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Ns strategies: a highly versatile synthetic method for amines

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A highly efficient and versatile synthetic method for amines was established using nitrobenzenesulfonamides (Ns-amides) as both a protecting and activating group. The alkylation of *N*-monosubstituted Ns-amides either proceeded conventionally or under Mitsunobu conditions to provide the *N*,*N*-disubstituted sulfonamides, and the Ns group was removed easily with soft nucleophiles *via* Meisenheimer complexes to give the corresponding secondary amines. The major advantage of this protocol is that both alkylation and deprotection proceed under mild conditions. Thus, with this methodology, the total synthesis of linear and/or macrocyclic natural polyamines can be accomplished efficiently.

Introduction

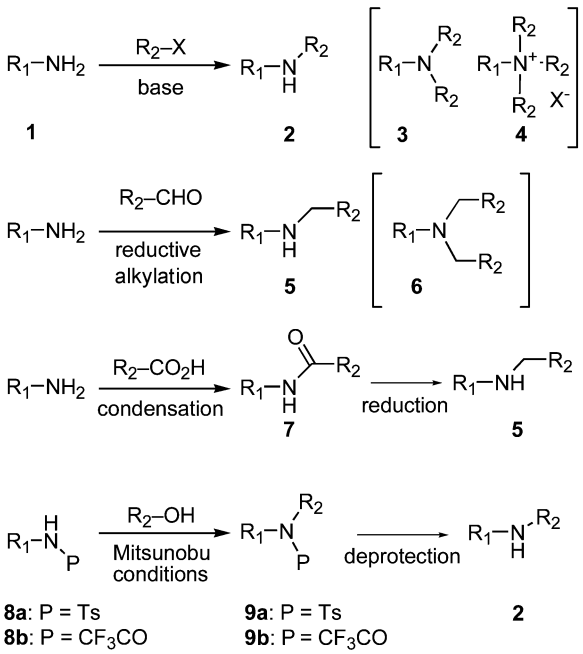
The development of an efficient synthetic method for amines has been an important subject of research, not only in organic chemistry but also in related fields, because these compounds possess an array of interesting biological activities. Although many synthetic investigations have been reported to date,[1,2] there have been only a few efficient installations of a nitrogen atom on to functionalized substrates. The highly polar nature of these compounds makes their handling difficult, and in addition, their instability to oxidation conditions limits their use. Protection of the nitrogen atom would be indispensable in normal chemical transformations and purification and the selection of a proper protecting group would play a vital role.[3]

Professor Toshiyuki Kan was born in Kushiro, Hokkaido, in 1964. He received his Ph.D. in 1993 from Hokkaido University under the direction of Professor H. Shirahama. After spending three years (1993–1995) at the Suntory Institute for Bioorganic Research, he was appointed Assistant Professor of Pharmaceutical Sciences in Professor Fukuyama's group at the University of Tokyo. He received the Incentive Award in Synthetic Organic Chemistry, Japan, in 2002. His current research interest centers on the total synthesis of bioactive natural products and bioorganic chemistry.

Professor Tohru Fukuyama was born in Anjo, Aichi, in 1948. He received his B.A. in 1971 and M.A. in 1973 from Nagoya University. In 1977, he received his Ph.D. from Harvard University under the direction of Professor Y. Kishi. After a year of postdoctoral study at Harvard, he joined the faculty of Rice University as Assistant Professor, and rose to the rank of Full Professor in 1988. In 1995, he moved to the University of Tokyo, where he is currently Professor of Pharmaceutical Sciences. He is the recipient of the ACS Arthur C. Cope Scholar Award (1993), the Synthetic Organic Chemistry Award, Japan (2001), and the ISHC Senior Award in Heterocyclic Chemistry (2003). His research interest is focused on the total synthesis of complex natural products.

Preparation of secondary amines from primary amines

The conversion of primary amines to the corresponding secondary amines appears to be simple, as shown in Scheme 1. Alkylation of



Scheme 1 Conversion of primary amines to the corresponding secondary amines.

primary amines **1** with alkyl halides or sulfonates would seem to provide the desired secondary amines **2**. However, the reaction frequently leads to the formation of the undesired tertiary amines **3** and/or the quaternary ammonium salts **4**. Furthermore, reductive alkylation with aldehydes or ketones using $NaBH_3CN$[4] often produces tertiary amines **6** (to a varying degree), unless the desired secondary amine **5** is sterically hindered. After condensation with a carboxylic acid, reduction of the *N*-monoalkyl amides **7** with strong reducing agents such as $LiAlH_4$, DIBAL, or boranes, appeared to be the most reliable procedure. A recent report described the Mitsunobu alkylation[5] of toluenesulfonamides **8a**[6,7] and trifluoroacetamides **8b** as a method to circumvent these problems. However, due to the relatively harsh deprotection conditions (from **9a**, **b** to **2**), these methods were not suitable for the preparation of base sensitive secondary amines.

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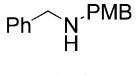
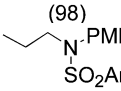
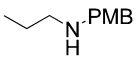
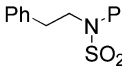
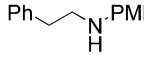
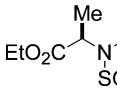
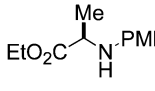
2- or 4-Nitrobenzenesulfonamides[8–10]

Recently, we developed an efficient synthetic methodology for amines by means of nitrobenzenesulfonamides (Ns-amides).[9] An example of the general conversion of primary amines to secondary amines *via* an Ns-group is described in Scheme 2. Protection of the primary amines **10** was performed by treatment with 2-nitrobenzenesulfonyl chloride **11a** and base (triethylamine or pyridine) to give the *N*-monosubstituted nitrobenzenesulfonamides **12** in high yields. The alkylation of the *N*-monosubstituted nitrobenzenesulfonamides **12** proceeded smoothly under either conventional alkylation (R–X) or Mitsunobu conditions (R–OH) to give the *N*,*N*-disubstituted sulfonamides **13** in excellent yields. Facile deprotection of **13** was accomplished by treatment with thiolate nucleophiles, presumably *via* the formation of the Meisenheimer complex (**14**), and produced the desired secondary amines **15**. Representative examples of this method are summarized in Table 1. It should be noted that no racemization was observed with this procedure during reactions with (−)-ethyl lactate. Although 4-nitrobenzenesulfonyl chloride (**11b**) has a reactivity similar to that of **11a**, we recommend the use of **11a** because it is inexpensive.

Table 1 Alkylation of **12** and deprotection of **13**

RX or ROH	Alkylation conditions[a]	**13** (%)	**15**[b] (%)
Ph–Br	A	 (98)	 (94)
Br	B	 (98)	 (94)
Ph–OH	C	 (91)	 (88)
Me, CO_2Et	D	 (87)	 (93)

[a] A: RX (1.1 equiv.), K_2CO_3 (2 equiv.), DMF. B: RX (1.1 equiv.), K_2CO_3 (2 equiv.), DMF, 60 °C. C: ROH (1.3 equiv.), DEAD (1.3 equiv.), PPh_3 (1.3 equiv.), CH_2Cl_2. [b] Deprotection conditions: PhSH (1.2 equiv.), K_2CO_3 (3 equiv.), DMF.

2,4-Dinitrobenzenesulfonamides[11]

2,4-Dinitrobenzenesulfonamides also share a similar reactivity with the Ns-group in alkylations, as shown in Table 2. However, because of the instability of the DNs-group under basic conditions at high temperatures, deprotection was carried out under milder conditions, MA ($HSCH_2CO_2H$ and Et_3N). This procedure is convenient because the by-product, 2,4-dinitrophenylthioacetic acid, can be removed by washing the ethereal layer with an aqueous $NaHCO_3$ solution. Thus the amine can be obtained almost pure without chromatographic separation. The particular advantage of the DNs-group is its selective deprotection in the presence of an Ns-group. As shown in Scheme 3, treatment of the dinitrobenzenesulfonamide **16** with $HSCH_2CO_2H$ and Et_3N gave the desired amine **17** in nearly quantitative yield.

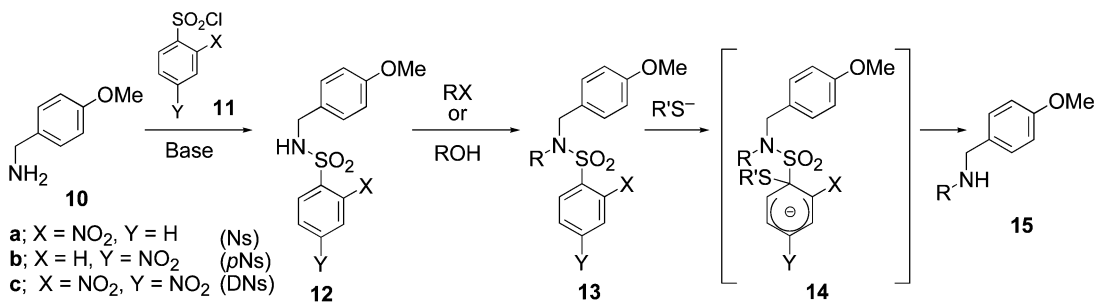
Table 2 Alkylation and deprotection of 2,4-dinitrobenzenesulfonamide **12c**

R′X or R′OH	Alkylation[a] Yield (%)	Deprotection[b] Yield (%) PA	MA
Ph–Br	A 87	91	91
I	B 89	91	97
Me, CO_2Et, OH	C 96	92	94

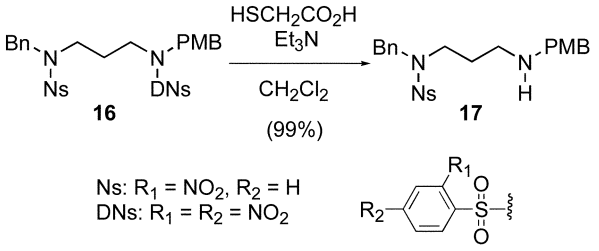
[a] Alkylation conditions, A: R′X (1.5 equiv.), K_2CO_3 (5 equiv.), DMF. B: R′OH (2 equiv.), DEAD (2 equiv.), PPh_3 (2 equiv.), benzene. [b] Deprotection conditions, PA: *n*-$PrNH_2$ (20 equiv.), CH_2Cl_2. MA: $HSCH_2CO_2H$ (1.3 equiv.), LiOH (2 equiv.), CH_2Cl_2.

Synthesis of protected primary amines (*N*-carboalkoxy-2-nitrobenzenesulfonamides)[12]

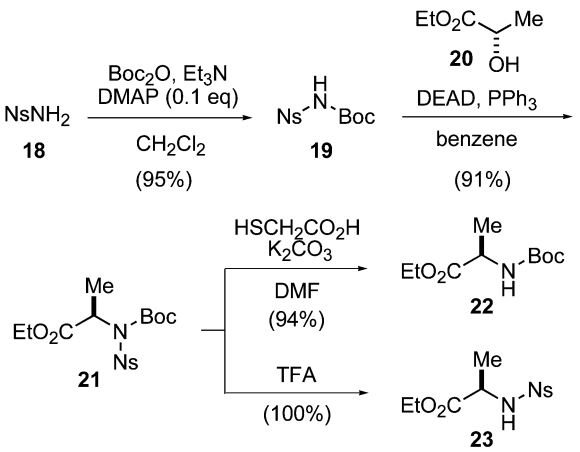
The transformation of primary alcohols and alkyl halides to the corresponding amines also has been an important subject in organic chemistry. While the Gabriel synthesis[13] and direct conversion to azides have been occasionally used, few practical methods for the direct preparation of *N*-protected primary amines are available. Recently, alkylation of *N*-Boc-*p*-toluenesulfonamide[6] and *p*-toluenesulfonamide, by means of the Mitsunobu and the modified Mitsunobu reactions[14] respectively, has been reported. However, these methods are limited in scope because deprotection of *p*-toluenesulfonamides required harsh conditions. We expected that the mild deprotection conditions of the Ns-group would allow the use of more valuable nitrogen nucleophiles. 2-Nitrobenzenesulfonamide (**18**), readily available from NsCl and NH_3, was converted to the corresponding carbamate **19**. Alkylation of **19** was performed by conventional alkylation and under Mitsunobu conditions. An example of a Mitsunobu reaction of **19** with (−)-ethyl lactate (**20**) is described in Scheme 4. Both the 2-nitrobenzenesulfonamide and the Boc group of alkyl sulfonamide **21** can be selectively deprotected without affecting other functional groups. Deprotection of the Ns-group of **21** was achieved by treatment with $HSCH_2CO_2H$ and K_2CO_3 in DMF to give the *N*-Boc amine **22**. Alternatively, treatment of **21** with excess trifluoroacetic acid afforded the *N*-monoalkylated sulfonamide **23**. The *N*-Boc amine **22** can be converted to primary amines, and the sulfonamide **23** in turn could serve as a precursor for secondary amines. Additionally,



Scheme 2 Conversion of primary amines to the corresponding secondary amines *via* nitrobenzenesulfonamides.



Scheme 3 Selective deprotection of DNs group.



Scheme 4 Alkylation and deprotection of *N*-Boc-Ns-amides.

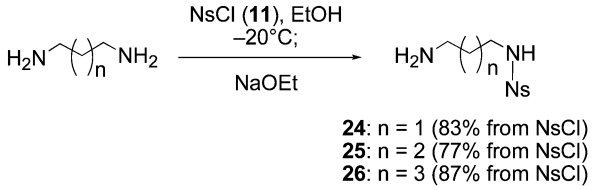
N-Alloc and *N*-Cbz protected sulfonamides were also readily prepared from **18** and possessed a reactivity similar to that of **19**. However, selective deprotection of the Cbz group in the presence of the Ns group required the use of BCl_3, because the nitro group could not survive the hydrogenolysis conditions.

Synthesis of polyamine natural products

With the recent advance of micro-analytical technology, many polyamines have been isolated from natural sources.[15] These polyamines are responsible for a variety of important biological activities, yet in spite of the many reports on the synthetic studies of these compounds, few versatile syntheses of secondary amines exist. We anticipated that the use of the Ns-strategy would enable a highly efficient synthesis.

Selective mono-nosylation of diamines[16,17]

Monoprotected diamines seemed to be ideal starting materials for incorporation into a polyamine chain. Though selective protection and purification of diamines is reported to be difficult,[18] the Ns-group provided good results. As shown in Scheme 5, treatment of



Scheme 5 Selective mono-nosylation of diamines.

1,3-diaminopropane with NsCl (**11**), followed by neutralization with NaOEt afforded the monosulfonyl adduct **24** in high yield. This procedure was applied to other diamines to provide the sulfonamides **25** and **26**. These compounds could be useful as key building blocks for the preparation of polyamines.[19]

Total synthesis of spider toxin HO-416b (27)[16,17]

Polyamine toxins derived from spider venom have been shown to be specific glutamate receptor blockers.[20] They are expected to be useful as tools for studying neurophysiology and as lead structures for pharmacological and agrochemical agents.[21] Recently, we accomplished the efficient total synthesis of HO-416b (**27**; Fig. 1),[22] which was isolated from the venomous spider *Hololena curta*, utilizing the Ns-strategy.

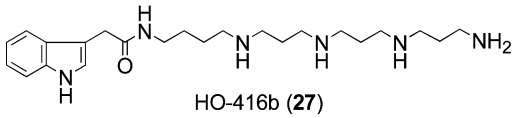
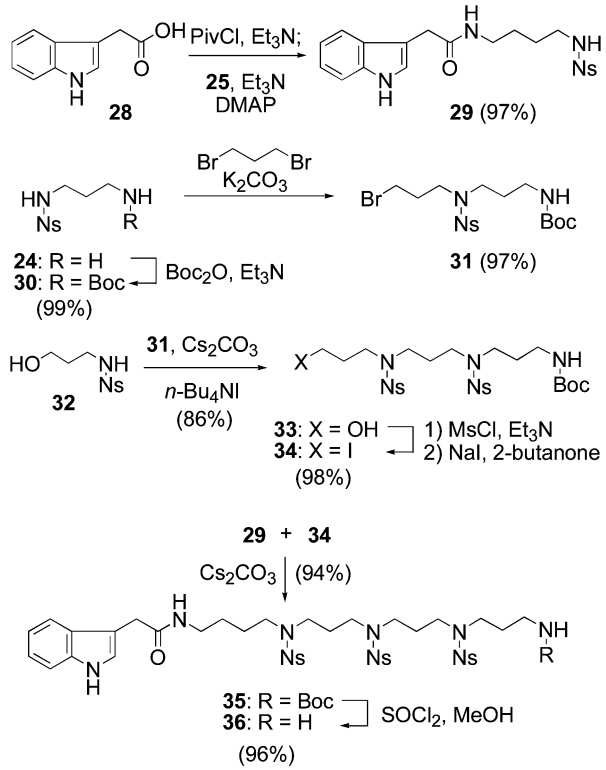


Fig. 1 Structure of HO-416b (**27**).

As shown in Scheme 6, the left-hand fragment **29** was obtained by condensation of 3-indoleacetic acid (**28**) and **25** under mixed-

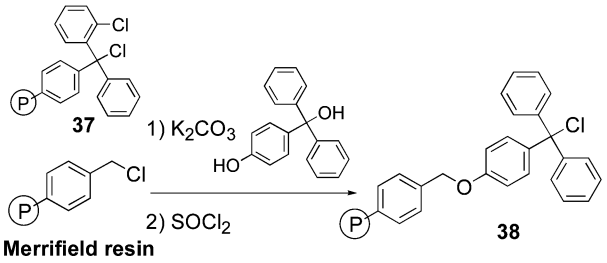


Scheme 6 Total synthesis of HO-416b.

anhydride conditions. The synthesis of the right-hand segment began with the monoprotected diamine **24**. Treatment of **24** with Boc_2O followed by selective alkylation with 1,3-dibromopropane afforded the bromide **31**. The sulfonamide **32** was converted to the right-hand triamine **34** by treatment with **31** and Cs_2CO_3. After conversion of the alcohol **33** to the iodide **34** by mesylation and iodide displacement, the alkylation of the sulfonamide **29** proceeded smoothly on treatment with Cs_2CO_3, to provide **35**. Subsequent removal of the Boc group under acidic conditions gave the primary amine **36**.

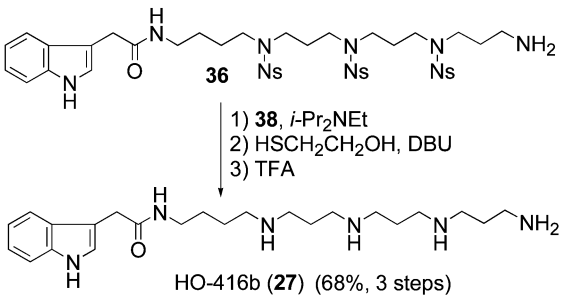
Removing the Ns-group of **36** readily provided the natural product, but the purification of the highly polar polyamine **27** was difficult. Usually, purification of water-soluble polyamines is carried out by reverse-phase HPLC and/or ion-exchange resins. In comparing these methods, the use of solid phase supports was attractive due to the simple isolation of highly polar compounds. Yet initial attempts to load **36** onto a commercially available 2-chlorotrityl chloride resin (**37**) were inefficient. Thus, we prepared the resin **38** with the hope that it would be more reactive,

since a phenol unit separated the bulky polystyrene support from the reactive site, and an alkoxy group stabilized the trityl cation. Treatment of Merrifield resin with *p*-hydroxytrityl alcohol[23] and K_2CO_3, followed by reaction with $SOCl_2$, afforded the desired resin **38** (Scheme 7).



Scheme 7 Synthesis of trityl-type resin.

Linkage of the Ns-protected HO-416b **36** to the resin **38** was induced by *i*-Pr_2NEt (Scheme 8). Upon treatment of the resin with



Scheme 8 Total synthesis of HO-416b (**27**).

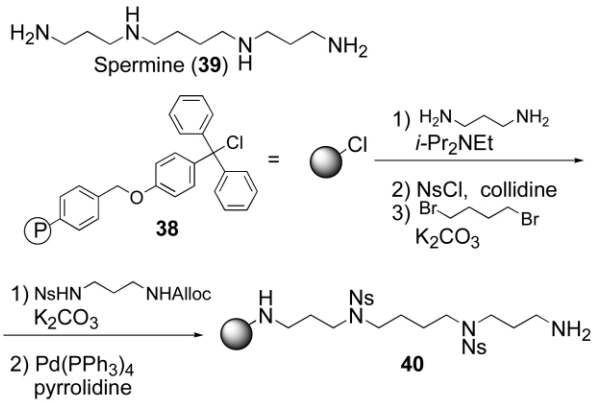
2-mercaptoethanol and DBU,[24] the Ns groups were removed. Cleavage from the resin under acidic conditions (1% TFA–CH_2Cl_2) and evaporation of the solvent provided **27** without the need for any chromatographic purification. The ^1H and ^{13}C NMR spectral data of **27** indicated the presence of highly pure material. Thus, we completed the total synthesis of HO-416b (**27**) in 11 steps and 41% overall yield from the diamine.

Solid-phase synthesis of philanthotoxin-343 (41)[25]

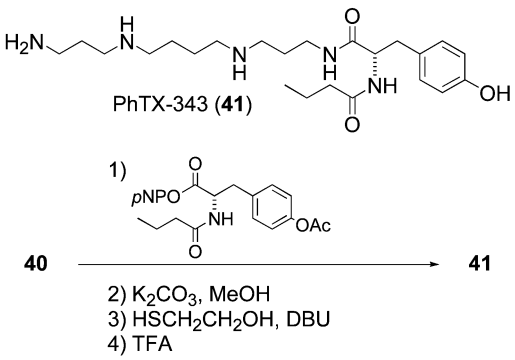
Polyamines, such as spermidine and spermine, are natural products found in microorganisms, plants, and animals and are responsible for a variety of important biological activities.[26] They interact with nucleic acids and play an important role in DNA synthesis and cell proliferation. In addition, many of their conjugates have potential for pharmacological use. Inspired by our development of a resin **38** that is easy to use, we set to work to develop a solid-phase synthesis of polyamines, which would enable the facile construction of a diverse library. To test the feasibility of our protocol, we decided to synthesize the spermine backbone **40**.

First, we attached 1,3-diaminopropane to the resin **38** in the presence of *i*-Pr_2NEt, and then activated the less-hindered amine with NsCl (Scheme 9). Elongation of the polyamine chain was performed by stepwise alkylation with 1,4-dibromobutane and the sulfonamide. Removal of the Alloc group of the spermine backbone gave the primary amine **40**. The polymer-bound **40** is a valuable intermediate for the synthesis of numerous spermine conjugates, since alkylation with R_1-X *via* the Ns-strategy, or acylation with R_2-COX of the primary amine **40** is expected to proceed smoothly.

To demonstrate the utility of this protocol, we investigated the synthesis of PhTX-343 (**41**). The spermine conjugate polyamine PhTX-343 (**41**) is a synthetic analogue of the natural toxin PhTX-433 isolated from the digger wasp *Philanthus triangulum*, which is known to be a noncompetitive antagonist for nicotinic acetylcholine receptors (nAChRs) and ionotropic glutamate receptors (iGluRs).[27] Our synthesis, which began with the condensation of **40** with the protected tyrosine activated ester (Scheme 10), proceeded



Scheme 9 Synthesis of polymer-bound spermine.



Scheme 10 Total synthesis of PhTX-343.

smoothly. Following methanolysis of the acetate, the deprotection of the Ns group was effected by treatment with 2-mercaptoethanol and DBU. Final cleavage from the resin was performed under acidic conditions (1% TFA–CH_2Cl_2). Upon removal of the solvent, **41** was obtained in high purity. The whole sequence of transformations from **38** to **41** (9 steps and 75% overall yield) was carried out without any purification.

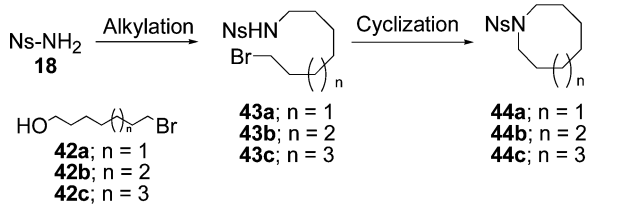
Synthesis of cyclic polyamines

The construction of cyclic amines also is an important task in organic synthesis, because these structural units often are found in the framework of a variety of medicinally interesting natural products. While many synthetic methods have been reported, few are available for the construction of medium- or large-sized rings. During the course of our total synthesis of lipogrammistin-A, we found that an intramolecular alkylation with the Ns-group provided an efficient method for macrocyclization.

Construction of medium-sized rings[28,29]

First, we investigated the construction of medium-sized cyclic amines, using non-branched, simple substrates, as shown in Table 3. Coupling between the sulfonamide **18** and the ω-bromoalcohols **42a–c** was carried out under Mitsunobu conditions to give predominantly the mono-alkylated products **43a–c**. Preliminary studies on the cyclization of **43a–c** revealed that to achieve reasonable yields, high-dilution conditions (0.01 M) are preferable. Thus, when an acetonitrile solution of **43a–c** was added slowly (2 h) by means of a syringe pump to a mixture of tetrabutylammonium iodide and Cs_2CO_3 in acetonitrile at 60 °C, the cyclization proceeded smoothly to give the desired products **44a–c** in good yields.

Table 3 Cyclization *via* conventional alkylation

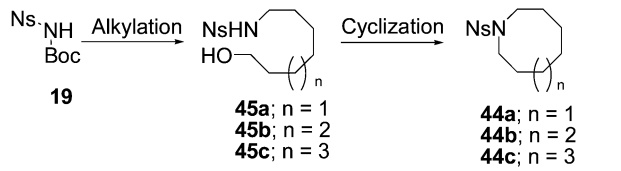


Ring size	Alcohol	Alkylation[a] (Yield %)	Cyclization[b] (Yield %)
		43a	**44a**
8	**42a**	(70)	(62)
		43b	**44b**
9	**42b**	(67)	(64)
		43c	**44c**
10	**42c**	(74)	(66)

[a] Alkylation conditions: PPh_3, DEAD, toluene–THF. [b] Cyclization conditions: Cs_2CO_3, CH_3CN, *n*-Bu_4NI, 60 °C.

In order to perform a similar cyclization under Mitsunobu conditions, the precursors **45a–c** were prepared from the *N*-Boc-nitrobenzenesulfonamide **19** (Table 4). When the mixture of **19** and

Table 4 Cyclization *via* Mitsunobu reaction



Ring size	Bromide	Alkylation[a] (Yield %)	Cyclization[b] (Yield %)
		45a	**44a**
8	**42a**	(66)	(59)
		45b	**44b**
9	**42b**	(85)	(57)
		45c	**44c**
10	**42c**	(62)	(62)

[a] Alkylation conditions: 1) K_2CO_3, *n*-Bu_4NI, DMF, 60 °C; 2) TFA, CH_2Cl_2; 3) K_2CO_3, MeOH. [b] Cyclization conditions: PPh_3, DEAD, toluene–THF.

the bromides **42a–c** was heated with K_2CO_3 in DMF, the alkylation proceeded smoothly to give the *N*-Boc protected precursors. Subsequent deprotection of the Boc group with trifluoroacetic acid and methanolysis of the trifluoroacetate, which was formed during the deprotection, provided the cyclization precursors **45a–c**. Upon treatment of **45a–c** with DEAD and triphenylphosphine in 0.01 M solution of toluene–THF at room temperature, the desired cyclization reaction afforded **44a–c** in moderate yields. In both ring closures (Tables 3 and 4), the cyclization successfully occurred without the aid of a branching effect.[30]

Thus, the Ns-strategy proved to be a powerful method for the construction of medium-sized rings, because it was able to override the inherent entropic disadvantage of the ring closure. With these successful results in hand, we turned our attention to applying the Ns-strategy to the synthesis of cyclic natural products, such as the many macrocyclic polyamine alkaloids which have been isolated from plants and marine sources and which have been shown to exhibit interesting biological activity.[31]

Total synthesis of lipogrammistin-A (46)[32]

Lipogrammistin-A (**46**; Fig. 2) was isolated from the skin mucus of the grammistid fish by Fusetani and Tachibana[33] on the basis of

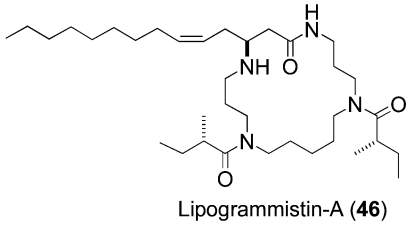
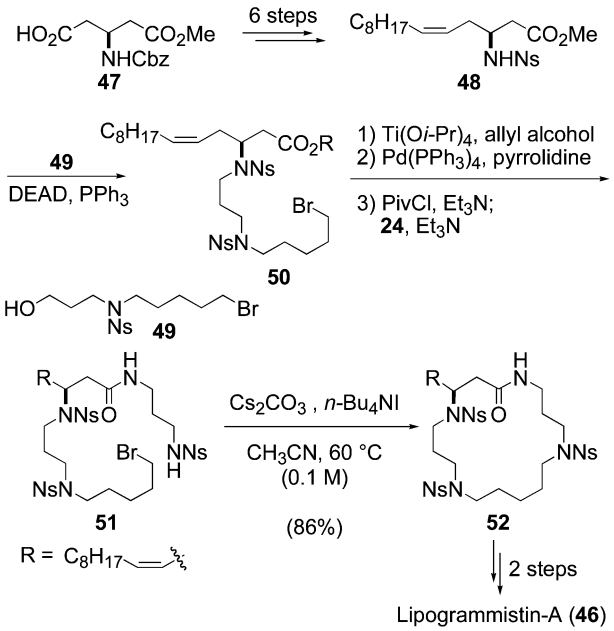


Fig. 2 Structure of lipogrammistin-A (**46**).

extensive NMR studies. One of the key structural features of **46** is the acylated polyamine lactam ring.

We began our total synthesis of lipogrammistin-A (**46**) with the carboxylic acid **47**[34] (Scheme 11). Preparation of the Ns-amide **48**

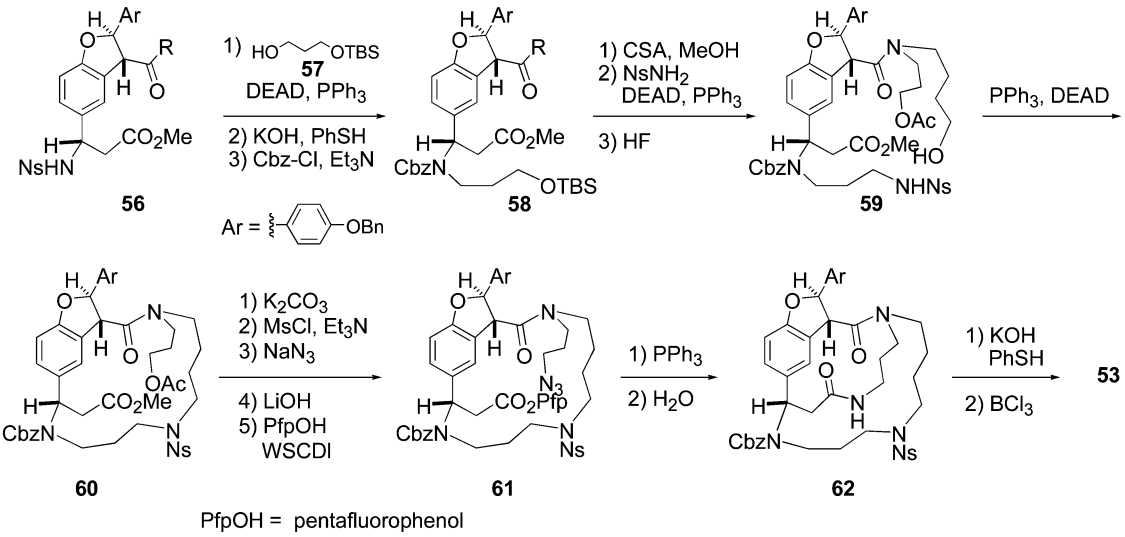


Scheme 11 Total synthesis of lipogrammistin-A.

from **47** was performed by reduction of the thiol ester with triethylsilane and 10% Pd on C and a Wittig reaction as the key steps. Coupling between the sulfonamide **48** and the alcohol **49** was effected under standard Mitsunobu conditions to give **50** in excellent yield. Since the undesired β-elimination of the alkylsulfonamide in **50** occurred under alkaline hydrolysis conditions, conversion of the methyl ester to the carboxylic acid was carried out in a two-step sequence. Condensation of the carboxylic acid and the amine **24** was done in a conventional manner to give the amide **51**. Upon heating a mixture of the sulfonamide **51**, tetrabutylammonium iodide, and Cs_2CO_3 in acetonitrile at 60 °C, the cyclization proceeded smoothly to give predominantly the desired product **52** in 86% yield. The ring closure was successfully performed even at 0.1 M concentrations, obviating the need for high-dilution conditions. Removal of the three Ns-groups and diacylation with (*S*)-2-methylbutyric acid and BOPCl gave **46**. Thus, we accomplished the total synthesis of lipogrammistin-A (**46**), starting with the carboxylic acid **47**, in a 13-step sequence in 12% overall yield.

Total synthesis of (−)-ephedradine A (53)[35]

(−)-Ephedradine A (orantine, **53**; Fig. 3) is a complex macrocyclic spermine alkaloid, which was isolated by Hikino and co-workers in 1979 as one of the hypotensive components of the traditional Chinese drug "mao-kon".[36,37] While the synthesis of the racemic



Scheme 12 Total synthesis of (−)-ephedradine A.

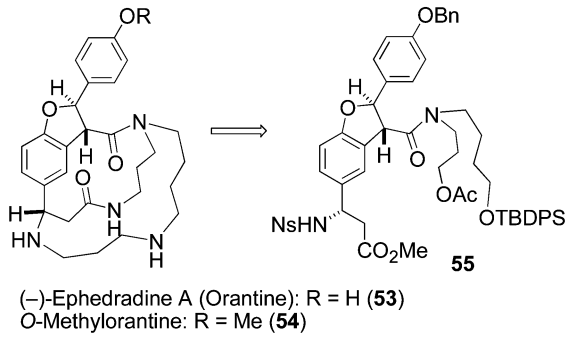


Fig. 3 Structure of (−)-ephedradine A.

O-methylated orantine (**54**) was achieved by Wasserman and co-workers in 1985,[38] no total synthesis of **53** has been reported to date. Clearly, construction of the two macrocyclic rings in the presence of a labile dihydrobenzofuran moiety constitutes the major challenge in the total synthesis of **53**. Recently, we accomplished an efficient total synthesis of (−)-ephedradine A (**53**) by the stereocontrolled synthesis of the optically active intermediate **55** and the subsequent construction of the macrocyclic polyamine ring using the Ns-strategy.

The key intermediate **56** was synthesized by the construction of the optically active dihydrobenzofuran ring, *via* an intramolecular C–H insertion reaction,[39,40] and the installation of the β-amino ester, utilizing the Sharpless asymmetric aminohydroxylation reaction.[41] As shown in Scheme 12, the construction of all the secondary amines of **53** was accomplished using the Ns-strategy, including macrocyclization. Coupling between the sulfonamide **56** and the alcohol **57** under Mitsunobu conditions, followed by switching the protecting group of the amine to the corresponding *N*-Cbz derivative yielded **58**. Acid-catalyzed selective deprotection of the TBS group, coupling with $NsNH_2$ under Mitsunobu conditions, and subsequent cleavage of the TBDPS ether, furnished the cyclization precursor **59**. Upon treatment of **59** with DEAD and PPh_3 in 0.05 M solution of toluene at room temperature, the desired cyclization proceeded smoothly to afford **60** in 77% yield. The construction of the 13-membered macrolactam ring was carried out using the Staudinger[42] and the intramolecular aza-Wittig reactions[43,44] of the azide-pentafluorophenyl ester **61**. Subsequent hydrolysis of the 13-membered iminoether by refluxing in H_2O afforded the desired macrolactam **62**. Finally, removal of the Ns group and simultaneous cleavage of the Cbz group and benzyl ether with BCl_3 yielded (−)-ephedradine A (**53**).

Conclusion

In this article, we report a highly efficient and versatile synthesis of amines by use of the nitrobenzenesulfonamide as both an activating and protecting group (Ns-strategy). Since the Ns-group is stable under acidic [HCl (10 equiv.), MeOH, 60 °C, 4 h] as well as basic [NaOH (10 equiv.), MeOH, 60 °C, 4 h] conditions, it can be used extensively for the protection of primary and secondary amines. Furthermore, the amazing alkylating ability of Ns-amides under mild conditions (solid-phase and macrocyclization[45]) makes possible the efficient total synthesis of natural products. Because the Ns-chemistry described here is applicable to amines in both natural products and medicinal chemistry,[46] we hope that this versatile method will be useful to many chemists.

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