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Expedient Synthesis of Chiral Homoallylamines via *N,O*-Acetal TMS Ethers and Its Application

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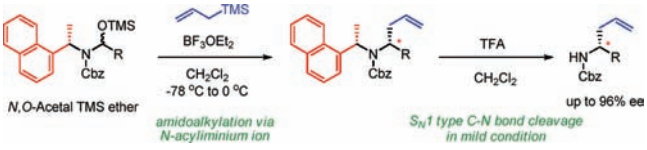
ABSTRACT



A highly stereoselective and efficient method for the synthesis of optically active homoallylamines was developed. Key features of the method include (1) the utilization of naphthylethylamine as both an excellent chiral auxiliary and the amine source, (2) the 1,3-chiral induction of the *N*-acyliminium ion with high stereoselectivity and high yield, and (3) facile auxiliary removal under mild conditions to liberate *N*-Cbz-protected homoallylamines. In addition, the total synthesis of the proposed novel tripeptide containing a β-amino acid has been achieved by applying this method.

Homoallylamines and acylated homoallylamines are some of the important structural subunits of biologically active compounds and are useful intermediates in a wide range of syntheses of alkaloids and nitrogen-containing heterocycles.[1] Thus, the enantio- and diastereoselective synthesis of homoallylamines has become one of the major goals in the fields of medicinal chemistry and organic synthesis. Consequently, the development of a new method for the synthesis of optically active homoallylamines has been continuously attempted by organic and synthetic chemists.[1a,2]

We have recently reported a new approach to the synthesis of the *N*-acyliminium ion from *N*,*O*-acetal TMS ether, which was conveniently prepared from acylcarbamate.[3] The *N*,*O*-acetal TMS ether proved to be an excellent acyliminium ion precursor in terms of convenience of preparation, chemical stability, and functional versatility in addition to the accessible structural diversity of cyclic and acyclic *N*-acyliminium ions. More recently, we have reported a novel asymmetric synthetic route for β-amino acids using this methodology.[3c] Herein, we describe an efficient and versatile method for the synthesis of various homoallylamines through chiral auxiliary-assisted diastereoselective allylation of *N*-acyliminium ions[3,4] prepared from *N*,*O*-acetal TMS ether and the facile removal of the naphthylethyl auxiliary (Figure 1).

As shown in Scheme 1, *N*,*O*-acetal TMS ethers were prepared in high yield according to the established

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(1) (a) Puentes, C. O.; Kouznetsov, V. *J. Heterocycl. Chem.* **2002**, *39*, 595. (b) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815. (c) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541.

(2) For recent example, see: (a) Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 3332. (b) Kim, S. J.; Jang, D. O. *J. Am. Chem. Soc.* **2010**, *132*, 12168. (c) Chakrabarti, A.; Konishi, H.; Yamaguchi, M.; Schneider, U.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1838.

(3) (a) Suh, Y.-G.; Shin, D.-Y.; Jung, J.-K.; Kim, S.-H. *Chem. Commum.* **2002**, 1064. (b) Suh, Y.-G.; Kim, S.-H.; Jung, J.-K.; Shin, D.-Y. *Tetrahedron Lett.* **2002**, *43*, 3165. (c) Shin, D.-Y.; Jung, J.-K.; Seo, S.-Y.; Lee, Y.-S.; Paek, S.-M.; Chung, Y. K.; Shin, D. M.; Suh, Y.-G. *Org. Lett.* **2003**, *5*, 3635. (d) Jung, J.-W.; Shin, D.-Y.; Seo, S.-Y.; Kim, S.-H.; Paek, S.-M.; Jung, J.-K.; Suh, Y.-G. *Tetrahedron Lett.* **2005**, *46*, 573.

(4) For α-amido sulfones as precursors of *N*-acylimino derivatives, see: (a) Giardinà, A.; Mecozzi, T.; Petrini, M. *J. Org. Chem.* **2000**, *65*, 8277. (b) Marcantoni, E.; Mecozzi, T.; Petrini, M. *J. Org. Chem.* **2002**, *67*, 2989. (c) Petrini, M. *Chem. Rev.* **2005**, *105*, 3949.

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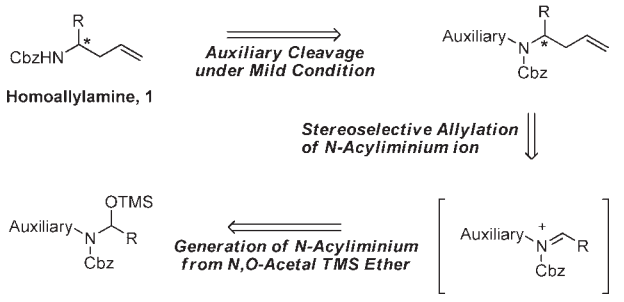
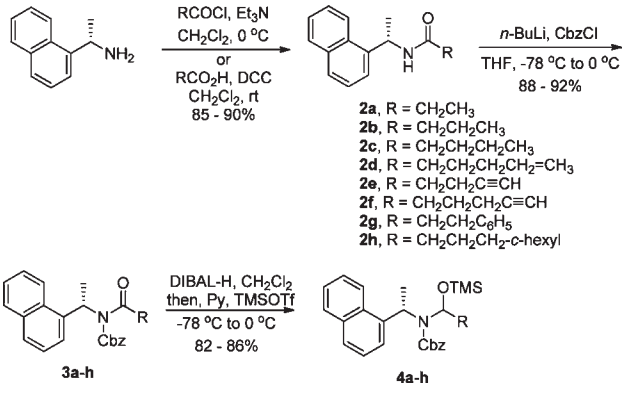


Figure 1. Strategy for the synthesis of optically active homoallylamines.

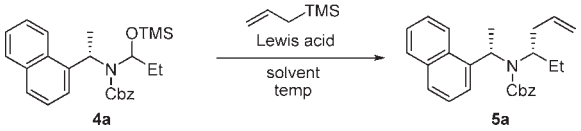
method.[3] After extensive preliminary investigation of chiral auxiliaries, we selected 1-(1-naphthyl)ethylamine based on (1) its ability to serve as an appropriate amine source, (2) the excellent 1,3-chiral induction in the allylation of *N*-acyliminium ions, and (3) the facile auxiliary removal. Thus, the commercially available chiral 1-(1-naphthyl) ethylamine was initially acylated, followed by Cbz-protection to afford the protected amide **3a**–**h**. The *N*,*O*-acetal TMS ether **4a**–**h** was successfully generated from the corresponding amide **3a**–**h** by DIBAL reduction and *in situ* trapping of the resulting alkoxide with TMSOTf. Fortunately, the *N*,*O*-acetal TMS ethers were successfully prepared in high yield irrespective of the steric effects of the substituents.[5]

Scheme 1. Preparation of *N*,*O*-Acetal TMS Ethers



We subsequently investigated the reaction conditions for the diastereoselective allylation of the *N*-acyliminium ion prepared from the *N*,*O*-acetal TMS ether **4a**, as illustrated in Table 1. We chose allylsilane as an allyl donor based on the synthetic efficiency and the low hazard to the public.[6] The chemical yields of the allylations of **5a** were generally good or excellent regardless of the Lewis acid, solvent or temperature used. However, the diastereoselectivity was quite sensitive to the reaction conditions. Reactions in methylene chloride in the presence of $BF_3 \cdot OEt_2$ provided the best results with respect to both diastereoselectivity and chemical yield (entries 1–6). Entries 7–10 revealed the decrease in the diastereoselectivity with increasing reaction temperature, whereas the stereochemical results were almost the same at temperatures less than −40 °C. We carried out all allylation reactions with $BF_3 \cdot OEt_2$ at −78 °C, followed by slow warming to 0 °C slowly as a standard procedure, although maintaining the reaction temperature at −78 °C for 1 day resulted in the highest diastereoselectivity (93:7).[7]

Table 1. Effects of the Lewis Acid, Solvent and Temperature on the Homoallylation of the *N*,*O*-Acetal TMS Ether[a]



entry	Lewis acid	solvent	temp	yield (%)[b]	dr[c]
1	$BF_3 \cdot OEt_2$	CH_2Cl_2	−78 to 0 °C[d]	95	92:8
2	$SnCl_4$	CH_2Cl_2	−78 to 0 °C[d]	75	87:13
3	TMSOTf	CH_2Cl_2	−78 to 0 °C[d]	51	92:8
4	$BF_3 \cdot OEt_2$	$PhCH_3$	−78 to 0 °C[d]	93	86:14
5	$BF_3 \cdot OEt_2$	CH_3CN	−78 to 0 °C[d]	95	75:25
6	$BF_3 \cdot OEt_2$	Et_2O	−78 to 0 °C[d]	94	89:11
7	$BF_3 \cdot OEt_2$	CH_2Cl_2	−78 °C[e]	88	93:7
8	$BF_3 \cdot OEt_2$	CH_2Cl_2	−40 °C	86	92:8
9	$BF_3 \cdot OEt_2$	CH_2Cl_2	−23 °C	90	90:10
10	$BF_3 \cdot OEt_2$	CH_2Cl_2	0 °C	80	78:22

[a] Reactions were performed at given conditions for 3 h and quenched with a sufficient amount of triethylamine unless otherwise noted. [b] Isolated yields. [c] Determined using chiral HPLC (Daicel, OD-H) after removal of the naphthylethyl moiety. (The racemate was prepared from commercially available (±)-1-(1-naphthyl)ethylamine). [d] Reaction temperature was slowly elevated during 3 h. [e] Stirred for 1 day at a given temperature and then quenched with triethylamine.

We then turned our attention to the removal of the 1-(1-naphthyl)ethyl moiety. The crucial C–N bond cleavage of the allylation products under mild conditions was intensively investigated. The *N*-Cbz-protected homoallylamine **1a** was finally obtained from **5a** in an excellent yield by TFA treatment in CH_2Cl_2 at room temperature. To the

(5) The spectral data (^1H NMR, ^{13}C NMR) were quite complicated due to the rotameric and/or diastereomeric nature of the *N*,*O*-acetal TMS ethers. Accordingly, the diastereomeric ratios were not determined at this stage, and the *N*,*O*-acetal TMS ethers were used for the next step without further purification.

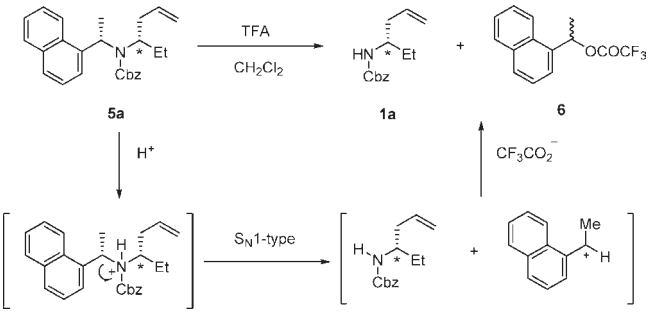
(6) Aoyama, N.; Hamada, T.; Manabe, K.; Kobayashi, S. *Chem. Commun.* **2003**, 676.

(7) Unfortunately, the chemical yields significantly dropped under the reaction conditions of entry 7 of Table 1.

(8) There have been only a few reports for C–N bond cleavages at the alpha position of the naphthyl moiety using methansulfonic acid. Acidity constant (K_a) of methanesulfonic acid is more than a hundred fold compared to that of TFA. pK_a (CH_3SO_3H) = −2.6, pK_a (CF_3CO_2H) = −0.25 based on pK_a values compiled by Prof. D. A. Evans at Harvard University: Sugiyama, S.; Morishita, K.; Ishii, K. *Heterocycles* **2001**, *55*, 353.

best of our knowledge, no information on the cleavage of the carbon–heteroatom at the α position of the naphthyl moiety has been published, although carbon–heteroatom cleavages at the benzylic position in various strongly acidic media are well known.[8] The removal of naphthylalkyl moieties has been infeasible[9] despite their excellent stereoinductions, primarily because of the limited functional group tolerances under harsh auxiliary cleavage conditions.[10] In the course of our mechanistic studies on naphthyl cleavage, we were able to easily isolate trifluoroacetate **6** as the sole side product, which was shown to be a racemate.[11] Consequently, the removal of the 1-(1-naphthyl)ethyl moiety could be mechanistically understood as an S_N1-type reaction (Scheme 2).

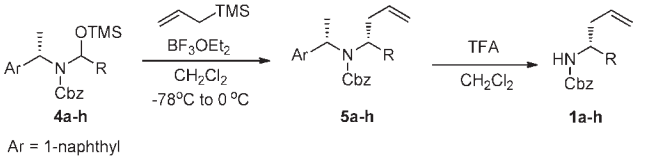
Scheme 2. S_N1-type Removal of the 1-(1-Naphthyl)ethyl Moiety



We also turned our attention to the scope of this established method. The stereoselective allylation of a variety of *N*,*O*-acetal TMS ethers under optimized conditions proceeded smoothly to afford the corresponding *N*-Cbz-protected homoallylamines (Table 2). Generally, an increase in the diastereoselectivity upon introduction of a longer alkyl substituent was observed (entries 1–3). Olefin and alkyne functional groups were well tolerated (entries 4–6), and even phenylethyl substituents survived under the established conditions (entry 7). The presence of branching with aliphatic substituents resulted in slight decrease in both yield and diastereoselectivity (entry 8).

To confirm the absolute configuration of the newly generated stereocenter, we converted homoallylamine **1a** into the known *β*-amino acid **7**. Dihydroxylation of **1a** under Upjohn conditions[12a] and subsequent 1,2-diol cleavage with sodium periodate followed by Pinnick oxidation[12b] gave the desired *β*-amino acid **7**. The absolute configuration of the new stereocenter was confirmed as (*S*)

Table 2. Allylation of *N*,*O*-Acetal TMS Ethers



entry	R, 4	yield %[a] on **5**	yield %[b] on **1**	er[c]
1	CH_2CH_3, **4a**	95	99	92:8
2	$CH_2CH_2CH_3$, **4b**	90	95	92:8
3	$CH_2CH_2CH_2CH_3$, **4c**	90	90	96:4
4	$CH_2CH_2CH_2CH_2{=}CH_2$, **4d**	86	90	98:2
5	$CH_2CH_2CH_2C{\equiv}CH$, **4e**	80	95	92:8
6	$CH_2CH_2CH_2CH_2C{\equiv}CH$, **4f**	88	92	96:4
7	CH_2CH_2Ph, **4g**	89	90	95:5
8	CH_2 CH_2CH_2c-hex[d], **4h**	82	95	90:10

[a] Isolated yield of the first step. [b] Isolated yield of the second step. [c] Determined with chiral HPLC (Daicel, OD-H). [d] Cyclohexyl.

based on the reported results.[13] A plausible transition state for the stereoselective allylation is suggested based on the stereochemical outcome (Figure 2). The Felkin–Ahn model, which is addressed in the 1,3-chiral induction of imine species,[14,15] was followed in this system.

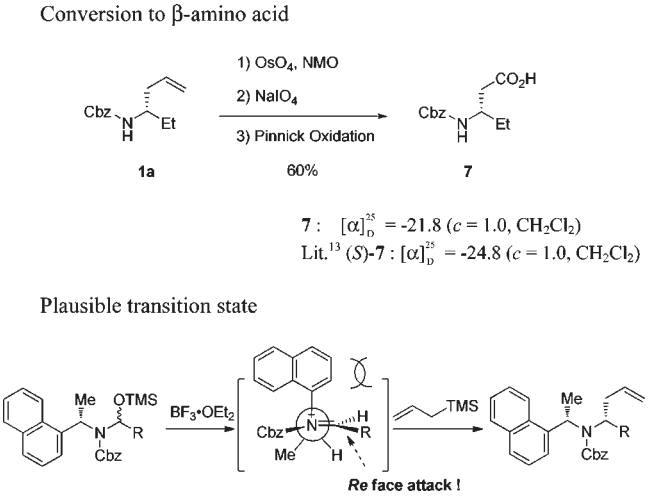


Figure 2. Confirmation of the absolute stereochemistry.

(9) In general, hydrogenation under high pressure was conducted to remove the auxiliaries with naphthyl group: (a) Jiang, W.; Suia, Z.; Chen, X. *Tetrahedron Lett*. **2002**, *43*, 8941. (b) Santos Fustero, S.; Soler, J. G.; Bartolome', A.; Rosello', M. S. *Org. Lett*. **2003**, *5*, 2707.

(10) (a) Paquette, L. A.; Rothhaar, R. R.; Isaac, M.; Rogers, L. M.; Rogers, R. D. *J. Org. Chem*. **1998**, *63*, 5463. (b) Takacs, J. M.; Weidner, J. J. *J. Org. Chem*. **1994**, *59*, 6480. (c) Bell b, A. S.; Fishwick, C. W. G.; Reed, J. E. *Tetrahedron Lett*. **1996**, *37*, 123. (d) Ghera, E.; Kleiman, V.; Hassner, A. *J. Org. Chem*. **1999**, *64*, 8. (e) Loh, T.-P.; Huang, J.-M.; Goh, S.-H.; Vittal, J. J. *Org. Lett*. **2000**, *2*, 1291. (f) Oh, B. H.; Nakamura, I.; Yamamoto, Y. *Tetrahedron Lett*. **2002**, *43*, 9625.

(11) Authentic trifluoroacetate **6** was alternatively prepared from commercially available (±)-1−1-(naphthylethyl)amine and trifluoroacetic acid.

(12) (a) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett*. **1976**, *17*, 1973. (b) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(13) Palomo, C.; Oiarbide, M.; Condepcion Gonzalez-Rego, M.; Sharma, A. K.; Garcia, J. M.; Gonzalez, A.; Landa, C.; Linden, A. *Angew. Chem., Int. Ed*. **2000**, *39*, 1063.

(14) For discussions about the 1,3-chiral induction to imine species, see: (a) Bellucci, C.; Cozzi, P. G.; Umani-Ronchi, A. *Tetrahedron Lett*. **1995**, *36*, 7289. (b) Nancy, Ghosh, S.; Singh, N.; Nanda, G. K.; Venugopalan, P.; Bharatam, P. V.; Trehan, S. *Chem. Commun*. **2003**, *12*, 1420. (c) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc*. **1986**, *108*, 7778. (d) Alvaro, G.; Savoia, D.; Valentinetti, M. R. *Tetrahedron* **1996**, *52*, 12571.

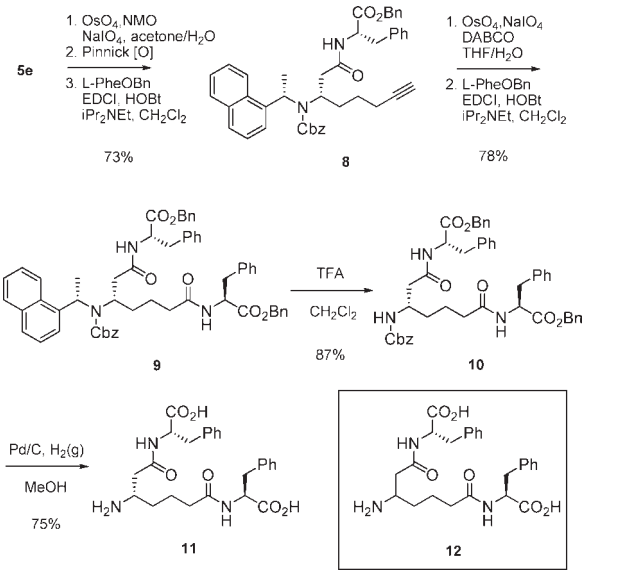
Having established a synthetic method for homoallylamines, we undertook the total synthesis of a marine natural product to validate the applicability of our method. The novel tripeptide **12** with the proposed structure was isolated from a bacterium identified as Pseudomonas or Alteromonas (DF-1).[16] This marine natural product, which consists of a β-aminopimelic acid was reported first from a natural source. Our curiosity about the biological role of the novel tripeptide based on the structural similarity of its fragments with α-aminopimelic acid and 1,6-diaminopimelic acid[17] and the desire to elucidate the undetermined chiral center led us to attempt the total synthesis of this compound.

Shown in Scheme 3, the concise synthesis commenced with the preparation of homoallylamine **5e** on a gram scale, followed by a sequence of oxidative olefin cleavage and coupling of phenylalanine.[18] Removal of the phenylethyl auxiliary with the established procedure and global deprotection by hydrogenolysis provided the desired novel tripeptide, which was further purified using ion-exchange resin and preparative HPLC. Epimerization was not observed after the removal of the 1-naphthylethyl moiety.

We have successfully synthesized the two diastereomeric tripeptides that have been proposed.[19] However, a comparison of the spectral data with the reported data revealed that the structure of **12** is not the same as that of the natural tripeptide[20] (see Supporting Information, this synthesis successfully showcases the synthetic utility of our asymmetric amidoalkylation protocol).

In conclusion, we have developed a reliable and stereoselective method for the synthesis of various homoallylamines. Allylsilane turned out to be an adequate allyl donor and 1-(1-naphthyl)ethylamine proved to be both an excellent chiral auxiliary and an excellent amine source. We also established an efficient and mild procedure for the facile removal of the 1-(1-naphthyl)ethyl moiety, which can be widely utilized in the asymmetric synthesis of amino acids and alkaloids. Our method was also successfully applied in the total synthesis of the proposed structure of a novel tripeptide containing β-amino acid.

Scheme 3. Total Synthesis of Novel Tripeptide



(15) We have suggested the kinetic generation of *N*-acyliminium ion from the dual acting oxazolidinone precursors in our previous report, which was supported by experimental and computational data.[2c]

(16) Rosa, S. D.; Giulio, A. D.; Tommonaro, G.; Popov, S.; Kujumgiev, A. *J. Nat. Prod.* **2000**, *63*, 1454.

(17) (a) Berges, D. A.; DeWolf, W. E., Jr.; Dunn, G. L.; Grappel, S. F.; Newman, D. J.; Taggart, J. J.; Gilvarg, C. *J. Med. Chem.* **1986**, *29*, 89. (b) Petra, S.; Maija, D. *Curr. Med. Chem.* **2004**, *11*, 945.

(18) Synthesis of the tripeptide utilizing homoallylamine **5d** was inefficient due to a difficulty in the similtaneous cleavage of both terminal olefins and in the phenylalanine coupling of the resulting diacid.

(19) Synthesis of only one tripeptide was shown in Scheme 3. The other diastereomer was synthesized by analogy to the synthesis from (*R*)-1-(1-naphthylethyl)amine. See, Supporting Information.

(20) ^{1}H NMR spectra of the synthetic tripeptide prepared from commercially available α-aminopimelic acid and phenylalanine derivatives were close to those of the tripeptide synthesized by us.

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Supporting Information Available. Experimental procedures, characterization data, and stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.