Asymmetric transformation of L-homoserine lactone to an optically active 2-substituted pyrrolidine for clemastine

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The asymmetric transformation of L-homoserine lactone to (R)-ethyl 2-(2-chloroethyl)pyrrolidine-1-carboxylate for clemastine has been accomplished by a combination of regioselective N-allylation and ring-closing metathesis. A key feature associated with the synthesis involved the racemization-minimized N-allylation of carbamate version of an amino ester by using P4-phosphazene as a base. This method might offer an alternative route to obtain optically active 2-substituted pyrrolidines from α-amino esters, not easily accessible from proline-based asymmetric transformations.

1. Introduction

Optically active pyrrolidine rings are a common structural motif found in alkaloid natural products and biomolecules. Our interest in chiral pyrrolidine 2 arose from the asymmetric synthesis of chiral clemastine 1 using our chelation-controlled asymmetric alkylation. Clemastine is an H1-receptor antagonist with excellent antihistaminic activity. Clemastine has two stereogenic centers, and is marketed as the (R,R)-form. This absolute configuration is crucial to its antihistaminic activity. Since clemastine should be accessible from the corresponding chiral pyrrolidine 2, we needed to develop a new and general synthetic method for chiral 2-substituted pyrrolidines (Fig. 1).1

Figure 1. Structures of clemastine and its key intermediate.

Proline-based asymmetric transformations have been one of the most popular methods for the synthesis of 2-substituted pyrrolidine derivatives. However, our target molecule has an (R)-configuration, which is not accessible from natural (S)-proline. In addition, considering the natural occurrence of these cyclic alkaloids, alternative and new synthetic approaches for the construction of pyrrolidine ring systems remain an area of intense research. Over the past few decades, coupled with the recent development of the ring-closing metathesis (RCM) reaction, many attempts have been made for the construction of chiral pyrrolidine ring systems. Some RCM approaches to pyrrolidines using N,N-diallylated α-amino esters have been reported, but they could not give us such pyrrolidines with a stereogenic center on the ring. Taking into account the utility of amino esters as chiral synths, general approaches using amino esters would be useful methods for the construction of chiral 2-substituted pyrrolidines. Thus, we envisioned that the RCM reaction of diallylamine 3 in which one of the two allyl groups comes from the ester group of an α-amino ester, would provide the requisite chiral pyrrolidine 2 (Scheme 1).

However, due to the chelation of a nitrogen lone pair to the Ru catalyst, the RCM reaction of diallylamines 3 (P = H) possessing a basic or nucleophilic nitrogen atom are rather difficult to carry out to obtain the desired pyrrolidines. Therefore, diallylcarbamates 3 (P = alkoxycarbonyl) or diallylamine 3 (P = acyl) could be a solution for the RCM reactions of α-amino esters, although their precursors 4 (P = acyl, alkoxycarbonyl) are easy to racemize during their preparation. The RCM reaction of the corresponding β-amino alcohol could be a solution for avoiding racemization. However, it sometimes requires additional manipulation steps, such as protection and deprotection. Despite the problem of racemization, we decided to find a racemization-minimized pathway to diallylcarbamate as a precursor for the RCM reaction.

2. Results and discussion

We chose commercially available (S)-(−)-α-amino-γ-butyrolactone hydrobromide (Aldrich®, L-homoserine lactone hydrobromide)
as a starting material due to its latent functionality favorable for clemastine synthesis and its potential for side chain modification of the pyrrolidine ring. Our synthesis began with the preparation of mono-allylated \((S)/(C0)\)-(\(S\))-α-amino-\(\gamma\)-butyrolactone 6. We chose an ethoxycarbonyl group as a protecting group for the amino group, since it can be easily converted to the methyl group necessary for clemastine. First, we attempted the sequential mono-allylation and ethoxycarbonylation process, and found the optimum conditions as shown below (Scheme 2).

Low chemical yields, careful control of the mono-allylation, and a wide range of racemization during the ethoxycarbonylation are the problems encountered in this process. Thus, we tried the direct N,N-diallylation process, and found the optimum conditions as shown below (Scheme 3).

Chemical yields were increased, but racemization was inevitable. In contrast to the mono-allylation process, racemization did not occur during the ethoxycarbonylation. This was presumably due to the hydrogen bonding between the acidic hydrogen on the nitrogen atom and the carbonyl oxygen, which enhances the enolization of carbonyl group, which resulted in racemization. The third process we chose was the sequential ethoxycarbonylation and allylation process as shown in Scheme 4.

In this process, ethoxycarbonylation proceeded cleanly in good yield under standard conditions, and the product was proven to be enantiomerically pure \([\alpha]D = -37.0 (c 1.0, MeOH)]\) by chiral HPLC analysis. However, subsequent allylation was accompanied with a wide range of racemization depending on the conditions, as shown in Table 1. The reactions using weak bases required an elevated temperature for allylation to occur. Treatment of 9 with Cs\(_2\)CO\(_3\) at 60°C afforded the allylated product 7 in a 95% yield, but with complete racemization. Low temperature allylations using strong bases, such as LDA and \(n\)-BuLi, proceeded in favor of the C-alkylation on \(\alpha\)-carbon over N-alkylation. Many attempts were made in order to favor N-alkylation over C-alkylation at low temperatures, but all were unsuccessful. After finding a report in which P4-phosphazene was an effective base for the regioselective N-alkylation of cyclic peptides, \(11\) treatment of 9 with P4-phosphazene at \(-78^\circ\text{C}\) (Table 1, entry 7), followed by addition of allyl

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**Scheme 1.** Retrosynthetic analysis of 2-substituted pyrrolidine 2.

\[
\begin{align*}
2 & \quad \Rightarrow \quad \begin{array}{c}
\text{H} \\
\text{\(R\)} \\
\text{\(P\)} \\
\end{array} \\
3 & \quad \Rightarrow \quad \begin{array}{c}
\text{H} \\
\text{\(R\)} \\
\text{\(\text{P} = \text{H, Acyl}\)} \\
\text{\(\text{Alkoxycarbonyl}\)} \\
\end{array} \\
4 & \quad \Rightarrow \quad \begin{array}{c}
\text{H} \\
\text{\(R\)} \\
\text{\(\text{NH}_2\)} \\
\end{array}
\]

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**Scheme 2.** Sequential allylation and ethoxycarbonylation processes toward 7.

\[
\begin{align*}
\text{NH}_3^+ & \quad \xrightarrow{\text{NaHCO}_3, \text{MeCN}} \quad \text{O} \\
\text{O} & \quad \xrightarrow{\text{ClCO}_2\text{Et}, \text{LiI}} \quad \text{O} \\
\text{N} & \quad \xrightarrow{\text{DMAP, pyridine}} \quad \text{O} \\
\text{O} & \quad \xrightarrow{\text{60 °C, 5h}} \quad \text{N} \\
\text{O} & \quad \xrightarrow{\text{(S) : (R) = 30 : 1}} \quad \text{O} \\
\text{O} & \quad \xrightarrow{\text{O} \quad \text{O} \quad \text{O} \quad \text{O} \quad \text{N} \quad \text{O}} \quad \text{O} \\
\text{O} & \quad \xrightarrow{\text{60 ºC, 5h}} \quad \text{O} \\
\text{O} & \quad \xrightarrow{\text{(S) : (R) = 12 : 1}} \quad \text{O}
\end{align*}

**Scheme 3.** Diallylation process toward 7.

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**Table 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Halide</th>
<th>Base</th>
<th>Solvent</th>
<th>Additive</th>
<th>°C</th>
<th>Time (h)</th>
<th>((S)/(R))^a</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Allyl iodide</td>
<td>K(_2)CO(_3)</td>
<td>DMF</td>
<td>None</td>
<td>60</td>
<td>12</td>
<td>NA</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>Allyl iodide</td>
<td>Cs(_2)CO(_3)</td>
<td>DMF</td>
<td>None</td>
<td>60</td>
<td>4</td>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>Allyl iodide</td>
<td>t-BuOK</td>
<td>DMF</td>
<td>None</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>Allyl iodide</td>
<td>t-BuOK</td>
<td>DMF</td>
<td>18-Crown-6</td>
<td>-20</td>
<td>1</td>
<td>1.2</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Allyl bromide</td>
<td>LDA</td>
<td>THF</td>
<td>None</td>
<td>-78</td>
<td>1</td>
<td>NA</td>
<td>Trace</td>
</tr>
<tr>
<td>6</td>
<td>Allyl bromide</td>
<td>n-BuLi</td>
<td>THF</td>
<td>None</td>
<td>-78</td>
<td>1</td>
<td>NA</td>
<td>Trace</td>
</tr>
<tr>
<td>7</td>
<td>Allyl bromide</td>
<td>P4-phosphazene</td>
<td>THF</td>
<td>None</td>
<td>-78</td>
<td>2</td>
<td>&gt;100</td>
<td>74</td>
</tr>
</tbody>
</table>

^a The ratio \((S)/(R)\) was determined by HPLC analysis (Chiralcel AD-H column) of the carbamate compound.

^b NA: not available.
bromide produced 7 and its enantiomer in a more than 100:1 ratio in favor of 7 in 74% combined yield. When a proton or metal cation derived from substrate 9 or base coordinates to the carbonyl oxygen on the lactone, enolization of 9 might be enhanced and result in racemization. However, it is anticipated that protonated P4-phosphazene obtained by deprotonation at low temperature is reluctant to serve as a proton source, coordinating to the carbonyl group for steric reasons.

After installing the N-allyl substituents successfully on α-amino lactone 5 without significant racemization, we next turned our attention to the synthesis of the requisite acyclic diene 3a for ring-closing metathesis. Subsequent reduction and a Wittig olefination process for the diene shown in Scheme 5.

Standard DIBAL-H reduction of 7 gave lactol 10 in an 82% yield. If we adopted the synthetic route via a β-amino alcohol instead of an α-amino ester, we have to differentiate the two primary alcohols. By forming lactol 10, we are able to bypass the highly selective protection and deprotection steps. Next, we explored the Wittig olefination of 10 with a variety of reagents and conditions. However, all attempts were unsuccessful. Only bicyclic compound 11 was obtained as the sole product instead of 3a. Presumably, the preferential formation of an O-alkoxide under basic conditions leads to produce bicyclic compound 11. Thus, we attempted the Wittig olefination under less basic conditions. Treatment of 10 with Ph3P=CHCO2Et in benzene at room temperature gave the desired diene 13 in a 90% yield. With diene 13 in hand, the stage was set for the RCM. Accordingly, exposure of 13 to 10 mol % of the Grubbs’ catalyst A or B as a 2.5 × 10−3 M solution in dichloromethane at room temperature cleanly produced 2-substituted pyrrolidine 15 in good yields, depending on the conditions as shown in Table 2.

We initially tried the RCM reaction without protection of the alcohol functionality. The chemical yields were sensitive to the alcohol functionality depending on the catalyst. Alcohol 13 was transformed into the chloride 14, followed by subjecting to a RCM reaction. It turned out that chloride 14 was less sensitive to the catalyst, and gave moderate chemical yields. However, treatment of alcohol 13 with Grubbs’ catalyst B was the best condition for our purposes. With pyrrolidine 15 in hand, the complete synthesis of 2 was accomplished in a straightforward manner (Scheme 6). Hydrogenation over palladium on carbon, followed by chloride formation using a Vilsmeier salt (dichloromethylene-dimethyliminium chloride) afforded 2 in a 72% yield over 2 steps.
3. Conclusion

In conclusion, we have shown that optically active (R)-ethyl 2-(2-chloroethyl)pyrrolidine-1-carboxylate 2 for cleomastine can be prepared efficiently from \( \gamma \)-homoserine lactone 5 via racemization-minimized and regioselective N-allylation, and ring closing metathesis. A high degree of enantiopurity could be retained during the allylation step by using P4-phosphazene as a base. The direct use of a \( \alpha \)-amino ester enabled us to bypass the highly selective protection and deprotection steps necessary for the \( \beta \)-amino alcohol pathway. Although we chose pyrrolidine 2 as an initial target to demonstrate our synthetic strategy, our synthetic method might offer an alternative route to obtain optically active and functionalized 2-substituted cyclic amines including pyrrolidines from \( \alpha \)-amino esters, not easily accessible from (S)-proline-based asymmetric transformations or other synthetic methods such as sparteine-mediated metallation method.\(^{12}\)

4. Experimental

4.1. General

Melting points were obtained using a Büchi 535 melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP 1000 digital polarimeter.\(^1\)\(^H\) NMR and \(^13\)C NMR apparatus and are uncorrected. Optical rotations were measured on a JASCO FT/IR-430 spectro-photometer. Thin layer chromatography (TLC) was carried out on 0.25 mm E. Merck precoated silica gel glass plates (60F254). Column chromatography was performed using the flow of indicated solvent on Merck Kieselgel 60 (230–400 mesh). Chiral HPLC was performed using a Shimadzu LC-10AS pumping system and Shimadzu SPD-10A UV detector with a chiral column (Chiralcel AD-H, 0.46 cm \( \times \) 25 cm, Daicel Chemical Ind., Ltd). Unless otherwise noted, the materials were obtained from commercially available sources and were used without further purification. THF was freshly distilled from sodium benzophenone ketyl under an argon atmosphere. Benzene, DCM, DMF, triethylamine (TEA), and toluene were freshly distilled under a nitrogen atmosphere with calcium hydride.

4.2. (S)-Ethyl allyl[(2-oxotetrahydrofuran-3-yl)carbamate 7

A solution of (S)-(2-oxotetrahydrofuran-3-yl)carbamate 7 (99% ee, 25.0 mg, 0.144 mmol, 1.0 equiv) in dry THF (4 mL) at −78 °C was treated with the dropwise addition of t-Bu solution (216.6 μL, 0.217 mmol, 1.5 equiv) under nitrogen. The resulting solution was stirred at −78 °C for 1 h, and then a solution of allyl bromide (44.3 μL, 0.288 mmol, 2.0 equiv) in dry THF (1 mL) was slowly added via syringe over 2 min. The reaction mixture was stirred at −78 °C for 2 h and then allowed to warm to −20 °C. The reaction mixture was quenched with water at −20 °C, and extracted with EtOAc. The organic layer was washed with brine, dried (\( \text{Na}_2\text{SO}_4 \)), filtered, and concentrated in vacuo. Purification by column chromatography (\( \text{SiO}_2, 33\% \text{EtOAc in hexane} \)) afforded 7 as a syrup (23.0 mg, 74%); \( \text{IR}\) (NaCl, neat) cm\(^{-1}\) 3531, 3082, 2983, 2918, 1780, 1698, 1460, 1418, 1382, 1255, 1178; \({}^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 5.72 (m, 1H), 5.14 (d, 1H, \( J = 17.2 \) Hz), 5.07 (d, 1H, \( J = 10.0 \) Hz), 4.35 (m, 1H), 4.10 (m, 2H), 4.03 (q, 2H, \( J = 7.2 \) Hz), 3.88 (m, 2H), 2.38 (m, 2H), 1.16 (t, 3H, \( J = 7.2 \) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 174, 155, 133, 117, 65, 62, 55, 27, 14; \( |\delta^J_{\text{H,H}}| = -4.8 \) (c 1.0, chloroform); HPLC (CHIRALCEL AD-H column) eluent = 5% isopropanol in n-hexane, flow rate = 0.5 mL/min; detection 254 nm light, \( t_R \) of (S)-major 40 min; \( t_R \) of (R)-minor 44 min (\( \Delta \) : \( R \)) = 140:1; HRMS (EI\(^+\)) calc for \( \text{C}_{10}\text{H}_{15}\text{NO}_4 \) [M\(^+\)] 213.1001, found 213.1001.

4.3. Ethyl allyl[(3S,2S)-2-hydroxytetrahydrofuran-3-yl]carbamate 10

To a solution of (S)-ethyl (2-oxotetrahydrofuran-3-yl)carbamate 7 (>98% ee, 191.7 mg, 0.899 mmol, 1.0 equiv) in CH\(_2\)Cl\(_2\) (10 mL) at −78 °C under a nitrogen atmosphere, diisobutylaluminium hydride (1 M in toluene, 1.6 mL, 1.619 mmol, 1.8 equiv) was added dropwise. The mixture was stirred for 90 min at this temperature, and then cautiously quenched with methanol (5 mL). The whole mixture was stirred at −78 °C for 90 min and allowed to warm to room temperature. The resulting colloidal suspension was filtered, and the solid was washed thoroughly with dichloromethane. The combined organic layer was washed successively with water and brine, dried over anhydrous \( \text{Na}_2\text{SO}_4 \), filtered, and then concentrated. The resulting crude residue was purified by column chromatography on silica gel (\( \text{SiO}_2, 50\% \text{ethyl acetate in hexane} \)) to give the title compound 10 as a syrup (150.9 mg, 82%); \( \text{IR}\) (NaCl, neat) cm\(^{-1}\) 3145, 3082, 2983, 2988, 1679, 1469, 1445, 1416, 1256, 1027; \({}^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 5.80 (m, 1H), 5.33 (m, 1H), 5.13 (m, 1H), 5.08 (m, 1H), 4.45 (m, 1H), 4.12 (q, 2H, \( J = 7.2 \) Hz), 4.03 (m, 2H), 3.81 (m, 2H), 3.13 (OH, br s, 1H), 2.24 (m, 1H), 1.94 (m, 1H), 1.23 (dt, 3H, \( J = 2.0, 7.2 \) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 156, 135, 116, 100, 66, 63, 47, 25, 14; \( |\delta^J_{\text{H,H}}| = -0.2 \) (c 1.2, chloroform); HRMS (EI\(^+\)) calc for \( \text{C}_{13}\text{H}_{25}\text{NO}_4 \) [M\(^+\)] 215.1158, found 215.1157.

4.4. (S,E)-ethyl 4-(allyloxycarbonyl)amino)-6-hydroxyhex-2-enoate 13

To a solution of ethyl allyl[(3S)-2-hydroxytetrahydrofuran-3-yl]carbamate 10 (46.5 mg, 0.216 mmol, 1 equiv) in benzene (5 mL) was added (carbethoxymethylene)triphenylphosphorane (113.0 mg, 0.324 mmol, 1.5 equiv). After the resulting mixture was stirred for 10 h at room temperature, the reaction mixture was diluted with ethyl acetate (30 mL). The organic layer was washed successively with water and brine, dried over anhydrous \( \text{Na}_2\text{SO}_4 \), filtered, and then concentrated. The resulting crude residue was purified by column chromatography on silica gel (\( \text{SiO}_2, 33\% \text{ethyl acetate in hexane} \)) to give the title compound 13 as an oil (55.4 mg, 90%); \( \text{IR}\) (NaCl, neat) cm\(^{-1}\) 3450, 3081, 2981, 2936, 2876, 1719, 1698, 1468, 1412, 1308, 1254, 1175, 1048; \({}^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 6.91 (dd, 1H, \( J = 5.2, 16.0 \) Hz), 5.87 (d, 1H, \( J = 16.0 \) Hz), 5.76 (m, 1H), 5.09 (m, 1H), 5.06 (m, 1H), 4.94 (m, 1H),...
4.14 (q, 2H, J = 7.2 Hz), 4.14 (q, 2H, J = 7.2 Hz), 3.61 (m, 2H), 3.60 (m, 2H), 3.00 (OH, 1H), 1.87 (m, 2H), 1.25 (t, 3H, J = 7.2 Hz), 1.23 (t, 3H, J = 7.2 Hz); 13C NMR (100 MHz, CDCl3) δ 166, 157, 146, 134, 122, 117, 62, 60, 58, 55, 53, 46, 33, 14: [x]D25 = −37.7 (c 1.4, chloroform); Ec = 96% by HPLC (CHIRALCEL AD-H column) analysis; HRMS (EI+) calc’d for C14H22NO3 [M+H]+ 285.156, found 285.1576.

4.5. (S)-Ethyl 2-(2-hydroxyethyl)-2,5-dihydro-1H-pyrrole-1-carboxylate 15

To a solution of (S,E)-ethyl 4-(allyl(ethoxycarbonyl)amino)-6-hydroxyhex-2-enoate 13 (96% ee, 38.5 mg, 0.135 mmol, 1 equiv) in dichloromethane (15 ml) was added 2nd generation Grubbs' catalyst (5.7 mg, 0.007 mmol, 0.005 equiv) at room temperature. After the resulting mixture was stirred for 5 h at room temperature, the reaction mixture was concentrated to dryness. The residue was purified by column chromatography on silica gel (SiO2, 33% ethyl acetate in hexane) to give the title compound 15 (33% yield, 55.4 mg, 0.094 mmol, 0.69 equiv) at room temperature. After the resulting mixture was stirred for 5 h at room temperature, the reaction mixture was concentrated to dryness, and then the resulting crude residue was purified by column chromatography on silica gel (SiO2, 25% ethyl acetate in hexane) to give the title compound 2 as an oil (40.8 mg, 90%); IR (NaCl, neat) cm⁻¹ 2973, 2934, 2876, 1697, 1414, 1379, 1335 1188, 1116, 1027; 1H NMR (400 MHz, CDCl3) δ 4.09 (q, 2H, J = 7.0 Hz), 3.97 (m, 1H), 3.54 (m, 2H), 3.34 (m, 2H), 2.16 (m, 1H), 1.98 (m, 1H), 1.84 (m, 2H), 1.77 (m, 1H), 1.66 (m, 1H), 1.23 (t, 3H, J = 7.0 Hz); 13C NMR (100 MHz, CDCl3) δ 155, 59, 55, 46, 42, 38, 31, 23, 14: [x]D25 = +32.5 (c 1.4, chloroform); Ec = 96% by HPLC (CHIRALCEL AD-H column) analysis; HRMS (CI+) calc’d for C14H22CINO3 [M+H]+ 206.0948, found 206.0948.

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References


