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# Total synthesis of the alkaloid (−)-codonopsinine from L-xylose☆

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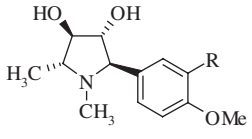
**Abstract**—The enantiopure total synthesis of (−)-codonopsinine is described from commercially available L-xylose in 20% overall yield. The key steps included Julia *trans* olefination and cascade epoxidation–cyclisation strategies.


The total synthesis of alkaloids has always fascinated synthetic organic chemists, not only because many have significant biological activity, but also due to their complex structures and the synthetic challenges they pose. (−)-Codonopsinine **1** and (−)-codonopsine **2** are two such alkaloids isolated from *Codonopsis clematidea*[1] in 1969, their structures with absolute stereochemistry being reported in 1972 by the same group.[2] Despite the fact that these compounds were isolated three decades ago, they continue to attract both synthetic and medicinal chemists due to the challenging penta-substituted pyrrolidine nucleus (four asymmetric carbons with substituents *trans* relative to each other) and varied biological activity as antibiotics and as antihypertensive agents without any effect on the central nervous system.[3] Some elegant synthetic approaches for the synthesis of (−)-codonopsinine **1** have been described.[4]




**1:** R = H (-)-codonopsinine

**2:** R = OMe (-)-codonopsine

Our continued interest in the chiral synthesis of bioactive compounds following a chiron approach prompted us to explore the possibility of synthesising (−)-codonopsinine starting from a pentose sugar namely L-xylose (Scheme 1).

For the synthesis of (−)-codonopsinine **1**, L-(−)-xylose was transformed by a known route in to 1,2-*O*-isopropylidine-α-L-xylofuranose **7**.[5] The primary alcohol in **7** was selectively tosylated by treating with *p*-tosyl chloride and triethylamine in dichloromethane giving **8** in 90% yield, which on reduction with lithium aluminium hydride in THF afforded **9** in 88% yield. Protection of the hydroxy group in **9** using *p*-methoxybenzyl bromide (PMBBr) and NaH in THF gave **5** in 94% yield, which on hydrolysis of the 1,2-acetonide with catalytic $H_2SO_4$ and 60% aq AcOH furnished **10** in 87% yield. Oxidative cleavage of **10** with $NaIO_4$ in MeOH–$H_2O$ (8:2) and subsequent Julia olefination of the unstable aldehyde **11** with sulfone **12** which was prepared from *p*-methoxybenzyl bromide and mercaptobenzothiazole[6] gave **4** in 72% yield. The formyl group in compound **4** was subjected to de-*O*-formylation with $NaBH_4$ in MeOH to afford **13** in 97% yield. The hydroxy group in compound **13** was treated with mesyl chloride and triethylamine in dichloromethane and subsequent azidation with $NaN_3$ in hot DMF (70 °C) gave **14** in 89% overall yield.

Removal of the PMB group in **14** with $ZrCl_4$ in $CH_3CN$ gave allyl alcohol[7] **15** in 86% yield. The azide group in **15** was subjected to reduction and protection using $PPh_3$ in benzene and water at 45 °C followed by exposure to $(Boc)_2O$ furnishing **3** in 88% yield. The allyl alcohol in **3** was epoxidised with *m*-CPBA in $CH_2Cl_2$ to furnish

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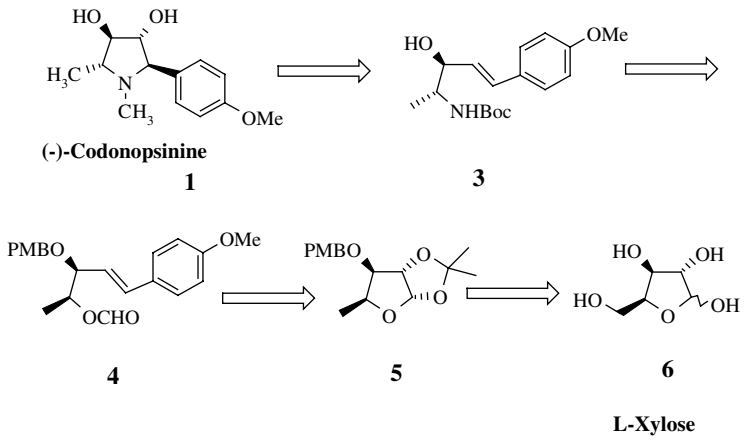
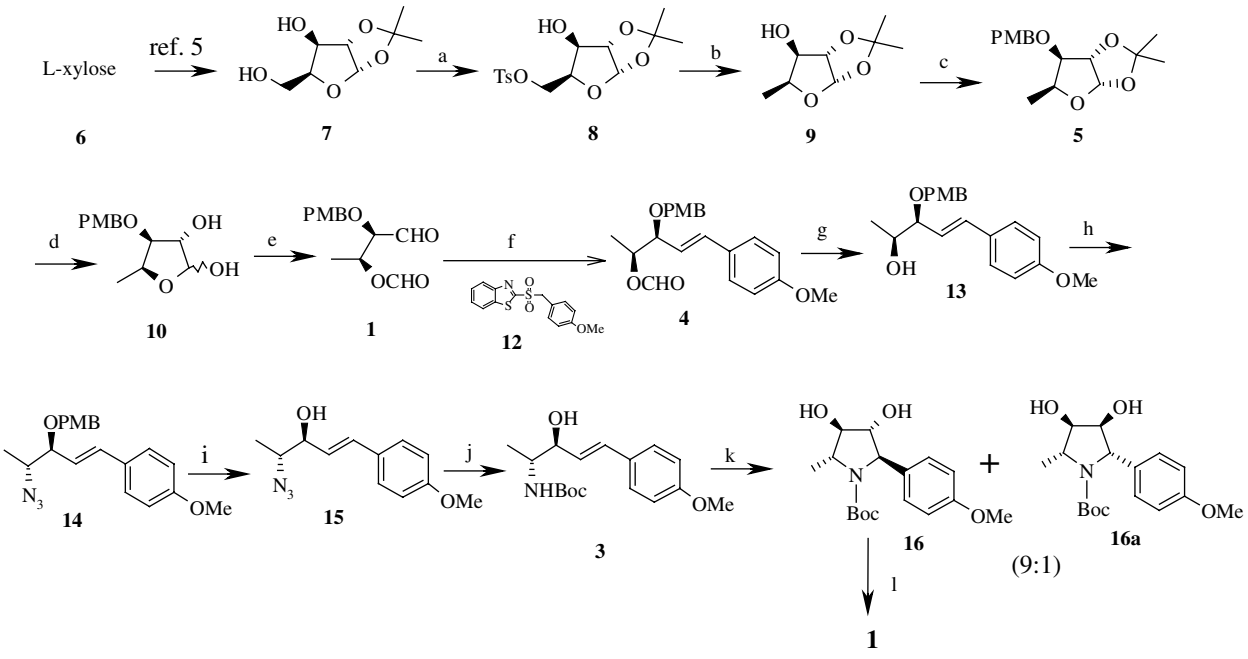



**Scheme 1.**




**Scheme 2.** Reagents and conditions: (a) TsCl, $Et_3N$, $CH_2Cl_2$, 0 °C to rt, 90%; (b) $LiAlH_4$, THF, 0 °C to rt, 88%; (c) PMBBr, NaH, THF, 94%; (d) 60% aq AcOH, cat. $H_2O_4$, 87%; (e) $NaIO_4$, MeOH–$H_2O$; (f) NaHMDS, THF, −78 °C, 72% (for two steps); (g) $NaBH_4$, MeOH, 97%; (h) (i) MsCl, $Et_3N$, 0 °C; (ii) $NaN_3$, DMF, 70 °C, 89% (for two steps); (i) $ZrCl_4$, acetonitrile, 86%; (j) (i) TPP, benzene, $H_2O$, 45 °C; (ii) $(Boc)_2O$, $Et_3N$, 88% (for two steps); (k) *m*-CPBA, $CH_2Cl_2$, 0 °C, 89%; (l) red-Al, toluene, reflux, 83%.

pyrrolidine diols, **16** and **16a** in a ratio of 9:1 with a combined yield of 89% in a single pot transformation. The absolute stereochemistry of the newly created diol was confirmed based on literature precedence[8] and by the spectral data of the final compound. The major comparison with isomer was easily isolated by flash column chromatography using 38% EtOAc in hexane. Finally, the Boc group in **16** was converted to a methyl group using red-Al in toluene under reflux[9] for 2 h yielding (−)-codonopsinine[10] in 83% yield (Scheme 2).

In conclusion, we have shown how a Julia olefination and epoxidation–intramolecular cyclisation cascade can provide an extremely convenient strategy for the synthesis of polyhydroxylated pyrrolidines. The total synthesis of similar molecules using this strategy is currently being pursued.

## Acknowledgements

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## Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.02.140.

## References and notes

1. (a) Matkhalikova, S. F.; Malikov, V. M.; Yunusov, S. Y. *Khim. Prir. Soedin* **1969**, *5*, 606–607; *Chem. Abstr.* **1970**,

*73*, 25712d; (b) Matkhalikova, S. F.; Malikov, V. M.; Yunusov, S. Y. *Khim. Prir. Soedin* **1969**, *5*, 30–32; *Chem. Abstr.* **1969**, *71*, 13245z.
2. Yagudaev, M. R.; Matkhalikova, S. F.; Malikov, V. M.; Yunusov, S. Y. *Khim. Prir. Soedin* **1972**, *8*, 495–498, *Chem. Abstr.* **1972**, *77*, 16490m.
3. (a) Matkhalikova, S. F.; Malikov, V. M.; Yugadaev, M. R.; Yunosov, S. Y. *Farmakol. Alkaloidov Serdech. Glikoyidov* **1971**, 210, *Chem. Abstr.* **1972**, *77*, 135091r; (b) Iida, H.; Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1986**, *27*, 5393–5396.
4. (a) Haddad, M.; Larcheveque, M. *Synlett* **2003**, 274–276; (b) Toyao, A.; Tamura, O.; Takagi, H.; Ishibashi, H. *Synlett* **2003**, 35–38; (c) Yoda, H.; Nakajima, T.; Takabe, K. *Tetrahedron Lett.* **1996**, *37*, 5531–5534; (d) Severino, E. A.; Correia, C. R. D. *Org. Lett.* **2000**, *2*, 3039–3042; (e) Goti, A.; Cicchi, S.; Mannucci, V.; Cardona, F.; Guarna, F.; Merino, P.; Tejero, T. *Org. Lett.* **2003**, *5*, 4235–4238; (f) Oliveira, D. F.; Severino, E. A.; Correia, C. R. D. *Tetrahedron Lett.* **1999**, *40*, 2083–2086.
5. (a) Wang, Z.; Wiebe, L. I.; Balzarini, J.; Clercq, E. D.; Knaus, E. E. *J. Org. Chem.* **2000**, *65*, 9214; (b) Joseph, R.; Snyder; Serianni, A. S. *Carbohydr. Res.* **1987**, *163*, 169–188.
6. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28.
7. Sharma, G. V. M.; Reddy, C. G.; Krishna, P. R. *J. Org. Chem.* **2003**, *68*, 4574–4575.
8. Benedetti, F.; Berti, F.; Dinon, F.; Nardin, G.; Norbedo, S. *Org. Lett.* **2004**, *6*, 1017–1019.
9. Tsuzuki, Y.; Tomita, K.; Sato, Y.; Kashimoto, S.; Chiba, K. *J. Med. Chem.* **2004**, *47*, 2097–2109.
10. Spectral data for selected compounds: compound **1**: white solid, mp 168–171 °C; $[\alpha]_D^{25}$ −12.4 (*c* 0.4, MeOH), lit.[1]; mp 169–170 °C, $[\alpha]_D^{20}$ −8.8 (*c* 0.1, MeOH); $^1$H NMR (300 MHz, pyridine-$d_5$): $\delta$ 7.60 (d, 2H, $J$ = 8.4 Hz), 6.96 (d, 2H, $J$ = 8.4 Hz), 4.63 (br t, 1H, $J$ = 3.0, 7.2 Hz), 4.38 (br t, 1H, $J$ = 3.0, 7.2 Hz), 4.08 (br d, 1H, $J$ = 6.0 Hz), 3.70–3.60 (m, 4H), 2.22 (s, 3H), 1.30 (d, 3H, $J$ = 6.0 Hz); $^{13}$C NMR (75 MHz pyridine-$d_5$): $\delta$ 159.5, 135.3, 130.0, 114.2, 86.7, 84.7, 74.2, 65.2, 55.1, 34.7, 13.8; MS (FAB): *m*/*z* $M^+$ 238, 222, 176, 121, 107, 95. HRMS (FAB) for $C_{13}H_{20}NO_3$, calculated (M+1) 238.1443. Found 238.1439.
Compound **4** $[\alpha]_D^{25}$ −17.40 (*c* 1, MeOH); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 8.10 (s, 1H), 7.39–7.20 (m, 4H), 6.86–6.82 (m, 4H), 6.58 (d, 1H, $J$ = 15.5 Hz), 5.94 (dd, 1H, $J$ = 8.1, 14.6 Hz), 5.18–5.02 (m, 1H), 4.62 (d, 1H, $J$ = 9.79 Hz), 4.38 (d, 1H, $J$ = 9.79 Hz), 3.86 (t, 1H, $J$ = 4.0 Hz), 3.80 (s, 6H), 1.28 (d, 3H, $J$ = 6.5 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$): 160.8, 159.7, 159.2, 130.2, 129.9, 129.4, 129.3, 127.8, 126.9, 113.8, 113.6, 81.0, 74.5, 72.4, 55.3, 55.2, 16.3; MS (EI): *m*/*z* $M^+$ 356. HRMS (EI) for $C_{21}H_{24}O_5$, calculated 356.1624. Found 356.1621.
Compound **14** $[\alpha]_D^{25}$ −70.20 (*c* 0.5, MeOH); $^1$H NMR (200 MHz, $CDCl_3$): $\delta$ 7.35–7.18 (m, 4H), 5.96 (m, 4H), 6.48 (d, 1H, $J$ = 15.5 Hz), 6.00–5.90 (dd, 1H, $J$ = 8.1,14.6 Hz), 4.58 (d, 1H, $J$ = 8.9 Hz), 4.35 (d, 1H, $J$ = 8.9 Hz), 3.88–3.77 (m, 7H), 3.58–3.49 (m, 1H), 1.22 (d, 3H, $J$ = 7.3 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ 159.5, 159.0, 134.5, 130.1, 129.2, 128.9, 127.8, 123.4, 114.0, 113.7, 82.7, 69.9, 60.7, 55.3, 55.2, 15.2; MS (EI): *m*/*z* $M^+$ 353.
Compound **16** $[\alpha]_D^{25}$ −50.18 (*c* 1, MeOH); $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.16 (d, 2H, $J$ = 9.2 Hz), 6.88 (d, 2H, $J$ = 9.2 Hz), 4.55 (br s, 1H), 3.99 (m, 2H), 3.80 (m, 4H), 1.38 (d, 3H, $J$ = 6.0 Hz), 1.25 (s, 9H); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 158.7, 154.0, 134.6,127.3, 113.8, 81.7, 79.6, 60.6, 59.3, 55.2, 28.0, 18.5, 17.7; MS (EI): *m*/*z* $M^+$ 323.