# TANDEM REDUCTIVE AMINATION AND MICHAEL ADDITION. SYNTHESIS OF OPTICALLY ACTIVE PYRROLIDINE NUCLEUS

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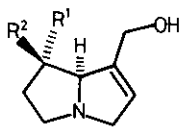
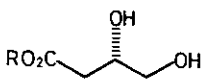
Abstract —— Reductive amination of ethyl (E)-(4S)-4-methoxymethoxy-6-oxo-2-hexenoate, derived from (S)-malic acid, with glycine ethyl ester was relayed intramolecularly by Michael-type addition, which has led, in one pot, to N-substituted (2R,3S)-2-ethoxycarbonylmethyl-3-hydroxypyrrolidine skeleton, a promising precursor for optically active necine bases such as (+)-heliotridine.

Optically active necine bases such as (+)-retronecine (1a) or (+)-heliotridine (1b) have recently drawn widespread interest in organic synthesis.[1] In these molecules two contiguous asymmetric centers appear at C(7) and C(8) positions and, especially, C(8) is adjacent to the nitrogen atom, which seems to make it highly challenging to develop the methods for the chiral synthesis of necine bases. Thus, although many methods or the syntheses of these natural products in a racemic form have been described so far,[1] chiral version of these has still been limited to only recent developments.[2]



**1a** $R^1$=H $R^2$=OH
**1b** $R^1$=OH $R^2$=H



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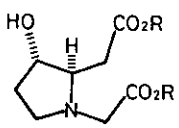

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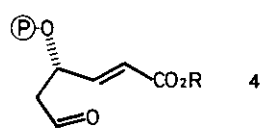
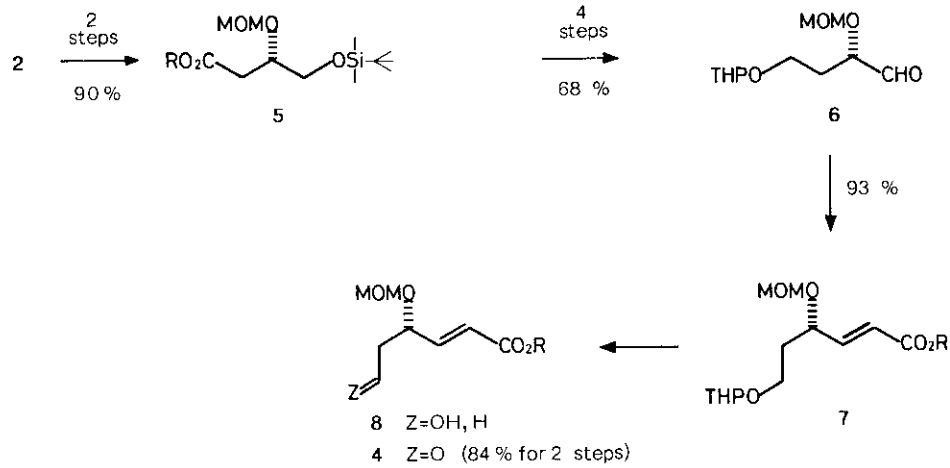
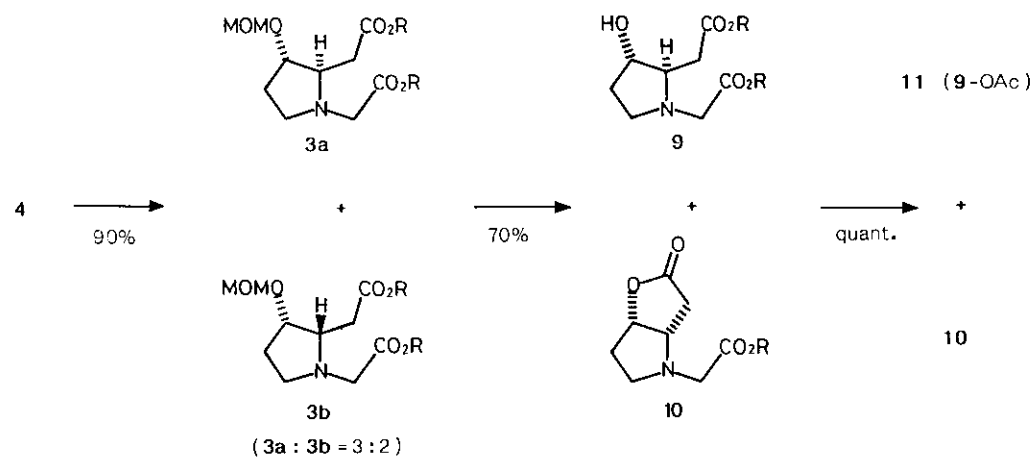


**4**

Recent communication from our laboratory has recorded the novel methodology for reducing the ester group α to the hydroxyl group of (S)-malic acid diesters in extremely selective manner which offers easy access to optically pure (3S)-3,4-dihydroxybutanoic acid esters (2).[3] Being encouraged by this new synthetic transformation, we have embarked in natural product synthesis utilizing 2 and, to our delight, will disclose herein a novel synthesis of optically pure N-substituted (2R,3S)-2-ethoxycarbonylmethyl-3-hydroxypyrrolidine (3) from 2 by means of tandem reductive amination and Michael addition of (E)-(4S)-4-methoxymethoxy-6-oxo-2-hexenoate (4) with glycine ethyl ester, which is a promising precursor for 1b.[2c]

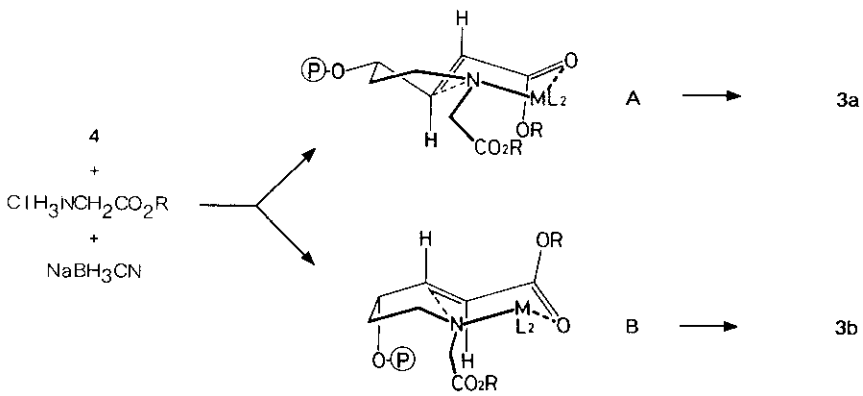


In the event, sequential protection of the primary and secondary hydroxyl groups of 2 with t-butyldimethylsilyl (TBDMS) [TBDMS-Cl/DMAP/$Et_3N$/$CH_2Cl_2$/0°C, 6 h] and methoxymethyl (MOM) groups [MOM-Cl/i-$Pr_2NEt$/$CH_2Cl_2$/0°C → rt, 6 h] gave fully protected diol ester (5) in 90% yield after silica gel ($SiO_2$) chromatography: $[\alpha]_D^{23}$ -23.2° (c 1.23, $CHCl_3$). A series of routine reactions from 5 involving reduction [$LiAlH_4$/THF/-40°C, 1 h], protection of resulting hydroxyl group as THP-ether [DHP/PPTs/$CH_2Cl_2$/rt, 12 h], deprotection of the TBDMS-group [n-$Bu_4NF$/THF/rt, 2.5 h], and Swern oxidation [$(COCl)_2$/DMSO/$Et_3N$/-60°C, 30 min], provided the aldehyde (6) in 68% yield (for 4 steps). Because of an instability of the aldehyde, a short-path column ($SiO_2$) chromatography was executed for purification of the aldehyde, which, accordingly, was quickly reacted with Wadsworth-Emmons reagent [(i-PrO)$_2$P(O)$CH_2CO_2Et$/NaH/THF/0°C, 45 min], giving rise to key intermediate (7) in 93% yield after $SiO_2$ chromatography, in which a proper arrangement of requisite carbon framework was established. On exposure to mild acid [PPTs/EtOH/50°C, 3 h], the THP-group of 7 was deprotected selectively to furnish the corresponding alcohol (8) almost quantitatively: $[\alpha]_D^{22}$ -123° (c 1.62, $CHCl_3$); $^1$H-nmr ($CDCl_3$) δ 1.30 (t, 3H, J=7.1 Hz), 1.7-1.95 (m, 2H), 2.12 (s, 1H, OH), 3.41 (s, 3H), 3.72-3.85 (m, 2H), 4.21 (q, 2H, J=7.1 Hz), 4.3-4.7 (m, 1H), 4.64 (s, 2H), 6.00 (dd, 1H, J=1.3 and 15.8 Hz), and 6.85 (dd, 1H, J=6.0 and 15.8 Hz) ppm.[4] Then, 8 was oxidized by Swern protocol [$(COCl)_2$/DMSO/$Et_3N$/-78°C, 2 h] to leave behind the aldehyde (4), immediate precursor for 3, in 84% yield after short-path column ($SiO_2$) chromatography, which was quickly treated with glycine ethyl ester hydrochloride [MeOH/0°C, 1 h], followed by reduction with $NaBH_3CN$ [1 mol eq/MeOH/0°C, 3 h] to generate secondary amine.[5] The reaction, however, never stopped at this stage but proceeded further in Michael-type fashion under given reaction conditions: the amine attacked intramolecularly to α,β-unsaturated ester moiety, ending up with the formation of pyrrolidine nucleus (3) in 90% yield after $SiO_2$ chromatography.

Diastereofacial selectivity of this Michael-type addition reaction turned out to be only in the neighborhood of 3 : 2 (3a : 3b) as verified on the basis of $^1$H- and $^{13}$C-nmr spectra. However, to our satisfaction, simple two-step chemical transformation from 3 involving MOM-deprotection [HCl/THF/EtOH/rt, 12 h] and subsequent acetylation [$Ac_2O$/DMAP/$CH_2Cl_2$/rt, 1 h] led a mixture of lactone (10) and acetate (11), a separation of which has been easily achieved even by usual gravity-type column chromatography. Thus, 10 and 11 were obtained in optically pure state (70% yield totally from 3): 10 $^1$H-nmr ($CDCl_3$) δ 1.28 (t, 3H, J=7.1 Hz), 2.1-2.4 (m, 2H), 2.5-2.6 (m, 2H), 2.6-2.9 (m, 1H), 3.0-3.8 (m, 4H), 4.18 (q, 2H, J=7.1 Hz), 5.00 (m, 1H); $[\alpha]_D^{23}$ +27.0° (c 2.27, $CHCl_3$); ir ($\nu_{C=O}$) 1775 and 1740 $cm^{-1}$: 11 $^1$H-nmr ($CDCl_3$) δ 1.25 and 1.27 (t, 3H for each, J=7.1 Hz), 1.6-2.3 (m, 2H), 2.05 (s, 3H), 2.5-2.75 (m, 2H), 2.75-3.70 (m, 5H), 4.18 and 4.21 (q, 2H for each, J=7.1 Hz), 5.09 (m, 1H); $^{13}$C-nmr ($CDCl_3$) δ 171.4 (C=O), 170.6 (C=O), 170.5 (C=O), 79.00 (AcO$\underline{C}$H), 65.55 (N-$\underline{C}$H), 60.48 (O-$\underline{C}H_2$x2), 54.29 (N-$\underline{C}H_2$COOR), 51.90 (N-$\underline{C}H_2$), 38.06 (C-$\underline{C}H_2$COOR), 30.60 (ring $\underline{C}H_2$), 21.15 (CO$\underline{C}H_2$), 14.23

($CH_2\underline{CH}_3$x2); $[\alpha]_D^{25}$ -25.3° (c 1.28, $CHCl_3$). When glycine methyl ester was employed in place of the ethyl ester, the similar conversion as 4→3b→10 gave again bicyclic lactone in which the methyl ester moiety stemmed from glycine methyl ester remained intact, whereas the ethyl group, which was present in 4, disappeared. This means unequivocally that the lactone should not be bicyclo[3.2.1]octyl system but the Geissman-Waiss-type[6] as 10. An attempt to remedy diastereofacial selectivity of this reaction in terms of steric effects exposed by γ-alkoxy substituent in 4 has been in vain. Nevertheless, the present method for the synthesis of pyrrolidine nucleus in optically pure form seems highly useful because of its operational simplicity, ready availability of 4 in optically pure state, and easiness of the separation between 10 and 11. As the exocyclic diester system in 3 or 11 has already proven to be potent functional groups for B-ring closure as demonstrated by Rueger and Benn,[2c] present approach should lead to 1b in a formal sense.




We believe tentatively that the formation of 3a or 3b involves a hypothetical transition state A or B respectively in which metal (M), assumed to be boron in this case, plays an important role in making the nitrogen atom and the β-carbon of α,β-unsaturated ester functionality come close to each other. This idea partly stemmed from the fact that the ω-amino-α,β-unsaturated ester corresponding to an intermediate intervened during the conversion 4→3, which was prepared independently, failed to undergo Michael-type addition reaction when it was treated with various bases.[7] The transition state A seems more favorable than B for the pyrrolidine ring closure because the latter might suffer from destabilizing non-bonded interactions.

ACKNOWLEDGMENTS

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REFERENCES AND NOTES

1) For review, see R. V. Stevens, 'Alkaloid Synthesis' in Total Synthesis of Natural Products, Vol. 3, ed. by J. ApSimon, John Wiley & Sons, Inc., 1977, p. 439 and K. Narasaka, J. Synth. Org. Chem. Japan, 1985, 43, 464 .

2) a) D. J. Robins and S. Sakdarat, J. Chem. Soc., Chem. Commun., 1979, 1181; J. Chem. Soc., Perkin Trans. I, 1981, 909; b) S. Takano, N. Ogawa, and K. Ogasawara, Heterocycles, 1981, 16, 915; c) H. Rueger and M. Benn, ibid., 1982, 19, 23, 1677; 1983, 20, 1331; d) K. Tatsuta, S. Miyashita, K. Akimoto, and M. Kinoshita, Bull. Chem. Soc. Jpn., 1982, 55, 3254; e) K. Tatsuta, H., Takahashi, Y. Amemiya, and M. Kinoshita, J. Am. Chem. Soc., 1983, 105, 4096; f) D. J. Hart and T. K. Yang, Tetrahedon Lett., 1982, 23, 2761; J. Chem. Soc., Chem. Commun., 1983, 135; J. Org. Chem., 1985, 50, 235; g) S. Takano, S. Otaki, and K. Ogasawara, J. Chem. Soc., Chem. Commun., 1983, 1172; h) A. R. Chamberlin and J. Y. L. Chung, J. Am. Chem. Soc., 1983, 105, 3653; J. Org. Chem., 1985, 50, 4425; i) J. G. Bachanan, G. Singh, and R. H. Wightman, J. Chem. Soc., Chem. Commun., 1984, 19, 1299; j) K. Shishido, Y. Sukegawa, K. Fukumoto, and T. Kametani, Heterocycles, 1985, 23, 1629; 1986, 24, 641.

3) S. Saito, T. Hasegawa, M. Inaba, R. Nishida, T. Fujii, S. Nomizu, and T. Moriwake, Chem. Lett., 1984, 1389.

4) $^{13}$C-nmr ($CDCl_3$) of 8 indicated the presence of very small amount (<2%) of (Z)-olefin: 166.2 (C=O), 147.6 ($\underline{C}_{\beta}$=C), 121.8 (C=$\underline{C}_{\alpha}$), 94.94 (O$\underline{C}H_2$O), 73.15 (MOMO$\underline{C}$H), 60.53 (HO$\underline{C}H_2$), 58.58 (O$\underline{C}H_2CH_3$), 55.65 (O$\underline{C}H_3$), 37.52 (t), 14.8 (q); signals due to (Z)-isomer appeared at 148.0 and 121.3 ppm.

5) When the reaction was quenched shortly after the addition of $NaBH_3CN$, the amine was obtained.

6) T. A. Geissman and A. C. Waiss, Jr., J. Org. Chem., 1962, 27, 139.

7) S. Saito, S. Matsumoto, M. Inaba, and T. Moriwake, unpublished observations.

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