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A facile approach to the synthesis of securinega alkaloids: stereoselective total synthesis of (−)-allonorsecurinine

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ABSTRACT

A concise stereoselective total synthesis of alkaloid (−)-allonorsecurinine is described utilizing classical reactions such as Grignard, Aldol and Horner–Wittig reactions as the key steps.

The securinega alkaloids isolated from plants of the Euphorbiaceae family have attracted significant interest from the synthetic chemistry community and biologist because of their complex ring systems and important biological activities exhibited by them.[1] Historically, many of the plants that produce these alkaloids have been used in traditional folk medicine.[2] Though securinine, the first alkaloid from this class was found to be a specific GABA receptor antagonist and displayed significant in vivo CNS activity,[3] further exploration of this class of compounds led to the identification of molecules exhibiting potent biological properties such as antimalarial,[4] antibiotic,[5] antifungal,[6] antipyretic,[7] diuretic,[8] and in the treatment of hepatic disorders.[9] Structurally, many of the molecules from this class have a common bridged tetracyclic ring system which forms a major back bone skeleton and based on the size of the heterocycle (ring A), they are classified into two main groups securinine (wherein a six-membered heterocycle, piperidine is present) and norsecurinine group (wherein a five-membered heterocycle, pyrrolidine is present). Owing to the unique structural feature (Fig. 1) and significant biological properties of these compounds, several synthetic efforts have been made and are well precedented in the literature.[10,11]

In continuation of our efforts on studies towards the total synthesis of lactone containing natural products[12] and as part of an academic exercise, we have initiated a programme to develop a general strategy for these complex and biologically interesting lactone containing alkaloids. We herein describe a strategy involving the classical synthetic approach utilizing Grignard reaction, Aldol reaction and a Horner–Wittig reaction as the key steps for the total synthesis of (−)-allonorsecurinine

Initially, our intent was to elaborate the commercially available L-proline into a bicyclic compound **11** with A & C rings followed by the extension of the C ring to form the CD ring **10** with appropriate stereogenicity. Finally, the pyrrolidine ring A and bicyclic CD ring can be bridged together using an intramolecular nucleophilic substitution reaction to form the B ring affording the tetracyclic framework of norsecurinine (Scheme 1). The strategy can be potentially extended to the synthesis of securinines by starting with an appropriate enantiopure pipecolinic acid.

Our synthesis began with Boc protection of secondary amine L-proline with di-*tert*-butyl dicarbonate[13] to get carbamate **14**

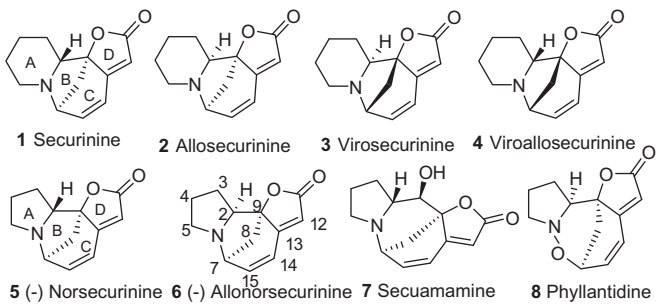

Figure 1. Structures of a few securinega alkaloids.

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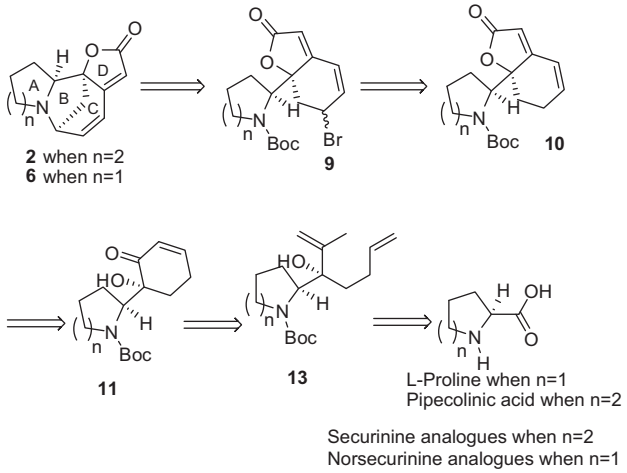
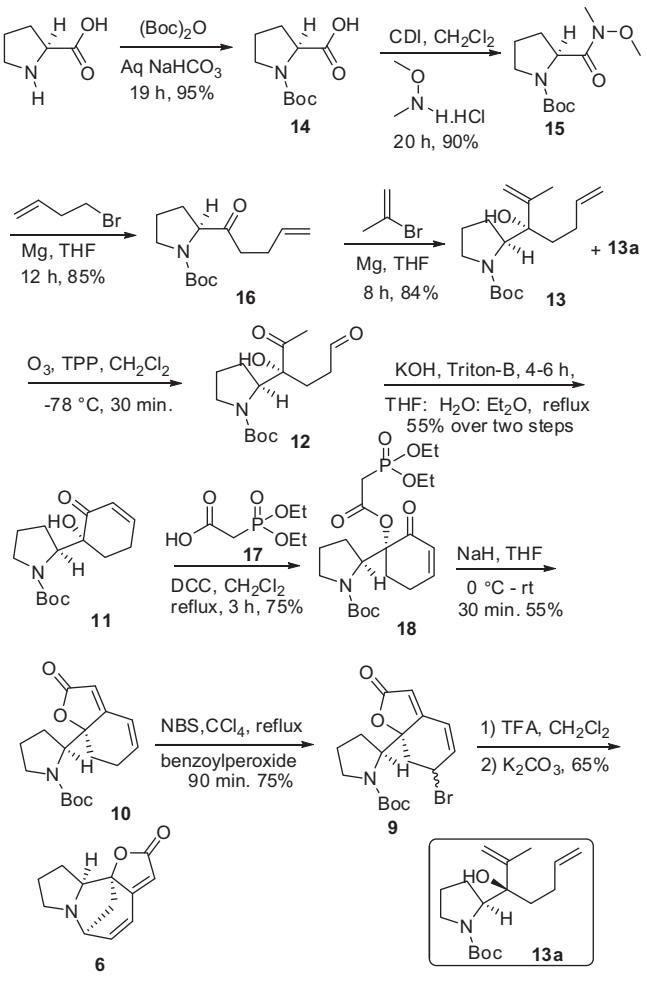


Scheme 1. General retrosynthetic strategy for securinine and norsecurinine analogues.



Scheme 2. Synthesis of (−)-allonorsecurinine.

which was converted to the corresponding Weinreb amide **15** with *N*,*O*-dimethylhydroxylamine hydrochloride using 1,1′-carbonyl diimidazole (CDI).[14] Weinreb amide **15** was subjected to Grignard reaction with homoallyl magnesium bromide (generated in situ with homoallyl bromide and magnesium) to yield ketone **16**. Ketone **16** when subjected to Grignard reaction with the isopropenyl magnesium bromide (prepared by 2-bromo-1-propene and magnesium) gave the mixture of diastereomers **13** and **13a** in 95:5 ratio.[15] Though, we could not establish the stereochemistry of the products based on NOE studies at this stage, later it was confirmed that the major product has 2*S*,9*S* configuration based on the final product synthesized (vide infra). The major diastereomer **13** was subjected to ozonolysis to get the crude dicarbonyl compound **12** which was directly treated with KOH in the presence of triton-B to yield the aldol product enone **11** (C ring formation) in 55% over-all yield.[16] Utilizing the free tertiary alcohol adjacent to carbonyl functionality in **11**, we proceeded further for the construction of the D ring. The tertiary alcohol **11** was coupled with phosphonate derived acetic acid **17** employing standard DCC coupling protocol[17] to get the ester **18** and was then subjected to the Horner–Wittig reaction[18] with NaH to yield the product butenolide **10** (D ring) affording product with bridged CD ring skeleton. The spectral data of this compound was found to be identical to that of the reported structure.[10f] With the three rings in the skeleton (A and BC), next was to complete the synthesis of the tetracyclic core by bridging the A ring with the C ring to form the B ring. Accordingly, we proceeded with allylic bromination of the product **10** with NBS in the presence of benzoyl peroxide to yield the corresponding bromide **9**. The compound **9** upon TFA mediated Boc deprotection followed by base (K_2CO_3) induced nucleophilic substitution reaction[10f] produced the B ring affording the tetracyclic core **6** thus accomplishing the total synthesis of (−)-allonorsecurinine **6** (Scheme 2). The spectral data of our compound were identical with those of the reported data[10f] (^{1}H and ^{13}C NMR) with a variation in the optical rotation.[19]

In conclusion, the total synthesis of (−)-allonorsecurinine has been accomplished. The adopted strategy is very facile and paves the way for the synthesis of other natural and unnatural securinine and norsecurinine analogues by starting with the appropriate chiral proline or pipecolinic acids involving a similar set of reaction sequences. Further application of this strategy towards the synthesis of other analogues is currently being investigated.

Acknowledgments

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Supplementary data

Supplementary data (Experimental details and analytical data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.088.

References and notes

1. (a) For reviews on Securinega alkaloids, see. Snieckus, V.; The Securinega Alkaloids In *The Alkaloids:The Alkaloids Manske*; R. H. F.; Academic Press: New York, 1973; Vol. 14, pp 425–503; (b) Buetler, J. A.; Brubaker, A. N. *Drugs Fut.* **1987**, *12*, 957–976; (c) Bayon, P.; Busque, F. M.; Figueredo *Targets Hetercocyclic System* **2005**, *9*, 281–310.
2. (a) Nakano, T.; Terao, S.; Lees, K. H.; Saeki, Y.; Durham, L. J. *J. Org. Chem.* **1966**, *31*, 2274–2279; (b) Horii, Z.; Imanishi, T.; Yamauchi, M.; Hanaoka, M.; Parello, J.; Munavalli, S. *Tetrahedron Lett.* **1972**, *13*, 1877–1880.
3. Beutler, J. A.; Karbon, E. W.; Brubaker, A. N.; Malik, R.; Curtis, D. R.; Enna, S. J. *Brain Res.* **1985**, *330*, 135–140.
4. Weenen, H.; Nkunya, M. H. H.; Bray, D. H.; Mwasumbi, L. B.; Kinabo, L. S.; Kilimali, V. A.; Wijnberg, J. B. *Planta Med.* **1990**, *56*, 371–373.
5. Mensah, J. L.; Lagarde, I.; Ceschin, C.; Michel, G.; Gleye, J.; Fouraste, I. *J. Ethnopharmacol.* **1990**, *28*, 129–133.
6. (a) Singh, A. K.; Pandey, M. B.; Singh, U. P. *Mycobiology* **2007**, *35*, 62–64; (b) Sangita, S.; Maurya, S.; Singh, U. P.; Singh, A. K.; Singh, V. P.; Pandey, V. B. *Mycobiology* **2005**, *33*, 97–103.
7. Serra, R. M. *An. Univ. Santo Domingo.* **1944**, *8*, 295–297.
8. Van der Woerd, L. A.; Geneeskd *Tijdschr. Ned. -Indie* **1941**, *81*, 1963–1980.

9. Nadkarni, A. K. *Indiana Materia Medica*; Popular Prakashan Prt. Ltd: Bombay, 1976.
10. For review on total synthesis of Securinega alkaloids see (a) Weinreb, S. M. *Nat. Prod. Rep.* **2009**, *26*, 758–775; For other publications of securinines (b) Satoda, I.; Murayama, M.; Tauji, J.; Yoahii, E. *Tetrahedron Lett.* **1962**, *3*, 1199–1206; (c) Honda, T.; Namiki, H.; Kudoh, M.; Watanbe, N.; Nagase, H.; Mizutani, H. *Tetrahedron Lett.* **2000**, *41*, 5927–5930; (d) Liras, S.; Davoren, J.; Bordner, J. *Org. lett.* **2001**, *3*, 703–706; (e) Honda, T.; Namiki, H.; Watanbe, M.; Mizutani, H. *Tetrahedron Lett.* **2004**, *45*, 5211–5213; (f) Honda, T.; Namiki, H.; Kaneda, K.; Mizutani, H. *Org. lett.* **2004**, *6*, 87–89; (g) Alibes, R.; Ballbe, M.; Busque, F.; March, P.; Elias, L.; Figuredo, M.; Font, J. *Org. Lett.* **2004**, *6*, 1813–1816; (h) Bardaji, G. G.; Canto, M.; Alibes, R.; Bayon, P.; Busque, F.; March, D. D.; Figueredo, M.; Font, J. *J. Org. Chem.* **2008**, *73*, 7657–7662; (i) Leduc, A. B.; Kerr, M. A. *Angew. Chem.* **2008**, *47*, 7945–7948; (j) Dhudshia, B.; Cooper, B. F. T.; Macdonald, C. L. B.; Thadani, A. N. *Chem. Commmun.* **2009**, *45*, 463–465; (k) Gonzalez-Galvez, D.; Garcia-Garcia, E.; Alibes, R.; Bayon, P.; March, P.; Figueredo, M.; Font, J. *J. Org. Chem.* **2009**, *74*, 6199–6211.
11. Other syntheses for norsecurinines (a) Jacobi, P. A.; Blum, C. A.; Desimome, R. W.; Udodong, U. E. S. *Tetrahedron Lett.* **1989**, *30*, 7173–7176; (b) Han, G.; Laporte, M. G.; Folmer, J. J.; Werner, K. M.; Weinreb, S. M. *J. Org. Chem.* **2000**, *65*, 6293–6306; (c) Alibes, R.; Bayon, P.; March, P. D.; Figueredo, M.; Font, J.; Garcia-Garcia, E.; Gonzalez-Galvez, D. *Org. Lett.* **2005**, *7*, 5107–5109; (d) Medeiros, M. R.; Wood, J. L. *Tetrahedron* **2010**, *66*, 4701–4709; Other analogues (e) Magnus, P.; Lopez, J. R.; Mulholland, K.; Matthews, I. *Tetrahedron* **1993**, *49*, 8059–8072; (f) Han, G.; Laporte, M. G.; Folmer, J. J.; Werner, K. M.; Weinreb, S. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 237–240; (g) Carson, C. A.; Kerr, M. *Angew. Chem.* **2006**, *118*, 6710–6713; (h) Liu, P.; Hong, S.; Weinreb, S. M. *J. Am. Chem. Soc.* **2008**, *130*, 7562–7756.
12. (a) Srihari, P.; Mahankali, B.; Rajendra Prasad, K. *Tetrahedron Lett.* **2012**, *53*, 56–58; (b) Srihari, P.; Satyanarayana, K.; Ganganna, B.; Yadav, J. S. *J. Org. Chem.* **2011**, *76*, 1922–1925; (c) Yadav, J. S.; Mandal, S. S.; Reddy, J. S. S.; Srihari, P. *Tetrahedron* **2011**, *67*, 4620–4627; (d) Srihari, P.; Maheswar Rao, G.; Srinivasa Rao, R.; Yadav, J. S. *Synthesis* **2010**, 2407–2412; (e) Srihari, P.; Kumaraswamy, B.; Shankar, P.; Ravishashidhar, V.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 6174–6176; (f) Srihari, P.; Kumaraswamy, B.; Bunia, D. C.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 2903–2905; (g) Srihari, P.; Kumaraswamy, B.; Maheswar Rao, G.; Yadav, J. S. *Terahedron: Asymmetry* **2010**, *21*, 106–111.
13. Huy, P.; Neudorfl, J. M.; Schmalz, H. G. *Org. Lett.* **2011**, *13*, 216–219.
14. Moldvai, I.; Domyei, G.; Major, E. T.; Szantay, C. *Org. Prep. Proc. Int* **2007**, *39*, 503–508.
15. The diastereomeric ratio was calculated based on the isolated yields after column chromatography. Based on the stereochemistry of final product, we believe that Grignard reaction might have proceeded by facial selectivity that is, *si* face attack.
16. (a) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1780–1783; (b) Yadav, J. S.; Tirupataiah, B.; Srihari, P. *Tetrahedron* **2010**, *66*, 2005–2009. The reaction worked well when Triton-B was utilized as a catalyst.
17. Clive, D. L. J.; Huang, X. *Tetrahedron* **2002**, *58*, 10243–10250.
18. (a) Horner, L.; Hoffmann, H.; Wippel, H. G. *Chem. Ber.* **1958**, *91*, 61–63; (b) Wordswoth, W. S.; Emmons, W. D., Jr. *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738; (c) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405–4408.
19. *Selective analytical data; Allonorsecurinine* ***6***: $[\alpha]_D^{25}$ −40.0 (*c* 0.53, EtOH); lit.[10f] $[\alpha]_D^{25}$ −441.3 (*c* 0.3, EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.83 (dd, *J* = 9.0, 6.0 Hz, 1 H), 6.73 (dd, *J* = 9.0, 0.7 Hz, 1H), 5.80 (s, 1H), 4.18 (t, *J* = 7.0 Hz, 1H), 4.04 (t, *J* = 5.0 Hz, 1H), 2.98–2.89 (m, 2H), 2.88–2.80 (m, 1H), 2.05 (d, *J* = 10.0 Hz, 1H), 1.92–1.85 (m, 1H), 1.83–1.76 (m, 1H) 1.72–1.65 (m, 1H), 1.31–1.23 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 166.5, 147.8, 124.2, 110.3, 90.5, 68.8, 57.6, 49.1, 46.6, 27.7, 25.3; **10**: $[\alpha]_D^{20}$ −151.9 (*c* 0.7, $CHCl_3$); Lit.[10f] $[\alpha]_D^{25}$ −166.8 (*c* 0.56, $CHCl_3$). IR (NEAT): 2927, 2856, 1753, 1695, 1650, 1452, 1390, 1249, 1166, 1104, 1027, 922, 852, 764, 648 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.57 (d, *J* = 9.8 Hz, 1H), 6.22 (dt, *J* = 9.8, 3.8 Hz, 1H), 5.57 (s, 1 H), 4.31 (dd, *J* = 5.7, 1.5 Hz, 1H), 3.53–3.46 (m, 1H), 3.27–3.17 (m, 1H), 2.50–2.37 (m, 3H), 2.18–1.73 (m, 5H), 1.38 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 166.1, 154.8, 135.3, 122.6, 109.8, 87.5, 79.3, 58.1, 47.1, 30.1, 26.2, 24.4, 24.3. MS (ESI): *m/z* 328 $[M+Na]^+$. HRMS (ESI): *m/z* calculated for $C_{17}H_{23}O_4NNa$ 328.15193, found 328.15195; **11**: $[\alpha]_D^{20}$ −85.4 (*c* 0.68, $CHCl_3$). IR (KBr): 3413, 2977, 2932, 1685, 1407, 1361, 1252, 1092, 981, 879, 654, 568 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.89–6.81(m, 1H) 6.17 (d, *J* = 9.5 Hz, 1H), 4.36 (d, *J* = 4.0 Hz, 1H), 4.16 (s, 1H), 3.54–3.46 (m, 1H), 3.26–3.21 (m, 1H), 2.50-2.37 (m, 2H), 2.20–2.15 (m, 1H), 2.07–1.91 (m, 4H), 1.74–1.67 (m, 1H), 1.38 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.1, 155.2, 147.0, 128.5, 79.4, 77.4, 59.6, 47.5, 32.5, 28.1, 26.1, 24.7, 24.1 ppm. MS (ESI): *m/z* 304 $[M+Na]^+$. HRMS (ESI): *m/z* calculated for $C_{15}H_{23}O_4NNa$ 304.15193, found 304.15188.