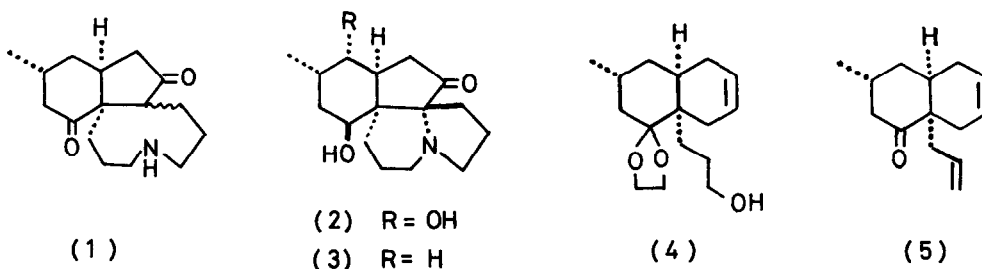


STEREOSELECTIVE SYNTHESSES OF LYCOPODIUM ALKALOIDS,  
(+)-FAWCETTILINE AND (+)-8-DEOXYSERRATININE

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Lycopodium alkaloids, (+)-fawcettimine(1) and (+)-8-deoxyseerratine(3) were stereoselectively synthesized through the stereoselective Diels-Alder reaction and the regioselective aldol condensation reaction of the dialdehyde(8).

Among lycopodium alkaloids, those of the serratinine group<sup>1)</sup> have unique skeletal structures and the possible biogenetic relationship between members of the serratinine group and 12-hydroxylycopodine was suggested.<sup>1)</sup> In these biogenetic schemes, fawcettimine(1) possessing a nitrogen containing nine membered ring was supposed to be the precursor of serratinine group alkaloids. Although chemical correlation of serratinine(2) with fawcettimine(1)<sup>2)</sup> and 8-deoxyseerratine(3)<sup>3)</sup> has been achieved, total syntheses of these alkaloids have not been accomplished. We wish to report here stereoselective syntheses of (+)-fawcettimine(1) and (+)-8-deoxyseerratine(3).



We reported that Diels-Alder addition of butadiene to 2,5-dialkylcyclohex-2-en-1-ones took place stereoselectively from the opposite side to the C<sub>5</sub>-substituent of dienophile.<sup>4),5)</sup> By taking advantage of this type of Diels-Alder reaction, the key intermediate(4) possessing the desired stereostructure was stereoselectively synthesized. Thus, Diels-Alder reaction of 2-allyl-5-methylcyclohex-2-en-1-one<sup>6)</sup> with butadiene in the presence of 0.5 eq. of BF<sub>3</sub>·Et<sub>2</sub>O gave the adduct(5)<sup>\*1</sup>, bp 133-135°/5 mmHg, in 29% yield (53% yield based on the consumed starting material). After acetalization, hydroboration of (5) with disiamylborane, followed by oxidation with H<sub>2</sub>O<sub>2</sub>-NaOH afforded the acetal-alcohol (4), bp 149°/0.14 mmHg, in 50.6% yield. The stereochemistry of (4) was

confirmed by conversion of (4) to the keto-acetate(6)<sup>6)</sup> via acetylation and deacetalization. Benzylolation of (4) with NaH-(n-Bu)<sub>4</sub>Ni-benzyl bromide in THF-HMPA provided the benzyl ether(7)<sup>\*2</sup>, bp 190°/0.08 mmHg, in 82.8% yield, which was successively treated with OsO<sub>4</sub>-N-methylmorpholine N-oxide<sup>7)</sup>, and HIO<sub>4</sub>·2H<sub>2</sub>O to give the dialdehyde(8) in 91.8% yield.

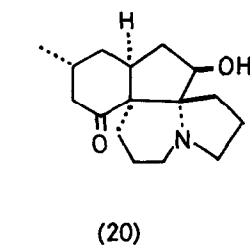
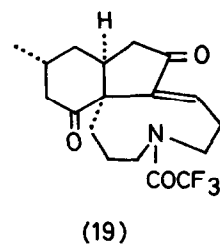
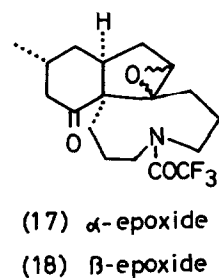
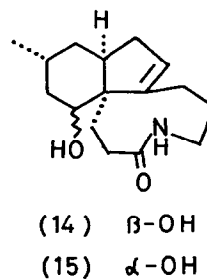
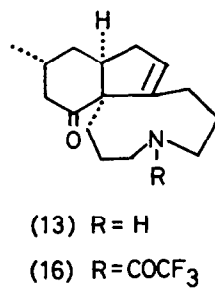
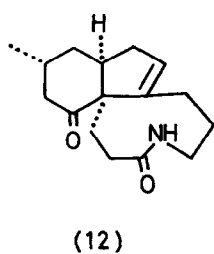
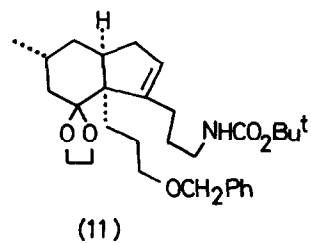
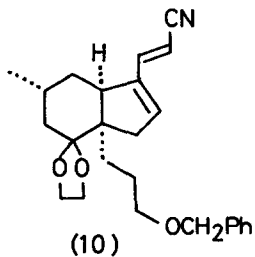
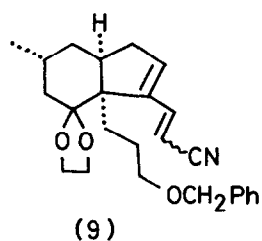
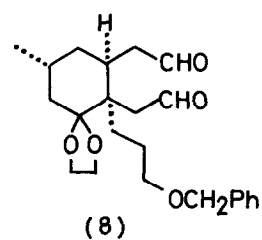
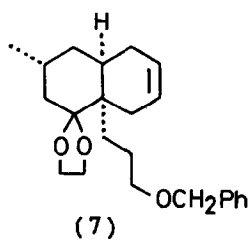
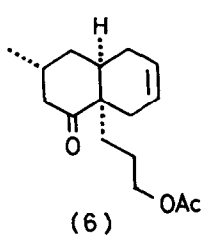
Next, the reaction condition of the regioselective intramolecular aldol condensation of (8) was investigated. The condensation of (8) by the Woodward's method (a catalytic amount of piperidine acetate in benzene)<sup>8)</sup> and subsequent treatment with (EtO)<sub>2</sub>POCH<sub>2</sub>CN by the Wadsworth-Emmons' method provided unfavorably (9) and (10)<sup>\*3</sup> in a 1:22 ratio (50.3% total yield). After examination of a variety of reaction conditions, the desired regioselectivity was obtained under the following reaction condition. Thus, treatment of (8) with excess of morpholine-camphoric acid in ether-HMPA, followed by Wadsworth-Emmons' reagent gave the conjugated nitrile(9) (a mixture of E and Z isomers), and (10) in 37.5% and 1.5% yield, respectively.<sup>\*4</sup>

Selective hydrogenation of (9) on (Ph<sub>3</sub>P)<sub>3</sub>RhCl, followed by reduction with LiAlH<sub>4</sub> and treatment of the product with N<sub>3</sub>CO<sub>2</sub>Bu<sup>t</sup> yielded the carbamate(11) in 71.9% yield, which was successively treated with Li-liq. NH<sub>3</sub>, Jones' reagent, N-hydroxysuccinimide-DCC, CF<sub>3</sub>CO<sub>2</sub>H, and (n-Bu)<sub>3</sub>N in CH<sub>3</sub>CN (high dilution method) to give the nine membered lactam(12), mp 196.5 -197.5°, in 40.9% yield.

Acetalization of (12) was unsuccessful and reduction of thioamide of (12) on Raney Ni gave the amine(13) only in a very low yield. Therefore, the lactam (12) was reduced with NaBH<sub>4</sub> to afford the alcohol A(14), mp 191-192°, and B(15)<sup>\*5</sup>, mp 169-171°, in 66.2% and 30.5% yield, respectively. Successive treatments of (14) with LiAlH<sub>4</sub>, (CF<sub>3</sub>CO)<sub>2</sub>O-Py., 0.2N KOH-MeOH, and Jones' reagent provided the N-trifluoroacetate(16) in 60.5% yield. Using the same sequence of reactions, (15) was also transformed into (16) in 56.1% yield.

Oxidation of (16) with m-chloroperbenzoic acid afforded the epoxide A(17) and B(18)<sup>\*5</sup>, mp 145-146°, in 57.8% and 40% yield, respectively. Treatment of the epoxide A(17) with BF<sub>3</sub>·Et<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub>, followed by oxidation with Jones' reagent provided the enone(19), mp 158-158.5°, in 57.7% yield. After hydrogenation on 10% Pd-C, (19) was hydrolyzed with 1N KOH-MeOH to afford (+)-fawcettimine(1), oil, in 60.7% yield, the sample of which was identical with an authentic sample by comparison of IR (in CCl<sub>4</sub> and CHCl<sub>3</sub>) and tlc behavior.

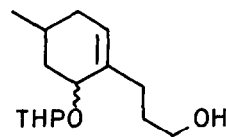
The epoxide B(18) was treated with BF<sub>3</sub>·Et<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub> to give an unidentified complex mixture. Treatment of (18) with 1N KOH-MeOH, however, caused simultaneously removal of N-protective group and ring closure to yield the alcohol (20), mp 91-92°, quantitatively. Oxidation of (20) with Jones' reagent, followed by reduction with NaBH<sub>4</sub> afforded (+)-8-deoxyserratinine(3), mp 217-218°, in 54.5% yield. A synthetic sample of 8-deoxyserratinine was identical with an authentic specimen.



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## Footnotes and References

- \*1 All new compounds gave satisfactory analytical and spectroscopic data.
- \*2 Our first attempt for getting the benzyl ether(7) was made to start from the alcohol(21).<sup>6)</sup> [(1) NaH-benzyl chloride; (2) 4% HCl-THF; (3) Jones' reagent; (4) Diels-Alder reaction with butadiene in the presence of 0.5 eq. of AlCl<sub>3</sub>; (5) ethylene-glycol-p-TsOH]. The yield(8.4%), however, was unsatisfactory.
- \*3 The structure assignment of the compounds (9) and (10) depended on the signal pattern due to allylic methylene protons and details will be reported in a full paper.
- \*4 Our method used for synthesis of serratinine (excess of pyrrolidine acetate in MeOH)<sup>9)</sup> gave an unsatisfactory regioselectivity in the present case. [(9) and (10) were obtained in a 1/1 ratio(18.3% total yield)] Interestingly, use of excess of l-proline as aldol condensation reagent gave (9) and (10) in a ratio of 1:30(23.7% total yield). The Corey's method (0.2 eq. of dibenzylamine trifluoroacetate in benzene)<sup>10)</sup> gave (9) and (10) in a ratio of 1:19(76.4% total yield). Details of examination of aldol condensation reaction conditions will be reported elsewhere.
- \*5 The stereochemistry of the alcohols, (14) and (15), and the epoxides, (17) and (18), will be discussed in a full paper.
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