (m, 2H), 2.07-1.92 (m, 3H), 1.88-1.83 (m, 1H).  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$ : 190.3 and 190.1 (1C), 154.4 and 154.1 (1C), 96.3, 52.9 and 52.5 (1C), 50.3 and 50.0 (1C), 47.3 and 46.7 (1C), 45.0 and 44.5 (1C), 40.5 and 40.3 (1C), 37.1 and 36.8 (1C), 27.8 and 27.3 (1C), 26.2 and 26.1 (1C). HRMS (EI):  $m/z$  calcd for  $C_{12}H_{15}^{35}Cl_4NO_3$  [ $M^+$ ] 360.9806, found 360.9805.

**(1S,2S,5S,7S)-2,9-Bis(methoxycarbonyl)-7-chloro-9-azabicyclo[3.3.1]nonane (10b).** Colorless oil.  $[\alpha]_D^{23} +35.9$  ( $c$  1.00,  $CHCl_3$ ). IR (neat): 2950, 1730  $cm^{-1}$ .  $[\alpha]_D^{23} +35.9$  ( $c$  1.00,  $CHCl_3$ ).  $^1H$ -NMR (300 MHz,  $CDCl_3$ )  $\delta$ : 4.76-4.61 (m, 2H), 4.46 and 4.34 (brs, 1H), 3.73-3.68 (m, 6H), 2.86-2.77 (m, 1H), 2.62-1.55 (m, 8H).  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$ : 172.5 and 172.4 (1C), 154.2 and 154.0 (1C), 52.9 and 52.4 (1C), 49.0 and 48.5 (1C), 47.3 and 46.7 (1C), 44.0 and 43.3 (1C), 42.8 and 42.5 (1C), 40.7 and 40.2 (1C), 37.4 and 37.1 (1C), 27.8 and 27.4 (1C), 25.4 and 25.1 (1C), 22.6 and 21.6 (1C). HRMS (EI):  $m/z$  calcd for  $C_{12}H_{18}^{35}ClNO_4$  [ $M^+$ ] 275.0924, found 275.0910.

**(1S,2S,5S,7S)-7-Chloro-9-(methoxycarbonyl)-2-(phenylcarbamoyl)-9-azabicyclo[3.3.1]nonane (10c).** Colorless oil.  $[\alpha]_D^{23} +81.3$  ( $c$  1.00,  $CHCl_3$ ). IR (neat): 3310, 2950, 1670  $cm^{-1}$ .  $^1H$ -NMR (300 MHz,  $CDCl_3$ )  $\delta$ : 8.60 (s, 1H), 7.54 (d,  $J = 5.9$  Hz, 2H), 7.33-7.27 (m, 2H), 7.12-7.08 (m, 1H), 4.89-4.80 (m, 1H),



4.64-4.36 (m, 2H), 3.74 (s, 3H), 2.85-2.69 (m, 1H), 2.59-2.45 (m, 1H), 2.33-1.80 (m, 7H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 170.4, 154.9 and 154.3 (1C), 138.0 and 137.6 (1C), 128.9 (2C), 124.6 and 124.2 (1C), 120.0-119.8 (2C), 53.0, 50.0 and 49.8 (1C), 47.8 and 47.1 (1C), 46.9 and 46.0 (1C), 40.7 and 40.4 (1C), 37.5 and 37.4 (1C), 27.9 and 27.6 (1C), 23.2 and 22.4 (1C). HRMS (EI):  $m/z$  calcd for  $\text{C}_{17}\text{H}_{21}^{35}\text{ClN}_2\text{O}_3$  [ $\text{M}^+$ ] 336.1241, found 336.1233.

**(1S,2S,5S,7S)-2-(Benzylcarbamoyl)-7-chloro-9-(methoxycarbonyl)-9-azabicyclo[3.3.1]nonane (10d).**

White solids of mp 44-45 °C.  $[\alpha]_{\text{D}}^{19}$  +33.5 ( $c$  1.00,  $\text{CHCl}_3$ ). IR (neat): 3310, 2950, 2930, 2360, 1670, 1650  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.38-7.24 (m, 5H), 6.17-5.87 (m, 1H), 4.85-4.33 (m, 5H), 3.80-3.55 (m, 4H), 2.65-1.56 (m, 8H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 171.8, 154.3, 138.0, 128.3, 127.2-127.0 (3C), 53.0, 52.4, 49.5, 47.4, 45.3, 44.7, 43.1, 40.4, 37.0, 27.7, 22.4. HRMS (EI):  $m/z$  calcd for  $\text{C}_{18}\text{H}_{23}^{35}\text{ClN}_2\text{O}_3$  [ $\text{M}^+$ ] 350.1397, found 350.1417.

**(1S,2S,5S,7S)-7-Chloro-9-(methoxycarbonyl)-2-(*n*-pentylcarbamoyl)-9-azabicyclo[3.3.1]nonane**

**(10e).** Colorless oil.  $[\alpha]_{\text{D}}^{19}$  +43.2 ( $c$  1.00,  $\text{CHCl}_3$ ). IR (neat): 3310, 2950, 2930, 1680, 1650  $\text{cm}^{-1}$ .  $^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.73-5.49 (m, 1H), 4.86-4.74 (m, 1H), 4.45-4.32 (m, 2H), 3.73-3.71 (m, 3H), 3.31-3.19 (m, 2H), 2.60-2.39 (m, 2H), 2.25-1.25 (m, 12H), 0.90 (t,  $J$  = 6.6 Hz, 3H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 171.7, 154.7, 53.2-52.7 (2C), 50.1 and 50.0 (1C), 47.7 and 47.0 (1C), 45.8 and 45.2 (1C), 40.8 and 40.4 (1C), 39.4, 37.5 and 37.2 (1C), 29.0-28.9 (2C), 27.9 and 27.6 (1C), 23.1-22.1 (2C), 13.8. HRMS (EI):  $m/z$  calcd for  $\text{C}_{16}\text{H}_{27}^{35}\text{ClN}_2\text{O}_3$  [ $\text{M}^+$ ] 330.1710, found 330.1711.

**Procedure for synthesis of 10b from 10a.** To **10a** (363 mg, 1 mmol) in MeOH (5 mL) was added saturated aqueous  $\text{NaHCO}_3$  solution (1 mL), and the reaction mixture was stirred at room temperature for 6 h. After MeOH was removed under reduced pressure, the resulting mixture was extracted with AcOEt. The combined organic layers were dried over  $\text{MgSO}_4$ . Concentration and purification through silica gel column chromatography gave desired product **10b**.

**Procedure for synthesis of 10d-e from 10a.** To **10a** (363 mg, 1 mmol) in MeCN (3 mL) were added an amine (1.5 mmol) and  $\text{Et}_3\text{N}$  (0.279 mL, 2 mmol), and the reaction mixture was stirred at room temperature for 6 h. After MeCN was removed under reduced pressure and aqueous 3% HCl solution was added, the resulting mixture was extracted with  $\text{CHCl}_3$ . The combined organic layers were dried over  $\text{MgSO}_4$ . Concentration and purification through silica gel column chromatography gave the desired product.

**(1S,2S,5S,7S)-7-Chloro-2-(hydroxycarbonyl)-9-(methoxycarbonyl)-9-azabicyclo[3.3.1]nonane (10f).**

To **10a** (363 mg, 1 mmol) was added aqueous 1 M NaOH solution (2 mL), and the reaction mixture was stirred at room temperature for 6 h. After the resulting mixture was washed with  $\text{Et}_2\text{O}$ , the aqueous layer

was acidified to a pH of 2 and extracted with AcOEt. The combined organic layers were dried over MgSO<sub>4</sub>, and concentration gave desired product **10f** (259 mg, 99%) as a white syrup. [ $\alpha$ ]<sub>D</sub><sup>19</sup> +33.4 (*c* 1.00, CHCl<sub>3</sub>). IR (neat): 2960, 1730, 1700 cm<sup>-1</sup>. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$ : 11.13 (brs, 1H), 4.77-4.67 (m, 2H), 4.48-4.36 (m, 1H) 3.76-3.72 (m, 3H), 2.91-2.82 (m, 1H), 2.44-2.37 (m, 1H), 2.26-2.19 (m, 1H), 2.11-1.80 (m, 6H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ : 177.3, 154.7, 53.0, 49.0 and 48.5 (1C), 47.5 and 47.0 (1C), 44.0 and 43.5 (1C), 40.7 and 40.4 (1C), 37.4 and 37.1 (1C), 27.9 and 27.5 (1C), 22.6. HRMS (EI): *m/z* calcd for C<sub>11</sub>H<sub>16</sub><sup>35</sup>ClNO<sub>4</sub> [M<sup>+</sup>] 261.0768, found 261.0760.

**Procedure for synthesis of 10c from 10f.** To **10f** (330 mg, 1.26 mmol) in MeCN (15 mL) were added PhNH<sub>2</sub> (176 mg, 1.89 mmol), EDC (290 mg, 1.5 mmol), HOBT (205 mg, 1.5 mmol), and Et<sub>3</sub>N (0.264 mL, 1.89 mmol). After the reaction mixture was stirred at room temperature for 24 h, the solvent was removed under reduced pressure and AcOEt was added. The resulting mixture was washed with saturated aqueous NaHCO<sub>3</sub> solution, water, and brine. After the organic layer was dried over MgSO<sub>4</sub>, concentration and purification through silica gel column chromatography gave desired product **10c**.

**Typical procedure for synthesis of azabicyclo-*N*-oxyls (11).** To **10a** (246 mg, 0.68 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> was added TMS-I (0.290 mL, 2.04 mmol). The reaction mixture was stirred at room temperature for 12 h. Then, saturated aqueous NaHCO<sub>3</sub> solution (10 mL) and saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution (10 mL) were added, and the resulting mixture was extracted with CHCl<sub>3</sub>. The combined organic layers were dried over K<sub>2</sub>CO<sub>3</sub>, and concentration and gave a crude product. This crude product was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL), and *m*-CPBA (187 mg, 0.82 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. Saturated aqueous NaHCO<sub>3</sub> solution (5 mL) was added, and the resulting mixture was extracted with CHCl<sub>3</sub>. The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration and purification through silica gel column chromatography gave desired product **11a**.

**(1*S*,2*S*,5*S*,7*S*)-7-Chloro-2-(2,2,2-trichloroacetyl)-9-azabicyclo[3.3.1]non-9-yloxy (11a).** Red oil. [ $\alpha$ ]<sub>D</sub><sup>23</sup> -20.4 (*c* 1.00, CHCl<sub>3</sub>). IR (neat): 2930, 2850, 1740, 1700 cm<sup>-1</sup>. HRMS (FAB): *m/z* calcd for C<sub>10</sub>H<sub>13</sub><sup>37</sup>Cl<sub>4</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 326.9582, found 318.9595.

**(1*S*,2*S*,5*S*,7*S*)-7-Chloro-2-(methoxycarbonyl)-9-azabicyclo[3.3.1]non-9-yloxy (11b).** Yellow solids of mp 95-99 °C. [ $\alpha$ ]<sub>D</sub><sup>23</sup> -74.0 (*c* 1.00, CHCl<sub>3</sub>). IR (neat): 2950, 1730 cm<sup>-1</sup>. HRMS (EI): *m/z* calcd for C<sub>10</sub>H<sub>15</sub><sup>35</sup>ClNO<sub>3</sub> [M<sup>+</sup>] 232.0740, found 232.0729.

**(1*S*,2*S*,5*S*,7*S*)-7-Chloro-2-(phenylcarbamoyl)-9-azabicyclo[3.3.1]non-9-yloxy (11c).** Red solids of mp 68-71 °C. [ $\alpha$ ]<sub>D</sub><sup>23</sup> -3.3 (*c* 1.00, CHCl<sub>3</sub>). IR (neat): 3310, 2950, 2360, 1740, 1680 cm<sup>-1</sup>. HRMS (EI): *m/z* calcd for C<sub>15</sub>H<sub>18</sub><sup>35</sup>ClN<sub>2</sub>O<sub>2</sub> [M<sup>+</sup>] 293.1057, found 293.1071.

(1*S*,2*S*,5*S*,7*S*)-2-(Benzylcarbamoyl)-7-chloro-9-azabicyclo[3.3.1]non-9-yloxy (**11d**). Red oil.  $[\alpha]_{\text{D}}^{23}$   $-23.6$  ( $c$  1.00,  $\text{CHCl}_3$ ). IR (neat): 3290, 2930, 2850, 1650, 1530  $\text{cm}^{-1}$ . HRMS (EI):  $m/z$  calcd for  $\text{C}_{16}\text{H}_{20}^{35}\text{ClN}_2\text{O}_2$  [ $\text{M}^+$ ] 307.1213, found 307.1191.

(1*S*,2*S*,5*S*,7*S*)-7-Chloro-2-(*n*-pentylcarbamoyl)-9-azabicyclo[3.3.1]non-9-yloxy (**11e**). Red oil.  $[\alpha]_{\text{D}}^{23}$   $-2.4$  ( $c$  1.00,  $\text{CHCl}_3$ ). IR (neat): 3300, 2950, 2930, 2860, 1640, 1540  $\text{cm}^{-1}$ . HRMS (EI):  $m/z$  calcd for  $\text{C}_{14}\text{H}_{24}^{35}\text{ClN}_2\text{O}_2$  [ $\text{M}^+$ ] 287.1526, found 287.1531.

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9. Crystallographic data for **10a**: CCDC 1859773 contains the supplementary crystallographic data, which will be obtained free of charge from The Cambridge Crystallographic Data Center. Formula: C<sub>12</sub>H<sub>15</sub>Cl<sub>4</sub>NO<sub>3</sub>. M<sub>r</sub>: 363.07. Crystal system: orthorhombic. Space group: P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub> (#19). *a*: 8.3208(15) Å. *b*: 9.6938(17) Å. *c*: 19.293(3) Å.  $\alpha = \beta = \gamma$ : 90°. *V*: 1556.1(5) Å<sup>3</sup>. *Z*: 4.  $\mu$ : 7.639 (cm<sup>-1</sup>). R<sub>1</sub> (*I*>2 $\sigma$ (*I*)): 0.0336. R (*I*>0.5 $\sigma$ (*I*)): 0.0426. wR<sub>2</sub> (*I*>0.5 $\sigma$ (*I*)): 0.0764. *D*: 1.550 (g/cm<sup>3</sup>). *S*: 1.012.
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