TOTAL SYNTHESIS OF (±)-NORSECURININE

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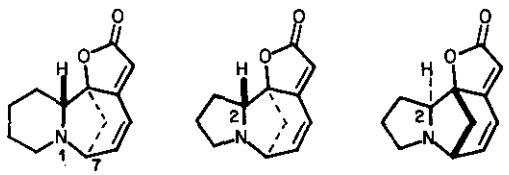
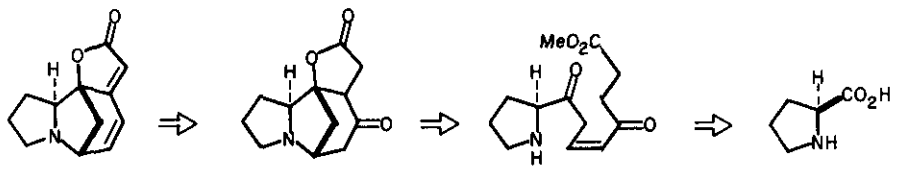
Abstract—The structures of the enantiomeric norsecurinines (2 and 3) have been confirmed by a total synthesis of (±)-2, starting with L-proline.

The Securinega alkaloids consist of a total of seventeen compounds isolated from several species of the Securinega and Phyllanthus genera of Euphorbiaceae.[1] These plants have a notably high concentration of alkaloids; in a number of cases the major alkaloid component comprises 0.25% of the dry plant weight.[2] Securinine (1) is the most abundant member of the group, the first to be identified,[3] and the only Securinega alkaloid to have been prepared by total synthesis.[4,5] Most of the Securinega alkaloids are either securinine stereoisomers or have the securinine skeleton. Four, however, have the ring-A nor structure. The most well characterized of this group are the enantiomeric norsecurinines, 2[6] and 3.[7] In this Communication, we report a total synthesis of (±)-2, which corroborates the assigned structure.



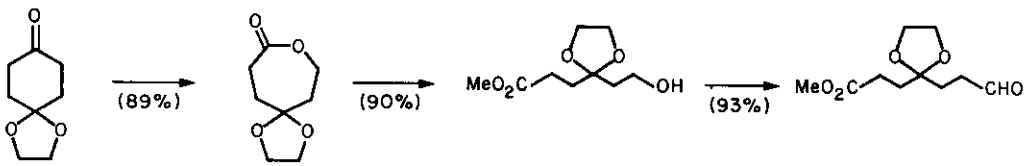
1 2 3

Our retrosynthetic plan is outlined in eq 1. The key maneuver was to be construction of three of the four rings by a series of reactions involving tandem Michael and aldol cyclization, followed by lactonization.



2 (1)

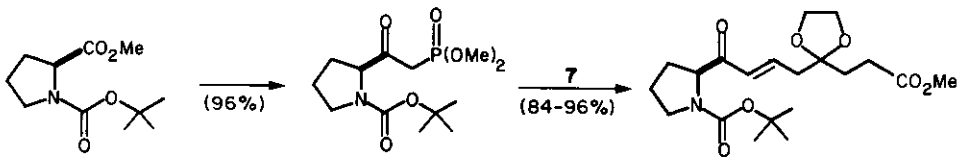
The actual synthesis begins with the monoketal of 1,4-cyclohexanedione (4), which is subjected to Baeyer-Villiger oxidation (CF_3CO_3H, Na_2HPO_4, CH_2Cl_2) to obtain lactone 5 (eq 2). This substance is converted to hydroxy ester 6 (NaOMe, MeOH), which is oxidized by pyridinium dichromate[8] in methylene chloride to secure aldehyde 7.



(2)

4 5 6 7

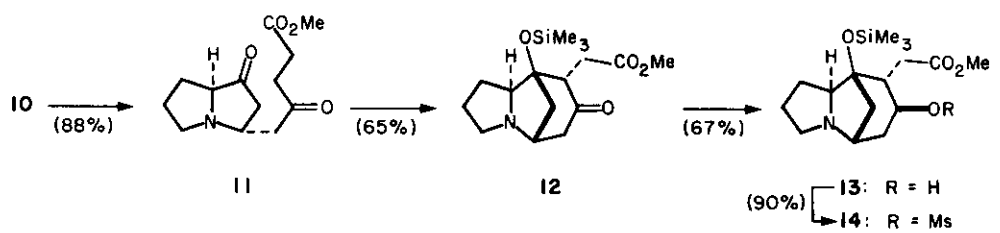
The tert-butoxycarbonyl derivative of methyl prolinate (8) reacts with dimethyl lithiomethylphosphonate to give keto phosphonate 9 (eq 3). When this material is condensed with aldehyde 7 using potassium tert-butoxide as base, enone 10 is obtained in 96% yield and in essentially racemic form. If the Wadsworth-Emmons reaction is carried out under the conditions recently introduced by Masamune, Roush, and coworkers,[9] enone 10 is obtained in enantiomerically enriched (93% ee) form, albeit in only 84% yield.



(3)

8 9 10

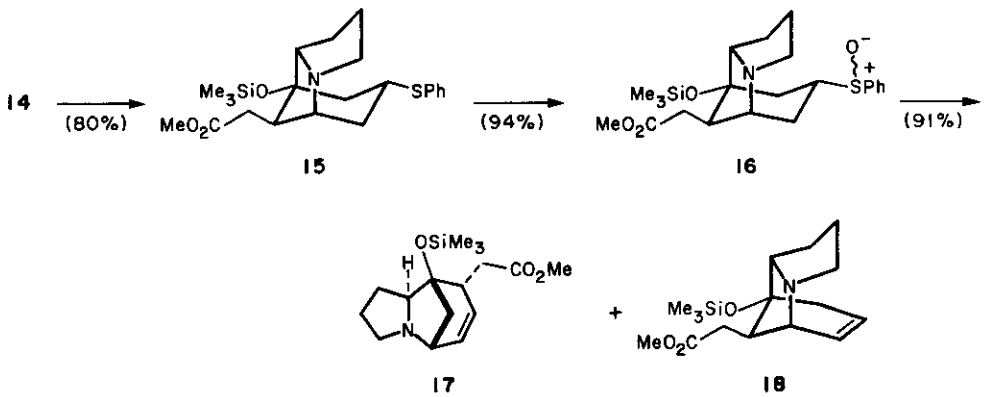
Treatment of enone (±)-10 with HCl in acetic acid gives pyrrolizidone (±)-11 (picrate salt, mp 166-7 °C) in excellent yield. Diketo ester 11 reacts with lithium imidazolide and N-trimethylsilylimidazole to provide tricyclic ketone (±)-12 in 57% overall yield from enone 10 (eq 4). Reduction of the carbonyl group by catecholborane occurs exclusively from the more hindered side, presumably due to prior coordination of the nitrogen with boron, providing equatorial alcohol (±)-13 (rhombic prisms, mp 125-6 °C) in 67% yield. The stereostructure of 13 was fully elucidated by single crystal x-ray analysis.[10] Treatment of alcohol 13 with methanesulfonyl chloride and triethylamine affords mesylate (±)-14 (mp 125-9 °C).



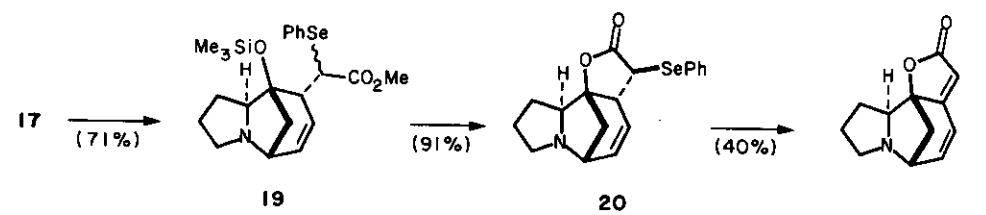
(4)

11 12

As shown in eq 5, rearranged sulfide (±)-15 is obtained when mesylate 14 is heated with thiophenoxide in DMF; the mechanism of the formation of 15 in this reaction has been discussed elsewhere.[11] Oxidation of 15 with m-chloroperoxybenzoic acid gives sulfoxide (±)-16 (1:1 mixture of diastereomers because of the new stereocenter) which is pyrolyzed by heating in toluene. The product, obtained in 91% yield, is a 45:55 ratio of tricyclic amines (±)-17 and (±)-18. Control experiments showed that this ratio is kinetic in nature (e.g., the identical 45:55 ratio is obtained after 1% conversion, and throughout the reaction; added 17 is not converted into 18 during the course of the reaction). This evidence, plus that from other control experiments, suggests that the sulfoxide pyrolysis is not fully concerted, but rather that initial ionization of the carbon-sulfur bond leads to an ion pair in which the cation is the azetidinium ion invoked in our earlier publication on the skeletal rearrangements of 14 and related compounds.[11]



Ester 17 is deprotonated with potassium bis(trimethylsilyl)amide and the resulting enolate selenylated with diphenyl diselenide to obtain (±)-19 as a 6:1 mixture of diastereoisomers. Lactonization is accomplished by heating 19 with p-toluenesulfonic acid in benzene solution; lactone 20 and its diastereomer (6:1 ratio) are produced in good yield. Oxidation of the mixture of lactones with m-chloroperoxybenzoic acid in methanol at -78 °C gives (±)-norsecurinine in 40% yield. The ^{1}H NMR spectrum of the synthetic material was identical to the published spectrum of (2R)-norsecurinine.[6] The synthesis requires 14 steps from the 1,4-cyclohexanedione monoketal and proceeds in 2.0% overall yield.



Optically active 10, $[\alpha]_D$ -23.2° (c = 0.15, $CHCl_3$), has been similarly transformed into 11, $[\alpha]_D$ +3.1° (c = 0.0065, $CHCl_3$), 12, $[\alpha]_D$ +2.0° (c = 0.45, $CHCl_3$), and 13, $[\alpha]_D$ +9.8° (c = 0.13, $CHCl_3$). The latter compound was shown by ^{1}H NMR

and ^{19}F NMR spectroscopic analysis of the derived ester with (+)-2-methoxy-2-trifluoromethyl-2-phenylacetic acid ester to be of 87% enantiomeric excess.[12] We have not yet carried this enantiomerically enriched material through the rest of the synthesis, but is should provide (2S)-norsecurinine.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

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5) The Horii synthesis of securinine roughly traces a reverse degradative path; the key construction is formation of the N-1,C-7 bond by intramolecular displacement of an allylic bromide. Although the synthesis is relatively brief (12 steps from the monoketal of 1,2-cyclohexanedione, the overall yield is only 0.4%, primarily because of a low yield (7.5%) in the final ring-closure reaction.

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