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Novel Route to the Synthesis of Hydroxylated Piperidine and Pyrrolidine Derivatives via the Intramolecular Reaction of γ-Aminoallylstannane with Aldehyde

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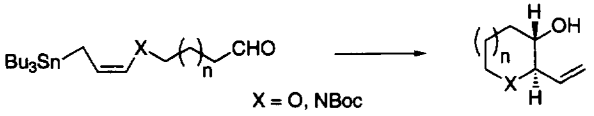
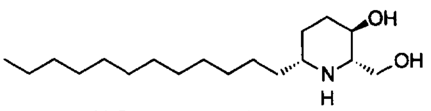
Abstract: The Lewis acid mediated intramolecular reaction of gamma-aminoallylstannane **6** gave *trans*-beta-hydroxypiperidine derivative **7a** as a major product. On the other hand, the thermal cyclization of **6** and **8** afforded *cis*-beta-hydroxypiperidine **7b** and pyrrolidine derivative **9b**, respectively, with very high stereoselectivity.

Recently, we have developed an efficient method for the synthesis of medium sized cyclic ether via the intramolecular reaction of γ-alkoxyallylstannane with aldehyde (eq 1; X = O, n = 1, 2).[1] The usefulness of this methodology has been demonstrated by the total synthesis of hemibrevetoxin B[2] and related polycyclic ethers.[3]

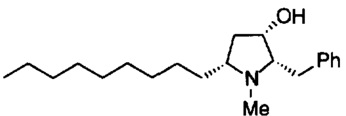


(1)

It occurred to us that replacement of the oxygen to nitrogen would produce the corresponding β-hydroxy nitrogen heterocycle (eq 1, X = NBoc). The structural framework of hydroxylated nitrogen heterocycle is widely found in naturally occurring piperidine/pyrrolidine alkaloids such as (-)-desoxoprosophilline[4] and (+)-preussin.[5] In this paper, we wish to report the stereoselective synthesis of β-hydroxypiperidine and pyrrolidine derivatives via the intramolecular reaction of γ-aminoallylstannane with aldehyde. To the best of our knowledge, this is the first example of a successful use of γ-aminoallylstannane in organic synthesis.[6]



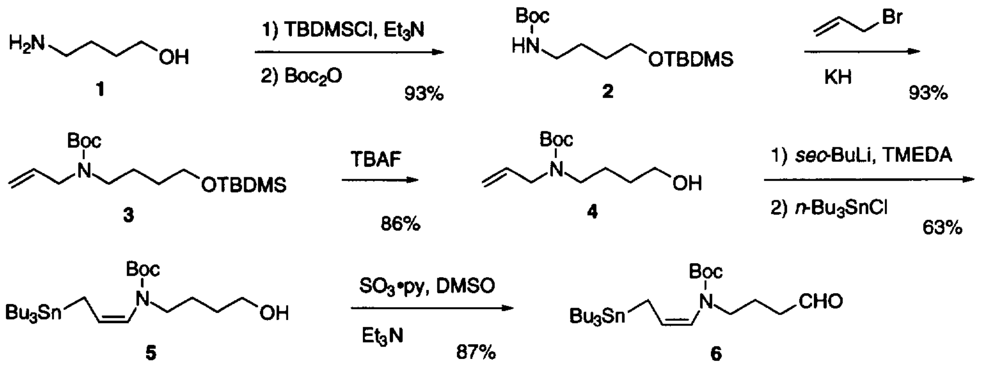
(-)-Desoxoprosophilline



(+)-Preussin

The γ-aminoallylstannane **6**, bearing aldehyde group at the terminus of the carbon chain, was prepared as shown in Scheme 1. The reaction of 4-amino-1-butanol **1** with TBDMSCl/Et_3N followed by the treatment with Boc_2O gave *N*-protected silyl ether **2** in 93% yield. The allylation of **2** was performed by allyl bromide/KH to give **3** in 93% yield. Desilylation of **3** with TBAF afforded primary alcohol **4** in 86% yield. Treatment of **4** with *sec*-BuLi/TMEDA followed by trapping with *n*-Bu_3SnCl gave *Z*-γ-aminoallylstannane **5** (63%) and recovered **4** (20%). Oxidation of alcohol **5** produced aldehyde **6** in 87% yield.

Scheme 1



The results of the cyclization of **6** are summaried in Table 1.[7] The use of $TiCl_4$ and/or $BF_3{\bullet}OEt_2$ gave trans-β-hydroxypiperidine **7a**, predominantly (entries 1 and 10). Interestingly, although the reason is not clear, the reaction mediated by titanium chloride (entries 2-4), tin chloride (entries 7 and 8), and ZnI_2 (entry 14) afforded *cis* isomer **7b** as a major product. Similar *cis* selectivity was observed in the protic acid promoted cyclization (entries 15 and 16) which would proceed via a cyclic transition state as proposed previously.[1b] The cyclization of **6** did not proceed in the presence of weak Lewis acids such as $Ti(O^iPr)_4$ (entry 5) and Bu_2SnCl_2 (entry 9). As expected, the thermal reaction afforded **7b** with very high stereoselectivity (entry 17).

We next examined the synthesis of pyrrolidine derivative using **8** which was prepared by the similar procedure as shown in Scheme 1. All reactions were carried out immediately after preparation of the substrate **8** owing to its low stability. The results are summarized in Table 2.[8] Although the Lewis and protic acid mediated reactions gave unsatisfactory results, quite high stereoselectivity was observed in the thermal cyclization. Trans isomer **9a** was not detected. The stereoselective formation of the *cis* isomer **9b** is highly promising as a methodology for the synthesis of nitrogen heterocycles, since (+)-preussin possesses *cis*-sterochemistry between α- and β-substituents.

In conclusion, we have not only developed a new method for the synthesis of hydroxylated nitrogen heterocycles but also demonstrated the first example of a successful use of γ-aminoallylstannane in organic synthesis. Application of this technology to natural product synthesis is in progress.

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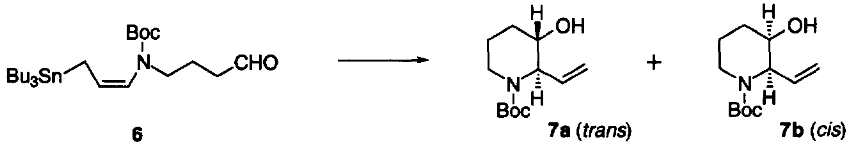
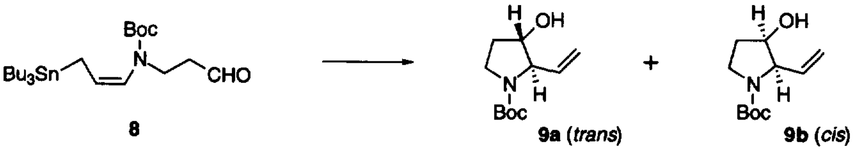
Table 1. Cyclization of **6**[a]



entry	reagent (equiv)	temp (°C)	time (h)	ratio (**7a**:**7b**)[b]	yield (%)[c]
1	$TiCl_4$ (1.5)	-78	0.7	69:31	63
2	$TiCl_3(O^iPr)$ (1.5)	-78	0.5	38:62	46
3	$TiCl_2(O^iPr)_2$ (1.5)	-78	1.5	29:71	89
4	$TiCl(O^iPr)_3$ (1.5)	rt	8.0	31:69	56
5	$Ti(O^iPr)_4$ (3)	rt	24	-	0[d]
6	$ZrCl_4$ (1.5)	-78	2.5	53:47	65
7	$SnCl_4$ (1.5)	-78	1.0	34:66	41
8	$BuSnCl_3$ (1.5)	-78	0.5	28:72	20
9	Bu_2SnCl_2 (1.0)	rt	15	-	0[d]
10	$BF_3 \cdot OEt_2$ (2.0)	-78	0.5	70:30	60
11	$AlCl_3 \cdot OEt2$ (1.2)	-78	0.5	64:36	45
12	$AlBr_3 \cdot OEt2$ (1.5)	-78	0.7	50:50	69
13	$MgBr_2 \cdot OEt_2$ (1.5)	0	2.0	61:39	92
14	ZnI_2 (1.5)	rt	7.0	36:64	45
15	HCl (2.0)	-78	1.0	27:73	48
16	CF_3SO_3H (2.0)	-78	3.0	43:57	21
17	-[e]	120	36	2:98<	67

[a] The reactions were carried out with 0.1 M substrate in CH_2Cl_2 under the conditions indicated in the table, and quenched with aqueous saturated $NaHCO_3$ at the reaction temperature. [b] Ratios were determined by a capillary GC analysis. [c] Isolated yields. [d] No reaction took place. [e] Toluene was used as a solvent.

Table 2. Cyclization of **8**[a]



entry	reagent (equiv)	temp (°C)	time (h)	ratio (**9a**:**9b**)[b]	yield (%)[c]
1	$TiCl_4$ (1.2)	-78	0.5	10:90	48
2	$BF_3 \cdot OEt_2$ (1.2)	-78	0.5	64:36	70
3	CF_3CO_2H (2.0)	-78	0.5	49:51	70
4	-[d]	120	1.0	2:98<	67

[a] The reactions were carried out with 0.1 M substrate in CH_2Cl_2 under the conditions indicated in the table, and quenched with aqueous saturated $NaHCO_3$ at the reaction temperature. [b] Ratios were determined by a capillary GC analysis. [c] Isolated yields. [d] Toluene was used as a solvent.

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(6) In general, γ-aminoallylstannanes exhibit lower reactivity toward aldehydes than γ-alkoxyallylstannanes.

(7) Typical procedure: To a stirred solution of **6** (156 mg, 0.30 mmol) in 3 mL of dry CH_2Cl_2 under Ar at -78 °C was added $TiCl_4$ (1.0 M solution in CH_2Cl_2, 0.45 mL, 0.45 mmol), and the mixture was stirred for 1 h at the same temperature. The reaction mixture was quenched with Et_3N (0.3 mL) and saturated aqueous $NaHCO_3$ (1 mL), extracted with ether, and dried over $MgSO_4$. Following solvent removal, the residue was dissolved in ether and was vigorously stirred with saturated aqueous KF. The organic layer was separated and dried. Following solvent removal, the residue was purified by silica gel column chromatography to give a mixture of **7a** and **7b** (44 mg, 63%).

7a: IR (neat) 3600-3200, 3084, 2977, 2933, 2871, 1699, 1422, 1418, 1367, 1174, 986 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.73 (ddd, J = 17.2, 10.6, 4.2 Hz, 1H), 5.24 (ddd, J = 10.6, 2.2, 1.5 Hz, 1H), 5.12 (ddd, J = 17.2, 2.2, 1.5 Hz, 1H), 4.78-4.70 (br, 1H), 4.03-3.89 (m, 1H), 2.88 (ddd, J = 12.9, 12.9, 3.2 Hz, 1H), 1.46 (s, 9H), 2.06-1.20 (m, 4H).

7b: IR (neat) 3600-3200, 3081, 2978, 2940, 2868, 1695, 1668, 1456, 1290, 1158, 665 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.99 (ddd, J = 16.9, 10.5, 6.1 Hz, 1H), 5.36 (ddd, J = 10.5, 1.7, 1.7 Hz, 1H), 5.25 (ddd, J = 16.9, 1.7, 1.7 Hz, 1H), 4.87-4.78 (m, 1H), 3.96-3.84 (brd, J = 14.0 Hz, 1H), 3.83-3.70 (m, 1H), 2.77 (ddd, J = 12.9, 12.9, 3.4 Hz, 1H), 2.24-2.14 (brs, 1H), 1.46 (s, 9H), 1.76-1.25 (m, 4H).

(8) **9a:** IR (neat) 3600-3200, 3084, 2977, 2932, 2895, 1697, 1668, 1479, 1413, 1365, 1256, 1168, 1124, 989 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.80-5.60 (m, 1H), 5.20-5.10 (m, 2H), 4.35-4.10 (m, 2H), 3.65-3.40 (m, 2H), 2.10-1.95 (m, 1H), 1.90-1.75 (m, 1H), 1.40 (s, 9H).

9b: IR (neat) 3600-3200, 3080, 2978, 1670, 1412, 1366, 1167, 1067, 897 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 5.80 (ddd, J = 17.0, 11.0, 6.0 Hz, 1H), 5.34 (brd, J = 11.0, Hz, 1H), 5.26 (brd, J = 17.0 Hz, 1H), 4.42-4.22 (m, 2H), 3.59-3.36 (m, 2H), 2.16-1.96 (m, 1H), 1.95-1.74 (m, 1H), 1.44 (s, 9H).

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