Total synthesis of (−)-codonopsinine via regioselective and diastereoselective amination using chlorosulfonyl isocyanate

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ABSTRACT
The total synthesis of (−)-codonopsnine (1) from the readily available (S)-3-chloropropan-1,2-diol is described. The key steps for the preparation of (−)-codonopsnine (1) involve the regioselective and diastereoselective amination of anti-1,2-dibenzyl ether 11 using chlorosulfonyl isocyanate and intramolecular amidomercuration to form the pyrrolidine ring. Notably, the reaction between anti-1,2-dibenzyl ether and chlorosulfonyl isocyanate in toluene at 0 °C produced the corresponding anti-1,2-amino alcohol 12a as a major product with excellent diastereoselectivity (anti:syn = 29:1). This observation can be explained by the neighboring group participation leading to the retention of stereochemistry.

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1. Introduction
Polyhydroxylated alkaloids are among the most notable achievements in the field of natural products due to remarkable therapeutic potential for the treatment of viral infections, cancer, AIDS, diabetes, and etc. With considerable progress in medicinal chemistry, a range of natural and unnatural polyhydroxylated alkaloids have been prepared and evaluated for clinical trial. Indeed, miglitol (Glyset™) and N-butyldeoxyxojirimycin (Zavesca™) are currently on the market as commercial drugs for the treatment of type II diabetes and Gaucher’s disease. In particular, polyhydroxylated pyrrolidine alkaloids are widely found to be biologically relevant scaffolds in natural products and pharmaceuticals.

Representative examples of polyhydroxylated pyrrolidine alkaloids, (−)-codonopsnine (1) and (−)-codonopsnine (2) are first isolated from Codonopsis clematidea in 1969 and their absolute stereochemistry was determined by the same group in 1972 (Fig. 1). Notably, these compounds have attracted considerable attention due to the challenging penta-substituted pyrrolidine core containing four stereogenic centers with indiscrète trans-stereochemistry and diverse biological activities as antibiotic and antihypertensive effects without affecting the central nervous system. Owing to interesting biological activity and unique structural feature, various synthetic routes for the preparation of (−)-codonopsnine (1) have been studied. For example, Rao have been reported the total synthesis of (−)-codonopsnine (1) via the DDQ-promoted benzylic sp³ C–H activation reaction and acid-catalyzed amidocyclization for the stereoselective intramolecular C–N bond formation. Davies described the ring-closing iodination reaction of homoallylic amines for the synthesis of polysubstituted pyrrolidines and its application to the asymmetric synthesis of 1. Ooi demonstrated the efficient synthesis of 1 through the organocatalytic asymmetric Henry reaction between ynals and nitromethane leading to the formation of anti-vinyl amino alcohols. Goti and Merino disclosed the construction of (−)-codonopsnine (1) and its analog based on the iterative organometallic addition to chiral hydroxylated cyclic nitrones.

As part of an ongoing research program aimed at developing asymmetric total synthesis of biologically active compounds via the stereoselective amination of chiral allylic and benzylic ethers using chlorosulfonyl isocyanate (CSI), we herein describe an asymmetric total synthesis of (−)-codonopsnine (1) starting from commercially available (S)-3-chloropropan-1,2-diol via chelation-controlled Grignard reaction, diastereoselective amination of anti-vinyl dibenzyl ether and intramolecular cyclization by amidomercuration as the key steps.
2. Results and discussion

Total synthesis of (−)-codonopsinine (1) was accomplished by using anti-vicinal dihydroxy ester 6 as a starting material, which can be readily prepared from (S)-3-chloropropan-1,2-diol (5) as reported in the literature (Scheme 1). The diol 6 was easily converted into anti-1,2-dibenzyl ether 7 upon treatment with sodium hydride and benzyl bromide. The reduction of 7 and subsequent Swern oxidation afforded the corresponding aldehyde 9 in 77% yield for two steps. Next, we screened the Lewis acid-mediated Grignard-type addition reaction of 9 with vinylmagnesium bromide to yield 1,2-syn-allyl alcohol 10a. The selected results are summarized in Table 1.

As shown in entry 1, in the absence of Lewis acid, the addition of vinylmagnesium bromide to aldehyde 9 provided a mixture of 10a and 10b with 2:1 ratio in 58% yield. In addition, MgBr2·OEt2 as a Lewis acid in THF or CH2Cl2 solvents afforded our desired product 10a, albeit resulting in low diastereoselectivity (Table 1, entries 2 and 3). After further evaluation of Lewis acids, we found that a combination of ZnCl2 and THF solvent proved to be the most effective reaction condition furnishing 10a as a major product with excellent diastereoselectivity of 13.9:1 (Table 1, entry 6). These results suggest that ZnCl2 can initiate the formation of chelation complex between aldehyde group and α-OBn group, which smoothly participates in nucleophilic addition with vinylmagnesium bromide to deliver syn-isomer 10a as a major diastereomer (Fig. 2). The stereochemistry of 10a can be confirmed by the full agreement of spectral data between our synthesized (−)-codonopsinine (1) and reported literature.

As illustrated in Scheme 2, protection of the hydroxyl group of 10a was subjected with Ac2O to give the corresponding acetate 11 in 91% yield. Next, the reactivity and diastereoselectivity of 11 with chlorosulfonyl isocyanate were examined under various reaction conditions, and the selected results are summarized in Table 2. The reaction of 11 with CSI in CH2Cl2 at 0°C gave the inseparable mixture of desired product 12a and its diastereomer 12b in 6:1 ratio in 84% yield (Table 2, entry 1). The screening of other solvents under identical reaction conditions showed that toluene was the most effective solvent for this reaction (Table 2, entry 4) to afford anti-vicinal amino alcohol 12a in 73% yield with excellent diastereoselectivity (anti:syn = 29:1 as obtained by 1H NMR and HPLC analysis), which was directly used in the next step. The diastereoselectivity of this reaction can be explained by the neighboring group effect, where the NHCbz group orientation retained its original conﬁguration in benzyl ether via double inversion of the conﬁguration (Fig. 3).

Next, we focused on the synthesis of (−)-codonopsinine (1) from Cbz-protected amine 12a, as illustrated in Scheme 3. The intramolecular amidomercurative cyclization of 12a with Hg(CF3SO3)2, NaHCO3 and KBr in nitromethane furnished the

![Fig. 1. Structure of representative polyhydroxylated pyrrolidines.](image)

**Scheme 1.** Synthesis of 1,2-syn-allyl alcohol 10a.
corresponding organomercuric bromides 13a and 13b in 70% combined yield with diastereoselectivity of 3:1 between 2,5-trans and 2,5-cis. The demercuration reaction of 13a with NaBH4 followed by reduction of a Cbz group led to the formation of compound 15. Finally, the benzyl group was removed via hydrogenation to yield (−)-codonopsinine (1), which has spectral properties (1H and 13C NMR) and specific rotation in full agreement with previous reports.8a,e

3. Conclusions

In conclusion, we have developed a method for a highly regioselective and diastereoselective introduction of an NHCbz group to anti-vicinal dibenzyl ethers using chlorosulfonyl isocyanate (CSI). Moreover, we illustrated the application of this methodology to the total synthesis of (−)-codonopsinine (1). We believe that this synthetic strategy can be applied to the preparation of various polyhydroxylated alkaloids or other natural products containing a nitrogen atom in the ring.

4. Experimental section

4.1. General

Commercially available reagents were used without additional purification, unless otherwise stated. All reactions were performed under an inert atmosphere of nitrogen or argon. Nuclear magnetic resonance spectra (1H and 13C NMR) were recorded on a Varian Unit 400 (400 MHz for 1H NMR and 100 MHz for 13C NMR) or Bruker Unit 400 (400 MHz for 1H NMR and 100 MHz for 13C NMR) instrument with CDCl3 or CD3OD as solvent and residual CHCl3 (δ 7.26 ppm) or CH3OH (δ 3.31 ppm) as internal standard for 1H NMR and CDCl3 (δ 77.0 ppm) or CD3OD (δ 49.0 ppm) as internal standard for 13C NMR. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation br is used to indicate a broad signal. Coupling constants (J) are reported in hertz (Hz). IR spectra were recorded on a JASCO FT/IR-4600 and reported as cm⁻¹. Optical rotations were measured with a JASCO P1020 polarimeter and are reported as [α]D (concentration g/100 mL, solvent). Thin layer chromatography was carried out using plates coated with Kieselgel 60F254 (Merck). For flash column chromatography, E. Merck Kieselgel 60 (230–400 mesh) was used. High-performance liquid chromatography (HPLC) was recorded on an Agilent 1200 series. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-700 mass spectrometer.

4.2. Methyl-(2R,3R)-2,3-bis(benzyloxy)-3-(4-methoxyphenyl)propanoate (7)

To a suspension of NaH (3.6 g, 89.1 mmol, 60% in mineral oil) in DMF (150 mL) was added dropwise a solution of 6 (6.72 g, 29.7 mmol) in DMF (60 mL) at 0°C. After stirring for 30 min at the same temperature, benzyl bromide (8.12 mL, 68.3 mmol) was added slowly over 10 min, and stirred further for 1 h at 0°C. The temperature was slowly raised to 0°C over 30 min, and the reaction mixture was further stirred for 30 min at 0°C. The reaction mixture was quenched with saturated solution of NH4Cl (150 mL) and the solution was extracted with CH2Cl2 (200 mL × 2). The combined

Table 2

Diastereoselective amination of 11 with chlorosulfonyl isocyanate.a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Ratio (12a:12b)b</th>
<th>Yield (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH2Cl2</td>
<td>6</td>
<td>6:1</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>Et2O</td>
<td>8</td>
<td>19:1</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>n-hexane</td>
<td>24</td>
<td>20:1</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>toluene</td>
<td>10</td>
<td>29:1</td>
<td>73</td>
</tr>
</tbody>
</table>

a Reaction conditions: (i) 11 (1 equiv.), chlorosulfonyl isocyanate (4.5 equiv.), Na2CO3 (6.8 equiv.) at 0°C, 10 h; (ii) aqueous solution of 25% Na2SO3 at room temperature for 24 h.
b Diastereomeric ratio was determined by HPLC analysis.
c Isolated yield by flash column chromatography.
organic layers were washed with water and brine, dried over Na2SO4, and concentrated in vacuo. The residue was purified by flash column chromatography (n-hexanes/EtOAc = 5:1) to afford compound 7 (9.4 g, 78%) as a colorless oil; [α]D20 = -35.1 (c 1.0, CHCl3); IR (neat) ν 3061, 3028, 2899, 1741, 1609, 1509, 1453 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 7.23 (d, J = 8.0 Hz, 2H), 7.18 (m, 10H), 7.08 (m, 2H), 6.95 (d, J = 8.0 Hz, 2H), 4.65 (d, J = 7.6 Hz, 1H), 4.51 (d, J = 7.6 Hz, 1H), 4.37 (m, 2H), 4.29 (m, 2H), 4.11 (d, J = 7.6 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 171.7, 159.7, 137.8, 136.9, 130.1, 129.2, 128.3, 128.2, 127.9, 127.8, 127.7, 127.6, 113.7, 81.9, 80.5, 72.8, 70.5, 55.2, 51.9; HRMS (EI) calcd for C25H26O5 [M]+ 406.1780, found 406.1779.

4.3. (2S,3R)-2,3-Bis(benzyloxy)-3-(4-methoxyphenyl)propan-1-ol (8)

To a stirred solution of 7 (8.0 g, 19.7 mmol) in THF (80 mL) was added LiAlH4 (1.12 g, 29.5 mmol) slowly at 0°C. The mixture was stirred for 1 h at room temperature and quenched with 3 M HCl (15 mL). The resulting mixture was extracted with EtOAc (160 mL). The organic layer was washed with H2O (2 × 60 mL), brine (60 mL), dried over MgSO4, and concentrated in vacuo. The residue was purified by flash column chromatography (n-hexanes/EtOAc = 3:1) to afford 8 (6.8 g, 91%) as a colorless oil; [α]D20 = -48.8 (c 1.0, CHCl3); IR (neat) ν 3493, 3026, 2907, 1609, 1587, 1509, 1450 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 7.39 (d, J = 8.8 Hz, 2H), 7.25 (m, 10H), 7.10 (m, 2H), 6.97 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 7.6 Hz, 1H), 4.65 (d, J = 7.6 Hz, 1H), 4.53 (d, J = 11.6 Hz, 1H), 4.46 (d, J = 7.6 Hz, 1H), 4.37–4.29 (m, 2H), 4.23 (d, J = 11.2 Hz, 1H), 3.89 (s, 3H), 3.87–3.84 (m, 2H), 3.66–3.62 (m, 1H), 2.49 (br s, 1H); 13C NMR (100 MHz, CDCl3) δ 159.5, 138.0, 137.9, 131.2, 129.0, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 113.8, 82.4, 81.2, 72.9, 70.4, 62.5, 55.3; HRMS (EI) calcd for C24H26O4 [M]+ 378.1831, found 378.1827.

4.4. (2R,3R)-2,3-Bis(benzyloxy)-3-(4-methoxyphenyl)propanal (9)

To a stirred solution of oxalyl chloride (2.01 mL, 23.78 mmol) in CH2Cl2 (50 mL) was added dropwise DMSO (3.38 mL, 47.55 mmol) and CH2Cl2 (50 mL) at 78°C. The reaction mixture was stirred for 1 h at 78°C and 8 (6.0 g, 15.85 mmol) in CH2Cl2 (100 mL) was added to resulting solution. After stirring for 1 h at same temperature, Et3N (11.04 mL, 79.24 mmol) was added dropwise. The reaction mixture was further stirred for 0.5 h at 78°C and carefully quenched with H2O (100 mL). The organic layer was washed, washed with brine (100 mL), dried over MgSO4, and concentrated in vacuo. The residue was purified by flash column chromatography...
To a stirred solution of aldehyde 9 (5.97 g, 15.85 mmol) in THF (50 mL) was slowly added ZnCl2 (3.24 g, 23.78 mmol) at 0 °C under N2 atmosphere. Then, vinylmagnesium bromide solution (47.55 mL, 47.56 mmol, 1.0 M in THF) was added at 0 °C and stirred for 1 h at 0 °C. The reaction mixture was quenched with saturated solution of NH4Cl (100 mL) and the aqueous layer was washed with dichloromethane (2 × 100 mL). The organic layer was washed with H2O (2 × 100 mL) and brine (100 mL), dried over MgSO4, and concentrated in vacuo. The residue was purified by flash column chromatography (n-hexanes/EtOAc = 8:1) to afford 5.14 g of 10a (12.71 mmol, 80%) and 0.37 g of 10b (0.91 mmol, 5.8%), respectively. Colorless oil; 78.33 (d, 137.0), 6.93 (d, 7.2 Hz, 3H), 3.87 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 27.3 (d, 7.2 Hz, 1H), 1.83 (s, 3H); HRMS (ESI) calcd for C29H31O6NBrHg [M]+ 646.2093, found 646.2097.

A stirred solution of compound 12a (2.70 g, 3.86 mmol) in nitromethane (30 mL) was added mercury trflate (4.13 g, 8.27 mmol) at room temperature. After the reaction mixture was stirred for 30 min and then saturated solution of KBr (13.7 mL) and NaHCO3 (13.7 mL) was added. The resulting mixture was further stirred for 30 min and the resulting solution was extracted with EtOAc (2 × 30 mL). The organic layer was washed with H2O, dried over MgSO4, and concentrated in vacuo. The residue was purified by flash column chromatography (n-hexanes/EtOAc = 8:1) to afford a separable mixture of 13a and 13b (2.97 g, 3.86 mmol, 70% combined yield of 13a and 13b) as a yellowish syrup. The diastereomer ratio of 13a and 13b was determined to be 3:1 by NMR spectra with the crude material before purified; 78.33 (d, 137.0), 6.93 (d, 7.2 Hz, 3H), 3.87 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 27.3 (d, 7.2 Hz, 1H), 1.83 (s, 3H); HRMS (ESI) calcd for C29H31O6NBrHg [M]+ 646.2093, found 646.2097.

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