Tetrahedron Letters, Vol. 34, No. 17, pp. 2729-2732, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

Tandem N-Acyliminium-Michael Addition Reaction. An Efficient Total Synthesis of the Quinolizidine Alkaloids (+/-)-Myrtine And (+/-)-Lasubine II.

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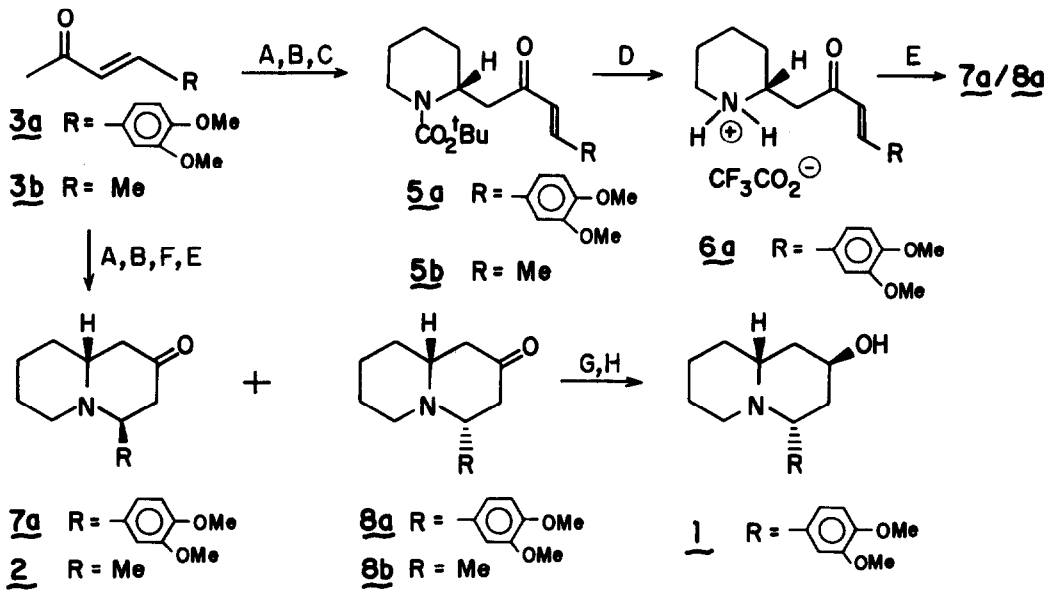
Abstract: A short and efficient preparation of the quinolizidine alkaloids (±)-lasubine II (1) and (±)-myrtine (2) is described featuring the tandem N-acyliminium ion- Michael addition of 2-trimethylsilyloxy butadienes to ethoxycarbamate 4 promoted by TMSOTf.

Among the several methodologies available for the total synthesis of quinolizidine alkaloids, the intramolecular addition to N-acyliminium ions has proven to be a versatile protocol.[1] Far less explored is the intermolecular version of this reaction which has been recently employed in the total synthesis of (+/-)-myrtine and (+/-)-epimyrtine.[2]

Our search for highly efficient methodologies for the construction of quinolizidine systems, led us to investigate the tandem N-acyliminium ion-Michael addition sequence described below. Here we disclose our preliminary results which have been applied to the total synthesis of (+/-)-lasubine II (**1**)[3] and (+/-)-myrtine (**2**).[2,4]

Based on our previous studies on the addition of silylenolethers to N-aryl and N-acyliminium ions under trimethylsilyl trifluoromethanesulfonate (TMSOTf) catalysis[5] and on the in situ preparation of silylenolethers,[6] we explored the one-pot preparation of carbamate **5a** from enone **3a**, N-carbo-tert-butoxy-2-ethoxypiperidine (**4**) and TMSOTf. Addition of freshly distilled TMSOTf (1.6 mmol) to a stirred solution of **3a** (1.0 mmol) and Et_3N (2.0 mmol) in CH_2Cl_2 (3.0 mL) at 0°C, followed by a CH_2Cl_2 soln. of **4** (1.1 mmol), additional TMSOTf (0.6 mmol), quenching with satd. aq. $NaHCO_3$ after 1 hour at 0°C and normal workup, afforded carbamate **5a**,[7] in 87% yield (Scheme 1).



Scheme 1. A. TMSOTf (1.5 equiv.), Et_3N (2.0 equiv.), CH_2Cl_2, 0°C; B. **4** (1.0 equiv.); C. TMSOTf (0.6 equiv.), 0°C; D. CF_3CO_2H, CH_2Cl_2,0°C; E. satd. $NaHCO_3$, rt, 36h; F.TMSOTf (1.1 equiv.), 0°C,1h; G. 2N NaOH/MeOH or 2N NH_4OH/MeOH, rt, 48h; H.LS-Selectride^R, THF,-78°C; MeOH, rt, 36h, 77%.

Deprotection of N-BOC-carbamate **5a** with trifluoroacetic acid in CH_2Cl_2, at 0°C, followed by quenching with satd. $NaHCO_3$ until pH 6.0 led to the isolation of ammonium salt **6a**[8] (83% yield). At pH 7.5, its conjugate base was isolated (contaminated with quinolizidin-2-ones **7a/8a**[9]) and it was converted to a 3:2 mixture of **7a/8a** (85% yield) upon standing in CH_2Cl_2 solution (4 days, rt). The smooth cyclization observed above prompted us to attempt the **in situ** decarboxylation of **5a**[10] in order to trigger the intramolecular Michael addition[11] which would ultimately lead to the quinolizidin-2-one system in a one-pot transformation from enone **3a** and ethoxycarbamate **4**. After several experiments, a slight modification in the above procedure provided a 3:2 mixture of quinolizidin-2-ones **7a/8a**, in 90% yield: an additional amount of TMSOTf (1.1 mmol) was added to the reaction mixture immediately after the addition of **4** (1.1 mmol), which was let to stir 1 hour at 0°C, followed by treatment with satd. aq. $NaHCO_3$ during 36 hours at room temperature. Under basic conditions (2N

NaOH/MeOH, rt, 48 h or 2N NH_4OH/MeOH, rt, 48 h), the above mixture afforded trans-quinolizidin-2-one **8a**[12] (90% yield) which was reduced with LS- Selectride^R/THF, at -78°C, to yield (+/-)-lasubine II (**1**),[13] after treatment of the crude reduction mixture with MeOH, evaporation and column chromatography on silica gel (77% yield).

The same methodology was also applied to enone **3b** (i. TMSOTf (1.5 equiv.), Et_3N (2.0 equiv.), CH_2Cl_2, 0°C; ii. (+/-)- **4** (1.0 equiv.); iii. TMSOTf (1.3 equiv.), 0°C, 30 min.; iv. satd. $NaHCO_3$, 36 h) to produce a 5.5:1.0 mixture of (+/-)-myrtine (**2**)[13] and its epimer **8b**, in 67% yield, after column chromatography on neutral alumina.

The tandem N-acyliminium ion addition-decarboxylation-Michael addition described here represents a novel and efficient one-pot route to quinolizidin-2-ones with promising applications in the total synthesis of other quinolizidine alkaloids.

Acknowledgements

Financial support from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and International Foundation for Science (IFS) are gratefully acknowledged.

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7. **4a:** pale yellow oil, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.43 (s,10H), 1.63 (s,br, 5H), 2.8-2.9 (m,3H), 3.92(s,6H), 4.0 (m,1H), 4.79 (m,1H), 6.67 (d, J=16.0 Hz,1H), 6.88 (d, J=8.3 Hz,1H), 7.09 (d, J=1.7 Hz,1H), 7.14 (dd, J=8.3 and 1.9, 1H), 7.56 (d,J=16.0, 1H).^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 18.90, 25.34, 28.15 (br), 28.42, 39.49 (br), 41.51, 47.96 (br), 55.89, 55.96, 79.56, 109.82, 111.11, 123.20, 124.11, 127.46, 143.15, 149.27, 151.40, 154.80, 198.32. Elemental analysis : calcd. for $C_{22}H_{31}NO_5$, C-67.86, H-7.97, N-3.60. Obsd.: C-67.78, H-8.14, N-3.32.
8. **5a:** white solid, m.p. 144.8-146.3°C, ^{1}H-NMR (300 MHz,$CDCl_3$): δ 1.4- 1.6 (m,1H), 1.7-2.0 (m,5H), 2.8-3.0 (m,1H), 3.00 (dd, J=17.6 and 6.2 1H), 3.27 (dd, J=17.6 and 6.2,1H), 3.4-3.6 (m,2H), 3.90(s,3H), 3.91(s,3H), 6.57 (d, J=16 Hz, 1H), 6.85 (d, J=8.3 Hz, 1H), 7.04 (9d, J=1.9 Hz, 1H), 7.11 (dd, J=8.4 and 1.9 Hz, 1H), 7.54 (d, J=16 Hz, 1H), 8.93 (s, br, 1H), 9.60 (s, br, 1H).^{13}C-NMR (75.5 MHz, $CDCl_3$): δ 22.25, 22.40, 28.48, 42.62, 45.07, 53.73, 56.03, 56.10, 110.27, 111.36, 123.57, 123.78, 127.11, 145.22, 149.65, 152.20, 162.42 (br), 197.10. Elemental analysis : calcd. for $C_{19}H_{24}O_5NF_3$: C-56.57, H-5.99, N-3.47. Obsd : C- 56.70, H-6.05, N-3.14.
9. The mixture of quinolizidin-2-ones **7a/8a** was readly separated on column chromatography (SiO_2, $CHCl_3$/MeOH 30:1). The ^{1}H- and ^{13}C-NMR spectral data were identical to those described in ref. 3c and 3d.
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13. (+/-)- Lasubine II (1) and (+/-)-myrtine (2) were characterized by comparison of their spectroscopic data (^{1}H- and ^{13}C-NMR, mass and infrared spectra) with those reported in ref. 3d and 4c, respectively.

(Received in USA 30 December 1992; accepted 18 February 1993)