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A New Method for Introducing Some Active Methylene or Methine Groups to the 3-Position of Pyrrolidine or Piperidine Skeleton, and Its Application to Preparation of a Key Intermediate for (±)-Eburnamonine Synthesis[1)]

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A new method for introducing a bis(methoxycarbonyl)methyl or 2-oxopropyl group to the 3-position of pyrrolidine or piperidine skeleton has been exploited, and this method could be used in the synthesis of a key intermediate for the (±)-eburnamonine synthesis.

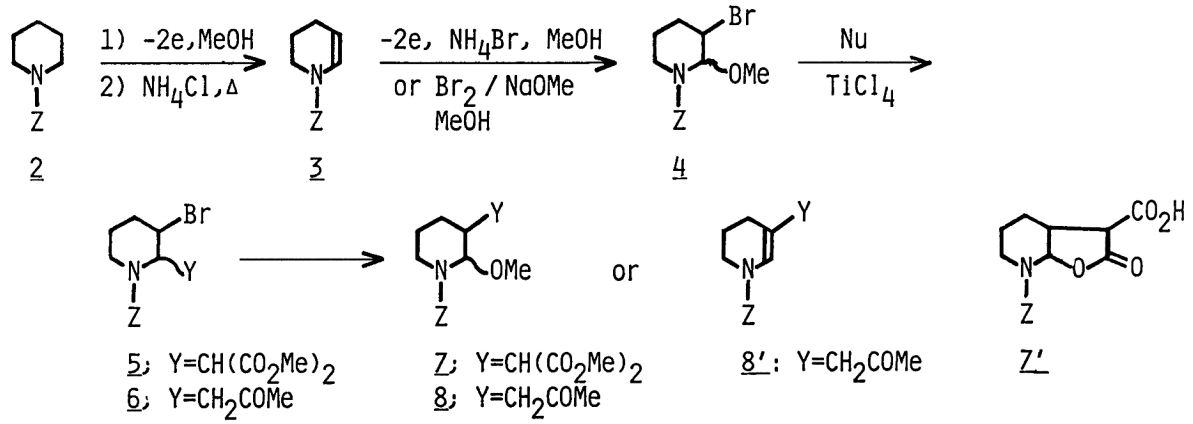
Introducing a variety of substituents to certain positions of pyrrolidine or piperidine skeleton is worthwhile in organic synthesis since substituted pyrrolidine or piperidine skeleton is found in many types of alkaloid.[2)]

In continuing our studies carried out from this standpoint,[3)] we found a new method for the introduction of some active methylene or methine groups (Y) such as a bis(methoxycarbonyl)methyl or 2-oxopropyl group to the 3-position of pyrrolidine or piperidine skeleton and succeeded in its application to synthesis of 26, a key intermediate in the synthesis of (±)-eburnamonine 1,[4)] an indole alkaloid isolated from *Hunteria eburnea* Pichon.[5)]

Out method for introducing Y group to the 3-position of piperidine skeleton is shown in Scheme 1 which consists of the following four steps: (1) the synthesis of 1,2,3,4-tetrahydro-1-methoxycarbonylpyridine 3 from 1-methoxycarbonylpiperidine 2, (2) the bromomethoxylation of 3 yielding 3-bromo-2-methoxy-1-methoxycarbonylpiperidine 4, (3) the introduction of Y group to the 2-position of 4 affording 2-Y-3-bromo-1-methoxycarbonylpiperidine 5 or 6, and (4) the base treatment of 5 or 6 giving piperidine derivatives 7 or 8 bearing a substituent Y at the 3-position.

The experimental procedures of these steps were very simple as described below. The preparation of 4 from 2 has already been reported (3,[3b,c)] 83% yield from 2: 4,[3d)] 81% yield from 3).[6)] Subsequent introduction of Y group to the 2-position of 4 was achievable according to our reported method.[3a)] That is, a solution of 4 in methylene chloride and a solution of a mixture of dimethyl malonate (1.5 equiv.) and triethylamine (1.5 equiv.) in methylene chloride were successively added into a solution of titanium tetrachloride (1.0 equiv.) in methylene chloride at -78 °C, and then the resulting solution was warmed to room temperature. The usual working up gave 5 in 75% yield. Compound 6 was obtained in 78% yield by the reaction of 4 with isopropenyl acetate (1.5 equiv.) in

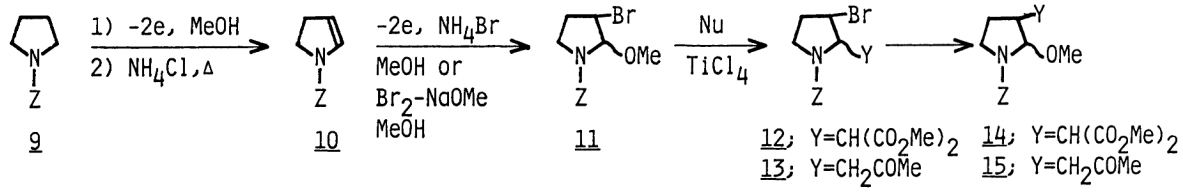
the presence of titanium tetrachloride (1.0 equiv.).



Scheme 1.

The final step was the rearrangement of the substituent Y from the 2-position to the 3-position. The rearrangement of 5 yielding 7 was found to be easily achieved by treating 5 with NaOMe (1.2 equiv.) in methanol. Similar treatment of 5 with aqueous methanol containing NaOH gave an amino lactone 7'. On the other hand, the transformation of 6 to 8 required the treatment of 6 with NaOMe (1.2 equiv.) in methanol followed by acidifying the resulting solution with conc. HCl, and the compound 8' was obtained instead of 8.

Our method is also applicable to the introduction of Y group to the 3-position of pyrrolidine skeleton (Scheme 2). That is, compounds 14 and 15 were preparable from 9 through intermediates 10-13 which were formed by similar procedures to the preparation of 3-6 (10, 91% yield:[3c] 11, 42% yield:[3d,6] 12, 81% yield: 13, 82% yield).



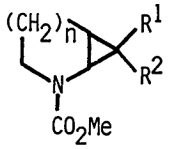
Scheme 2.

The yields of 7, 7', 8', 14, and 15, and the reaction conditions for the rearrangement are summarized in Table 1.

Table 1. Rearrangement of 5, 6, 12, and 13 to 7, 7', 8', 14, and 15

Substrate	Reaction conditions	Product	Isolated yield/%
5	NaOMe/MeOH, r.t., 22 h	7	59
5	NaOH/MeOH-H_2O (2:1), r.t., 5 h	7'	68
6	NaOMe/MeOH, r.t., 15 h, then conc. HCl, r.t., 18 h	8'	72
12	NaOMe/MeOH, r.t., 22 h	14	82
13	NaOMe/MeOH, r.t., 12 h, then conc. HCl, r.t., 15 h	15	48

The rearrangement of Y group from 2-position to 3-position in compounds 5, 6, 12, and 13 may proceed through the formation of cyclopropane intermediates 16-19. In fact, the formation of 18 or 19 was observed in the reaction of 6 or 13 with bases, whereas 16 or 17 was not detected in the reaction of 5 or 12 with bases.



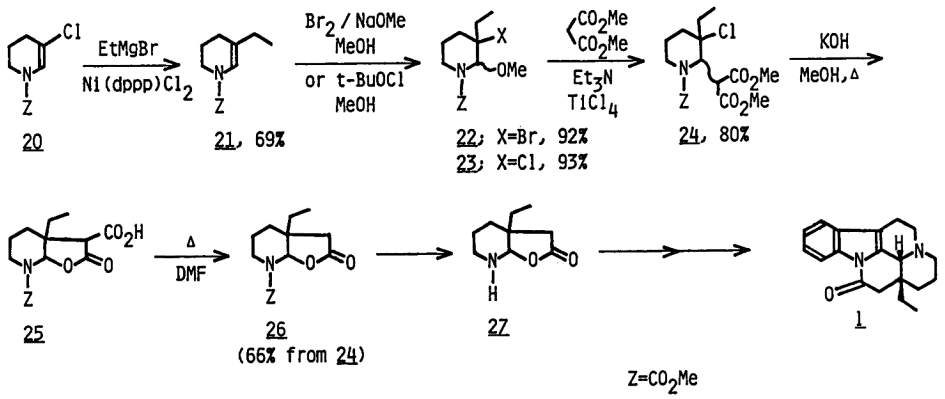
16; n=1, $R^1=R^2=CO_2Me$ 17; n=2, $R^1=R^2=CO_2Me$

18; n=1, $R^1=COMe$, $R^2=H$ 19; n=2, $R^1=COMe$, $R^2=H$

Among the products, the structure of 7' is interesting since it is similar to an amino lactone 27 which is a key intermediate in the synthesis of 1. Wenkert *et al.* have reported the synthesis of 27 using a cyclopropane intermediate prepared by copper-catalyzed reaction of ethyl diazoacetate with 21.[7] Ban *et al.* have synthesized 26 by utilizing anodic oxidation of 3-ethyl-3-carboxymethyl-1-methoxycarbonylpiperidine, and converted 26 to 1 through 27.[8] More recently, Hanaoka *et al.* have also succeeded in the synthesis of 27 starting from 1,6-dihydro-3(*2H*)-pyridinone.[4]

Thus, our effort has been directed toward the application of our method to the synthesis of 27 (Scheme 3). The starting compound 21 was prepared in 69% yield by Ni-catalyzed reaction of 3-chloro-1-methoxycarbonyl-1,4,5,6-tetrahydropyridine 20[3d] with ethylmagnesium bromide.[9,10] The bromomethoxylation of 21 giving 22 was easily carried out by treating 21 with bromine (1.1 equiv.) in methanol containing NaOMe (1.1 equiv.) (92% yield). However, in contrast with the transformation of 4 to 5, introducing a bis(methoxycarbonyl)methyl group to the 2-position of 22 was unsuccessful possibly because of the steric constraints of substituents at the 3-position of 22. On the other hand, fortunately, chloromethoxylated compound 23, prepared by the reaction of 21 with *t*-butyl hypochlorite (1.2 equiv.) in methanol (93% yield), reacted with dimethyl malonate affording 24 (80% yield). Compound 24 was transformed to 25 on treatment with KOH (20 equiv.)

in methanol for 20 h at 65 °C, and 25 was decarboxylated by heating 25 in DMF for 11 h to give 26 (66% yield from 24). The hydrolysis of 26 giving 27 and the easy transformation of 27 to 1 have already been reported.[4,7,8]



Scheme 3.

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5) M. F. Bartlett, W. I. Taylor, and R. Hamet, *C. R. Acad. Sci., Ser. C*, 249, 1259 (1959).
6) The transformation of 3 to 4 or of 10 to 11 was also achieved by adding bromine (1.2 equiv.) to a solution of 3 or 10 in methanol containing NaOMe (1.2 equiv.) (4, 80% yield: 11, 71% yield).
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9) The yield of 21 described in a literature[7] was very low (14% yield starting from 3-acetyl-1,4,5,6-tetrahydropyridine).
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