

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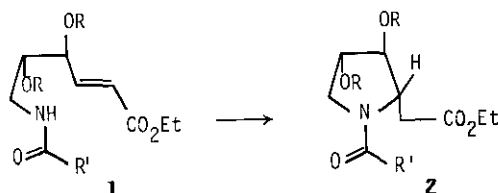
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Abstract — An enantioselective synthesis of the title compound, a precursor for the Geissman lactone, from S-(-)-malic acid is described. The synthesis features the diastereoselective intramolecular Michael reaction of the carbamate (3).

We recently introduced¹ the intramolecular Michael reaction-based² 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)

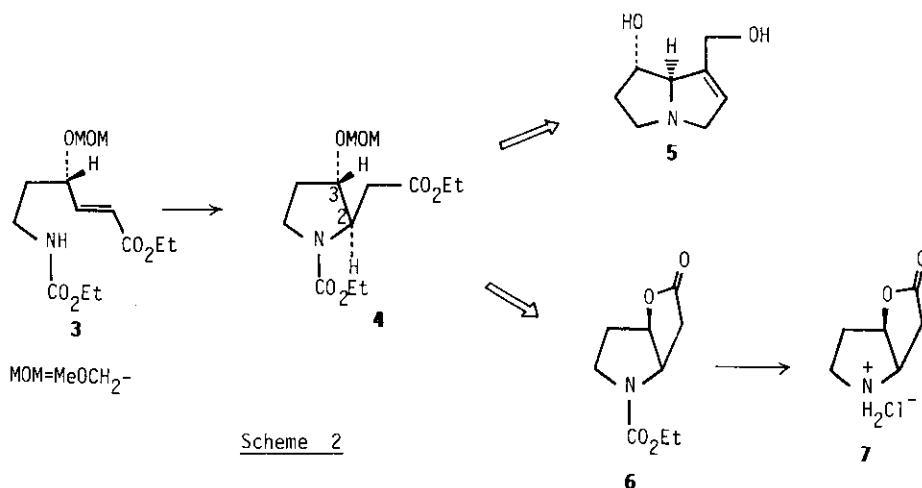


Scheme 1

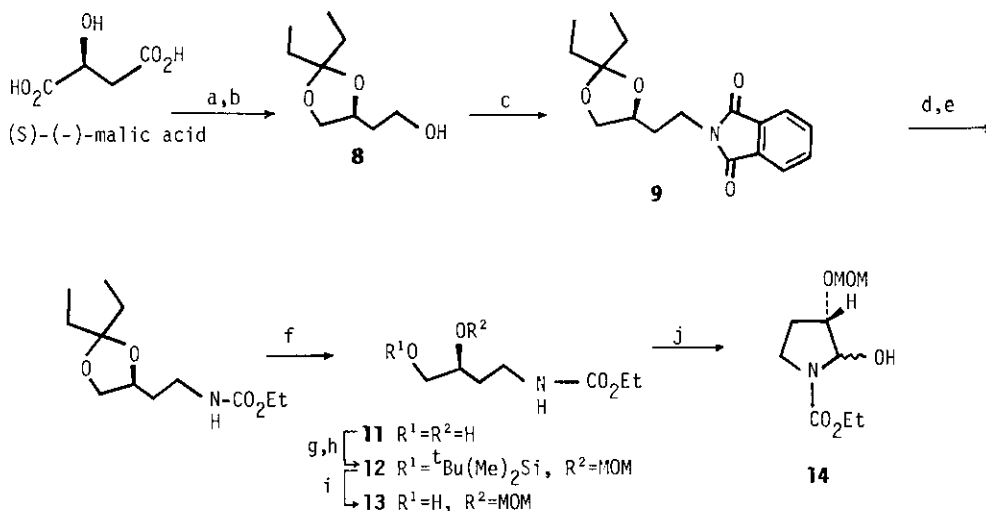
In the conversion, it was found that the nitrogen nucleophile might attack the β -carbon of the unsaturated ester preferentially from the si-face by steric reason. It is interesting to note that if the mechanistic rationale was acceptable, the intramolecular Michael reaction of 3 should lead to a preference 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 2*R*,3*S*-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 retronecine⁵, 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 reduction⁷ and protection⁶ of the 1,2-diol function of the resulting triol⁸, with the well-established condition of Mitsunobu⁹ afforded 9¹⁰



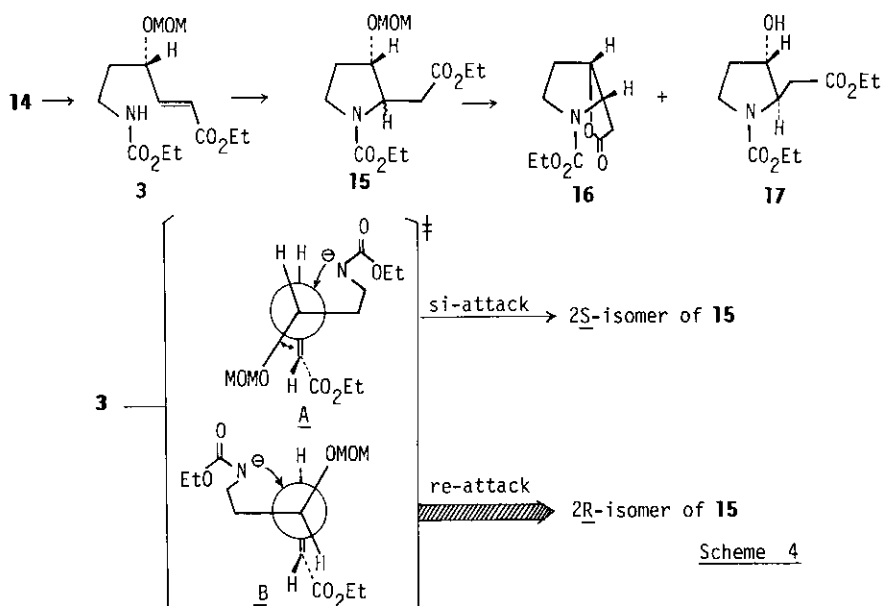
$[[\alpha]_D + 11.77^\circ$ ($c=1.45$, CHCl_3)]. The Ing-Manske hydrazinolysis¹¹ followed by carbamate formation with ethyl chloroformate gave the carbamate (10) $[[\alpha]_D + 1.85^\circ$ ($c=1.26$, CHCl_3)] which was then exposed to 6N-HCl in THF to afford the diol (11) $[[\alpha]_D + 1.15^\circ$ ($c=0.59$, CHCl_3)] in 91 % yield from malic acid. Selective silylation and methoxymethylation of the resulting secondary alcohol cleanly generated 12 $[[\alpha]_D - 50.00^\circ$ ($c=0.61$, CHCl_3)]. Subsequent desilylation and Swern oxidation¹² of the resulting primary alcohol moiety in 13 $[[\alpha]_D + 11.97^\circ$ ($c=0.75$, 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) $\text{B}(\text{OMe})_3$, $\text{BH}_3 \cdot \text{SMe}_2$, THF then MeOH, 100% b) $\text{Et}_2\text{C}(\text{OMe})_2$, $p\text{-TsOH}$ (cat.), DMF, 100% c) Ph_3P , EtO_2CN , phthalimide, THF, 100% d) $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, EtOH e) ClCO_2Et , NEt_3 , CH_2Cl_2 , 91% from 9 f) 6N-HCl, THF, 100% g) $t\text{Bu}(\text{Me})_2\text{SiCl}$, imidazole, 4-DMAP, CH_2Cl_2 , 95% h) MOMCl, $i\text{Pr}_2\text{NEt}$, CH_2Cl_2 , 100% i) $n\text{Bu}_4\text{NF}$, THF, 100% j) $(\text{COCl})_2$, DMSO, NEt_3 , CH_2Cl_2 , 96%.

Scheme 3

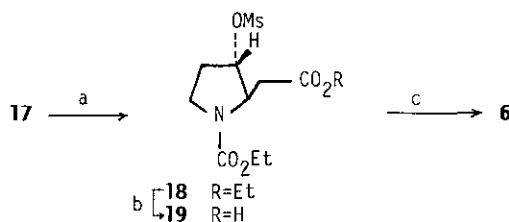
On treatment with triethyl phosphonoacetate $[(\text{EtO})_2\text{POCH}_2\text{CO}_2\text{Et}]$ (2.3 eq) in the presence of sodium hydride (2.5 eq) in dimethoxyethane (DME) at room temperature for 13 h, the diastereomeric hemiacetal (**14**) could be converted into the cyclized product (**15**) as an inseparable diastereomeric mixture. Cleavage of the methoxymethyl (MOM) function in the crude **15** with ethanethiol and boron trifluoride etherate¹³ provided an easily separable 1:2 mixture of the lactone (**16**) $[[\alpha]_D^{+144.1^\circ} (c=0.52, \text{CHCl}_3)]$ and the hydroxy ester (**17**)¹⁴ $[[\alpha]_D^{-44.04^\circ} (c=1.28, \text{CHCl}_3)]$ in 65 % yield. To circumvent the lower selectivity, the transformation was attempted by a kinetic condition. Thus, treatment of **14** with $(\text{EtO})_2\text{POCH}_2\text{CO}_2\text{Et}$ 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**) $[[\alpha]_D^{-4.30^\circ} (c=0.66, \text{CHCl}_3)]$ which was hydrolyzed 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 rotation¹⁶ 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.

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- 8) $[\alpha]_D^{25} -25.8^\circ$ ($c=0.65$, MeOH). [lit.⁷ $[\alpha]_D^{28} -28^\circ$ ($c=1.07$, MeOH)].
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- 14) $\text{IR}(\text{CHCl}_3)\text{cm}^{-1}$ 3400, 1720, 1690; $^{13}\text{CNMR}(\text{Pyridine-}d_5, 80^\circ\text{C})$ 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; 1H NMR($CDCl_3$, 100 MHz) δ 1.25(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 1H NMR of 3, contamination of a trace amount of Z-isomer was observed.
- 16) $[\alpha]_D -144.9^\circ$ ($c=0.64$, $CHCl_3$) [lit.¹ $[\alpha]_D -146.7^\circ$ ($c=1.61$, $CHCl_3$)].
- 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