AN ENANTIOSELECTIVE SYNTHESIS OF (-)-6-AZA-6-CARBETHOXY-2-OXA-BICYCLO[3.3.0]OCTAN-3-ONE FROM S-(-)-MALIC ACID

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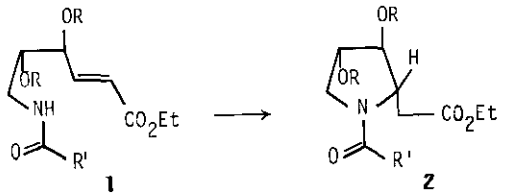
Abstract —— An enantioselective synthesis of the title compound, a precursor for the Geissman lactone, from S-(-)-malic acid is described. The synthesis features the diastereoselective intramolecular Michael reaction of the carbamate (3).

We recently introduced[1] the intramolecular Michael reaction-based[2] 1,2-asymmetric induction, exemplified by the conversion of **1** into **2**, for the synthesis of a synthon for certain biologically active natural products containing pyrrolidine ring.[1] (Scheme 1)

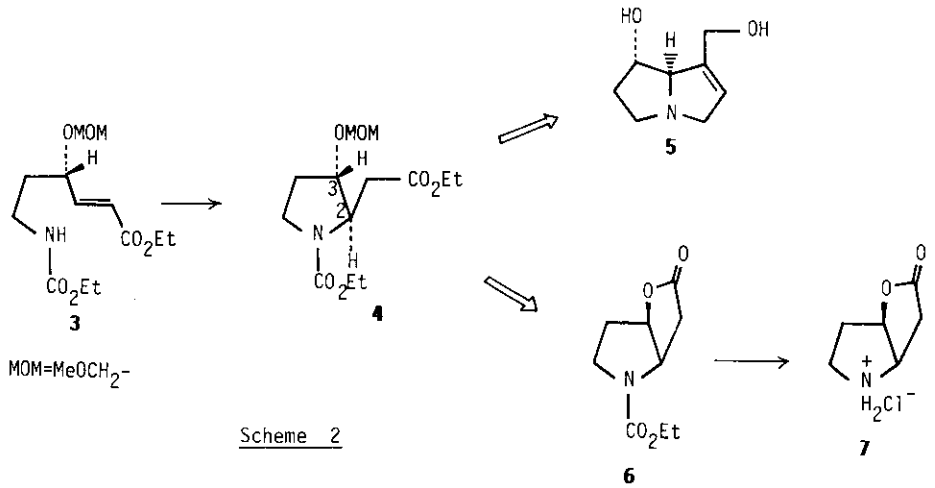


Scheme 1

In the conversion, it was found that the nitrogen nucleophile might attack the β-carbon of the unsaturated ester preferencially from the si-face by steric reason. It is interesting to note that if the mechanistic rationale was acceptable, the intramolecular Michael reaction of **3** should lead to a preference for the formation of **4** via re-face attack. The resulting functionalized pyrrolidine (**4**) seemed to be transformed not only into some kinds of pyrrolizidine alkaloids with 2R,3S-configuration, such as heliotridine (**5**)[3], but also into the lactone (**6**), a precursor for the Geissman lactone (**7**)[1,4] which was a potential intermediate for the synthesis of retronecine[5], via internal lactonization with inversion of the configuration at C-3. (Scheme 2)

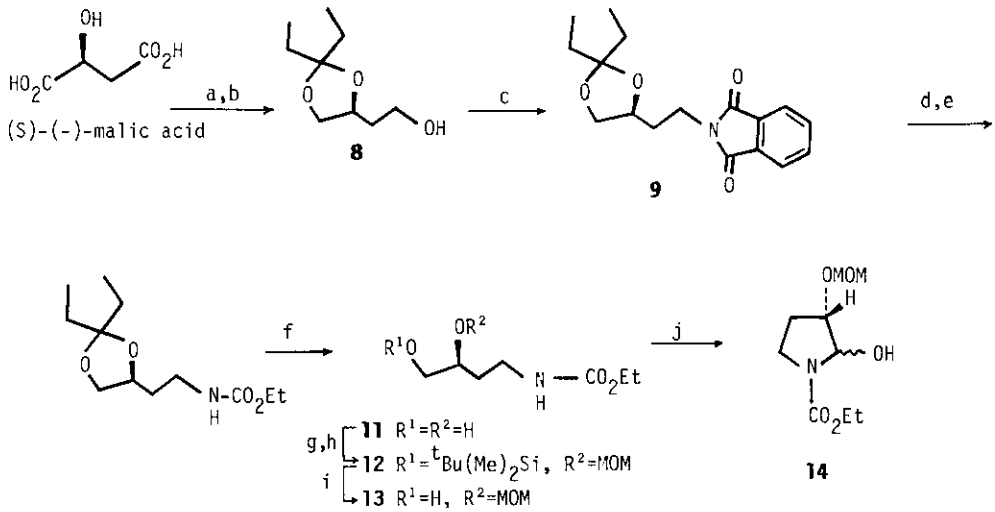
We now wish to report the realization of the diastereoselective conversion of **3** into **4** and a high-yield synthesis of (-)-6-aza-6-carbethoxy-2-oxabicyclo[3.3.0]-octan-3-one (**6**) from an inexpensive enantiomer of malic acid.

Treatment of the alcohol (**8**)[6], readily derivable from S-(-)-malic acid by sequential borane reduction[7] and protection[6] of the 1,2-diol function of the resulting triol[8], with the well-established condition of Mitsunobu[9] afforded **9**[10]



Scheme 2

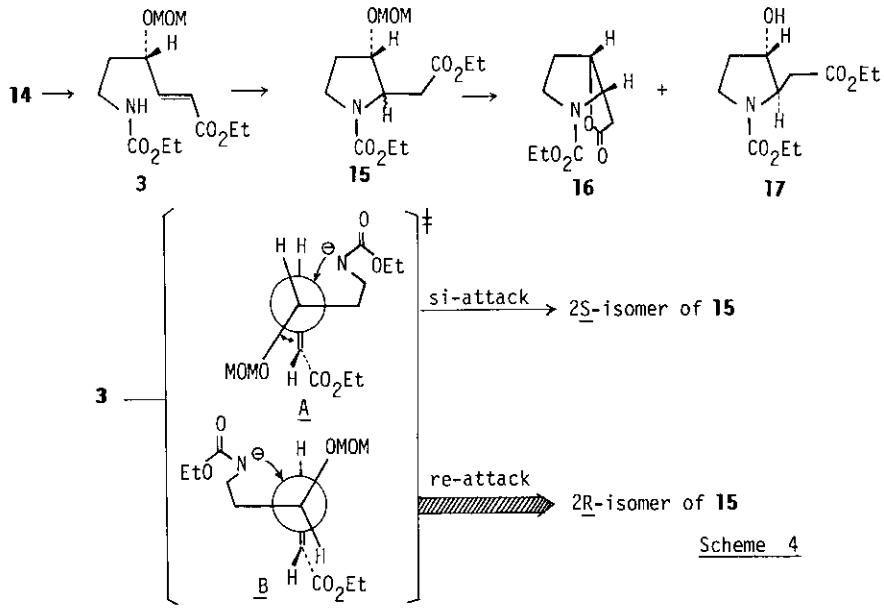
$[\alpha]_D$+11.77° (c=1.45, $CHCl_3$)]. The Ing-Manske hydrazinolysis[11] followed by carbamate formation with ethyl chloroformate gave the carbamate (**10**) $[\alpha]_D$+1.85° (c=1.26, $CHCl_3$)] which was then exposed to 6N-HCl in THF to afford the diol (**11**) $[\alpha]_D$+1.15° (c=0.59, $CHCl_3$)] in 91 % yield from malic acid. Selective silylation and methoxymethylation of the resulting secondary alcohol cleanly generated **12** $[\alpha]_D$-50.00° (c=0.61, $CHCl_3$)]. Subsequent desilylation and Swern oxidation[12] of the resulting primary alcohol moiety in **13** $[\alpha]_D$+11.97° (c=0.75, $CHCl_3$)] proceeded smoothly to furnish the hemiacetal (**14**) as a mixture of two diastereomers in yield of 91 % from **11**. (Scheme 3)



Reagents: a) $B(OMe)_3$, BH_3•SMe_2, THF thenMeOH, 100% b) $Et_2C(OMe)_2$, p-TsOH(cat.), DMF, 100% c) Ph_3P, $EtO_2CN{=}NCO_2Et$, phthalimide, THF, 100% d) $NH_2NH_2H_2O$, EtOH e) $ClCO_2Et$, NEt_3, CH_2Cl_2, 91% from **9** f) 6N-HCl, THF, 100% g) $^tBu(Me)_2SiCl$, imidazole, 4-DMAP, CH_2Cl_2, 95% h) MOMCl, $^iPr_2NEt$, CH_2Cl_2, 100% i) $^nBu_4NF$, THF, 100% j) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, 96%.

Scheme 3

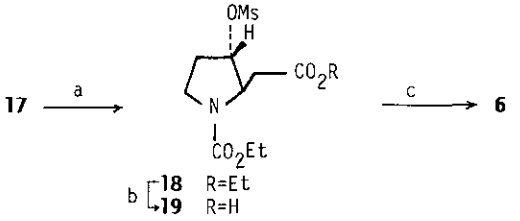
On treatment with triethyl phosphonoacetate [$(EtO)_2POCH_2CO_2Et$] (2.3 eq) in the presence of sodium hydride (2.5 eq) in dimethoxyethane (DME) at room temperature for 13 h, the diastereomeric hemiacetal (**14**) could be converted into the cyclized product (**15**) as an inseparable diastereomeric mixture. Cleavage of the methoxymethyl (MOM) function in the crude **15** with ethanethiol and boron trifluoride etherate[13] provided an easily separable 1:2 mixture of the lactone (**16**) [$[\alpha]_D$+144.1° (c=0.52, $CHCl_3$)] and the hydroxy ester (**17**)[14] [$[\alpha]_D$-44.04° (c=1.28, $CHCl_3$)] in 65 % yield. To circumvent the lower selectivity, the transformation was attempted by a kinetic condition. Thus, treatment of **14** with $(EtO)_2POCH_2CO_2Et$ and potassium hydride (KH) in DME at 0°C for 45 min afforded the unsaturated ester (**3**)[15] in 92 % yield. Attempted Michael reaction of **3** using KH (1.1 eq) in DME at 0°C for 10 min followed by cleavage of the MOM function gave **16** and **17** in a ratio of 1:5.2 in 81 % overall yield. The anticipated preferential formation of **17** via re-face attack of the nitrogen nucleophile can be rationalized by considering the transition states A and B. In the event, our mechanistic presumption could thus be supported by the result. (Scheme 4)



Scheme 4

With the suitably functionalized pyrrolidine (**17**) in hand, we decided to prepare the lactone (**6**). Mesylation of **17** gave quantitatively the mesylate (**18**) [$[\alpha]_D$-4.30° (c=0.66, $CHCl_3$)] which was hydrolized with lithium hydroxide to afford the corresponding carboxylic acid (**19**). The crude acid was then treated with potassium carbonate in the presence of catalytic 18-crown-6 in acetonitrile to furnish the lactone (**6**), which has already been converted into **7** by basic hydrolysis followed by acid treatment, in 86 % yield from **17**. The spectroscopic properties including optical rotation[16] of **6** were identical with those of a sample prepared previously.[1,17] (Scheme 5)

In conclusion, we have shown that the intramolecular Michael reaction of **3**, easily available from S-(-)-malic acid, can be used to prepare the optically pure pyrrolidine (**17**) with controlled stereochemistry and **17** can further be converted into **6**



Reagents: a) MsCl, NEt_3, 4-DMAP, CH_2Cl_2, 100% b) LiOH, dioxane(aq.)
c) K_2CO_3, 18-crown-6, CH_3CN, 86% from **18**.

Scheme 5

in high yield (45 % overall) in an enantioselective manner. Further conversion of **17** into heliotridine (**5**) is in progress and will be reported in due course.

ACKNOWLEDGEMENT

This work was financially supported in part by a grant from The Sendai Institute of Heterocyclic Chemistry, which is gratefully acknowledged.

REFERENCES AND NOTES

1) K. Shishido, Y. Sukegawa, K. Fukumoto, and T. Kametani, Heterocycles, 1985, **23**, 1629.
2) For recent intramolecular Michael approach to amino sugars, see: M. Hirama, T. Shigemoto, Y. Yamazaki, and S. Ito, J. Amer. Chem. Soc., 1985, **107**, 1797; idem, Tetrahedron Letters, 1985, **26**, 4133; M. Hirama, T. Shigemoto, and S. Ito, ibid., 1985, **26**, 4137.
3) Synthesis of (+)-heliotridine from S-malic acid, see; A. R. Chamberlin and J. Y. L. Chung, J. Amer. Chem. Soc., 1983, **105**, 3653. Recent synthesis of (-)-heliotridine, see: D. J. Hart and T. K. Yang, J. Org. Chem., 1985, **50**, 235.
4) T. A. Geissman and A. C. Waiss, Jr., J. Org. Chem., 1962, **27**, 139; H. Rüeger and M. Benn, Heterocycles, 1982, **19**, 23.
5) During the preparation of our manuscript, Professor Chamberlin reported the enantioselective conversion of S-malic acid into (+)-retronecin, see; A. R. Chamberlin and J. Y. L. Chung, J. Org. Chem., 1985, **50**, 4425.
6) S. Masamune, P. Ma, H. Okumoto, J. W. Ellingboe, and Y. Ito, J. Org. Chem., 1984, **49**, 2834.
7) S. Hanessian, A. Ugolini, D. Dubé, and A. Glamyan, Canad. J. Chem., 1984, **62** 2146.
8) $[\alpha]_D$-25.8° (c=0.65, MeOH). [lit.[7] $[\alpha]_D$-28° (c=1.07, MeOH)].
9) O. Mitsunobu, M. Wada, and T. Sano, J. Amer. Chem. Soc., 1972, **94**, 679.
10) All new compounds gave satisfactory spectral and analytical (combustion and/or high resolution mass spectral) data consistent with the structures shown.
11) H. R. Ing and R. H. Manske, J. Chem. Soc., 1926, 2348.
12) A. J. Mancuso, S. L. Huang, and D. Swern, J. Org. Chem., 1978, **43**, 2480.
13) K. Fuji, K. Ichikawa, M. Node, and E. Fujita, J. Org. Chem., 1979, **44**, 1661.
14) IR($CHCl_3$)cm^{-1} 3400, 1720, 1690; ^{13}CNMR(Pyridine-d_5, 80°C) δ 14.207(q),

14.853(q), 32.173(t), 38.102(t), 45.089(t), 60.413(t), 60.941(t), 63.935(d), 74.914(d), 155.465(s), 171.200(s); MS(m/z) 227(M^+-H_2O). For the acetate of **17**: IR($CHCl_3$)cm^{-1} 1735, 1695; ^{1}HNMR($CDCl_3$, 100 MHz) δ1.25(3H, t, J=7.0 Hz), 1.26(3H, t, J=7.0 Hz), 2.04(3H, s), 2.00-3.00(4H, m), 3.50(2H, m), 4.12(4H, q, J=7.0 Hz), 4.00-4.23(1H, m), 5.12(1H, m, $W_{1/2}$ 8.0 Hz); MS(m/z) 227(M^+-HOAc).

15) From the ^{1}HNMR of **3**, contamination of a trace amount of Z-isomer was observed.

16) $[\alpha]_D$-144.9° (c=0.64, $CHCl_3$) [lit.[1] $[\alpha]_D$-146.7° (c=1.61, $CHCl_3$)].

17) For an another chiral synthesis of **6**, see; J. G. Buchanan, G. Singh, and R. H. Wightman, J. Chem. Soc. Chem. Commun., 1984, 1299.

Received, 6th December, 1985