Efficient and Practical Method for Synthesizing N-Heterocyclic Compounds Using Intramolecular Nucleophilic Acyl Substitution Reactions Mediated by Ti(O-*i*-Pr)$_4$/2*i*-PrMgX Reagent. Synthesis of Quinolones, Pyrroles, Indoles, and Optically Active N-Heterocycles Including Allopumiliotoxin Alkaloid 267A

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Abstract: Treatment of *N*-(2- or 3-alkynyl)amino esters with a low-valent titanium reagent diisopropoxy(η^2-propene)-titanium (**1**), generated *in situ* by the reaction of Ti(O-*i*-Pr)$_4$ and 2*i*-PrMgCl, resulted in an intramolecular nucleophilic acyl substitution (INAS) reaction to afford α-alkylidene-pyrrolidinones or -piperidinones. Thus, treatment of *N*-propargyl-anthranilates **5**, -indole-2-carboxylates **10**, or -pyrrole-2-carboxylates **13** with **1** gave 4-quinolones **7**, [1,2-*a*]indoles, or [1,2-*a*]pyrroles, respectively. Similarly, N-alkynylated α- or *β*-amino esters **14** or **15** with **1** afforded N-heterocycles **18** or **19**. In the reaction of *N*-(2- or 3-alkenyl)amino esters with **1**, the resulting INAS product underwent intramolecular carbonyl addition (ICA) reaction to afford the N-heterocyclic compounds having a cyclopropanol moiety in good to excellent yields. Thus, the treatment of *N*-alkenyl-anthranilate **4a**, -indole-2-carboxylates **8** and **9**, or -pyrrole-2-carboxylates **11** and **12** with **1** gave the corresponding quinoline derivative **6a**, [1,2-*a*]indoles, or [1,2-*a*]pyrroles, respectively. The optically active N-heterocyclic compounds **20** and **21** were obtained from N-alkenylated α- or *β*-amino esters **16** or **17**. A highly efficient total synthesis of allopumiliotoxin alkaloid 267A has also been accomplished. Thus, the *N*-propargyl-2[(1-hydroxy-1-methoxycarbonyl)ethyl]pyrrolidine **24** (from L-proline in six steps) reacted with **1** to afford the corresponding indolidinone **25** in 67% yield, which has previously been converted to allopumiliotoxin 267A.

Heterocyclic compounds containing nitrogen are widely distributed in nature, many of which display important biological activities; moreover, a vast number of natural and synthetic N-heterocyclic compounds have found applications as pharmaceuticals and agricultural chemicals. A large number of N-heterocycles also have found practical uses as dyestuffs, copolymers, antioxidants, and vulcanization accelerators in the rubber industry and as valuable intermediates in synthesis. The synthesis of N-heterocyclic compounds, therefore, has attracted much interest and a variety of synthetic methodologies have been developed, as many reviews, monographs, and reports have been released.[1] Despite the wide availability of synthetic methods for these compounds, there still exists a need for developing more efficient new procedures or methods which allow the synthesis of optically active compounds. Recent efforts in this research field have focused on the use of transition metals.[2] However, in comparison with transition-metal-based routes to carbocyclic systems, routes to N-heterocyclic compounds so far have been explored to a much lesser extent.

Recently, we have found that the reaction of Ti(O-*i*-Pr)$_4$ with 2 equiv of *i*-PrMgX (X = Cl or Br) provides (η^2-propene)Ti-(O-*i*-Pr)$_2$ (**1**) in an essentially quantitative yield and that **1** acts as a versatile titanium(II) equivalent.[3] In the course of our studies to develop synthetic methodology based on this reagent, we have revealed that the reaction with acetylenic esters **2** results in an intramolecular nucleophilic acyl substitution (INAS) reaction to afford organotitanium compounds having a carbonyl functional group in good to excellent yields.[4] We[5] and the Cha group[6] also independently found that in the reaction with olefinic ester **3**, the resulting INAS products undergo intramolecular carbonyl addition (ICA) reaction to afford cyclopropanol derivatives. The mechanistic sequence responsible for these processes is shown in Scheme 1.

We have now found that these titanium-mediated INAS and tandem INAS-ICA reactions open up a method for synthesizing a variety of N-heterocyclic compounds.[2,7] Reported herein are (i) the synthesis of quinolone, pyrrole, and indole derivatives,

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(1) General reviews: *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press, New York, 1984. *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1963−1996.

(2) For reviews: Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. Harvey, D. F.; Sigano, D. M. *Chem. Rev.* **1996**, *96*, 271. Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. Fürstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2442. Ohshiro, Y.; Hirao, T. *Heterocycles*, **1984**, *22*, 859. For leading references: Buchwald, S. L.; Wannamaker, M. W.; Watson, B. T. *J. Am. Chem. Soc.* **1989**, *111*, 776. Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1996**, *61*, 2594 and see also ref 10b.

(3) The generation of olefin(derived from the added Grignard reagent)-titanium complexes of the type (η^2-olefin)Ti(O-*i*-Pr)$_2$ from Ti(OR)$_4$ and Grignard reagents was first reported by Kulinkovich *et al*. They utilized this complex as 1,2-bis-anionic species; see: Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A. *Synthesis* **1991**, 234. For the initial reports on the use of the olefin−titanium complex as a divalent titanium reagent, see: Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881. Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203. See, also: Takayanagi, Y.; Yamashita, K.; Yoshida, Y.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1996**, 1725.

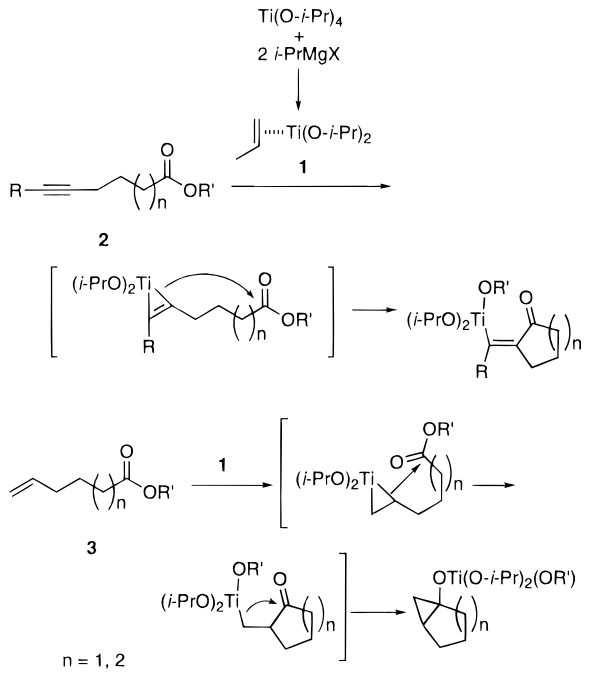
(4) (a) Kasatkin, A.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6075. (b) Zubaidha, P. K.; Kasatkin, A.; Sato, F. *J. Chem. Soc., Chem. Commun.* **1996**, 197. (c) Okamoto, S.; Kasatkin, A.; Zubaidha, P. K.; Sato, F. *J. Am. Chem. Soc.* **1996**, *118*, 2208. (d) Yoshida, Y.; Okamoto, S.; Sato, F. *J. Org. Chem.* **1996**, *61*, 7826.

(5) (a) Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 6079. (b) Kasatkin, A.; Kobayashi, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 1849.

(6) Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291.

S0002-7863(97)00810-X CCC: $14.00

Scheme 1

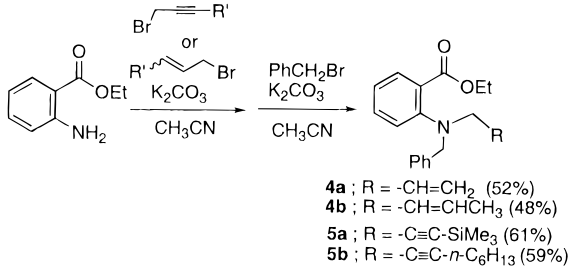


(ii) the synthesis of optically active N-heterocycles from chiral α- and β-amino acids, and (iii) the application of the reaction for preparing allopumiliotoxin 267A, a dendrobatid alkaloid.

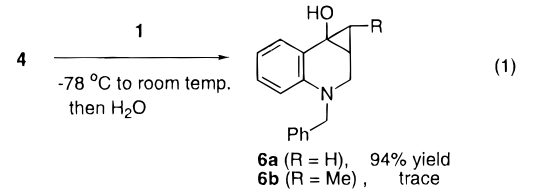
Results and Discussion

Synthesis of Quinolone, Pyrrole, and Indole Derivatives.[8] As N-allylated and -propargylated anthranilic acid derivatives **4** and **5** can be readily prepared from anthranilic acid ethyl ester according to the procedure shown in Scheme 2, we carried out

Scheme 2

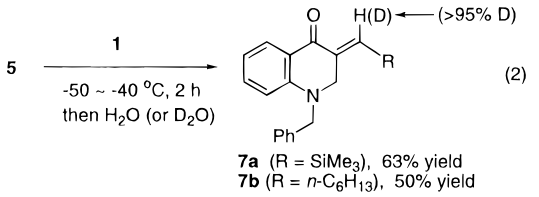


their reactions with **1**, in anticipation that the reaction might afford quinolone derivatives.[9] When a mixture of the N-allylated derivative **4a** and Ti(O-*i*-Pr)$_4$ was treated with 2 equiv of *i*-PrMgCl in ether at −78 °C to room temperature over 2 h, the expected tandem INAS-ICA reaction product **6a** was obtained in excellent yield, after hydrolysis, as shown in eq 1. On the other hand, the N-crotylated substrate **4b** which has the



(1)

disubstituted double bond did not afford the corresponding INAS-ICA product. This may be due to steric hindrance as was observed in the reaction of **1** with olefinic esters **3**.[4c] The reaction with the N-propargylated compounds **5a,b** also proceeded as expected to afford the corresponding INAS reaction products **7** in good yields by the reaction with **1**; the presence of an intermediate alkenyltitanium species before the aqueous workup of the reaction mixture was confirmed by deuterolysis (eq 2).



(2)

Fused [1,2-*a*]indoles (annulated indoles) represent the basic skeleton of many naturally occurring indole alkaloids and pharmaceutically important compounds.[10] One attractive method to construct the [1,2-*a*]indole-nucleus is annulation of a new ring to the skeleton of indoles. Since indole 2-carboxylic acid easily undergoes N-alkylation, thus providing **8**, **9**, and **10**, we carried out their reaction with **1**. As can be seen from Table 1 (entries 1−4), the expected tandem INAS-ICA or INAS reaction products were obtained in good to excellent yields from **8**, **9**, and **10**. Similarly, the reaction of **1** with methyl 2-pyrrolecarboxylate derivatives having an *N*-allyl, homoallyl, or propargyl

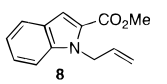
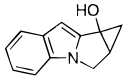
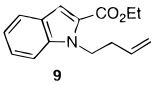
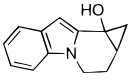
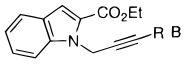
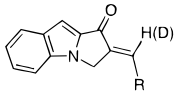
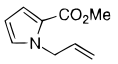
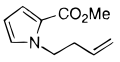
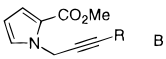
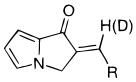
(7) For the transition-metal-based routes to N-heterocyclic compounds *via* the intramolecular carbon-carbon bond forming reaction, see the following most recent papers and references cited therein: Ti: Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11688. Pd: Goeke, A.; Sawamura, M.; Kuwano, R.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 662. Comins, D. L.; Joseph, S. P.; Zhang, Y.-mei *Tetrahedron Lett.* **1996**, *37*, 793. Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genêt, J.-P. *Tetrahedron Lett.* **1996**, *37*, 2003. Yun, W.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*, 7189. McAlonan, H.; Montgomery, D.; Stevenson, P. J. *Tetrahedron Lett.* **1996**, *37*, 7151. Rigby, J. H.; Mateo, M. E. *Tetrahedron*, **1996**, *52*, 10569. Jiang, H.; Ma, S.; Zhu, G.; Lu, X. *Tetrahedron* **1996**, *52*, 10945. Grigg, R.; Sansano, J. M. *Tetrahedron* **1996**, *52*, 13441. Boger, D. L.; Tarby, C. M.; Myers, P. L.; Caporale, L. H. *J. Am. Chem. Soc.* **1996**, *118*, 2109. Latham, E. J.; Stanforth, S. P. *J. Chem. Soc., Chem. Commun.* **1996**, 2253. Ni: Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Org. Chem.* **1996**, *61*, 5895. Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1996**, *61*, 824. Rh: Burgess, K.; Lim, H.-J.; Porte, A. M.; Sulikowski, G. A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 220. McMills, M. C.; Wright, D. L. Zubkowski, J. D.; Valente, E. J. *Tetrahedron Lett.* **1996**, *37*, 7205. Doyle, M. P.; Kalinin, A. V. *J. Org. Chem.* **1996**, *61*, 2179. Huwe, C. M.; Velder, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2376, and see also ref 10b. Ru: Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356. Maarseveen, van J. H.; Hartog, den J. A. J.; Engelen, V.; Finner, E.; Visser, G.; Kruse, C. G. *Tetrahedron Lett.* **1996**, *37*, 8249. Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606. Mo: Barrett, A. G. M.; Baugh, S. P. D.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; Procopiou, P. A. *J. Chem. Soc., Chem. Commun.* **1997**, 55. Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Päzel. M. Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251. Co: Krafft, M. E.; Wilson, A. M.; Dasse, O. A.; Shao, B.; Cheung, Y. Y.; Fu, Z.; Bonaga, L. V. R.; Mollman, M. K. *J. Am. Chem. Soc.* **1996**, *118*, 6080. Alcaide, B.; Polanco, C.; Sierra, M. A. *Tetrahedron Lett.* **1996**, *37*, 6901. Cu: Kondo, Y.; Matsudaira, T.; Sato, J.; Murata, N.; Sakamoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 736. Baldovini, N.; Bertrand, M.-P.; Carriere, A.; Nouguier, R.; Plancher, J.-M. *J. Org. Chem.* **1996**, *61*, 3205. Lim, H.-J.; Sulikowski, G. A. *Tetrahedron Lett.* **1996**, *37*, 5243. Mn: Galazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1996**, *52*, 1069. Sm, Y: Ha, D.-C.; Yun, C.-S.; Yu, E. *Tetrahedron Lett.* **1996**, *37*, 2577. Aoyagi, Y.; Manabe, T.; Ohta, A.; Kurihara, T.; Pang, G.-L.; Yuhara, T. *Tetrahedron* **1996**, *52*, 869. Molander, G. A.; Nichols, P. J. *J. Org. Chem.* **1996**, *61*, 6040.

(8) For a preliminary account of this work, see ref 5b.

(9) Reviews on synthesis and utility of quinolones, see: Meth-Cohn, O. *Heterocycles* **1993**, *35*, 539. Radl, S.; Bouzard, D. *Heterocycles* **1992**, *34*, 2143. Jones, G. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 2, pp 395−510. For some recent examples for synthesis of quinolones: Roy, K.; Srivastava, R. P.; Tekwani, B. L.; Pandey, V. C.; Bhaduri, A. P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 121. Gao, F.; Johnson, K. F.; Schlenoff, J. B. *J. Chem. Soc., Perkin Trans. 2* **1996**, 269.

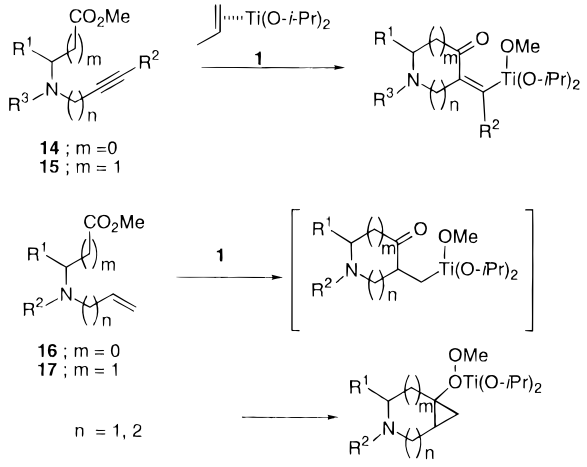
(10) For some recent approaches to fused [1,2-*a*]indoles, see: (a) Caddick, S.; Aboutayab, K.; Jenkins, K.; West, R. I. *J. Chem. Soc., Perkin Trans. 1* **1996**, 675. (b) Wee, A. G. H.; Slobodian, J. *J. Org. Chem.* **1996**, *61*, 2897 and references cited therein. For a review of earlier approaches, see: Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 199.

Table 1. Synthesis of [1,2-*a*]Indoles and [1,2-*a*]Pyrroles by Titanium(II)-Mediated INAS and INAS-ICA Reactions

Entry	Substrate[a]	Conditions[b]	Product	Yield, %[c]
1	 **8**	A		94
2	 **9**	A		74
		B		
3	**10a** : R = $SiMe_3$			62[d]
4	**10b** : R = *n*-C_6H_{13}			53
5	 **11**	A		80
6	 **12**	A		80
		B		
7	**13a** : R = $SiMe_3$			76[d]
8	**13b** : R = *n*-C_6H_{13}			65

[a] Prepared from pyrrole- or indole-2-carboxylate by the reaction with the corresponding allyl, homoallyl, propargyl, or homopropargyl bromide in the presence of K_2CO_3 in CH_3CN (65−89% yield). [b] Conditions: A; −78 °C to room temperature over 2 h then H_2O, B; −78 to −50 °C over 1 h, −50 °C to −40 °C for 2 h and then H_2O at −40 °C. [c] Isolated yield. [d] Deuterolysis of the reaction mixture gave the product containing >98% D.

Scheme 3



moiety, *i.e.*, **11**, **12**, or **13** (prepared from pyrrole-2-carboxylate),[11] proceeded as expected to afford, after hydrolysis, [1,2-*a*]pyrrole derivatives in good to excellent yields.[12] The results are also shown in Table 1 (entries 5−8).

In summary, the INAS and INAS-ICA reactions mediated by **1** allow practical access to quinolone, pyrrole, and indole derivatives from readily available starting materials. Noteworthy also is the fact that the products thus synthesized have a versatile 1-hydroxybicyclo[*n*.1.0]alkane[13] or conjugated enone[14] moiety, thus allowing further structural manipulation.

Scheme 4

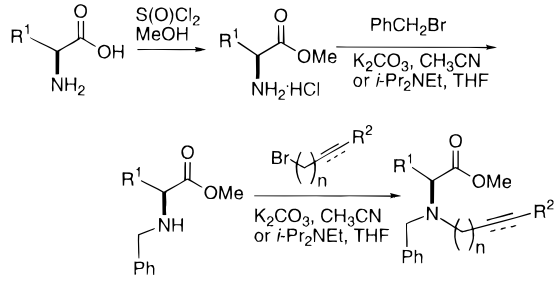
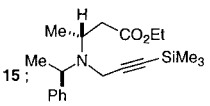
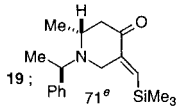
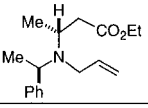
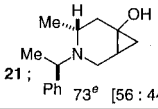


Table 2.[a] Synthesis of Optically Active N-Heterocycles from N-Alkylated α- or β-Amino Acid Esters and **1**

Entry	Substrate[b]	Product, % Yield
	14 ; R^1 R^3 R^2 n	**18** ;
1	**a** ; Bn Bn $SiMe_3$ 1	74[c,d]
2	**b** ; Bn Bn $SiMe_3$ 2	75[e]
3	**c** ; CH_2OTBS Bn $SiMe_3$ 1	73[c,d,f]
4	**d** ; CH_2OTBS Bn C_5H_{11} 1	72[c,f]
5	**e** ; $(CH_2)_2CO_2Me$ Bn $SiMe_3$ 1	78[c]
6	**f** ; $-(CH_2)_3-$ $SiMe_3$ 1	0
7	**g** ; $-(CH_2)_3-$ $SiMe_3$ 2	75[c]
8	 **15** ;	**19** ;  71[e]
	16 ; R^1 R^2 n	**20** ;
9	**a** ; Bn Bn 1	75[e] [73 : 27][g]
10	**b** ; Bn Bn 2	76[e] [92 : 8][g]
11	**c** ; CH_2OTBS Bn 1	86[e] [75 : 25][g]
12	**d** ; $-(CH_2)_3-$ 1	0
13	**e** ; $-(CH_2)_3-$ 2	0
14	**17** ; 	**21** ;  73[e] [56 : 44][g]

[a] Reaction conditions: Ti(O-*i*-Pr)$_4$ (1.3 equiv), *i*-PrMgCl (2.6 equiv), ether, −78 °C to room temperature, over 4 h for **16** and **17** or −50 to −40 °C, 1.5 h for **14** and **15**. [b] The substrates **14** and **16** were prepared from the corresponding L-amino acids. [c] Yield was determined by ^{1}H NMR analysis (by using an internal standard) of the crude product which was obtained by passing through a pad of silica gel after usual workup followed by concentration in vacuo and had >90% purity (wt %). Owing to somewhat low stability on column chromatography, the pure product could not be isolated. The identification of the product was also carried out by converting into the corresponding allyl alcohols by treatment with $NaBH_4$ and $CeCl_3$ in methanol (48−74% yield).[18] [d] Deuterolysis with D_2O gave the product with >95% D. [e] Isolated yield. [f] >98% ee.[18] [g] Ratio of two diastereomers. Their relative stereochemistries were not determined.

Synthesis of Optically Active Pyrrolidine and Piperidine Derivatives. Many naturally occurring N-heterocyclic compounds have stereogenic center(s) in the heterocyclic ring; thus, the development of an enantioselective route to access to N-heterocycles from readily available nonracemic starting

(11) Tietze, L. F.; Kettschau, G.; Heitmann, K. *Synthesis* **1996**, 851 and references cited therein.

(12) For a review for synthesis of fused [1,2-*a*]pyrroles, see: Flitsch, W. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; Vol. 3, pp 443−495. For recent syntheses, see: Barluenga, J.; Tomás, M.; Kouznetsov, V.; Suárez-Sobrino, A.; Rubio, E. *J. Org. Chem.* **1996**, *61*, 2185 and references cited therein.

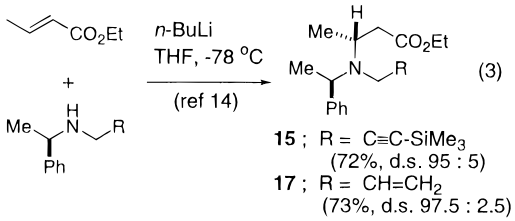
(13) For the synthetic utility of 1-hydroxybicyclo[*n*.1.0]alkanes: Reviews: Ryu, I.; Sonoda, N. *J. Syn. Org. Chem. Jpn.* **1985**, *43*, 112. Nakamura, E. *J. Syn. Org. Chem. Jpn.* **1989**, *47*, 931. Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *133*, 1. Kuwajima, I.; Nakamura, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, UK, 1991; Vol. 2, pp 441−454. A leading reference: Sugimura, T.; Futagawa, T.; Mori, A.; Ryu, I.; Sonoda, N.; Tai, A. *J. Org. Chem.* **1996**, *61*, 6100.

(14) For the reaction of conjugated enones, see: Patai, S.; Rappoport, Z., Eds. *The Chemistry of Enones*; Wiley: Chichester, 1989; Vol 1. Ullenius, C.; Christenson, B. *Pure Appl. Chem.* **1988**, *60*, 57.

materials has attracted much interest. Starting from optically active α- and *β*-amino acids and/or their esters, we planned the reaction sequence shown in Scheme 3 in anticipation that the reaction might afford nonracemic N-heterocycles.

Starting from natural α-amino acids such as L-phenylalanine, L-serine, L-gultamic acid, and L-proline, the corresponding N-allylated, -homoallylated, -propargylated, and/or -homopropargylated methyl esters were synthesized according to the conventional reaction sequence shown in Scheme 4 and were subjected to the reactions with **1**. The results are summarized in Table 2. The reaction with the phenyl alanine derivatives **14a** and **14b** resulted in a smooth INAS reaction providing the corresponding pyrrolidine and piperidine derivatives **18a** and **18b** after hydrolysis (entries 1 and 2 in Table 2), while the corresponding olefinic derivatives **16a** and **16b** furnished the INAS-ICA reaction products **20a** and **20b**, respectively, in excellent yields (entries 9 and 10). Similarly, from the serine and glutamic acid derivatives, the corresponding INAS and/or INAS-ICA products were obtained (entries 3−5 and 11). In the reaction with proline derivatives, however, only N-homopropargylated compound **14g** provided the expected indolizine derivative **18g** (entry 7). The results that **14f**, **16d**, and **16e** did not afford the expected products (entries 6, 12, and 13) may be attributable to the fact that the formation of the corresponding bicyclic transition state leading to INAS products is disfavored conformationally, because the side chains containing a carbon−carbon unsaturated bond and an ester group are situated anti to each other.[4c]

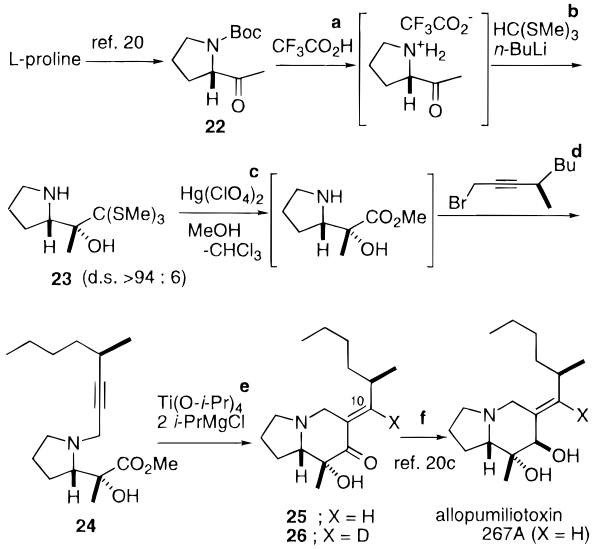
N-Propargylated and -allylated *β*-amino esters **15** and **17**, readily prepared by diastereoselective Michael addition of N-propargylated and -allylated α-phenylethylamine to crotonic acid ester according to the Davies protocol (eq 3),[15] also afforded the corresponding piperidine derivatives by treatment with **1**. The results are shown in entries 8 and 14 in Table 2.



The reaction developed here, which allows the synthesis of optically active pyrrolidine and piperidine derivatives, is practical since the starting materials are readily available, and the reaction is operationally simple. Noteworthy also is the fact that the synthesis reported here represents one of the most straightforward routes to N-heterocycles from α- or *β*-amino acids[16] and involves a carbon−carbon bond connection at an unprecedented position.[17]

Total Synthesis of Allopumiliotoxin Alkaloid 267A. In an extension of our methodology for preparation of N-heterocycles from α- and *β*-amino acids, we carried out the total synthesis of a (+)-allopumiliotoxin alkaloid 267A from L-proline (Scheme 5). The target substance is one of the pumiliotoxin A class of

Scheme 5[a]



[a] (a) Anisole, CH_2Cl_2, room temperature, 30 min; (b) THF, −78 °C, 1 h; (c) room temperature, 12 h; (d) *i*-Pr_2NEt, THF, room temperature, 2 days; (e) ether, −50 °C to −5 °C over 3 h then H_2O or D_2O; (f) $Me_4NBH(OAc)_3$, acetone-HOAc, room temperature, 2 days.

amphibian (*Dendrobatidae*) alkaloids and displays significant cardiotoxic activity.[19]

The reaction of the N-Boc-protected (*S*)-2-acetylpyrrolidine (**22**)[20c] with trifluoroacetic acid in the presence of anisole provided (*S*)-2-acetylpyrrolidine trifluoroacetate salt which was treated with an excess of tris(methylthio)methyl lithium (5 equiv) in tetrahydrofuran at −78 °C to give the tertiary alcohol **23** in 78% yield with >94:6 diastereoselectivity.[21] The tris(methylthio)methyl group of **23** was converted to a methyl ester group by treatment with $Hg(ClO_4)_2$-H_2O in methanol−chloroform, and then the resulting hydroxyl ester was N-alkylated by the reaction with (*R*)-1-bromo-4-methyl-2-octyne[22] (65% yield from **23**). The hydroxyl ester **24** thus prepared was subjected to the titanium-mediated INAS reaction. Accordingly, **24** was reacted with 1.5 equiv of Ti(O-*i*-Pr)$_4$ and then 4.0 equiv of *i*-PrMgCl[23] in ether at −78 °C to −5 °C to provide the indolidinone **25** in 67% yield. The compound **25** has already been synthesized by Overman as a precursor of allopumiliotoxin 267A, and identity was established by comparison of the spectral data (^{1}H and ^{13}C NMR, MS, IR).[20c] Finally, a stereospecific reduction of the keto group in **25** under the Overman conditions afforded (+)-allopumiliotoxin 267A (96%).[24] So far, total syntheses of allopumiliotoxin 267A have been accomplished by three groups, and all of them started with N-protected L-proline.[20] Compared

(15) Davies, S. G.; Hedgecock, C. J. R.; McKenna, J. M. *Tetrahedron: Asymmetry* **1995**, *6*, 827 and references cited therein.

(16) Recent review: Tisler, M.; Kolar, P. *Adv. Heterocycl. Chem.* **1995**, *64*, 1.

(17) Synthesis of N-heterocycles from amino acids by Dieckmann condensation which involves the connection at the acid group directly by using its reactivity has been reported: King, F. E.; King, T. J.; Warwick, A. J. *J. Chem. Soc.* **1950**, 3590. Brochmann, H.; Stahler, E. A. *Naturwissenschaften* **1965**, *52*, 391. Katz, E.; Mason, K. T.; Mauger, A. B. *Biochem. Biophys. Res. Commun.* **1975**, *63*, 502. Hershenson, F. M. *J. Org. Chem.* **1975**, *40*, 1260. Imai, N.; Terao, Y.; Achiwa, K.; Sekiya, M. *Tetrahedron Lett.* **1984**, *25*, 1579.

(18) See Experimental Section.

(19) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1. Daly, J. W.; Garraffo, H. M.; Spande, T. F. *Alkaloids* **1993**, *43*, 185.

(20) (a) Overman, L. E.; Goldstein, S. W.; *J. Am. Chem. Soc.* **1984**, *106*, 5360. (b) Overman, L. E.; Robinson, L. A.; Zablocki, J. *J. Am. Chem. Soc.* **1992**, *114*, 368. (c) Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, *57*, 1179. (d) Caderas, C.; Lett, R.; Overman, L. E.; Rabinowitz, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9073. (e) Trost, B. M.; Scanlan, T. S. *J. Am. Chem. Soc.* **1989**, *111*, 4988. (f) Aoyagi, S.; Wang. T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1992**, *114*, 10653. (g) Aoyagi, S.; Wang, T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1993**, *115*, 11393. For a review of the total synthesis of pumiliotoxin A and allopumiliotoxin alkaloids: Franklin, A. S.; Overman, L. E. *Chem. Rev.* **1996**, *96*, 505.

(21) Similar high diastereoselectivity was reported in the reaction of **22** with 1-lithio-1-methoxyallene[20c] or 2-lithio-1,3-dithiane.[20f,g]

(22) Prepared from (*R*)-4-methyloct-2-yn-1-ol[20g] by treatment with CBr_4 and PPh_3.

(23) Because of the presence of a hydroxyl group in **24**, 1 equiv excess of *i*-PrMgCl was used.

(24) The spectroscopic data were in good agreement with those reported in the literature.[20c,g]

to these methods, the present synthesis was the shortest (seven steps) and gave the highest overall yield (27% from N-protected L-proline). Noteworthy also is the fact that, as deuterolysis of the reaction mixture of **1** and **24** gave a deuterated compound **26** (>98% D), the present method enables the synthesis of C(10) deuterium (and probably tritium) labeled allopumiliotoxin 267A.

Conclusion

We have developed a highly efficient method for the preparation of N-heterocyclic compounds such as quinolone, indole, and pyrrole derivatives and optically active pyrrolidine and piperidine derivatives by using the titanium(II)-mediated INAS or INAS-ICA reaction. The reaction is practical since the starting organic substrates are readily available. Nontoxic, inexpensive metallic starting materials are used, and the procedure is operationally simple. Moreover, the N-heterocycles obtained here contain a versatile 1-hydroxybicyclo[*n*.1.0]-alkane[13] or conjugated enone[14] moiety. Thus, the reaction may find wide applicability for synthesizing a variety of N-heterocyclic compounds.

Experimental Section

General Methods. Infrared spectra were reported in cm^{-1}. ^1H NMR spectra were measured at 300 MHz with $CDCl_3$ as a solvent at ambient temperature and the chemical shifts were described in parts per million downfield from tetramethylsilane ($\delta = 0$ ppm) or based on residual $CHCl_3$ ($\delta = 7.26$ ppm) as an internal standard. ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$ as a solvent and referenced to the central line of the solvent ($\delta = 77.0$ ppm). The coupling constants (J) are reported in hertz. All experiments were conducted under argon atmosphere in oven-dried flasks. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl immediately prior to use. The procedure for preparation of the starting materials **4**, **5**, **8**, **9**, **10**, **11**, **12**, **13**, **14**, **15**, **16** and **17** and their spectroscopic data were given in Supporting Information.

Synthesis of Quinolone, [1,2-*a*]Indole and [1,2-*a*]Pyrrole Derivatives by Titanium-Mediated INAS or Tandem INAS-ICA Reaction. Procedure for the Reaction of Olefinic Substrates. To a stirred solution of *N*-allyl- or *N*-homoallyl compound **4**, **8**, **9**, **11**, **12**, **16**, or **17** (1.0 mmol) and Ti(O-*i*-Pr)$_4$ (385 μL, 1.30 mmol) in ether (6−8 mL) was added *i*-PrMgCl or *i*-PrMgBr (1.1−1.8 M in ether, 2.60 mmol) at −78 °C. The resulting mixture was gradually warmed to room temperature over 2−2.5 h. After addition of tetrahydrofuran (5 mL) and water (2.4 mL), the mixture was stirred for 30 min. The organic layer was separated, and the residue was washed with ether (2 × 10 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel to give the N-heterocyclic compound having a cyclopropanol moiety.

1-Benzylbenzo[*b*]cyclopropa[3,4]piperidin-4-ol (6a): ^1H NMR (300 MHz) δ 7.62 (dd, $J = 1.7$, 7.5, 1H), 7.28 (m, 5H), 7.05 (dt, $J =$ 1,7, 7.8, 1H), 6.83 (t, $J = 7.2$, 1H), 6.61 (d, $J = 8.3$, 1H), 4.46 (d, $J = 15.5$, 1H), 4.22 (d, $J = 15.5$, 1H), 3.14 (d, $J = 2.1$, 2H), 1.88 (m, 1H), 1.51 (t, $J = 5.5$, 1H), 1.23 (dd, $J = 5.0$, 9.6, 1H); ^{13}C NMR (75 MHz) δ 142.32, 138.21, 128.83, 128.48, 127.37, 126.91, 126.66, 124.30, 118.00, 112.22, 54.55, 53.27, 45.20, 28.95, 16.47; IR (neat) 3250, 2980, 2950, 1320, 1210. Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 80.91; H, 7.20; N, 5.78.

Indolo[1,2-*a*]cyclopropa[3,4]pyrrolidin-3-ol (entry 1, Table 1): ^1H NMR (300 MHz) δ 7.54 (dd, $J = 7.5$, 1.5, 1H), 7.09 (m, 3H), 6.33 (s, 1H), 4.18 (dd, $J = 10.7$, 5.5, 1H), 3.83 (d, $J = 10.7$, 1H), 2.90 (br s, 1H), 2.31 (m, 1H), 1.76 (dd, $J = 9.4$, 5.9, 1H), 1.01 (t, $J = 5.4$, 1H); ^{13}C NMR (75 MHz) δ 145.46, 132.88, 132.56, 120.97, 120.81, 119.38, 108.98, 91.99, 60.81, 46.38, 28.42, 24.00; IR (neat) 3340, 2960, 1615, 1332, 1225. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.62; H, 6.31; N, 7.83.

Indolo[1,2-*a*]cyclopropa[3,4]piperidin-3-ol (entry 2, Table 1): yellow crystalline (recrystallized from hexane); mp 52.0−53.5 °C; ^1H NMR (300 MHz) δ 7.56 (dd, $J = 7.0$, 1.2, 1H), 7.15 (m, 3H), 6.57 (s, 1H), 4.21 (dt, $J = 13.1$, 3.8, 1H), 3.41 (dt, $J = 11.9$, 9.2, 1H), 2.81 (br s, 1H), 2.16 (m, 2H), 1.81 (m, 1H), 1.40 (dd, $J = 10.0$, 6.2, 1H), 1.13 (t, $J = 6.3$, 1H); ^{13}C NMR (75 MHz) δ 140.64, 136.05, 128.03, 120.63, 119.93, 119.52, 108.54, 96.23, 52.98, 36.74, 21.99, 21.18, 17.02; IR (Nujol) 3380, 2950, 1625, 1325. Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.33; H, 6.73; N, 6.89.

Pyrrolo[1,2-*a*]cyclopropa[3,4]pyrrolidin-3-ol (entry 5, Table 1): ^1H NMR (300 MHz) δ 6.46 (dd, $J = 3.0$, 1.2, 1H), 6.18 (t, $J = 3.0$, 1H), 6.00 (dd, $J = 3.4$, 1.2, 1H), 4.23 (dd, $J = 11.4$, 5.7, 1H), 3.70 (d, $J = 11.4$, 1H), 2.76 (br s, 1H). 2.17 (m, 1H), 1.67 (dd, $J = 9.3$, 5.7, 1H), 0.91 (t, $J = 5.3$, 1H); ^{13}C NMR (75 MHz) δ 138.48, 113.89, 112.04, 98.35, 61.14, 48.47, 27.48, 23.63; IR (Nujol) 3800, 1580, 1330. Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.01; H, 7.10; N, 7.39.

Pyrrolo[1,2-*a*]cyclopropa[3,4]piperidin-3-ol (entry 6, Table 1): ^1H NMR (300 MHz) δ 6.51 (dd, $J = 2.6$, 1.8, 1H), 6.22 (dd, $J = 3.5$, 1.7, 1H), 6.12 (t, $J = 3.2$, 1H), 3.88 (ddd, $J = 12.9$, 5.9, 1.9, 1H), 3.43 (dt, $J = 4.7$, 12.9, 1H), 2.16 (ddt, $J = 3.3$, 5.6, 13.0, 1H), 2.00 (m, 1H), 1.64 (m, 1H), 1.30 (dd, $J = 9.9$, 6.0, 1H), 1.00 (t, $J = 6.0$, 1H); ^{13}C NMR (75 MHz) δ 132.86, 119.08, 107.05, 102.87, 52.95, 40.56, 21.51, 21.04, 16.24; IR (Nujol) 3150, 2890, 1630, 1319. Anal. Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 71.97; H, 7.61; N, 9.51.

Procedure for the Reaction of Acetylenic Substrates. To a stirred solution of *N*-propargyl- or *N*-homopropargyl compound **5**, **10**, or **13** (1.0 mmol) and Ti(O-*i*-Pr)$_4$ (325 μL, 1.3 mmol) in ether (8−10 mL) was added *i*-PrMgCl or *i*-PrMgBr (1.1−1.7 M in ether, 2.6 mmol) at −78 °C. The resulting mixture was gradually warmed to −50 °C over 0.5−1 h and stirred for 1−2 h at −50 °C ∼ −40 °C. After addition of saturated aqueous $NaHCO_3$ (1.0 mL) at −40 °C, the mixture was warmed to ambient temperature. NaF (2 g) and Celite (2 g) were added, and the resulting mixture was stirred for 1 h at room temperature. The mixture was filtered through a pad of Celite, and the filterate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel to afford the N-heterocycles having a α-alkylidene ketone moiety.

(*E*)-1-Benzyl-1,2,3,4-tetrahydro-3-trimethylsilylmethylene-4-quinolone (7a): ^1H NMR (300 MHz) δ 8.04 (dd, $J = 1.8$, 7.8, 1H), 7.31 (m, 6H), 6.98 (t, $J = 1.8$, 1H), 6.75 (m, 2H), 4.54 (s, 2H), 4.24 (d, $J = 1.7$, 2H), 0.07 (s, 9H); ^{13}C NMR (75 MHz) δ 189.42, 151.86, 145.91, 138.05, 136.96, 135.49, 129.65, 128.92, 127.44, 127.28, 117.76, 113.12, 54.49, 53.87, −0.74; IR (neat) 2980, 1630, 1583, 1300. Anal. Calcd for $C_{20}H_{23}NOSi$: C, 74.72; H, 7.21; N, 4.36. Found: C, 74.61; H, 7.38; N, 4.67.

(*E*)-1-Benzyl-1,2,3,4-tetrahydro-3-heptylidene-4-quinolone (7b): ^1H NMR (300 MHz) δ 8.04 (dd, $J = 1.7$, 7.9, 1H), 7.31 (m, 6H), 6.87 (t, $J = 7.7$, 1H), 6.75 (t, $J = 7.4$, 1H), 6.68 (d, $J = 8.4$, 1H), 4.59 (s, 2H), 4.22 (s, 2H), 2.06 (q, $J = 7.4$, 2H), 1.43 (m, 2H), 1.25 (m, 6H), 0.87 (t, $J = 6.8$, 3H). Anal. Calcd for $C_{23}H_{27}NO$: C, 82.84; H, 8.16; N, 4.20. Found: C, 82.11; H, 8.35; N, 4.59.

(*E*)-4-Trimethylsilylmethyleneindolo[1,2-*a*]pyrrolidin-3-one (entry 3, Table 1): yellow crystalline (recrystallized from hexane); mp 125.0−126.5 °C; ^1H NMR (300 MHz) δ 7.77 (d, $J = 8.3$, 1H), 7.41 (m, 2H), 7.20 (m, 1H), 7.15 (s, 1H), 7.11 (t, $J = 2.3$, 1H), 4.99 (d, $J = 2.3$, 2H), 0.29 (s, 9H); ^{13}C NMR (75 MHz) δ 181.10, 148.91, 135.73, 134.90, 132.10, 131.80, 125.46, 124.14, 121.68, 110.47, 100.86, 45.59, −1.09; IR (Nujol) 1702, 1630, 1543, 1353. Anal. Calcd for $C_{15}H_{17}NOSi$: C, 70.54; H, 6.71; N, 5.48. Found: C, 70.17; H, 6.98; N, 5.66.

(*E*)-4-Heptylideneindolo[1,2-*a*]pyrrolidin-3-one (entry 4, Table 1): ^1H NMR (300 MHz) δ 7.76 (d, $J = 8.2$, 1H), 7.38 (m, 2H), 7.19 (m, 1H), 7.09 (d, $J = 1.1$, 1H), 6.88 (tt, $J = 7.8$, 2.2, 1H), 4.91 (d, $J = 2.2$, 2H), 2.30 (q, $J = 7.4$, 2H), 1.57 (m, 2H), 1.33 (m, 6H), 0.90 (t, $J = 6.7$, 3H); ^{13}C NMR (75 MHz) δ 182.00, 138.10, 137.79, 136.24, 134.57, 131.72, 125.18, 124.03, 121.44, 110.33, 99.96, 43.96, 31.62, 29.83, 29.09, 28.33, 22.53, 14.03; IR (Nujol) 1708, 1652, 1543, 1350. Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.58; H, 8.20; N, 5.27.

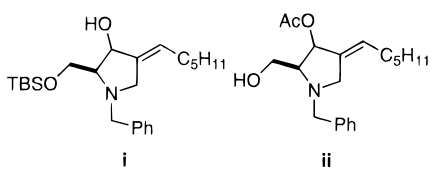
(*E*)-4-Trimethylsilylmethylenepyrrolo[1,2-*a*]pyrrolidin-3-one (entry 7, Table 1): ^1H NMR (300 MHz) δ 7.08 (dd, $J = 2.2$, 1.1, 1H), 6.94 (t, $J = 2.2$, 1H), 6.86 (dd, $J = 4.4$, 1.1, 1H), 6.52 (dd, $J = 4.0$, 2.2, 1H), 4.86 (d, $J = 2.3$, 2H), 0.22 (s, 9H); ^{13}C NMR (75 MHz) δ 177.69, 149.37, 133.08, 122.15, 116.64, 109.46, 107.79, 47.66, −1.08; IR (Nujol) 1725, 1660, 1560, 1348. Anal. Calcd for $C_{11}H_{15}NOSi$: C, 64.35; H, 7.36; N, 6.82. Found: C, 64.15; H, 7.46; N, 6.71.

(*E*)-4-Heptylidenepyrrolo[1,2-*a*]pyrrolidin-3-one (entry 8, Table 1): ^1H NMR (300 MHz) δ 7.04 (d, $J = 1.7$, 1H), 6.81 (m, 1H), 6.70

(tt, J = 7.8, 2.1, 1H), 6.50 (dd, J = 4.0, 2.3, 1H), 4.86 (d, J = 2.2, 2H), 2.21 (q, J = 7.6, 2H), 1.52 (m, 2H), 1.42−1.25 (m, 6H), 0.89 (t, J = 6.6, 3H); ^{13}C NMR (75 MHz) δ 178.90, 136.34, 135.30, 135.25, 121.84, 116.26, 108.39, 45.89, 31.53, 29.50, 28.94, 28.30, 22.45, 13.95; IR (neat) 2960, 1718, 1663, 1543, 1329. Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.11; H, 9.11; N, 6.37.

Synthesis of Optically Active N-Heterocyclic Compounds from α- or *β*-Amino Acid Derivatives. Typical Procedure for the Reaction of Acetylenic Substrates 14 or 15. To a stirred solution of **14d** (432 mg, 1.0 mmol) and Ti(O-*i*-Pr)$_4$ (385 μL, 1.3 mmol) in ether (10 mL) was added *i*-PrMgCl (1.94 mL, 1.34 M in ether, 2.6 mmol) at −78 °C. The resulting mixture was gradually warmed to −50 °C over 1 h and stirred for 2 h at −50 °C ∼ −40 °C. After addition of aqueous saturated $NaHCO_3$ (0.8 mL) at −40 °C, the mixture was warmed to ambient temperature. NaF (3 g) and Celite (3 g) were added, and the resulting mixture was stirred for 30 min at room temperature and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to afford the crude product with >90% chemical purity (wt %, determined by ^{1}H NMR analysis). The yield of **18d** was 78% determined by ^{1}H NMR analysis of the crude residue using an internal standard. In this reaction procedure use of D_2O (0.8 mL) instead of aqueous saturated aqueous $NaHCO_3$ gave the product contained >98% D at the olefinic position which was determined by ^{1}H NMR analysis. Purification of **18d** proved difficult, as this compound decomposed on attempted silica gel chromatography as well as distillation. Thus the crude enone was reduced with $CeCl_3$−$NaBH_4$ in MeOH to the corresponding allylic alcohol (234 mg, 58% yield from **14d**, as a mixture of two diastereomers in a ratio of 70:30).

(*E*,*S*)-1-Benzyl-2-[(*tert*-butyldimethylsilyl)oxy]methyl-3-trimethylsilylmethylene-3-pyrrolidinone (18d): ^{1}H NMR δ 7.20−7.43 (m, 5H), 6.55 (tt, J = 2.5, 7.7, 1H), 4.40 (d, J = 13.4, 1H), 4.10 (dd, J = 2.5, 10.5, 1H), 3.86 (dd, J = 5.7, 10.5, 1H), 3.74 (d, J = 12.3, 1H), 3.67 (d, J = 13.4, 1H), 3.18 (m, 1H), 3.17 (dd, J = 2.2, 12.3, 1H), 2.03 (dt, J = 7.7, 7.4, 1H), 1.10−1.48 (m, 6H), 0.88 (s, 9H), 0.85 (t, J = 7.2, 3H), 0.09 and 0.05 (2s, each, 3H). Allylic alcohols derived from **18d** by treatment with $NaBH_4$−$CeCl_3$ in MeOH: for a major isomer; ^{1}H NMR δ 7.20−7.338 (m, 5H), 5.60 (t, J = 7.4, 1H), 4.46 (m, 1H), 4.09 (d, J = 13.3, 1H), 3.98 (dd, J = 5.8, 10.7, 1H), 3.86 (dd, J = 4.7, 10.7, 1H), 3.60 (d, J = 14.4, 1H), 3.39 (d, J = 13.3, 1H), 2.80 (d, J = 14.4, 1H), 2.73 (m, 1H), 1.88 (dt, J = 7.4, 6.7, 2H), 1.17−1.40 (m, 6H), 0.89 (s, 9H), 0.85 (t, J = 7.0, 1H), 0.08 and 0.07 (2s, 6H); ^{13}C NMR δ 140.3, 128.7, 126.9, 125.5, 123.2, 74.6, 68.7, 62.2, 58.6, 54.8, 31.5, 29.3, 28.8, 25.8, 22.5, 18.1, 14.0, −5.5; IR (neat) 3417, 2954, 2927, 2856, 1689, 1461, 1388, 1255, 1089, 837, 777, 739, 698; MS/EI *m/e* 403 (0.2), 385 (3.2), 328 (5.8), 312 (5.1), 258 (100), 91 (57), 75 (30), 55 (8.7); HRMS (CI) calcd for $C_{24}H_{42}NO_2Si$ (M^+ + H) 404.2985, found 404.2991. Optical purity of **18d** was determined by ^{1}H NMR analysis of the corresponding MTPA esters of the compound **ii** which was derived from **18d** according to the following procedure: A mixture of two diastereomers of allylic alcohols **i** prepared above was treated with Ac_2O in pyridine and then TBAF in THF to give the corresponding acetoxy-*primary*-alcohol derivatives **ii** which were separated from each other by column chromatography on silica gel. Thus, the resulting major diastereomer was converted to the corresponding MTPA-esters by using (*S*)- or (*R*)-MTPA-Cl. ^{1}H NMR 300 MHz analysis of each MTPA ester showed that no racemization occurred in these reactions.



i **ii**

Under the same reaction conditions (quantity, reaction temperature, and period) the following compounds were obtained by the same procedure described above.

(*E*,*S*)-1,2-Dibenzyl-4-trimethylsilylmethylene-3-pyrrolidinone (18a): ^{1}H NMR δ 7.10−7.40 (m, 10H), 6.73 (t, J = 2.5, 1H), 4.05 (d, J = 13.2, 1H), 3.75 (dd, J = 1.1, 13.7, 1H), 3.32 (d, J = 13.2, 1H), 3.27 (dd, J = 4.7, 13.7, 1H), 3.19 (dd, J = 5.4, 5.5, 1H), 3.07 (dd, J = 2.8, 14.4, 1H), 3.02 (dd, J = 5.3, 14.4, 1H), 0.07 (s, 9H); ^{13}C NMR δ 201.50, 146.70, 138.73, 137.50, 134.36, 129.63, 128.70, 128.33, 128.22, 127.22, 126.22, 70.05, 59.18, 54.43, 36.40, −1.34. Optical purity of **18a** was confirmed by the same method as used for **18d**, and it was found that no racemization occurred in these reactions.

(*E*,*S*)-1,2-Dibenzyl-4-trimethylsilylmethylene-3-piperidinone (18b): ^{1}H NMR δ 7.15−7.33 (m, 10H), 6.70 (s, 1H), 3.90 (d, J = 13.5, 1H), 3.56 (d, J = 13.7, 1H), 3.49 (t, J = 6.0, 1H), 3.13 (dd, J = 6.0, 13.7, 1H), 3.20 (dd, J = 5.5, 13.9, 1H), 3.05 (m, 1H), 3.04−3.14 (m, 1H), 2.55 (m, 1H), 2.51−2.73 (m, 2H), 0.13 (s, 3H); ^{13}C NMR δ 200.45, 148.24, 139.13, 138.31, 129.69, 128.58, 128.22, 127.96, 127.04, 126.12, 71.69, 58.28, 45.70, 36.14, 29.22, −0.85.

(*E*,*S*)-1-Benzyl-2-[(*tert*-butyldimethylsilyl)oxy]methyl-4-trimethylsilylmethylene-3-pyrrolidinone (18c): ^{1}H NMR δ 7.22−7.43 (m, 5H), 6.70 (t, J = 2.6, 1H), 4.34 (d, J = 13.4, 1H), 4.09 (dd, J = 2.5, 10.6, 1H), 3.85 (dd, J = 5.2, 10.6, 1H), 3.83 (dd, J = 2.5, 14.3, 1H), 3.75 (d, J = 13.4, 1H), 3.33 (dd, J = 2.7, 14.3, 1H), 3.17 (dd, J = 2.3, 5.2, 1H), 0.87 (s, 9H), 0.09 (s, 9H), 0.04 and 0.08 (2s, each 3H).

(*E*,*S*)-1-Benzyl-2-(2-methoxycarbonyl)ethyl-4-trimethylsilylmethylene-3-pyrrolidinone (18e): ^{1}H NMR δ 7.20−7.42 (m, 5H), 6.71 (dd, J = 2.3, 2.6, 1H), 4.16 (d, J = 13.2, 1H), 3.80 (dt, J = 14.6, 1.4, 1H), 3.64 (s, 3H), 3.42 (d, J = 13.2, 1H), 3.08 (dd, J = 3.3, 14.6, 1H), 2.93 (m, 1H), 1.90−2.60 (m, 4H), 0.08 (s, 9H).

(*S*)-1-Aza-4-trimethylsilylmethylenebicyclo[4.3.0]nonan-5-one (18g): ^{1}H NMR δ 6.78 (s, 1H), 3.03−3.25 (m, 2H), 2.72−2.88 (m, 3H), 2.53 (dt, J = 16.1, 8.9, 1H), 2.38 (q, J = 12.2, 1H), 1.55−2.18 (m, 4H), 0.17 (s, 9H); ^{13}C NMR δ 198.1, 148.0, 138.6, 71.1, 54.4, 49.7, 30.6, 25.3, 21.7, −0.8.

(*R*,*E*)-1-[(*R*)-1-phenylethyl]-2-methyl-5-trimethylsilylmethylene-4-piperidinone (19). The crude mixture was purified by column chromatography on silica gel (hexane−ether) to give pure **19** as a pale yellow oil; $[\alpha]^{25}_D$ +19.5 (*c* 2.22, THF), +23.9 (*c* 2.17, $CHCl_3$); ^{1}H NMR δ 7.19−7.44 (m, 5H), 6.62 (dd, J = 1.6, 1.7, 1H), 3.87 (q, J = 6.7, 1H), 3.49 (m, 1H), 3.38 (dd, J = 1.6, 15.1, 1H), 3.31 (dd, J = 1.7, 15.1, 1H), 2.78 (dd, J = 5.6, 17.0, 1H), 2.37 (dd, J = 5.0, 17.0, 1H), 1.37 (d, J = 6.7, 3H), 1.16 (d, J = 6.5, 3H), −0.15 (s, 9H); ^{13}C NMR δ 198.5, 147.8, 144.7, 136.2, 128.3, 127.3, 127.0, 58.8, 49.7, 48.7, 47.2, 16.6, 15.3, −1.2; IR (neat) 2965, 1691, 1590, 1319, 1249. Anal. Calcd for $C_{18}H_{27}NOSi$: C, 71.71; H, 9.03; N, 4.65. Found: C, 71.75; H, 9.12; N, 4.49.

Typical Procedure for the Reaction of Olefinic Substrates 16 or 17. To a stirred solution of **16c** (181.5 mg, 0.50 mmol) and Ti(O-*i*-Pr)$_4$ (192 μL, 0.65 mmol) in ether (5 mL) was added *i*-PrMgCl (0.970 mL, 1.34 M in ether, 1.30 mmol) at −78 °C. The resulting mixture was gradually warmed to room temperature over 2 h and stirred for additional 2 h. After addition of aqueous saturated $NaHCO_3$ (0.6 mL), the mixture was stirred for 30 min. To this were added NaF (2 g) and Celite (2 g). After stirring for 30 min, the mixture was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel to give **20c** (144.4 mg) in 86% yield as a 72:28 mixture of two diastereomers.

(*S*)-1-Benzyl-2-[(*tert*-butyldimethylsilyl)oxy]methylcyclopropa-[3,4]pyrrolidin-3-ol (20c): a 72:28 mixture of two diastereomers. For a major isomer: ^{1}H NMR δ 7.16−7.38 (m, 5H), 3.90 (dd, J = 4.3, 10.7, 1H), 3.82 (dd, J = 3.0, 10.7, 1H), 3.73 and 3.79 (2d, J = 13.8, each 1H), 3.09−3.17 (m, 2H), 2.51 (d, J = 8.7, 1H), 1.40−1.52 (m, 1H), 1.04 (dd, J = 5.0, 8.9, 1H), 0.81−0.98 (m, 1H), 0.89 (s, 9H), 0.06 and 0.11 (2s, each 3H); ^{13}C NMR δ 139.9, 128.5, 128.1, 126.7, 64.6, 62.3, 56.0, 54.1, 25.8, 24.3, 20.7, 17.9, 17.0, −5.4, −5.6; IR (neat, for a mixture of two diastereomers) 3420, 2950, 1360. Anal. Calcd for $C_{19}H_{31}NO_2Si$: C, 68.42; H, 9.37; N, 4.20. Found (for a mixture of two diastereomers): C, 68.40; H, 9.51; N, 4.12.

Under the same reaction conditions (quantity, reaction temperature and period) the following compounds were obtained by the same procedure described above.

(*S*)-1,2-Dibenzylcyclopropa[3,4]pyrrolidin-3-ol (20a): a 82:18 mixture of two diastereomers. For a major diastereomer: ^{1}H NMR (300 MHz) δ 7.10−7.40 (m, 10H), 3.66 and 3.61 (2d, each J = 13.9, each 1H) 3.38 (dd, J = 5.3, 6.6, 1H), 2.84−3.06 (m, 3H), 2.37 (d, J = 9.3, 1H), 2.27 (br s, 1H), 1.44−1.54 (m, 1H), 0.96 (dd, J = 4.7, 8.9, 1H), 0.90 (t, J = 4.5, 1H); ^{13}C NMR δ 140.9, 139.6, 129.4, 128.3,

128.2, 128.1, 126.8, 125.7, 67.6, 65.4, 56.7, 52.6, 34.3, 24.2, 19.9; IR (Nujol, for a mixture of two diastereomers) 2971, 2884, 1602.

(*S*)-1,2-Dibenzylcyclopropa[3,4]piperidin-3-ol (20b): a 92.5:7.5 mixture of two diastereomers. For a major diastereomer: ^{1}H NMR δ 7.10−7.40 (m, 10H), 3.69 (d, J = 13.8, 1H), 3.55 (d, J = 13.8, 1H), 3.49 (dd, J = 5.4, 6.1, 1H), 3.17 (dd, J = 6.5, 14.0, 1H), 3.14 (dd, J = 4.8, 14.0, 1H), 2.65 (ddd, J = 6.7, 6.8, 12.3, 1H), 2.23 (ddd, J = 3.8, 7.8, 12.3, 1H), 1.88−2.00 (m, 1H), 1.56−1.68 (m, 1H), 1.20−1.30 (m, 1H), 0.96 (dd, J = 4.5, 6.1, 1H), 0.75 (dd, J = 4.5, 10.6, 1H); ^{13}C NMR δ 142.07, 139.74, 129.34, 128.37, 128.31, 128.10, 126.77, 125.59, 63.85, 58.68, 58.17, 42.22, 32.95, 22.26, 19.30, 17.75. Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found (for a mixture of two diastereomers): C, 81.55; H, 7.86; N, 4.63.

(*R*)-1-[(*R*)-1-Phenylethyl]-2-methylcyclopropa[4,5]piperidin-4-ol (21): a 56:44 mixture of two diastereomers. The mixture was recrystallized from hexane to afford two different types of crystals which were partially separated by tweezers to give analytically pure samples. Major isomer: white needle, mp 133.5−134.5 °C; ^{1}H NMR δ 7.16−7.41 (m, 5H), 3.66 (q, J = 6.8, 1H), 2.89−3.00 (m, 1H), 2.66 (dd, J = 5.6, 11.8, 1H), 2.38 (dd, J = 5.4, 13.6, 1H), 2.31 (dd, J = 1.2, 11.8, 1H), 1.84 (ddd, J = 1.2, 4.6, 13.6, 1H), 1.22 (d, J = 6.8, 3H), 1.10 (d, J = 6.5, 3H), 1.03−1.17 (m, 1H), 0.77 (dd, J = 4.6, 10.4, 1H), 0.47 (dd, J = 4.6, 6.1, 1H); ^{13}C NMR δ 144.6, 128.0, 127.4, 126.4, 59.2, 52.1, 46.8, 43.5, 41.0, 20.3, 18.3, 18.1, 13.8. Minor isomer: pale yellow plates, mp 119.0−120.0 °C; ^{1}H NMR δ 7.16−7.41 (m, 5H), 4.18 (q, J = 7.0, 1H), 2.59−2.71 (m, 1H), 2.55 (dd, J = 3.7, 11.3, 1H), 2.36 (dd, J = 1.8, 11.3, 1H), 2.16 (dd, J = 6.1, 13.8, 1H), 1.97 (dd, J = 10.1, 13.8, 1H), 1.24 (d, J = 7.0, 3H), 1.03−1.17 (m, 1H), 1.09 (d, J = 6.2, 3H), 0.60−0.68 (m, 2H); ^{13}C NMR δ 144.7, 127.8 (2C), 126.2, 54.1, 53.0, 50.8, 43.13, 43.07, 21.5, 19.8, 17.7, 9.7. IR (KBr, for a mixture of two diastereomers) 3411, 2965, 1637,1367. Anal. Calcd for $C_{15}H_{21}NO$ (for a mixture of two diastereomers): C, 77.88; H, 9.15; N, 6.05. Found: C, 77.60; H, 9.27; N, 6.06.

Synthesis of Allopumiliotoxin 267A. (2*S*)-2-[(*R*)-1-(Hydroxy)-1-(trimethylthiomethyl)ethyl]pyrrolidine (23). The compound **22** (1.065 g, 5.0 mmol) prepared from L-proline (83% overall yield) according to the procedure reported by Overman[20c] and Kibayashi[20g] was deprotected by treatment with CF_3COOH (3.5 mL) and anisole (3.5 mL) in CH_2Cl_2 (3.5 mL) at room temperature for 30 min to give a trifluoroacetate salt of the amine which was dried by azeotroping with CH_2Cl_2 (3 × 3 mL) and then toluene (2 × 3 mL). To a solution of tris(methylthio)methane (3.326 mL, 25 mmol) in THF (50 mL) was added dropwise a solution of BuLi (11.7 mL, 2.14 M in hexane, 25 mmol) at −78 °C, and the resulting mixture was allowed to warm to −20 °C over 1 h. After the mixture was cooled to −78 °C, to it (a white suspension) was added dropwise a solution of the trifluoroacetate salt prepared above in THF (15 mL), and the resulting mixture was stirred for 1 h at −78 °C and gradually warmed to −40 °C over 1 h. After addition of water (30 mL), the mixture was extracted with ether (50 mL) and then $CHCl_3$ (20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on Chromatorex NH-gel (DM1020, Fuji Silysia Chemical Ltd.) using hexane−ether to afford **23** (1.043 g, 78% yield): a colorless oil; $[\alpha]^{25}_D$ −65.1 (*c* 2.196, THF); ^{1}H NMR δ 3.88 (dd, J = 6.4, 9.6, 1H, 2-H), 3.10 (ddd, J = 3.1, 7.6, 10.4, 1H, part of 5-H_2), 2.84 (ddd, J = 6.4, 9.1, 10.4, 1H, part of 5-H_2), 2.27 (s, 9H, 3SMe), 1.50−1.94 (m, 4H, 3-H_2 and 4-H_2), 1.47 (s, 3H, *Me*COH); ^{13}C NMR δ 81.3, 62.2, 50.9, 45.8, 28.7, 25.9, 22.9, 12.1.

(2*S*)-1-[(*R*)-4-Methyl-2-octynyl]-2-[(*R*)-1-(Hydroxy)-1-methoxycarbonyl]ethylpyrrolidine (24). To a solution of **23** (710 mg, 2.65 mmol) in MeOH (10 mL) and $CHCl_3$ (10 mL) was added dropwise a solution of $Hg(ClO_4)_2$−$3H_2O$ (3.606 g, 7.95 mmol) in MeOH (20 mL) at room temperature. The resulting white-pink suspension was stirred for 12 h at room temperature. After careful addition of saturated aqueous $NaHCO_3$ (20 mL), the mixture was extracted with $CHCl_3$ (3 × 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was passed through a short column of Chromatorex NH-gel with ether and concentrated *in vacuo* to give a semipurified methyl ester, (2*S*)-2-[(*R*)-1-(hydroxy)-1-methoxycarbonyl]ethylpyrrolidine (340 mg), which was subjected to the next reaction. To a solution of the methyl ester thus obtained and *i*-Pr_2NEt (0.94 mL) in THF (10 mL) was added (*R*)-1-bromo-4-methyl-2-octyne [400 mg, 1.97 mmol, prepared from (*R*)-4-methyl-2-octyn-1-ol (which was synthesized according to the procedure reported by Kibayashi[20g]) by treatment with triphenylphosphine and CBr_4 in CH_2Cl_2] at room temperature. After the mixture was stirred for 2 days at room temperature, to it was added saturated aqueous $NaHCO_3$ (10 mL), and the mixture was extracted with ether (2 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane−ether to hexane−AcOEt) to give **24** (509 mg, 65% yield): a colorless oil; $[\alpha]^{24}_D$ −59.8 (*c* 1.106, $CHCl_3$); ^{1}H NMR δ 3.75 (s, 3H, CO_2Me), 3.34 (dd, J = 2.1, 17.5, 1H, part of 1′-H_2), 3.30 (dd, J = 5.7, 8.2, 1H, 2-H), 3.12 (dd, J = 2.1, 17.5, 1H, part of 1′-H_2), 2.98 (ddd, J = 5.1, 5.6, 9.4, 1H, part of 5-H_2), 2.84 (ddd, J = 7.5, 7.7, 9.4, 1H, part of 5-H_2), 2.34−2.47 (m, 1H, 4′-H), 1.66−1.96 (m, 4H, 3-H_2 and 4-H_2), 1.34 (s, 3H, *Me*COH), 1.23−1.46 (m, 6H, $(CH_2)_3$Me), 1.14 (d, J = 7.0, 3H, $C_{4'}$-Me), 0.90 (t, J = 7.1, CH_2CH_3); ^{13}C NMR δ 176.9, 89.2, 75.1, 75.0, 66.7, 54.1, 51.9, 42.7, 36.7, 29.5, 27.0, 25.7, 24.5, 22.4, 22.2, 21.3, 13.9; IR (neat) 3510, 2958, 2929, 2871, 1743, 1457, 1375, 1322, 1253, 1211, 1191, 1116, 981, 723; MS (EI) *m/e* 295 (0.1), 236 (15.2), 192 (100), 134 (7.8), 126 (8.0), 112 (5.3), 81 (31.6), 70 (45.0), 67 (28), 55 (34), 53 (23); HRMS (CI) calcd for $C_{17}H_{30}NO_3$ (M^++H) 296.2226, found 296.2214.

(8*R*,8a*S*)-8-Hydroxy-8-methyl-6-[(*Z*)-2(*R*)-methylhexylidene]octahydroindolizin-7-one (25). To a solution of **24** (34.1 mg, 0.116 mmol) and Ti(O-*i*-Pr)$_4$ (47.8 μL, 0.174 mmol) in ether (1.16 mL) was added *i*-PrMgCl (386 μL, 1.20 M in ether, 0.464 mmol) at −78 °C and the resulting clear yellow solution was allowed to warm to −50 °C. After having been stirred for 1 h at −50 °C to −40 °C, the mixture was colored brown, and this was gradually warmed to −5 °C over 1 h. After addition of aqueous saturated $NaHCO_3$ (0.1 mL) and then stirring for 10 min at −5 °C, the cooling bath was removed. The mixture was dried by addition of anhydrous $MgSO_4$ and filtered through a pad of Celite with ether. The filtrate was concentrated under reduced pressure to give a crude oil which was purified by column chromatography on silica gel (Wako C-200, hexane−ether) to afford **25** (20.5 mg, 67% yield): $[\alpha]^{25}_D$ −6.4 (*c* 0.96, $CHCl_3$), lit.[20c] $[\alpha]^{25}_D$ −6.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 6.52 (d, J = 10.6, 1H, 10-H), 4.01 (d, J = 14.0, 1H, part of 5-H_2), 3.67 (br s, 1H, OH), 3.22 (ddd, J = 2.8, 5.3, 8.7, part of 3-H_2), 2.96 (dd, J = 2.6, 14.0, 1H, part of 5-H_2), 2.25−2.48 (m, 3H, part of 3-H_2, 11-H and 8a-H), 1.78−2.02 (m, 4H, 1-H_2 and 2-H_2), 1.10−1.43 (m, 6H, 12-H_2, 13-H_2 and 14-H_2), 1.25 (s, 3H, 9-H_3), 1.01 (d, J = 6.6, 3H, 16-H_3), 0.86 (t, J = 7.1, 3H, 15-H_3); ^{13}C NMR δ 197.1, 148.0, 129.6, 77.2, 73.1, 69.2, 55.2, 52.0, 36.3, 32.9, 29.7, 23.6, 22.7, 19.9, 17.8, 14.0; IR (neat) 3419, 2958, 2927, 2871, 2798, 2742, 1698, 1619, 1455, 1371, 1311, 1234, 1122, 979, 754; MS (EI) *m/e* 265 (7.5), 222 (6.1), 208 (3.1), 196 (2.0), 180 (9.5), 164 (4.0), 153 (1.5), 139 (18.8), 122 (1.9), 112 (14.0), 95 (2.8), 83 (10.0), 70 (100), 55 (18.9); HRMS (EI) calcd for $C_{16}H_{27}NO_2$ (M^+) 265.2042, found 265.2017.

The keto group of **25** thus obtained was reduced stereoselectively by treatment with tetramethylammonium triacetoxyborohydride and glacial acetic acid in acetone according to the procedure reported by Overman[20c] to provide (+)-allopumiliotoxin 267A [HRMS (EI) calcd for $C_{16}H_{29}NO_2$ (M^+) 267.2198, found 267.3266] in 72% yield (96% yield based on the conversion) with 25% of unreacted **25**. The spectroscopic data were in good agreement with those reported. The calculated overall yield of allopumiliotoxin 267A was 27% (based on conversion yield in the reaction of **25**) from *N*-Boc-L-proline.

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Supporting Information Available: The experimental procedure for preparation of the starting materials **4**, **5**, **8**, **9**, **10**, **11**, **12**, **13**, **14**, **15**, **16**, and **17** and their spectroscopic data, the spectroscopic data of the alcohols derived from **18** by treatment with $NaBH_4$−$CeCl_3$, and ^{1}H NMR charts of **6**, **7**, products from **8**−**13**, **18**−**21**, **25**, and (*R*)-1-bromo-4-methyl-2-octyne (27 pages). See any current masthead page for ordering and Internet access instructions.

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