SYNTHESIS OF (±)-LASUBINE I

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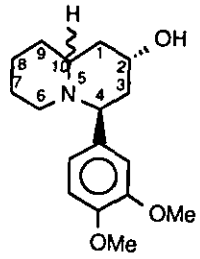
Abstract - Using N-acyliminium cyclization as a key-step, the total synthesis of (±)-lasubine I has been achieved in six steps starting from veratraldehyde.

Four new quinolizidine alkaloids have recently been isolated from the leaves of Lagerstroemia subcostata Koehne: lasubine I (1) and II (2) and their corresponding 3,4-dimethoxycinnamoyl esters subcosine I and II[1]. The total synthesis of (±)-lasubine I, based upon 1,3-dipolar cycloaddition of a nitrone, starting from veratraldehyde in 9.7% overall yield over 4 steps has been reported by Kibayashi[2].



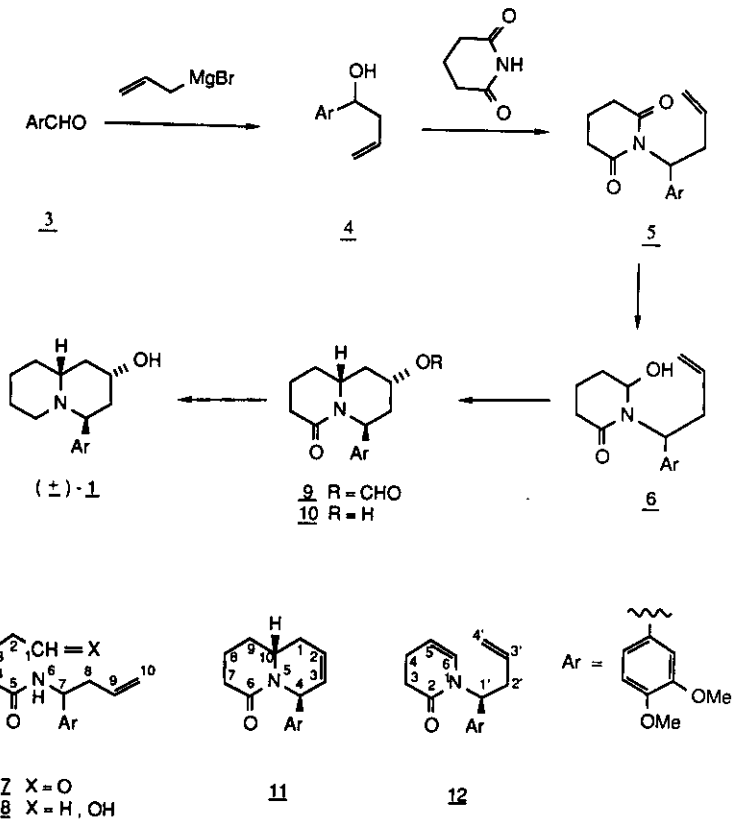
1 10 β-H

2 10 α-H

We describe here the highly stereoselective total synthesis of (±)-lasubine I starting from veratraldehyde in 15.4% overall yield over 6 steps, which utilizes as a key step the π-cyclisation of an *N-acyliminium ion*, the *intermediate* which has proved to be so versatile for the synthesis of a variety of heterocyclic systems under mild conditions[3].

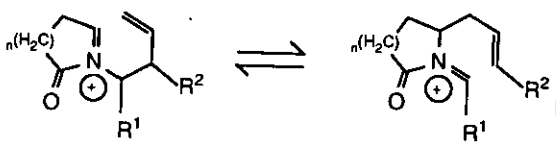
Treatment of veratraldehyde 3 with allylmagnesium bromide gave carbinol 4[4] (95%), which was converted into the glutarimide 5 (47%) by using the Mitsunobu oxidation-reduction coupling[5]; the coupling proceeded relatively slow because of the dimethoxyphenyl substituent in the α-position of the alcohol[6]. The imide 5 was partially reduced[7] with sodium borohydride in weakly alkaline medium to afford hydroxy lactam 6 (55%). The reduction had to be performed at -35/-30 °C in order to minimize ring opening of 6 to aldehyde 7, which is easily further reduced to alcohol 8. The over-reduction cannot be suppressed completely in this case of a six-membered ring hydroxy lactam with an alkoxyphenyl substituent in the α-position.

Treatment of hydroxy lactam 6 with formic acid gave a mixture of products, mainly consisting of formate 9, but presumably contaminated with olefin 11 and the C-2 epimer of 9[8]. Since direct reduction of this mixture with an excess of lithium



aluminium hydride in THF was unsuccessful in our hands, the crude product of the formic acid treatment was saponified with potassium hydroxide in aqueous ethanol and then flashchromatographed[9] to give the desired alcohol 10 (81%) and, in addition, olefin 11 (14%). The stereorelationship of the products as derived from the nmr-spectra was as expected from Hart's transition state model for cyclization via a chair conformation with the incipient C-4 substituent in axial position to avoid severe $A^{(1,3)}$-strain[10]. Reduction of 10 with lithium aluminium hydride afforded (±)-lasubine I (78%); ^{1}H nmr and mass spectral data were in agreement with those described in the literature[1,2b].

In view of the results obtained earlier in cyclizations of homoallylic substituted π-nucleophiles some additional experiments were conducted. Ring closure of hydroxy lactams proceeds via N-acyliminium ions of type A which, depending upon the substituents R^1 or R^2, rapidly may rearrange in a reversible 2-aza-Cope process to N-acyliminium ions of type B[11,12]. Even in the case where treatment with formic acid leads to the sole formation of cyclization products derived from A (e.g. for R^1=



A n = 1,2 B

vinyl, R^2=H, n=1[11b]) ions of type B can be trapped by carrying out the reaction in a 2:3 mixture of formic acid and acetic acid. Most remarkably, attempts to identify a 2-aza-Cope equilibrium in the cyclization of hydroxy lactam 6, containing a dimethoxyphenyl substituent in the α-position to the N-atom, were not successful. Upon reaction of 6 in a 2:3 mixture of formic acid and acetic acid for 1/4 h at 18 °C and saponification no products derived from an ion of type B could be detected; starting material 6 (7%), aldehyde 7 (17%) and enamide 12 (21%) could be isolated, along with an unidentified mixture of products. The latter results sharply contrast with the behaviour of systems like A (R^1=Ph, R^2=H, n=1[12]) and A (R^1=vinyl, R^2=H, n=1[11b] or n=2[13]). Further work on this aspect is in progress.
Cyclization of aldehyde 7 in formic acid gave, as expected, the same products as obtained from cyclization of hydroxy lactam 6.

EXPERIMENTAL

General. Melting points were measured with a Leitz hot stage microscope and are uncorrected. ^{1}H Nmr spectra were recorded on Varian XL-100-12, or Bruker WM-250 spectrometers with $CDCl_3$ as solvent, ^{13}C nmr spectra on Bruker WM-250. Ir spectra were taken with a Perkin-Elmer 257 spectrometer with $CHCl_3$ as solvent; absorptions are given in cm^{-1}. Mass spectra [reported as ms m/z (relative intensity)] were obtained with a Varian Mat 711 instrument at 70 eV ionization energy. Samples on which exact masses were measured exhibited no significant peaks at m/z greater than those of the parent peak. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ shortly before use. After work-up all organic layers were dried over anhydrous $MgSO_4$. The term "in vacuo" refers to solvent removal via a Büchi rotoevaporator at water aspirator pressure, followed by evacuation at 0.1 Torr when deemed necessary. Flashchromatography was performed over silica gel (E. Merck, Kieselgel 80, 230-400 mesh).

1-(3,4-Dimethoxyphenyl)but-3-en-1-ol 4

The reaction assembly, already containing the magnesium (5.47 g, 225 mmol), was flame-dried and cooled under N_2, after which dry ether (100 ml) was added. A solution of freshly distilled allyl bromide (4.23 g, 35 mmol) in dry ether (100 ml) was added dropwise over 3 h. The mixture was refluxed for 20 min and then a

solution of veratraldehyde 3 (4.32 g, 26 mmol) in dry ether (40 ml) was added dropwise under gentle reflux. After refluxing for another 20 min the mixture was cooled and decomposed with a satd. aqueous solution of ammonium chloride, followed by dilute hydrochloric acid to give a clear two-phase system. The organic layer was separated and the aqueous layer extracted with ether. The combined extracts were washed with satd. brine and satd. bicarbonate solution, dried and concentrated. The solid residue was recrystallized (diisopropyl ether) to give the arylbutenol 4[4] (5.12 g, 95%). *Colourless needles, mp 74-75.5 °C.* Ir 3596, 3420 (OH). ^{1}H Nmr 2.04 (d, J=2, OH), 2.48 (t, J=6.4, CH_2), 3.85 (s, OCH_3), 3.88 (s, OCH_3), 4.66 (dt, J=2, 6.4, CHOH), 5.10-5.18 (m, $=CH_2$), 5.71-5.87 (m, =CH), 6.80-6.91 (m, 3H, aromatic). *Ms 208 (6.5), 167 (100), 139 (64), 124 (17), 108 (14), 28 (57).* Exact mass calcd. for $C_{12}H_{16}O_3$ 208.1099; found 208.1087.

N-[1-(3,4-Dimethoxyphenyl)but-3-en-1-yl]glutarimide 5

To a stirred solution of alcohol 4 (2.08 g, 10 mmol), triphenylphosphine (3.33 g, 12.7 mmol) and glutarimide (1.58 g, 14 mmol) in THF (40 ml) under N_2, cooled in an ice-water bath, was slowly added a solution of dimethyl azodicarboxylate (1.85 g, 12.7 mmol) in THF (10 ml) over a 9 h-period. The mixture was allowed to warm to room temperature, stirred for 3 days, and concentrated in vacuo. To the residue, chloroform (100 ml) and 5% aqueous KOH (100 ml) were added, and the aqueous phase was extracted with 3x40 ml portions of chloroform. The combined organic extracts were dried and concentrated in vacuo. Flashchromatography (acetone/chloroform 1:100 → 1:20) afforded imide 5 as a solid (1.42 g, 47%), mp 95-96 °C, colourless plates (diisopropyl ether). Ir 1726, 1672 (C=O). ^{1}H Nmr 1.85 (qu, J=6.5, CH_2CH_2-CH_2), 2.58 (t, J=6.5, $CH_2CH_2CH_2$), 2.78-2.88 (m, =C-CH), 3.22 (dt, J=13.9, 9.7, =C--CH), 3.83 (s, OCH_3), 3.84 (s, OCH_3), 4.99-5.11 (m, $=CH_2$), 5.63-5.80 (m, =CH), 5.91 (dd, J=5.9, 10.4, NCH), 6.77 (d, J=8.7, 1H, aromatic), 6.98-7.01 (m, 2H, aromatic). Ms 303 (24), 282 (18), 262 (100), 190 (32), 166 (88), 55 (41), 31 (45), 28 (64). Exact mass calcd. for $C_{17}H_{21}NO_4$ 303.1470; found 303.1475.

Hydroxy Lactam 6

To a stirred solution of the imide 5 (606 mg, 2 mmol) in ethanol (80 ml) under N_2, $NaBH_4$ (1.2 g) was added at -35 to -30 °C. *The mixture was stirred for 5 h at -35* to -30 °C, adding 3 drops of 4M ethanolic HCl every 1/4 h. The mixture was poured into water (400 ml) and extracted with 7x100 ml portions of dichloromethane. The combined extracts were washed with satd. brine, dried, and concentrated in vacuo. Flashchromatography (acetone/dichloromethane 1:10) gave hydroxy lactam 6 (337 mg,

55%). Ir 3390 (OH), 1638 (C=O). ^{1}H Nmr 1.48-2.60 (m, $(CH_2)_3$, OH), 2.86 (dd, J=6.7, 7.9, $=CCH_2$), 3.82 (s, OCH_3), 3.84 (s, OCH_3), 4.73-4.78 (m, CHOH), 5.04-5.20 (m, $=CH_2$), 5.77-5.90 (m, NCH, =CH), 6.78-6.93 (m, 3H, aromatic). Ms 287 (14), 264 (10), 246 (100), 204 (24), 191 (95), 160 (23), 151 (18). Exact mass calcd. for $C_{17}H_{23}NO_4$ 305.1627; found 305.1639.

Cyclization of Hydroxy Lactam 6: Carbinol 10 and Olefin 11

A solution of hydroxy lactam 6 (85.5 mg, 0.28 mmol) in formic acid 98-100% (6 ml) was stirred for 1 h at room temperature. The mixture was poured into satd. brine and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with satd. bicarbonate solution and with satd. brine, dried, and concentrated in vacuo. The residue was dissolved in a cold solution of KOH (20.4 mg, 0.36 mmol) in 97% ethanol (20 ml) and stirred for 1½ h at 0-5 °C. Upon addition of water (100 ml) the mixture was extracted with dichloromethane and the combined extracts were washed with satd. brine, dried, and concentrated in vacuo. Flashchromatography (acetone/dichloromethane 2:9) gave olefin 11 (11.6 mg, 14%) and carbinol 10 (69.2 mg, 81%) in this order.

Carbinol 10: colourless oil. Ir 3600 (OH), 3400 (OH), 1620 (C=O). ^{1}H Nmr 1.37 (q, J=11.7, C(1)H_α), 1.51 (m, C(9)H), 1.57 (m, C(9)H), 1.64 (m, C(8)H), 1.66 (m, C(3)-H), 1.84 (m, C(8)H), 1.85 (m, C(1)H_β), 2.15 (br s, OH), 2.45-2.54 (m, C(7)H_2), 2.60-2.67 (m, C(3)H), 3.28-3.40 (m, C(10)H), 3.81 (s, OCH_3), 3.83 (s, OCH_3), 3.86-4.00 (m, C(2)H), 6.16-6.18 (m, C(4)H), 6.68-6.77 (m, 3H, aromatic); the absorptions were assigned using COSY; irradiation of C(2)H gives a positive NOE on C(10)H and aromatic H. ^{13}C Nmr 18.9, 30.0, 33.1, 36.2, 43.0, 50.2, 50.3, 55.9, 64.7, 109.7, 111.0, 118.3, 128.2, 131.1, 147.7, 149.2, 170.0. Ms 305 (46), 69 (83), 59 (100). Exact mass calcd. for $C_{17}H_{23}NO_4$ 305.1627; found 305.1639.

Olefin 11: Ir 1612 (C=O). ^{1}H Nmr 1.47-2.64 (m, 8H), 3.53-3.68 (m, C(10)H), 3.84 (br s, 6H, OCH_3), 5.80-5.85 (m, C(2)H), 5.92-6.02 (m, C(3)H), 6.20-6.27 (m, C(4)H), 6.73-7.08 (m, 3H, aromatic). Ms 287 (100), 272 (16), 256 (19), 228 (14), 216 (18), 189 (36). Exact mass calcd. for $C_{17}H_{21}NO_3$ 287.1521; found 287.1497.

(±)-Lasubine I (±)-1

A solution of carbinol 10 (34.8 mg, 0.114 mmol) in THF was slowly added to a solution of $LiAlH_4$ (110 mg) in THF at room temperature. The mixture was then refluxed for 2 h, cooled in ice and treated successively[14] with water (0.33 ml), 20% aqueous NaOH (0.16 ml), water (0.9 ml) and 40% aqueous NaOH (1.1 ml). The mixture was filtered through hyflo super cel, dried over K_2CO_3, and concentrated in vacuo.

Flashchromatography (chloroform/methanol 1:5) afforded (±)-lasubine I ((±)-1) as a colourless oil. Ir 3600, 3400 (OH). ^{1}H Nmr 1.2-2.11 (m, 11H), 2.24 (br dt, J=3.3, 11.7, C(6)H), 2.70 (br d, J~12, C(6)H), 2.92-3.00 (m, C(10)H), 3.85 (s, OCH_3), 3.86 (s, OCH_3), 4.08 (t, J=4.8, C(4)H), 4.16 (tt, J=4.5, 9, C(2)H), 6.76 and 6.80 (s each, ratio 29:71, total 1H, aromatic), 6.84, 6.87, 6.88 (s each, ratio 75:16:9, total 2H, aromatic); assignment of absorptions on the basis of COSY. Ms 291 (71), 164 (100), 154 (77). Exact mass calcd. for $C_{17}H_{25}NO_3$ 291.1834; found 291.1824.

Reaction of Hydroxy Lactam 6 in Formic Acid-acetic Acid: Aldehyde 7 and Enamide 12

A solution of hydroxy lactam 6 (122 mg, 0.4 mmol) in a 2:3 mixture (6 ml) of formic acid and acetic acid was stirred for 1/4 h at 18 °C. The mixture was worked-up and saponified as described above for 10. The residue was flashchromatographed to give enamide 12 (24 mg, 21%), aldehyde 7 (21 mg, 17%), starting material 6 (8 mg, 7%), and some fractions consisting of unidentified mixtures.

Aldehyde 7: colourless oil. Ir 3435 (NH), 2836, 2725 (HC=O), 1722 (C=O, aldehyde), 1665 (C=O, amide). ^{1}H Nmr 1.93 (qu, J=7, C(3)H_2), 2.21 (t, J=7, C(4)H_2), 2.49 (dt, J=1.4, 7.0, C(2)H_2), 2.53 (br t, J=7, C(8)H_2), 3.84 (s, OCH_3), 3.85 (s, OCH_3), 4.99 (q, J=7.5, C(7)H), 5.03-5.13 (m, C(10)H_2), 5.68 (ddt, J=17.2, 10.2. 7.0, C(9)H), 5.77 (br d, J=7.2, NH), 6.77-6.80 (m, 3H, aromatic), 9.73 (t, J=1.4, C(1)H). Ms 305 (5), 287 (49), 264 (49), 246 (37), 191 (42), 166 (100). Exact mass calcd. for $C_{17}H_{23}NO_4$ 305.1627; found 305.1615.

Enamide 12: colourless oil. Ir 1659 (C=O). ^{1}H Nmr 2.18-2.28 (m, C(4)H_2), 2.53 (dt, J=2.3, 8, C(2')H_2), 2.58-2.63 (m, C(3)H), 2.68-2.77 (m, C(3)H), 3.83 (s, OCH_3), 3.85 (s, OCH_3), 5.03-5.15 (m, C(5)H, C(4')H_2), 5.69-5.83 (m, C(3')H), 5.88-5.94 (m, C(6)H, C(1')H), 6.76-6.87 (m, 3H, aromatic). Ms 287 (14), 246 (97), 204 (12), 191 (100), 164 (7), 160 (14), 151 (11). Exact mass calcd. for $C_{17}H_{21}NO_3$ 287.1521; found 287.1506.

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