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

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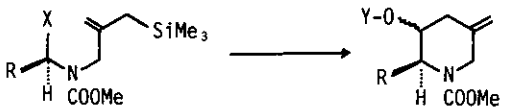
Abstract —— (2S,3S)-2-Alkyl-3-oxygenated 5-methylenepiperidines were obtained with high diastereoselectivity by cyclization of N-methoxycarbonyl-N-silylmethallyl-α-alkylaminoacetaldehyde ethyleneacetals with $TiCl_3(OPr^i)$.

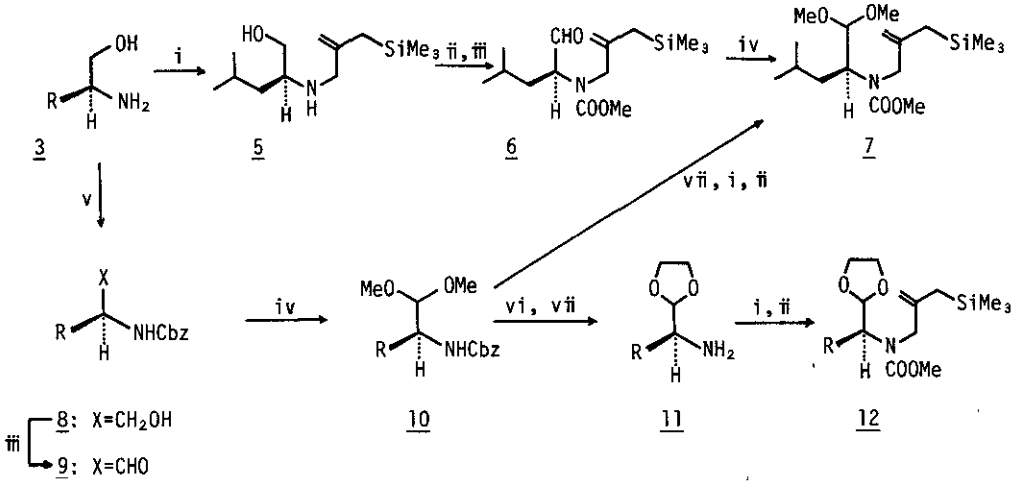
The enhanced π-bond nucleophilicity of allylsilanes[1] by Lewis acid has been widely applied to a synthesis of alcohols by addition to carbonyl compounds through C-C bond formation. Acetals were also used as an electrophile in the allylsilane-induced C-C bond formation.[2] Intramolecular allylation of α-amino aldehydes (or acetals), 1 ⟶ 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-functionallized piperidines. Although α-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.[3] We investigated a Lewis acid mediated intramolecular cyclization of α-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.



1: X=CHO or $CH(OR')_2$ 2: Y=H or R'

At first, the α-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 trimethylsilylmethallyl bromide (4)[4] gave 5[5] in 60 % yield. Methoxycarbonylation (ClCOOMe, CH_2Cl_2, Et_3N) of 5, followed by Swern oxidation[6] 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 ($ClCOOCH_2C_6H_6$, CH_2Cl_2, Et_3N) afforded 93 % yield of the aldehydes (9a-c) which were successively converted to the acetals (10a-c) by dimethylacetalizaiton in 90 -95 % yield, respectively. Transacetalizaiton of 10a-c (ethyleneglycohol, p-toluenesulfonic acid), followed by removal of benzyloxycarbonyl group by hydrogenolysis (H_2/Pd-C) gave the amine (11a-c) in 80-83 % yield, respectively. Condesation 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



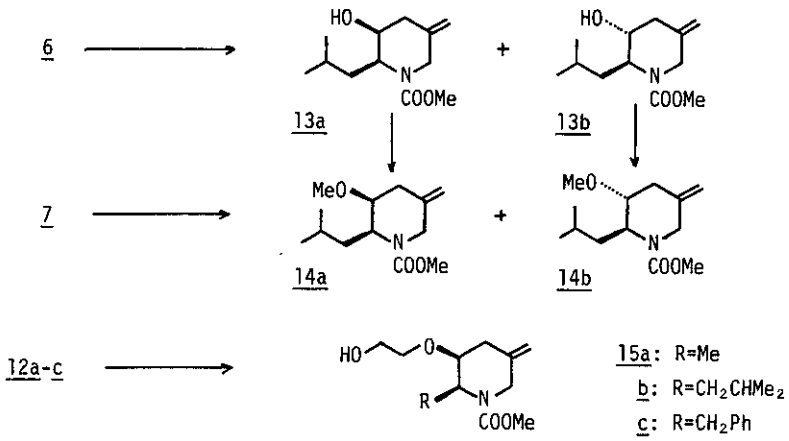
Cbz=$COOCH_2Ph$ For 3 and 8-12 a: R=Me; b: R=CH_2CHMe_2; c: R=CH_2Ph

Reagents and Conditions

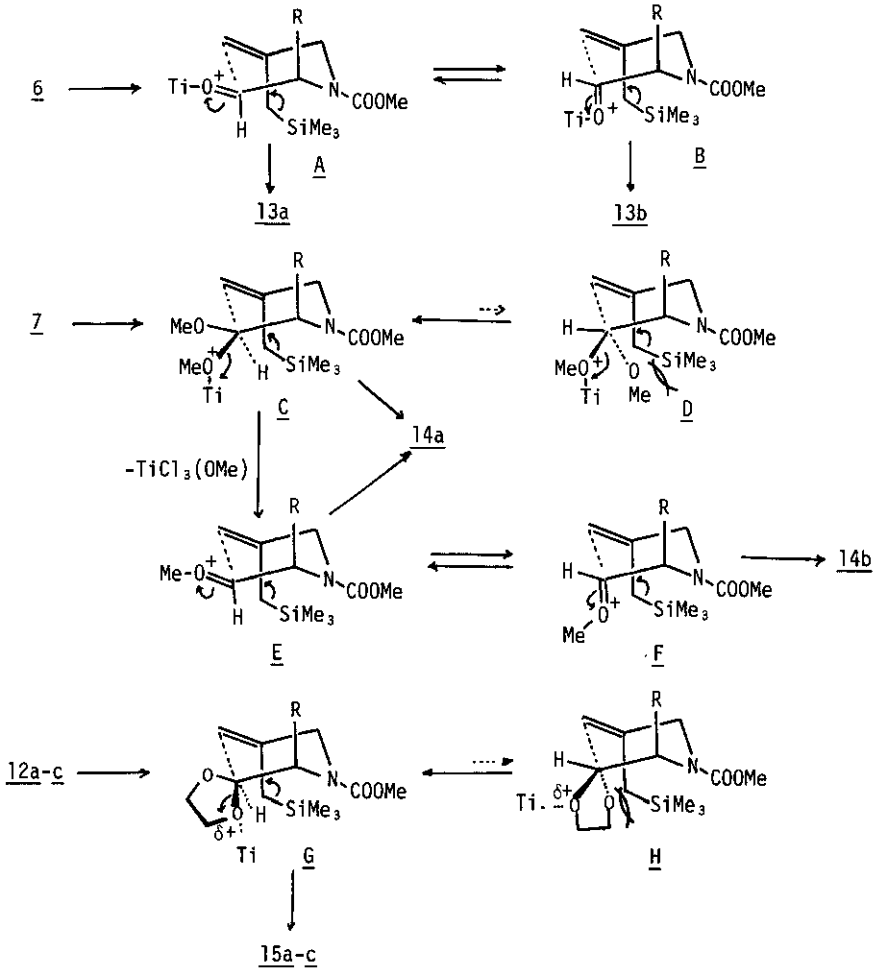
i. $CH_2=C(CH_2Br)CH_2SiMe_3$ (4), i-Pr_2NEt, CH_2Cl_2, room temperature ii. ClCOOMe, Et_3N, CH_2Cl_2
iii. $(COCl)_2$-Me_2SO, CH_2Cl_2, -78°C, Et_3N iv. MeOH, p-TsOH v. $ClCOOCH_2Ph$, Et_3N, CH_2Cl_2
vi. $HOCH_2CH_2OH$, p-TsOH vii. H_2/Pd-C

Cyclization of 6 ($TiCl_4$, CH_2Cl_2, -78°C, 1 h) yielded a 2:1 mixture of 13a and 13b in 43 % yield and in 95 % enantiomeric excess.[7] Two isomers were separated by column chromatography on silica gel; 13a: an oil, $[\alpha]_D^{20}$ -13.7° (c 1.86, $CHCl_3$), 13b, mp 58-60°C, $[\alpha]_D^{20}$ +29.4° (c 0.61, $CHCl_3$). Signals due to 4-H_2 of 13a and 13b are clearly visible in their ^1H nmr ($CDCl_3$, 400 MHz) spectra; 13a, δ 2.33 (4β-H, ddd, J=1.6, 11.6, 13.32 Hz),[8] 2.43 (4α-H, dd, J=4.90, 13.32); 13b, δ 2.31 (4β-H, broad d, 13.57 Hz), 2.56 (4α-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*[9] *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 $TiCl_4$ 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 (NaH, DMF, CH_3I, room temperature), respectively. Although the high diastereoselectivity was not observed in the cyclization of 6 and 7, clean diastereoselectivty was obtained in the cyclization of ethyleneacetals (12a-c). Cyclization of 12a-c by the use of $TiCl_3(O\text{-}Pr^i)$[10,11] generated from $TiCl_4$ and $Ti(OPr^i)_4$ *in situ* afforded 15a-c[12] in 82-83 % enantiomeric excess[13] 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[14,15] caused by the alkyl substituent and the carbonyl group. In the case of 6, among two posible 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. Cyclizaion proceeded *via* the transition state (G) to avoid the steric repulsion between acetal oxygen and trimethylsilylmethyl group.

Scheme 2



Scheme 3



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4. G. A. Molander and D. C. Shubert, Tetrahedron Lett., 27, 787 (1986).
5. Spectral data (ir. ^{1}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 (-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid esters, which were analyzed by ^{1}H nmr ($CDCl_3$, 400 MHz).
8. Small coupling constants (~1.6 Hz) are due to allylic coupling.
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11. Cyclization of 6 and 7 with $TiCl_3(OPr^i)$ was not successful.
12. 15a: 45 % yield, an oil, $[\alpha]_D^{20}$ +6.84°(c, 1.53, MeOH), ^{1}H nmr ($CDCl_3$, 400 MHz) δ 2.31 (4β-H, ddd, J=1.6, 11.74, 13.37 Hz),[8] 2.48 (4α-H, dd, J=4.59, 13.37 Hz). 15b: 43 % yield, an oil, $[\alpha]_D^{20}$ -8.33°(c, 1.44, $CHCl_3$), ^{1}H nmr ($CDCl_3$, 400 MHz) δ 2.31 (4β-H, ddd, J=1.49, 11.82, 13.30 Hz),[8] 2.49 (4α-H, dd, J=4.65, 13.30 Hz) 15c: 40 % yield, an oil, $[\alpha]_D^{20}$ -23.2°(c, 1.36, $CHCl_3$), ^{1}H nmr ($CDCl_3$, 400 MHz) δ 2.46 (4β-H, dd, J=11.83, 13.65 Hz), 2.56 (4α-H, dd, J=4.51, 13.65 Hz).
13. Determined by removal of hydroxyethyl group (i. $MeSO_2Cl$, CH_2Cl_2, Et_3N. ii. KCN, DMSO. iii. THF-MeOH-KOH), followed by esterification with (-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride.[7] The lower magnitude for the optical purity might be due to partial racemization during tranacetalization.
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