Tetrahedron Letters,Vol.30,No.51,pp 7173-7176,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

TOTAL SYNTHESIS OF (+)- AND (-)-NORSECURININE

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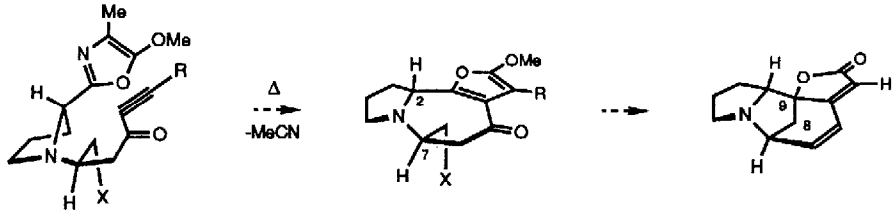
Summary: *(-)-Norsecurinine (**1a**) has been prepared in a stereospecific fashion beginning with the acetylenic oxazole **18**. Diels-Alder cyclization of **18** afforded the furanoketone **19**, which was transformed in five steps to the butenolide mesylate **24**. Transannular alkylation of **24** then afforded **1a**. In identical fashion, ent-**18** gave (+)-norsecurinine (**1b**).*

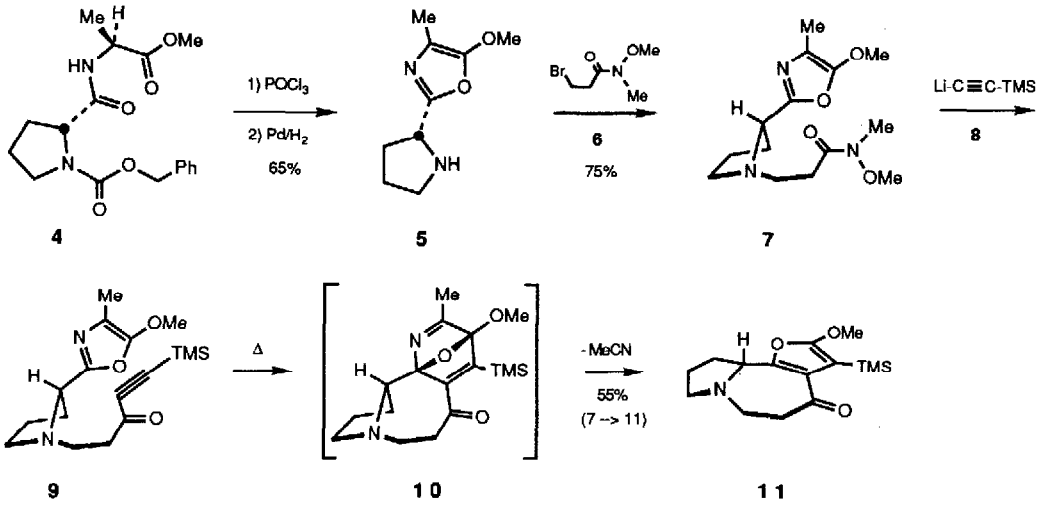
Norsecurinine (**1**) is a member of the *Securinega* class of alkaloids which was initially isolated in the levorotatory form **1a** from *Securinega virosa* by Iketubosin and Mathiesen,[1a] and subsequently in the dextrorotatory form **1b** from *Phylanthus niruri* by Rouffiac and Parello.[2] Interest in **1** derives mainly from the physiological activity exhibited by securinine itself (piperidine ring replaces pyrrolidine in **1a**), which acts as an inhibitor of the acetylcholinesterase system,[3] and produces a stimulant effect in the central nervous system similar to strychnine but possessing lower toxicity.[4] In contrast to the securinine type alkaloids, which are generally stable, crystalline solids, **1** polymerizes readily and is unstable as the free base. This lack of stability restricts the number of synthetic approaches available, and to date only one successful synthesis of (±)-**1** has appeared.[5a] In this note we describe efficient syntheses of both **1a** and **1b** which make use of the oxazole Diels-Alder methodology which we have previously employed for the synthesis of furanoterpenes and related materials.[6]



2 **3** (-)-Norsecurinine (**1a**)

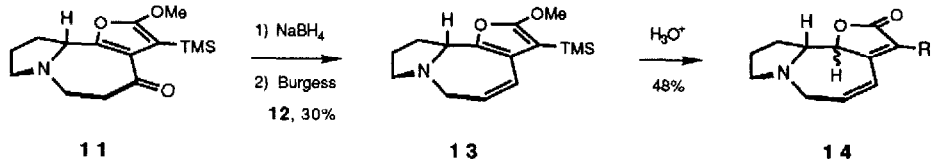
As indicated above, the key intermediate for our synthesis of **1a** was the acetylenic oxazole **2**, which incorporates the correct relative and absolute stereochemistry at C_2 and C_7 found in **1a**. Diels-Alder cyclization of **2** was expected to give the methoxyfuran **3**,[6] which upon hydrolysis and transannular alkylation would afford **1a** (X = leaving group). The feasibility of this approach was initially tested with the model system **9**, which was readily prepared from the known proline derivative **4**[7] (Scheme 1; initial experiments were carried out with **4** derived from

the more readily available L-proline. For convenience, structures are represented as those derived from the



Scheme 1

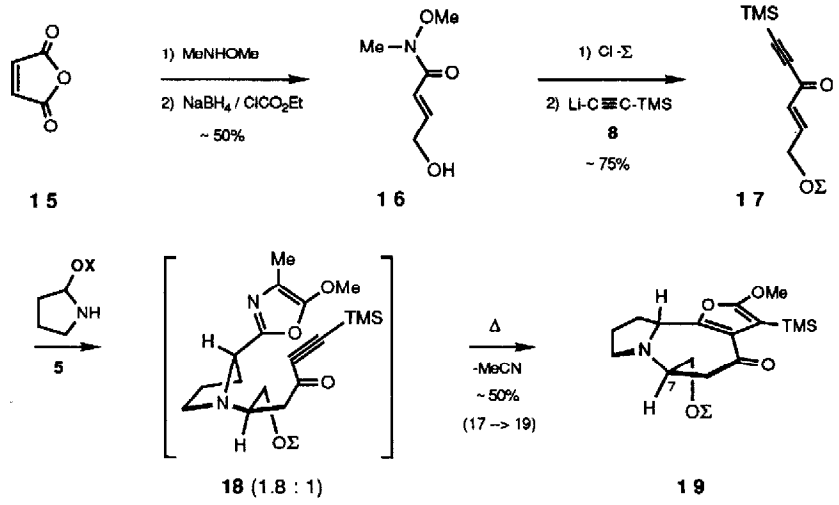
enantiomeric D-Proline[8]). Thus, **4** was first converted to the oxazole pyrrolidine derivative **5** by cyclodehydration followed by catalytic hydrogenation,[9] and **5** was directly alkylated with the bromoamide **6** prepared by reaction of 3-bromopropionyl chloride with N,O-dimethylhydroxylamine. Condensation of **7** with lithiotrimethylsilylacetylide (**8**) then proceeded routinely to afford the acetylenic ketone **9**,[10] which upon brief thermolysis (PhEt, 136° C) provided the furanoketone **11** in 55% overall yield from **7**. Finally, **11** was converted to the butenolide alkene **14** by a sequence of operations involving reduction and elimination to afford the methoxyfuran **13**, which upon acid hydrolysis gave **14** as a mixture of epimers at C_9 (R = H, TMS). Little effort was made to optimize these



transformations. It is worth noting, however, that the elimination step in the sequence **11** ---> **13** proved to be unexpectedly difficult, and of a variety of conditions explored, $Et_3N^+SO_2^-NCO_2Me$ (**12**, Burgess's reagent[11]) was the only reagent which afforded **13** in moderately acceptable yields.

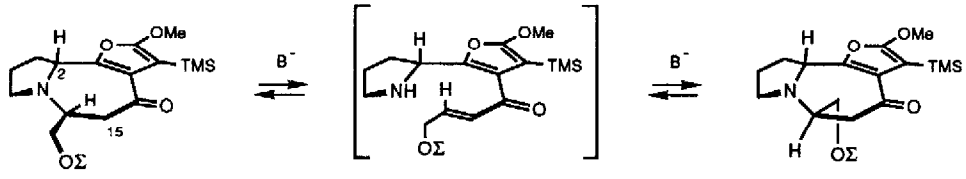
Extrapolation of these studies to the synthesis of (-)-norsecurinine (**1a**) required the preparation of a furanoketone of general structure **3** (*vide supra*). This was readily achieved, in a highly convergent fashion, as diagrammed in Scheme 2 (following page). Thus, maleic anhydride (**15**) was reacted with N,O-dimethylhydroxylamine, and the resulting E-amidoacid was reduced with $NaBH_4/ClCO_2Et$ to afford the E-alcohol **16** in ~50% overall yield. Silylation of **16** (*t*-butyldimethylsilyl chloride, Cl-Σ, 78%) followed by condensation with lithiotrimethylsilylacetylide (**8**) then gave the protected enynone **17** (98%),[10] which proved to be an

exceedingly reactive Michael acceptor. In protic solvents (*i*-PrOH) **17** underwent a rapid addition of the oxazole pyrrolidine **5** to afford the acetylenic ketone **18**,[12] which without purification was converted to the furanoketone **19** by brief thermolysis in mesitylene (~50% overall yield from **17**, 5 - 17 g scales based on **18**). The material thus



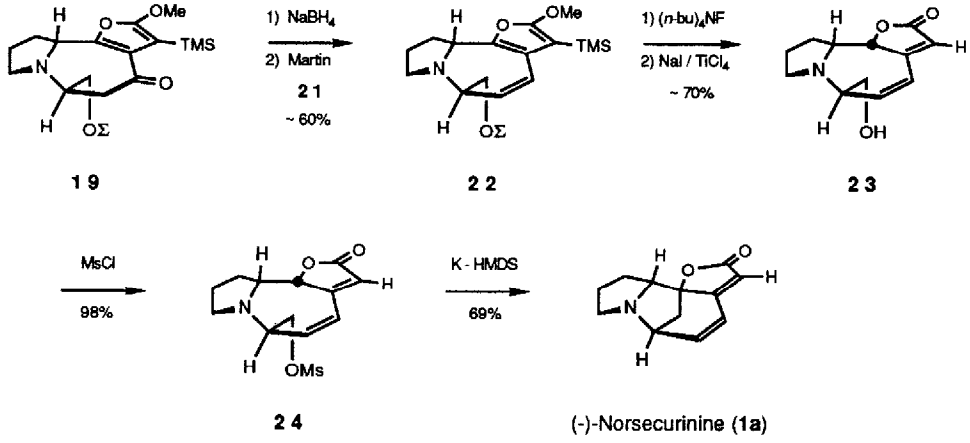
Scheme 2

obtained consisted of an ~ 2 : 1 mixture of **19** together with its C_7 epimer **19S**, which reflects the kinetic bias in the initial condensation of **5** and **17**. In addition, the undesired isomer **19S** could be conveniently recycled by epimerization with Na_2CO_3 in MeOH, which effected a Michael-retro-Michael sequence proceeding through the intermediacy of the enone **20** (see below; **19** : **19S** ≈ 50 : 50 at thermodynamic equilibrium). The mechanism for this interconversion was established by deuterium incorporation studies, which showed exclusive incorporation at C_{15}. An alternative mechanism, involving C_2 proton abstraction, would have yielded *ent*-**19** from **19S** and has been ruled out on the basis of specific rotations obtained in both the D- and L-proline series (*vide infra*).



Furanoketone **19** was next converted to the furanoalkene **22** by initial reduction with $NaBH_4$ (90%) followed by elimination with Martin's reagent ($[C_6H_5C(CF_3)_2O]_2S[C_6H_5]_2$, **21**, 65%) (Scheme 3, following page).[13] Deprotection of **22** (90%), followed by hydrolysis with NaI/$TiCl_4$ (75%),[14a] then afforded the butenolide alcohol **23** as a single isomer,[14b] which was converted to the mesylate **24** in virtually quantitative yield. Finally, transannular alkylation of **24** with K-HMDS gave a 69% yield of (-)-norsecurinine (**1a**), isolated as its HCl salt (mp

228-30° d, lit.[1b] mp 223-25° d), the free base of which had identical spectral data (NMR, IR, UV, mass spectrum) as that published for the naturally occurring substance ($[\alpha]_D$ = -262°, c = 0.06 [EtOH], synthetic; -272°, c = 6.9 [EtOH], natural).[1b] Repetition of the identical reaction sequence described for **1a**, but beginning with L-proline, afforded (+)-norsecurinine (**1b**), also in homochiral form ($[\alpha]_D$ = +268°, c = 0.085 [EtOH]).[15]



Scheme 3

References and Notes

1. (a) Iketubosin, G. O.; Mathieson, D. W. *J. Pharm. Pharmacol.* **1963**, *15*, 810. See also (b) Saito, S.; Tanaka, T.; Kotera, K.; Nakai, H.; Sugimoto, N.; Horii, Z.; Ikeda, M.; Tamura, Y. *Chem. Pharm. Bull.* **1965**, *13*, 786; (c) Snieckus, V. in "The Alkaloids"; Manske, R. H., Ed., Academic Press: New York, 1973, Vol. 14, p. 425.
2. Rouffiac, R.; Parello, J. *Plant. Med. Phytother.* **1969**, *3*, 220.
3. Friess, S. L.; Durant, R. C.; Whitcomb, E. R.; Reber, L. J.; Thommesen, W. C. *Toxicol. Appl. Pharmacol.* **1961**, *3*, 347; *CA* **1961**, *55*, 25053b.
4. Turova, A. D.; Aleshkina, Y. A. *Farmakol. Toksikol. (Moscow)* **1956**, *19*, 11; *CA* **1956**, *50*, 17201a.
5. (a) Heathcock, C. H.; von Geldern, T. W. *Heterocycles* **1987**, *25*, 75, and references cited therein. For an unsuccessful approach to (±)-**1**, see (b) Kucerovy, A. Ph.D. Thesis, Pennsylvania State University, University Park, 1984; *Diss. Abstr. Int. B.* **1984**, *45(6)*, 1780.
6. For a partial listing, see Reference 1 in Jacobi, P. A.; Armacost, L. M.; Kravitz, J. I.; Martinelli, M. J.; Selnick, H. G. *Tetrahedron Lett.* **1988**, *29*, 6865.
7. Savige, W. E. *Aust. J. Chem.* **1961**, *14*, 664.
8. Satisfactory spectral and analytical data were obtained for all new compounds reported.
9. Likhan, R.; Ternai, B. *Adv. Heterocycl. Chem.* **1974**, *17*, 99.
10. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
11. Burgess, E. M.; Penton, H. R., Jr.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.
12. The TMS protecting group in **17** served to prevent Michael addition to the normally more reactive triple bond.
13. Arhart, R. J.; Martin, J. C. *J. Amer. Chem. Soc.* **1972**, *94*, 5003.
14. (a) Mandal, A. K.; Mahajan, S. W. *Tetrahedron* **1988**, *44*, 2293. Direct hydrolysis of **22**, prior to desilylation, gave much lower yields of butenolides. The hydroxyl group may facilitate this reaction by initial ligand exchange with $TiCl_4$, followed by intramolecular complexation at C_9. (b) We are grateful to Ms. Gail Schulte, of Yale University, for carrying out an X-ray analysis of **23**.
15. Financial support of this work by the National Science Foundation, Grant No. CHE-8711922, is gratefully acknowledged.

(Received in USA 5 September 1989)