A CHIRAL ROUTE TO PYRROLIZIDINE ALKALOIDS VIA INTRAMOLECULAR MICHAEL REACTION

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Abstract - Wittig-Horner reaction of **10** gave the pyrrole (11) as a diastereomeric mixture via the intramolecular Michael reaction, one of the diastereomers could be converted to the Geissman lactone (4), a synthon for some pyrrolizidine alkaloids.

The intramolecular Michael reaction promises to be a useful tool in carbocyclic or heterocyclic synthesis. In particular, for constructing nitrogen heterocycles[1] this reaction can be considered useful not only because of the easy availability of substrates but also the proper nucleophilicity of the nitrogen towards the Michael acceptor.

As part of a synthetic program directed toward certain biologically active natural products containing pyrrolidine ring, e.g. anisomycin (1)[2], swainsonine(2)[3], retronecine(3)[4], etc.,

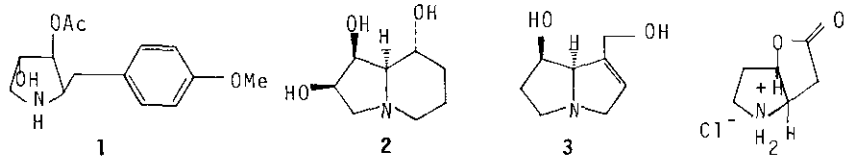
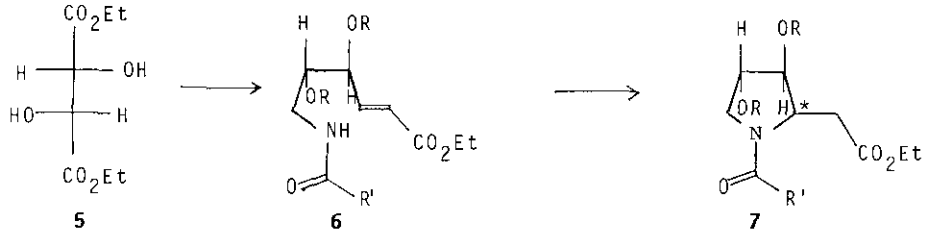


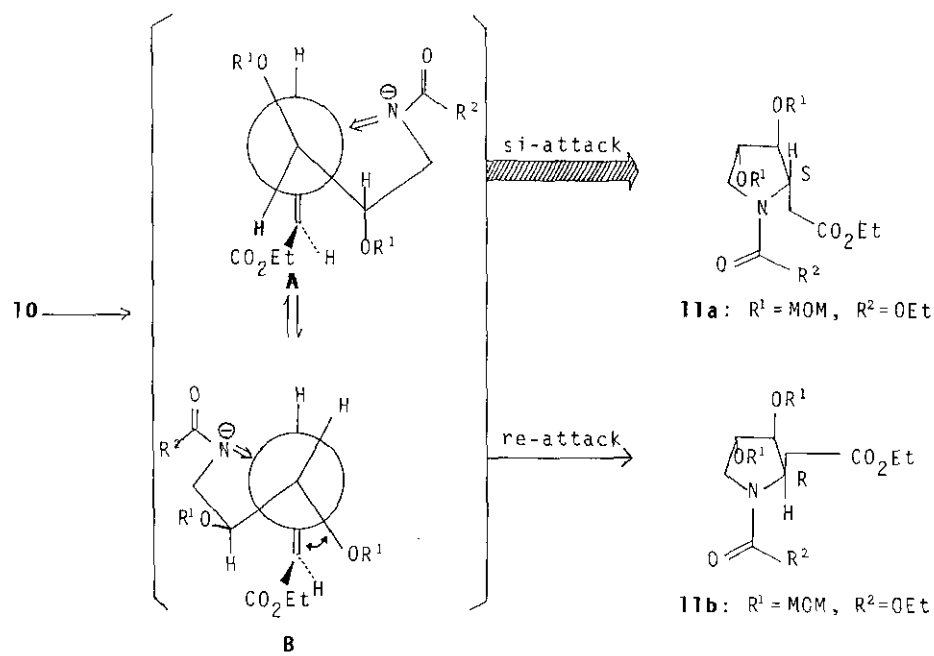
Fig I

we have examined α-asymmetric induction by the intramolecular Michael reaction of **6** which would be derivable from L-(+)-diethyl tartrate (5) as a chiral source. We report here the results of a stereoselectivity in the reaction [**6** ⟶ **7**] and a chiral synthesis of the Geissman lactone (4), an intermediate in the synthesis[5-7] of retronecine (3).

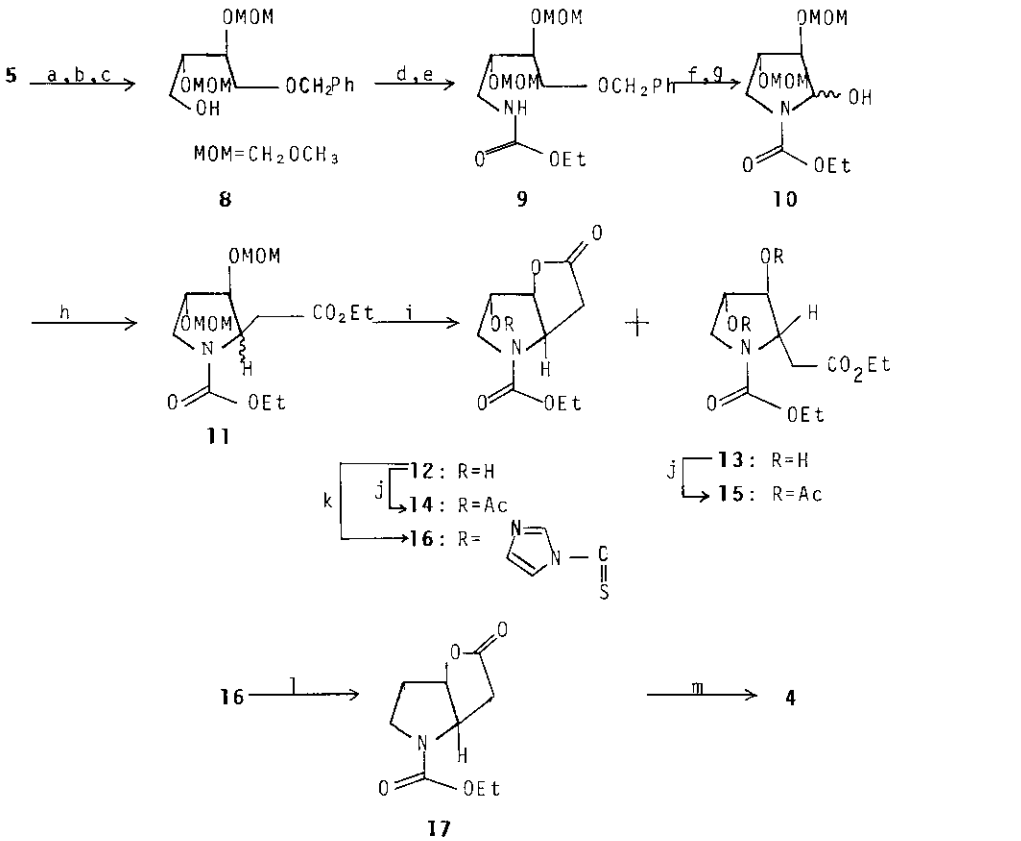


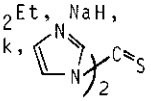
Scheme I

Protection of the diol of L-(+)-diethyl tartrate (5) as methoxymethyl(MOM) ether[8] followed by lithium aluminum hydride reduction and monobenzylation gave the alcohol (8)[9] in 85% yield. Introduction of an amino functionality could be accomplished by sequential Mitsunobu reaction[10] and Ing-Manske hydrazinolysis[11] of the alcohol (8). Acylation of the crude primary amine with ethyl chloroformate gave the carbamate (9) which was submitted to hydrogenolysis and Swern oxidation[12] to afford a mixture of the diastereomeric hemiacetal (10) in 79% overall yield from **8**. On treatment with triethyl phosphonoacetate in the presence of sodium hydride (2.3 eq.) in dimethoxyethane at room temperature for 39 h, the hemiacetal (10) was converted to the pyrrolidino ester (11) as an unseparable diastereomeric mixture in 70% yield. An examination of the proton NMR spectrum of the mixture showed a complete absence of vinyl protons, thus confirming that the initial reaction product (α, β-unsaturated ester) had undergone a spontaneous Michael type ring closure. Cleavage of MOM ether in **11** with ethanethiol in the presence of boron trifluoride etherate[13] provided a separable 2:3 mixture of the lactone (12) and the ester (13) in 74% yield. Both compounds were spectroscopically characterized as the acetates (14, 15)[14]. The prolonged reaction time [15] for the conversion of **10** to **11** resulted in no expected increase[16] of a ratio for the lactone (12) but a slight decomposition of the products. Furthermore, attempted treatment of **10** with triethyl phosphonoacetate uning potassium hydride[17] as a base led to the formation of both **12** and **13** in a ratio of 1:3.4 in 71% overall yield.



Scheme III



Reagents : a, $CH_2(OMe)_2$, P_2O_5, 100%; b, $LiAlH_4$, 85%; c, $PhCH_2Br$, NaH, 99%; d, phthalimide, Ph_3P, diethyl azodicarboxylate, 92%; e, N_2H_4 then $ClCO_2Et$, NEt_3, 89%; f, $Pd(OH)_2-C$, cyclohexene, 97%; g, $(COCl)_2$, DMSO, NEt_3, 100%; h, $(EtO)_2POCH_2CO_2Et$, NaH, 70%; i, EtSH, $BF_3 \cdot OEt_2$, 74%; j, Ac_2O, Py., 4-DMAP; k,  , 90%; l, $^nBu_3SnH$, 84%; m, $Ba(OH)_2 \cdot 8H_2O$ then HCl, 40%

Scheme II

This suggested that the 2S-isomer(11a) would be the kinetic product. The predominance of the 2S-isomer(11a) in the intramolecular Michael addition can be rationalized by considering the transition states (A) and (B). The steric congestion in the transition state (B) leading to 2R-isomer(11b) *via re*-face[18] attack of the nitrogen nucleophile makes it less favorable than the alternative transition state (A) which favors the 2S configuration in **11a** *via si*-face attack. The lactone (12) with a desired configuration at C-2 for synthesizing the target molecules (1,2, and 3) was then converted to the corresponding (thiocarbonyl)-imidazolide(16)[19] which was reduced with tri-n-butyltin hydride to give the deoxygenated lactone (17) whose spectral data (IR, ^{1}HNMR) and the TLC behavior[20] were indistinguishable from an authentic sample[6].

Finally, the lactone (17) was transformed into the Geissman lactone (4)[5,21],

intermediate for retronecine (3), by the literature[5] procedure. On the other hand, since the kinetic product (13) seems to be a useful precursor for constructing the necine bases with 7R, 8S-configuration such as hastanecine (18)[22] (Fig II), we are presently exploring the conversion.

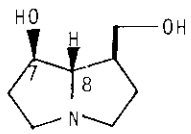


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Fig II

ACKNOWLEDGEMENT

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14. **14:** Colorless leaflets, mp 137-139°C; IR($CHCl_3$) 1795, 1745, 1695 cm^{-1}; ^{1}HNMR($CDCl_3$, 400 MHz) δ1.28(3H, t, J=7.5Hz), 2.10(3H, s), 2.81(1H, dd, J=18.5, 6.3Hz), 2.93(1H, d, J=18.5Hz), 3,67(1H, dd, J=13.1, 3.9 Hz), 3.75(1H, d, J=13.1Hz), 4.15(2H, q, J=7.5Hz), 4.64(1H, dd, J=6.3, 4.4Hz), 4.87(1H, d, J=4,4Hz), 5.34(1H, d, J=3.9Hz); MS(m/z) 257(M^+). $[\alpha]_D^{24}$+47.64°(c=0.96, $CHCl_3$)
15: Colorless oil; IR($CHCl_3$) 1740, 1695cm^{-1}; ^{1}HNMR($CDCl_3$, 100MHz) δ1.27(6H, t, J=7.5Hz), 2.08(3H, s), 2.11(3H, s), 2.62(1H, dd, J=15.5, 10.0Hz), 2.96(1H, m), 3.52(1H, d, J=12.5Hz), 3.85(1H, dd, J=12.5, 4.0Hz), 4.16(4H, t, J=7.5Hz), 5.10(1H, d, J=4.0Hz), 5.17(1H, s); MS(m/z) 300(M^+-OEt). $[\alpha]_D^{26}$+39.27°(c=0.48, $CHCl_3$).
15. In the presence of excess base, it was considered that the retro Michael-readdition sequence might result a preferential formation of the thermodynamic product.
16. When the conversion was stopped at the earlier stage (12 h), a 1:2 ratio of **12** and **13** could be realized. This indicates that there appears to be a slight thermodynamic preference for the 2R-isomer (11b).
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20. Three different kinds of solvent system for the developing were examined.
21. mp 185-186.5°C(lit.[7a] 185-186°C), $[\alpha]_D^{24.8}$+48.75°(c=0.2, MeOH) (lit.[7a] $[\alpha]_D$+48.5°(c=1.5, MeOH))
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