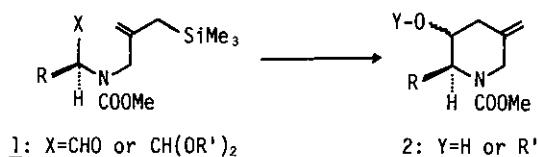


DIASTEREOSELECTIVE SYNTHESIS OF 2,3-CIS-2-ALKYL-3-OXYGENATED  
PIPERIDINE DERIVATIVES BY TITANIUM MEDIATED INTRAMOLECULAR  
CYCLIZATION OF  $\alpha$ -AMINOACETAL-ALLYLSILANE SYSTEM

Shinzo Kano,\* Tsutomu Yokomatsu, Haruo Iwasawa, and Shiroshi Shibuya  
Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji,  
Tokyo 192-03, Japan

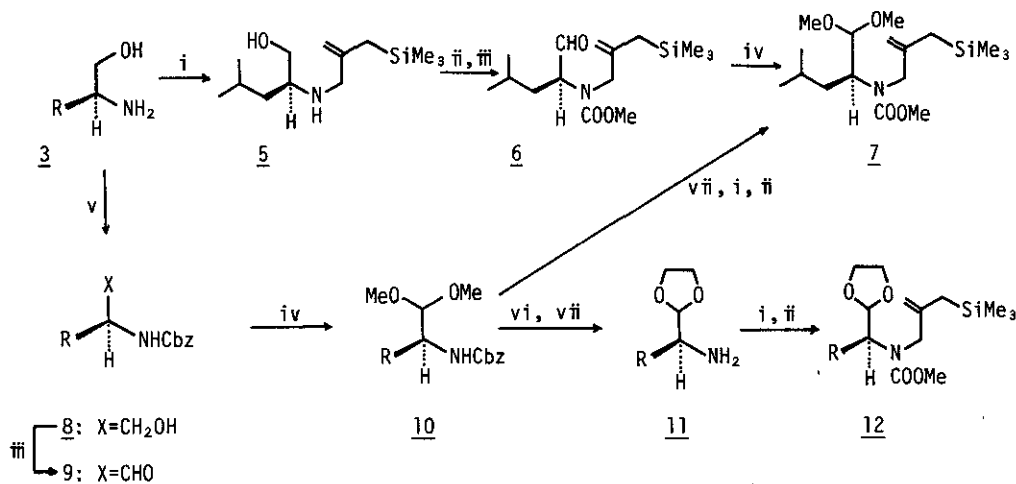
**Abstract** — (2S,3S)-2-Alkyl-3-oxygenated 5-methylenepiperidines were obtained with high diastereoselectivity by cyclization of N-methoxycarbonyl-N-silylmethyl- $\alpha$ -alkylaminoacetaldehyde ethyleneacetals with  $\text{TiCl}_3(\text{OPr}^i)$ .

The enhanced  $\pi$ -bond nucleophilicity of allylsilanes<sup>1</sup> by Lewis acid has been widely applied to a synthesis of alcohols by addition to carbonyl compounds through C-C bond formation. Acetals were also used as an electrophile in the allylsilane-induced C-C bond formation.<sup>2</sup> Intramolecular allylation of  $\alpha$ -amino aldehydes (or acetals), 1  $\rightarrow$  2, would constitute a new facile method for a synthesis of 2-alkyl-5-methylene-3-oxygenated piperidine derivatives, potentially useful intermediates for a synthesis of poly-functionalized piperidines. Although  $\alpha$ -amino aldehydes from L-amino acids have a remarkable ability to yield chiral 2-amino alcohols, it is known that the level of diastereoselectivity in a formation of 2-amino alcohols is not high.<sup>3</sup> We investigated a Lewis acid mediated intramolecular cyclization of  $\alpha$ -amino aldehyde (or acetals)-allylsilane systems (1) to examine the level of diastereoselectivity in a formation of type of compounds (2). The results of our studies are described in this paper.



At first, the  $\alpha$ -amino aldehydes and acetals, used in this study, were prepared as outlined in the Scheme 1. Condensation of the amino alcohol (3b), derived from L-leucine, with trimethylsilylmethyl bromide (4)<sup>4</sup> gave 5<sup>5</sup> in 60 % yield. Methoxycarbonylation (ClCOOMe, CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N) of 5, followed by Swern oxidation<sup>6</sup> and successive dimethylacetalization (methanol, p-toluenesulfonic acid) of the resulting aldehyde (6) gave the acetal (7) in 93 % yield from 5. Swern oxidation of the alcohols (8a-c), obtained from 3a-c in 95 % yield by benzyloxycarbonylation (ClCOOCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, CH<sub>2</sub>Cl<sub>2</sub>, Et<sub>3</sub>N) afforded 93 % yield of the aldehydes (9a-c) which were successively converted to the acetals (10a-c) by dimethylacetalization in 90-95 % yield, respectively. Transacetalization of 10a-c (ethyleneglycohol, p-toluenesulfonic acid), followed by removal of benzyloxycarbonyl group by hydrogenolysis (H<sub>2</sub>/Pd-C) gave the amine (11a-c) in 80-83 % yield, respectively. Condensation of 11a-c with 4, followed by methoxycarbonylation gave the corresponding carbamates (12a-c) in 60-62 % yield, respectively. Removal of benzyloxycarbonyl group of 10b by hydrogenolysis followed by condensation with 4 and successive methoxycarbonylation also afforded 7 in 57 % yield.

Scheme 1



Cbz=COOCH<sub>2</sub>Ph

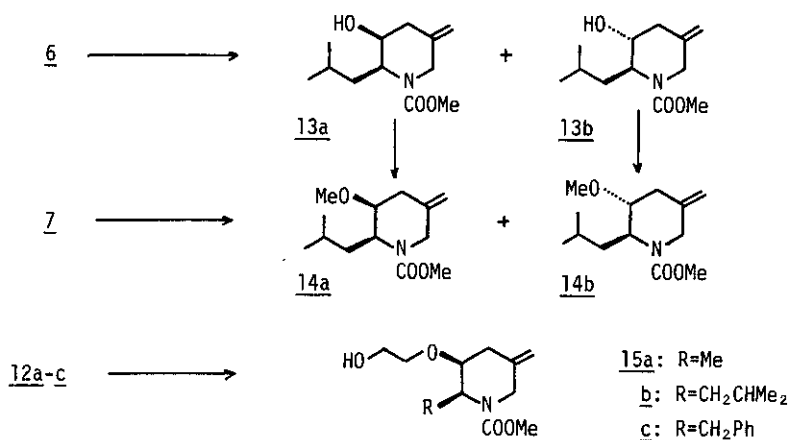
For 3 and 8-12 a: R=Me; b: R=CH<sub>2</sub>CHMe<sub>2</sub>; c: R=CH<sub>2</sub>Ph

Reagents and Conditions

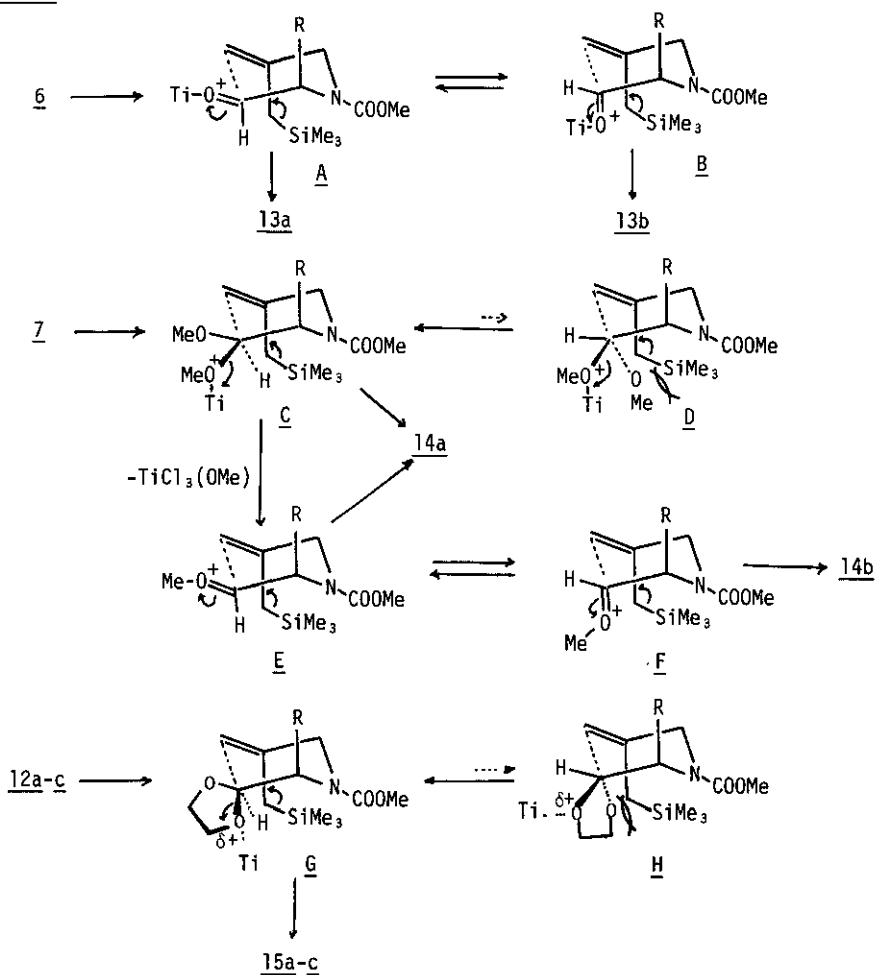
- i. CH<sub>2</sub>=C(CH<sub>2</sub>Br)CH<sub>2</sub>SiMe<sub>3</sub> (4), *i*-Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, room temperature ii. ClCOOMe, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>  
 iii. (COCl)<sub>2</sub>-Me<sub>2</sub>SO, CH<sub>2</sub>Cl<sub>2</sub>, -78°C, Et<sub>3</sub>N iv. MeOH, p-TsOH v. ClCOOCH<sub>2</sub>Ph, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>  
 vi. HOCH<sub>2</sub>CH<sub>2</sub>OH, p-TsOH vii. H<sub>2</sub>/Pd-C

Cyclization of 6 ( $\text{TiCl}_4$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 1 h) yielded a 2:1 mixture of 13a and 13b in 43 % yield and in 95 % enantiomeric excess.<sup>7</sup> Two isomers were separated by column chromatography on silica gel; 13a: an oil,  $[\alpha]_{\text{D}}^{20} -13.7^\circ$  (c 1.86,  $\text{CHCl}_3$ ), 13b, mp  $58-60^\circ\text{C}$ ,  $[\alpha]_{\text{D}}^{20} +29.4^\circ$  (c 0.61,  $\text{CHCl}_3$ ). Signals due to 4-H<sub>2</sub> of 13a and 13b are clearly visible in their <sup>1</sup>H nmr ( $\text{CDCl}_3$ , 400 MHz) spectra; 13a,  $\delta$  2.33 (4 $\beta$ -H, ddd,  $J=1.6, 11.6, 13.32$  Hz),<sup>8</sup> 2.43 (4 $\alpha$ -H, dd,  $J=4.90, 13.32$ ); 13b,  $\delta$  2.31 (4 $\beta$ -H, broad d, 13.57 Hz), 2.56 (4 $\alpha$ -H, broad d,  $J=13.57$  Hz). The  $J$  values of 11.6 and 4.90 Hz in 13a are due to a diaxial and an equatorial-equatorial interaction, respectively. On the other hand, each of two 4-H in 13b appeared as a pair of doublet caused by geminal coupling constants with only small equatorial-equatorial interaction. Based on these results, the absolute configuration of 13a was assigned as 2S,3S and that of 13b was as 2S,3R from Karplus relation<sup>9</sup> and the Dreiding model study. By conversion of aldehyde to dimethylacetal, the ratio of 2,3-cis/trans-isomer slightly increased. Cyclization of 7 with  $\text{TiCl}_4$  as above gave a 3:1 mixture of 14a and 14b in 43 % yield. Both isomers were separated and their structures were identified by comparison with the authentic samples obtained from 13a and 13b by O-methylation ( $\text{NaH}$ , DMF,  $\text{CH}_3\text{I}$ , room temperature), respectively. Although the high diastereoselectivity was not observed in the cyclization of 6 and 7, clean diastereoselectivity was obtained in the cyclization of ethyleneacetals (12a-c). Cyclization of 12a-c by the use of  $\text{TiCl}_3(\text{O-Pr}^i)$ <sup>10,11</sup> generated from  $\text{TiCl}_4$  and  $\text{Ti}(\text{OPr}^i)_4$  in situ afforded 15a-c<sup>12</sup> in 82-83 % enantiomeric excess<sup>13</sup> as 2,3-cis-diastereomers, respectively, without formation of the 2,3-trans-isomers. This stereoselectivity can be accounted for by the following reasons as depicted in the Scheme 3. The alkyl substituent at the 2-position can be assumed to take the axial configuration to avoid A-strain<sup>14,15</sup> caused by the alkyl substituent and the carbonyl group. In the case of 6, among two possible transition states (A and B), A leading 13a would be slightly predominant over B giving 13b. In the case of 7, the transition states (C and E) giving 14a should be more favorable than D and F. But comparable amounts of the two isomers were obtained in both cases. However, in the cases of 12a-c, cleavage of C-O bond was controlled by the use of the weaker Lewis acid in acidity. Cyclization proceeded via the transition state (G) to avoid the steric repulsion between acetal oxygen and trimethylsilylmethyl group.

Scheme 2



Scheme 3



## REFERENCES AND NOTES

1. T. K. Sarker and N. H. Anderson, Tetrahedron Lett., 1978, 3513; H.-F. Chow and I. Fleming, J. Chem. Soc. Perkin Trans. 1, 1984, 1815; M. T. Reetz, in "Organotitanium Reagents in Organic Synthesis", Springer-Verlag, Berlin, 1986, and references cited therein.
2. T. Tsunoda, M. Suzukim and R. Noyori, Tetrahedron Lett., 21, 71 (1980), and references cited therein.
3. D. H. Rich, E. T. Sun, and A. S. Boparai, J. Org. Chem., 43, 3624 (1978).
4. G. A. Molander and D. C. Shubert, Tetrahedron Lett., 27, 787\* (1986).
5. Spectral data (ir.  $^1\text{H}$  nmr, ms) and microanalyses (or high resolution ms) of all new compounds are consistent with their structures.
6. K. Omura and D. Swern, Tetrahedron, 34, 1651 (1978).
7. Determined by conversion to (-)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetic acid esters, which were analyzed by  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , 400 MHz).
8. Small coupling constants ( $\sim 1.6$  Hz) are due to allylic coupling.
9. L. M. Jackman and Sternhell, in "Application of Nuclear Magnetic Resonance in Organic Chemistry", 2nd Ed; Pergamon Press, Oxford, 1969, Chapter 4-2, pp 280.
10. T. Mukaiyama, Angew. Chem. Inter. Ed., 16, 817 (1977).
11. Cyclization of 6 and 7 with  $\text{TiCl}_3(\text{OPr}^i)$  was not successful.
12. 15a: 45 % yield, an oil,  $[\alpha]_D^{20} +6.84^\circ$  (c, 1.53, MeOH),  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  2.31 (4 $\beta$ -H, ddd,  $J=1.6, 11.74, 13.37$  Hz),  $^8$  2.48 (4 $\alpha$ -H, dd,  $J=4.59, 13.37$  Hz).  
15b: 43 % yield, an oil,  $[\alpha]_D^{20} -8.33^\circ$  (c, 1.44,  $\text{CHCl}_3$ ),  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  2.31 (4 $\beta$ -H, ddd,  $J=1.49, 11.82, 13.30$  Hz),  $^8$  2.49 (4 $\alpha$ -H, dd,  $J=4.65, 13.30$  Hz)  
15c: 40 % yield, an oil,  $[\alpha]_D^{20} -23.2^\circ$  (c, 1.36,  $\text{CHCl}_3$ ),  $^1\text{H}$  nmr ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  2.46 (4 $\beta$ -H, dd,  $J=11.83, 13.65$  Hz), 2.56 (4 $\alpha$ -H, dd,  $J=4.51, 13.65$  Hz).
13. Determined by removal of hydroxyethyl group (i.  $\text{MeSO}_2\text{Cl}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{Et}_3\text{N}$ . ii. KCN, DMSO. iii. THF-MeOH-KOH), followed by esterification with (-)- $\alpha$ -methoxy- $\alpha$ -(trifluoromethyl)phenylacetyl chloride.<sup>7</sup> The lower magnitude for the optical purity might be due to partial racemization during tranacetalization.
14. F. Johnson, Chem. Rev., 68, 375 (1969).
15. D. J. Hart, J. Am. Chem. Soc., 102, 397 (1980); D. J. Hart and K. Kanai, J. Org. Chem., 47, 1555 (1982).

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