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AN ASYMMETRIC SYNTHESIS OF THE TAKANO LACTONE. A FORMAL SYNTHESIS OF 9-(-)-EBURNAMINE[†]

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Abstract — The lactone **2** known as a precursor to the alkaloid eburnamine **1** has been prepared *via* chiral bicyclic lactam **4** in 4 steps in 35% overall yield and > 99% enantiomeric excess.

The synthetic efforts to reach the indole alkaloids eburnamine **1** and vincamine **1a** have a long and exciting history. However, the asymmetric synthetic route to these important systems has only recently been realized mainly through the elegant work of Takano[2] and Fuji.[3] These workers have prepared, in high enantiomeric excess, the requisite bicyclic lactone **2** via glutamic acid and 2-methoxymethylpyrrolidine, respectively. The lactone **2** has been adequately featured in a number of synthetic approaches to the indole alkaloids mentioned above.

We wish to describe our own efforts to reach this important intermediate, based on the ongoing research program[4] dealing with asymmetric quaternary carbon compounds. The scheme was initiated by metalation of the readily available bicyclic lactam[5] **3** with LDA (THF, -78 °C, 45 min) followed by addition of 1.0 equiv. of ethyl iodide (-78°→ 0 °C, 12 h) to give the monoethyl derivative **4** in 85% yield, as a 1:1 epimeric mixture. This mixture was again metalated (LDA) and treated with 1.5 equiv. of allyl bromide at -100 °C (slow addition with syringe pump for 2.5 h), and stirred for 16 h at 0 °C. Work-up gave the dialkylated lactam **5** in 99% yield as a 4.6:1 mixture favoring the *endo* allyl epimer. This mixture could not be readily separated and thus it was subjected directly to reaction with 9-BBN (0 °C, 16 h) and then with 3M NaOH-30% H_2O_2 (0 °C, 2 h, 84%). This 4.6:1 ratio of alcohols was readily separated by chromatography on Amicon Matrix® silica gel (pore size 60A, particle size 20-45 mµ) to give, in 70% yield, pure **6** ($[\alpha]_D$ = 16.02°, c 1.54, THF).[6]

The synthetic route to the Takano lactone was completed by heating **6** in 1M HCl at 95 °C for 18 h and isolating **2** in 62% yield, mp 87-89 °C; $[\alpha]_D$ = 5.58° (c 1.10 CH_2Cl_2).[7] The intermediate aldehydic acid **7** was never observed during the hydrolysis presumably due to very facile ring closure under the reaction conditions. The minor diastereomer, epi-**6** (*exo*-3-hydroxypropyl), was also isolated and on acidic hydrolysis gave (-)-**2**; $[\alpha]_D$ = -5.2° (c 0.5, CH_2Cl_2). The physical properties of **2** compared well with the literature values reported; mp 82-85 °C; $[\alpha]_D$ = 6.7° (c 0.42, CH_2Cl_2)[2]; mp 89-90 °C; $[\alpha]_D$ = 5.4° (c 1.47, CH_2Cl_2).[3]

In summary, we have shown that this versatile chiral lactone can be efficiently prepared in four steps from the lactam **3** in an overall yield of 35%. Further studies on these versatile lactams are continuing.

ACKNOWLEDGEMENTS

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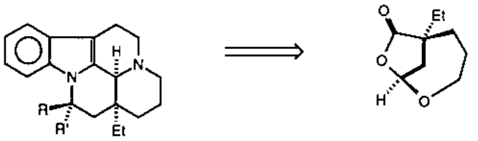
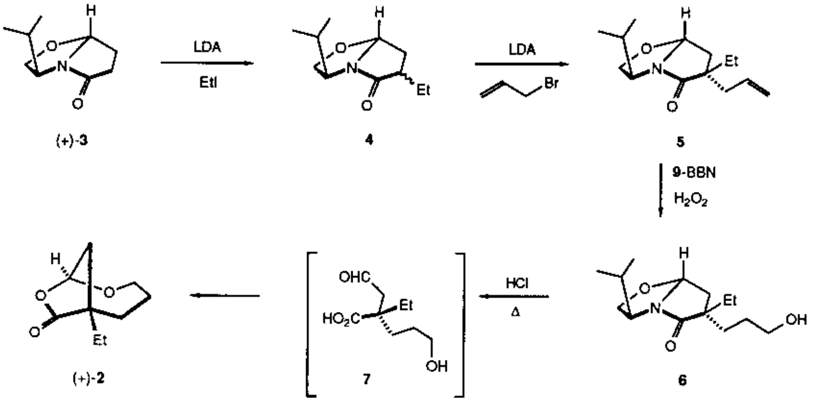
[†] This paper is dedicated to the memory of Professor Tetsuji Kametani.



1, R = OH, R' = H (eburnamine)
1a, R = OH, R' = CO_2Me (vincamine)

(+)-**2**



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6. Physical data for **6**: oil, ir (neat) 3435, 2963, 2871, 1692, 1461, 1405, 1256, 1056, 1005 cm^{-1}. ^1H-Nmr (270 MHz, $CDCl_3$) δ, ppm 4.96 (dd, J = 6.4, 2.6 Hz, 1 H), 4.14 (t, J = 7.0 Hz, 1 H), 3.69-3.56 (m, 5 H), 2.12-1.94 (m, 2 H), 1.65-1.46 (m, 7 H), 0.97 (d, J = 6.7 Hz, 3 H), 0.89 (d, J = 7.3 Hz, 3 H), 0.88 (t, J = 7.0 Hz, 3 H). ^{13}C-Nmr (75 MHz, $CDCl_3$) 182.55, 89.27, 70.88, 62.59, 60.80, 51.83, 34.86, 32.93, 32.03, 31.78, 27.74, 19.71, 18.54, 9.07. M/z 255 (0.6%), 237 (11.6%), 224 (7.9%), 212 (14%), 197 (19.7%), 182 (11.8%).
7. ^1H-Nmr of **2** (270 MHz, $CDCl_3$) δ, ppm 5.81 (d, J = 5.9 Hz, 1 H), 4.00-3.86 (m, 2 H), 2.37-2.18 (m, 2 H), 1.90-1.60 (m, 6 H), 0.92 (t, J = 7.4 Hz, 3 H).

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