Diastereocontrolled Synthesis of (–)-Codonopsinine

Mansour Haddad, Marc Larchevêque*

Laboratoire de Synthèse Organique associé au CNRS, ENSCP, 11 rue Pierre et Marie Curie, 75231 Paris Cedex 05, France
Fax +33(1)43257975; E-mail: larchm@ext.jussieu.fr

Received 11 December 2002

Abstract: An efficient process is described for the total synthesis of the alkaloid (–)-codonopsinine. The synthetic strategy is based on the diastereoselective hydrocyanation of a 2,3-dialkoxyaldehyde derived from L-threonine followed by a reductive alkylation of the nitrile function with a Grignard compound and sodium borohydride. The resulting aminotriol was then cyclized into the target molecule after selective mesylation.

Key words: alkaloid, aminoalcohol, cyanohydrine, pyrrolidine

Codonopsinine **1** and codonopsine **2**, antibiotics first isolated in 1969 from *Codonopsis clematidea* by a Russian group[1] exhibit hypotensive pharmacological activity with no effect on the central nervous system observed in animal tests.[2] After structural characterization,[1b,3] they revealed to be a new class of simple pyrrolidine alkaloids possessing 1,2,3,4,5 pentasubstituted structures. The absolute configuration of the natural antibiotic **1** (Figure 1) was determined unambiguously to be (2*R*,3*R*,4*R*,5*R*).[4] In addition, the structure of codonopsine **2** was recently confirmed by another group using X-ray crystallographic analysis.[5]

Despite interesting pharmacological activity and unique structural features, to our knowledge only two syntheses have been reported to date.[6]

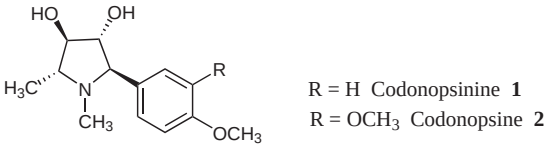
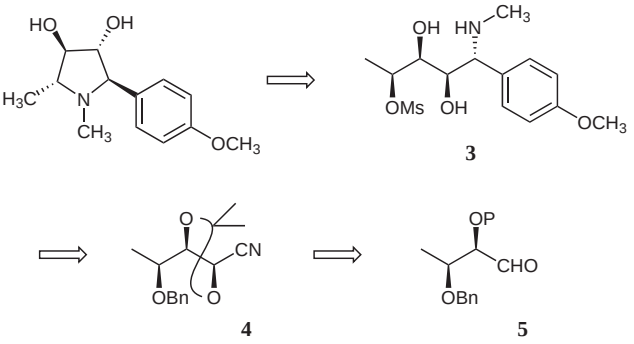


Figure 1

We wish to describe here a new approach to the natural codonopsinine **1** based on the stereocontrolled reductive alkylation of a trialkoxynitrile and further cyclization of the resulting aminotriol.

We planned to synthesize this alkaloid by cyclization of a linear aminotriol **3** in which the appropriate alcohol would be activated as a mesylate (Scheme 1). Such an intermediate could be obtained by a reductive alkylation of the nitrile **4** resulting from the condensation of an aromatic Grignard reagent followed by in situ reduction of the intermediate imine.[7] The required trihydroxynitrile with all *syn* stereochemistry would be obtained by diastereocontrolled hydrocyanation of a diprotected dihydroxyaldehyde of type **5**.[8] We have previously reported that the reductive alkylation of 2,3-dialkoxynitriles with alkyl Grignard reagents afforded protected aminodiols in good yields.[9] The relative stereochemistry between the oxygen at the α-position to the newly created amino function and this latter group was generally established as *syn*; however we recently observed that the use of aromatic Grignard reagents reversed the diastereoselectivity to give the aminoalcohols *anti* mainly.[10]



P : protective group

Scheme 1

The required trialkoxynitrile **4** was synthesized very easily starting from the monoprotected dihydroxyester **7a** (Scheme 2). This latter compound was obtained by regioselective opening of the (2*S*,3*S*) glycidic epoxide **6** derived from L-threonine.[11] The reaction of this epoxide with benzylalcohol in the presence of lithium perchlorate[12] afforded the ester **7a** exclusively.[13] The free hydroxy function of this compound was then protected as a MOM ether and the resulting ester **7b** was transformed into the aldehyde **9** by reduction of the ester function into the alcohol **8** with DIBAL-H followed by a Swern oxidation. The hydrocyanation of the resulting aldehyde with trimethylsilyl cyanide in the presence of $MgBr_2 \cdot OEt_2$ according Ward et al[14] and subsequent removal of the MOM protection conducted to compound **10** which was protected as an acetonide to give the nitrile **4**. This compound was obtained in 80% yield and in a diastereomeric ratio better than 98:2.

This nitrile was transformed into secondary amine in the following manner: 4-methoxyphenylmagnesium bromide in THF was reacted with nitrile **4**. After completion of the addition, the intermediate iminomagnesium compound was treated with methanol and the resulting primary imine

Synlett 2003, No. 2, Print: 31 01 2003.
Art Id.1437-2096,E;2003,0,02,0274,0276,ftx,en;D10202ST.pdf.

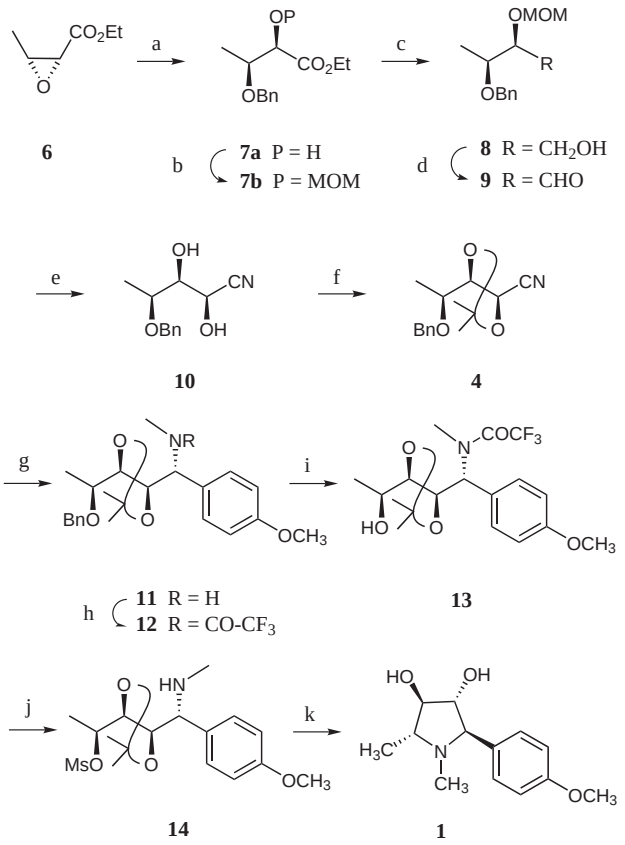
ISSN 0936-5214

was transiminated into secondary imine with methylamine in methanol[15] and reduced with sodium borohydride. This transimination allowed us to access directly to the *N*-methyl amine required for the synthesis of the target molecule. The amine **11** was isolated as a 8:2 mixture of diastereomers and in a 80% yield from nitrile **4**.[16]

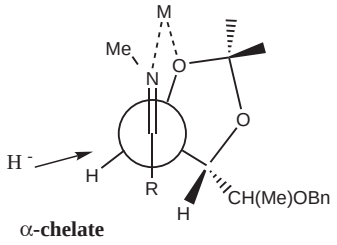
At this stage, we were unable to determine the relative stereochemistry of the aminotriol **11**. The synthesis of codonopsinine was carried on with the diastereomeric mixture. First attempts of debenzylation by catalytic hydrogenation or by elimination with dimethylsulfide–boron trifluoride diethyl etherate[17] failed, giving poor yields or non-reproducible results. However, a satisfactory result was obtained by protecting the secondary amine as its trifluoroacetamide. Removal of the benzyl group was then conducted without any problem by catalytic hydrogenation of **12** using10% palladium on charcoal as catalyst. The resulting free secondary alcohol was then transformed into mesylate and the amine was deprotected by hydrolysis with aqueous potassium carbonate. Due to the presence of the acetonide, the cyclization was impossible at this stage and it was necessary to remove this protection in acidic medium to obtain codonopsinine after treatment with potassium carbonate. The minor isomer was easily removed and pure codonopsinine **1** was isolated in 55% yield.[18] The relative stereochemistry was established by comparison of the ^{1}H NMR spectrum which was identical to the spectrum reported for the (–)-(2*R*,3*R*,4*R*,5*R*) isomer,[4b] Melting point and rotatory power were also in agreement with the reported values thus establishing the relative configuration of compound **11** to be 1,2 *anti*. Moreover, an accurate examination of the ^{1}H NMR spectrum showed that the minor isomer was the (2*S*,3*R*,4*R*,5*R*) epimer.

The stereochemical outcome is consistent with a chelation-controlled mechanism. Indeed, it is reasonable to assume that the species actually reduced is not the magnesioimine but more likely the hydrogenated or alkylated imine resulting from the methanolysis. A chelation of the solvated $MgBr_2$ magnesium atom by the oxygen in position α or β may be postulated and the formation of the β-chelate is probably disfavored by the steric hindrance generated by the presence of the acetonide, which increases the distance between the β-oxygen and the nitrogen atom (Figure 2). However, at present, we have no explanation for the reversal of the stereochemistry when moving from aryl to alkyl Grignard reagents. In order to rationalize these results, further exploration of these reactions are underway in our laboratory.

In summary, this synthesis demonstrates that the reductive alkylation of 2,3-dialkoxynitriles allows an efficient access to codonopsinine and could be applied to other polyhydroxylated pyrrolidines.



Scheme 2 (a) neat BnOH 3 equiv, $LiClO_4$ 0.5 equiv, 30 h, 60 °C, 67%; (b) MOMCl, *i*-Pr_2EtN, 12 h; r.t., 82%; (c) DIBAL-H, toluene, –30 °C to 20 °C, 12 h, 82%; (d) $(COCl)_2$, DMSO, Et_3N, 90%; (e) 1) TMSCN, $MgBr_2$–Et_2O 2 equiv, CH_2Cl_2, 0 °C, 3 h then r.t. (15 h), 2) 10% HCl–MeOH, r.t., 12 h, 85% (two steps); (f) Dimethoxypropane, cat. APTS, benzene azeotrope, 80 °C, 3 h, 77%; (g) cf Ref.[16] (h) $(CF_3CO)_2O$, Et_3N, r.t., 16 h, 91%; (i) H_2, 10% Pd/C, EtOH, r.t., 12 h, 90%; (j) MsCl, Et_3N–cat. DMAP, CH_2Cl_2, 20 °C, 12 h, then K_2CO_3, MeOH–H_2O, 10 h, 80%; (k) 10% aqueous HCl–THF 1:1, 65 °C, 12 h, then K_2CO_3, 20 °C, 18 h, 55%.



α-**chelate**

Figure 2

References

(1) (a) Matkhalikova, S. F.; Malikov, V. M.; Yunosov, S. Y. *Khim. Pri. Soedin* **1969**, *5*, 30. (b) Matkhalikova, S. F.; Malikov, V. M.; Yunosov, S. Y. *Khim. Prir. Soedin* **1969**, *5*, 607.

(2) Matkhalikova, S. F.; Malikov, V. M.; Yugadaev, M. R.; Yunosov, S. Y. *Farmakol. Alkaloidov Serdech. Glikoyidov.* **1971**, 210; *Chem. Abstr.* **1972**, 77, 135091r.

(3) Matkhalikova, S. F.; Malikov, V. M.; Yugadaev, M. R.; Yunosov, S. Y. *Khim. Prir. Soedin* **1971**, *7*, 210.

(4) (a) Iida, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1986**, *27*, 5393. (b) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 1956.
(5) Wang, C. L. J.; Calabrese, J. C. *J. Org. Chem.* **1991**, *56*, 4341.
(6) (a) Yoda, H.; Nakajima, T.; Takabe, K. *Tetrahedron Lett.* **1996**, *37*, 5531. (b) Severino, E. A.; Correia, C. R. D. *Org. Lett.* **2000**, *2*, 3039.
(7) (a) Krepski, L. R.; Jensen, K. M.; Heilmann, M.; Rasmussen, J. K. *Synthesis* **1986**, 301. (b) Brussee, J.; Dofferhoff, F.; Kruse, C. G.; Van der Gen, A. *Tetrahedron* **1990**, *46*, 1653. (c) Jackson, W. R.; Jacobs, H. A.; Jayatilafe, G. S.; Matthews, B. R.; Watson, K. G. *Aust. J. Chem.* **1990**, *43*, 2045. (d) Effenberger, F.; Gutterer, B.; Ziegler, T. *Liebigs Ann. Chem.* **1991**, 269. (e) Urabe, H.; Aoyama, Y.; Sato, F. *J. Org. Chem.* **1992**, *57*, 5056.
(8) (a) Reetz, M. T.; Kesseler, K.; Jung, A. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 989. (b) Gu, J.; Okamoto, M.; Terada, M.; Mikami, K.; Nakai, T. *Chem. Lett.* **1992**, 1169.
(9) Hutin, P.; Larchevêque, M. *Tetrahedron Lett.* **2000**, *417*, 2369.
(10) Haddad, M.; Larchevêque, M., unpublished results.
(11) Both enantiomers are commercially available from Acros Organics. Alternatively, they can be prepared according to: (a) Petit, Y.; Sanner, C.; Larchevêque, M. *Synthesis* **1988**, 538. (b) Cf also: Petit, Y.; Larchevêque, M. *Org. Synth.* **1998**, *75*, 37.
(12) Chini, M.; Crotti, P.; Flippin, L. A.; Gardelli, C.; Giovani, E.; Macchia, F.; Pineschi, M. *J. Org. Chem.* **1993**, *58*, 1221.
(13) (a) Riego, J.; Costa, A.; Saa, J. M. *Chem. Lett.* **1986**, 1565. (b) Haddad, M.; Larchevêque, M. *Synth. Commun*. **2003**, in press.
(14) Ward, D. E.; Hrapchak, M. J.; Sales, M. *Org. Lett.* **2000**, *2*, 57.
(15) Brussee, J.; van der Gen, A. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 25.
(16) Experimental procedure for **11**: Nitrile **4** (0.70 g, 2.68 mmol) was placed in anhydrous Et_2O (40 mL) and cooled to –13 °C. A 0.5 M solution of 4-methoxyphenylmagnesium bromide in THF (8 mL, 4.0 mmol) was added dropwise via a syringe through a septum and the reaction was allowed to warm to room temperature. Stirring was continued for 4 h before being cooled to –13 °C. Anhydrous methanol (5 mL) and a 1:1 (v/v)solution of methylamine in anhydrous methanol (5 mL) were added successively and the mixture was stirred for 45 min at room temperature. Sodium borohydride (254 mg, 6.7 mmol) was then added. The resultant mixture was stirred overnight and water (50 mL) was added. The mixture was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with brine. After the usual work-up, the residue was subjected to column chromatography (CH_2Cl_2 then CH_2Cl_2/MeOH, 95:5) to give 774 mg (80%) of a mixture of the amine **11** and its epimer.
(17) Fuji, K.; Ichikawa, K.; Node, M.; Fujita, E. *J. Org. Chem.* **1979**, *44*, 1661.
(18) Selected data: **14**: $[\alpha]_D^{20}$ –13.1 (*c* = 1.43, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 1.28–1.38 (m, 9 H), 1.60 (m, 1 H), 2.22 (s, 3 H), 3.06 (s, 3 H), 3.61 (d, 1 H, *J* = 5.2 Hz), 3.78 (s, 3 H), 3.88 (dd, 1 H, *J* = 3.4 Hz, 7.8 Hz), 4.19 (dd, 1 H, *J* = 5.2 Hz, 7.8 Hz), 4.58 (dq, 1 H, *J* = 3.4 Hz, 6.4 Hz), 6.88 and 7.22 (AB system, 2 H, *J* = 8.6 Hz). ^{13}C (50 MHz, $CDCl_3$): δ (ppm) 18.1, 26.6, 27.1, 27.8, 34.0, 38.5, 55.1, 78.0, 79.3, 80.0, 80.7, 109.3, 113.8, 129.0, 130.6, 159.0. MS (CI, NH_3) *m/z* (%) = 374 (MH^+, 100%).
1: mp: 170–171 °C: lit. 172.5–173.5 °C.[4b] $[\alpha]_D^{20}$ –10.5 (*c* = 1.1, MeOH): lit. +12.5 (c 2.55, MeOH) for the enantiomer.[4b] ^{1}H NMR (400 MHz, DMSO): δ (ppm) 1.18 (d, 3 H, *J* = 6.4 Hz), 2.00 (s, 3 H), 3.13 (dq, 1 H, *J* = 4.1 Hz, 6.7 Hz), 3.58 (d, 1 H, *J* = 6.3 Hz), 3.69 (t, 1 H, *J* = 4.1 Hz), 3.78 (s, 3 H), 3.96 (dd, 1 H, *J* = 4.0 Hz, 6.4 Hz), 6.91 and 7.28 (AB system, 4 H, *J* = 8.8 Hz). ^{13}C (50 MHz, DMSO): δ (ppm) 13.5, 35.0, 55.6, 65.6, 74.3, 84.7, 86.0, 114.7, 130.8, 133.0, 160.7. MS (EI) *m/z* (%) = 237 (11), 222 (5), 176 (100), 162 (26), 121 (23).