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A highly efficient synthesis of (*S*)-(+)-*N*-Boc-coniine using ring-closing olefin metathesis (RCM)

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Abstract

Optically active (*S*)-(+)-coniine as an *N*-Boc protected form was concisely prepared starting from an amino acid, L-norvaline. The key step involved a ring-closing olefin metathesis (RCM) of the dialkenyl compound **6** to give the corresponding cyclic olefin **8** in an essentially quantitative yield.

Alkaloids with a piperidine skeleton are widespread in important natural products. Numerous synthetic strategies for the construction of these physiologically important compounds have therefore been reported.[1] Optically active coniine (**1**, R=H), the poisonous hemlock alkaloid, has served as a building block for many different groups to demonstrate the utility of the synthetic methodologies developed.[2] Herein we report a highly concise synthesis of (*S*)-(+)-*N*-Boc-coniine using a ring-closing olefin metathesis reaction as a key step.

Reduction of a commercially available amino acid (**2**, L-norvaline) followed by *N*-protection in a one-pot operation provided the *N*-*tert*-butoxycarbonyl (*N*-Boc) amino alcohol **3** in 91% overall yield (Scheme 1).[3] The treatment of **3** with I_2 in the presence of Ph_3P and imidazole transformed the hydroxyl group of **3** to the iodide **4** in 74% yield.[4] The iodide **4** was then homologated by the use of vinylmagnesium bromide (2 equiv.) in combination with copper iodide (1 equiv.) to yield the olefin **5** (70%).[5] The use of either CuBr–SMe_2 or CuCN instead of CuI resulted in slightly lower yields (45–60%). *N*-Allylation of **5** with allyl bromide in DMF provided the dialkenyl compound **6** that served as the precursor for the ring formation reaction. Ring-closing metathesis (RCM)[6] of **6** was performed with the Grubbs' ruthenium benzylidene catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$ (**7**, 3 mol%) in CH_2Cl_2 under the atmosphere of nitrogen.[7] The diene **6** was completely consumed within 3 h at room temperature creating the cyclic olefin **8** in an essentially quantitative yield.[8] Palladium catalyzed hydrogenation of the olefin **8** using a hydrogen balloon furnished in 95% yield the *N*-Boc-protected (*S*)-(+)-coniine **1** (R=Boc, $[\alpha]_D^{20}=+32.8$ (*c* 0.43, $CHCl_3$)).[9] The spectral data for this compound matched in all aspects those reported in the literature.[2]

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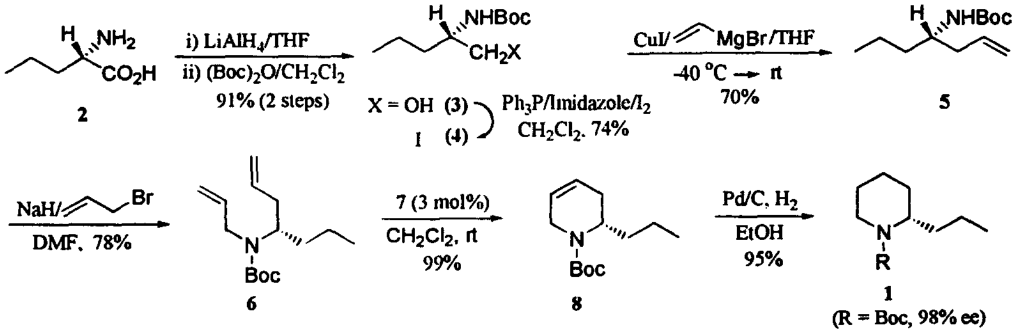

Scheme 1.

In conclusion, we present an efficient synthesis of (*S*)-(+)-*N*-Boc-coniine in seven steps with 35% total yield. If a suitable amino acid was chosen as a starting material, this approach should be amenable to the synthesis of a range of optically active piperidine moieties having a substituent at the 2-position.

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References

1. (a) Hammann, O. In *Organic Synthesis Highlights II*; Waldmann, H., Ed.; VCH: New York, 1995; p. 323. (b) Schneider, M. J. In *Alkaloids: Chemical & Biological Perspectives*; Pelletier, S. M., Ed.; Pergamon: Oxford, 1996; Vol 10, Chapter 2, p. 155.
2. (a) Enders, D.; Tiebes, J. *Liebigs Ann. Chem.* **1993**, 173. (b) Reding, M. T.; Buchwald, S. L. *J. Org. Chem.* **1998**, *63*, 6344. (c) Davies, S. B.; McKervey, M. A. *Tetrahedron Lett.* **1999**, *40*, 1229, and references cited therein.
3. All new compounds were fully characterized by spectroscopic means including ^{1}H and ^{13}C NMR, IR and HRMS.
4. Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198.
5. Kotsuki, H.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1990**, *55*, 4417.
6. For recent reviews on olefin metathesis see: (a) Ivin, K. J. *J. Mol. Cat. A-Chem.* **1998**, *133*, 1. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (c) Randall, M. L.; Snapper, M. L. *J. Mol. Cat. A-Chem.* **1998**, *133*, 29.
7. It was previously shown that piperidine ring systems could be either in general or for specific purposes constructed using ring-closing metathesis: (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324. (b) Huwe, C. M.; Kiehl, O. C.; Blechert, S. *Synlett* **1996**, 65. (c) Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677.
8. Representative procedure for the preparation of **8**: To a solution of **6** (0.13 g, 0.51 mmol) in methylene chloride (3 ml) was added the Ru–benzylidene complex **7** (12.6 mg, 0.015 mmol, 3 mol%) and the reaction mixture was stirred at room temperature for 3 h. After removal of the solvent under the reduced pressure, the residue was flash chromatographed on silica gel (ethyl acetate:hexanes=1:20) to afford the cyclic olefin **8** (114 mg, 99%) as a colorless liquid; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.71–5.66 (m, 2H), 4.29 (m, 2H), 3.45 (d, *J*=18.2 Hz, 1H), 2.43 (d, *J*=17.3 Hz, 1H), 1.90 (d, *J*=17.3 Hz, 2H), 1.55–1.49 (m, 2H), 1.48 (s, 9H), 1.11 (m, 4H), 0.91 (t, *J*=6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 155.5, 123.8, 123.3, 79.6, 48.6, 34.1, 28.6, 28.3, 20.1, 14.4; IR (in CH_2Cl_2, cm^{-1}) 3440, 2962, 2933, 1696, 1601, 1159; HRMS (CI) $C_{13}H_{22}NO_2$ $[M-H]^+$ 224.1650, found 224.1648.
9. The specific optical rotation measured in this work corresponds to 98% ee judging from the known value: Ref. 2a $[\alpha]_D^{20}$=+33.5 (*c* 0.43, $CHCl_3$), Ref. 2b $[\alpha]_D^{20}$=+29.8 (*c* 1.3, $CHCl_3$).