α-Lithioamine Synthetic Equivalents: Syntheses of Diastereoisomers from Boc Derivatives of Cyclic Amines

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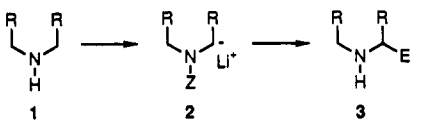
Sequences of α′-lithiations and electrophilic substitutions of Boc-pyrrolidines, Boc-piperidines, and Boc-hexahydroazepines that provide compounds which are substituted adjacent to nitrogen are reported, and the pathways of the reactions are discussed. By this methodology monosubstituted 2 and disubstituted 2,4, 2,6, and 2,5 Boc-piperidines are obtained as single or separable diastereoisomers consistent with equatorial lithiations and retentive electrophilic substitution in chair conformations. Both cis and trans 2,6-disubstituted diastereoisomers can be prepared, and control of diastereoselectivity is demonstrated by syntheses of solenopsin A, a 2,6-trans-disubstituted piperidine, and of Boc-dihydropinidine, a 2,6-cis-disubstituted piperidine. In the case of 3-methoxy-Boc-piperidine elimination of methoxide occurs upon lithiation, and with cis-2,4-disubstituted Boc-piperidines the electrophile is introduced with trans stereochemistry at C-6. These reactions are suggested to involve twist boat conformations consistent with an X-ray crystal structure of 2-methyl-6-(trimethylstannyl)-4-phenyl-*N*-Boc-piperidine. Boc-pyrrolidine lithiates more rapidly than Boc-piperidine, provides 2-substituted products with electrophiles, and on further lithiation–substitution gives 2,5-cis- and -trans-substituted products. Boc-perhydroazepine provides 2-substituted products by the sequence and on further lithiation–substitution gives 2,7-trans-disubstituted products.

Introduction

The elaboration of amines by the sequence of substitution of an activating group on nitrogen, α′-lithiation to give a dipole stabilized carbanion, electrophilic substitution, and removal of the activating group is illustrated for the conversion of 1 to 3 via the α-lithioamine synthetic equivalent 2. The advantages of this methodology over classical amine syntheses has led to investigation of the approach for a number of systems.[1] For saturated amines the sequence has been investigated most fully with the amide, formamidine, oxazoline, or nitroso functions as the activating groups.[1] Early work showed the amide to be effective in the combination of induction and complexation which is involved in dipole stabilization, and the stereochemical course of the sequence was investigated for piperidide derivatives.[1,2] However, the conditions required for the addition and removal of the amide were strenuous, and in recent years the formamidine group has been more fully developed for synthetic applications.[3,4] The experience in these studies has been that derivatives of cyclic secondary amines, particularly piperidine, are a demanding and informative test of the methodology.[2-6]



1 2 3

We have recently reported that the readily available *tert*-butoxycarbonyl (Boc) group, which is convenient to add and remove and safe to use, can be an effective activator for the elaboration of 1 to 3.[7] In this paper we report the preparation of single or separable diastereomers of mono-, di-, and trisubstituted Boc derivatives of saturated cyclic amines by this approach, illustrate the methodology by the syntheses of substituted piperidines, including three piperidine alkaloids, and discuss the course of these reactions.

Results

We prepared the Boc derivatives of the cyclic secondary amines by reaction of the amine with BocOBoc under standard conditions. The lithiations were carried out with *s*-BuLi/TMEDA at −78 °C in diethyl ether for 2 h and the electrophiles added to the cold reaction solutions before warming to ambient temperature and isolation of the products. The products were characterized by NMR, elemental analysis, and X-ray characterization as indicated, and the yields are for analytically pure material unless otherwise noted.

Boc-pyrrolidines. The lithiation and electrophilic substitutions of *N*-Boc-pyrrolidine (4) gives the 2-substituted products 5–8 in the yields indicated. Similar substitutions of trimethylsilyl and tributyltin groups have been reported previously.[7b] The alcohol 8 is an ca. equimolar mixture of anti and syn isomers, similar to our earlier experience.[7]

The lithiation of 2-methyl-*N*-Boc-pyrrolidine (5) takes place at the 5 position, and electrophilic substitutions give 9–11 as mixtures of cis and trans isomers. The assignment of stereochemistry to the mixture of 2,5-dimethyl-Boc-pyrrolidines was made by conversion to the *N*-benzyl derivatives which were separated and examined by ^{1}H NMR following the approach used by Hill for the

(1) (a) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* 1984, *84*, 471. (b) Gawley, R. E.; Rein, K. *Comprehensive Organic Chemistry*; Trost, B., Ed.; Pergamon Press: Oxford, England, 1991; Vol. 1., p 459, Vol. 3, p 65.

(2) (a) Beak, P.; Zajdel, W. J. *J. Am. Chem. Soc.* 1984, *106*, 1010. (b) Beak, P.; Reitz, D.; Tse, A. *J. Org. Chem.* 1981, *46*, 4316.

(3) Meyers, A. I. *Aldrichim. Acta* 1985, *18*, 59.

(4) Meyers, A. I.; Edwards, P. D.; Rieker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* 1984, *106*, 3270 and references cited therein.

(5) Gawley, R. E.; Hart, G. C.; Bartolotti, L. J. *J. Org. Chem.* 1989, *54*, 175 and references cited therein.

(6) Seebach, D.; Huber, I. M. P.; Syfrig, M. A. *Helv. Chim. Acta* 1987, *70*, 1357 and references cited therein.

(7) (a) Beak, P.; Lee, W. K. *Tetrahedron Lett.* 1989, *30*, 1197. (b) Beak, P.; Lee, W. K. *J. Org. Chem.* 1990, *55*, 2578.

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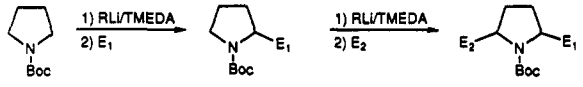
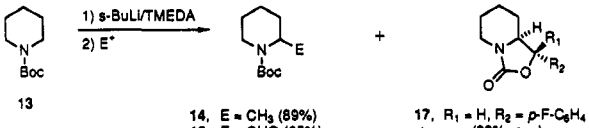
corresponding piperidines.[8] The cis compound, which has a plane of symmetry, shows equivalent benzylic protons in the ^1H NMR spectrum, whereas the trans compound, which is of C_2 symmetry, has nonequivalent benzylic protons. This assignment is supported by the ^{13}C NMR spectra of these isomers which shows the cis compound to have equivalent methyl groups at C-2 and C-5 carbons while the spectrum of the trans compound shows these position to be nonequivalent. Elaboration of a substituent was demonstrated by conversion of **7** to a 10:1 mixture of the *Z*:*E* isomers of **12** by a Wittig reaction.



4

5, E_1 = CH_3 (87%)
6, E_1 = CH_2-CH=CH_2 (34%)
7, E_1 = CHO (82%)
8, E_1 = p-$OCH_3C_6H_5CHOH$
12, E_1 = $CH=CH(CH_2)_2CH_3$ (63% from 7)
21, E_1 = $(CH_3)_3Si$ (92%)
9, E_1 = E_2 = CH_3 (72%, 2:1 *cis:trans*)
10, E_1 = CH_3, E_2 = $Si(CH_3)_3$ (93%)
11, E_1 = CH_3, E_2 = D (81%)

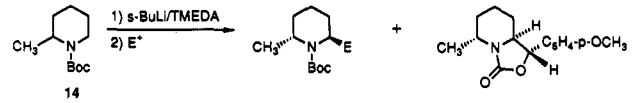
Boc-piperidine. Monosubstitutions of *N*-Boc-piperidine (**13**) are shown for the conversion of **13** to **14–17**. The 2-methyl-*N*-Boc-piperidine (**14**), obtained in 89% yield with dimethyl sulfate and in 54% yield with methyl triflate, was not a detectable product with methyl iodide as the electrophile. Reaction with dimethyl formamide gave the expected aldehyde **15** which can be elaborated via Wittig reactions to longer chain alkylated products (vide infra). The use of 4-fluorobenzaldehyde as the electrophile provided the anti and syn products **16** and **17**, respectively. Basic hydrolyses of these products gave the corresponding amino alcohols. Eight similar substitutions of **13** with other aldehydes and with trimethylsilyl, tributyltin, and thiophenyl groups have been reported.[7b] Formation of the α'-lithio-Boc-piperidide in the absence of TMEDA by tin–lithium exchange of **18** with *n*-BuLi and subsequent reaction with acetophenone and cyclohexanone gave **19** and **20**, respectively. A competitive lithiation between the pyrrolidine and piperidine derivatives was carried out by treatment of equimolar **4** and **13** with 0.5 equiv of *s*-BuLi/TMEDA followed by TMSCl. The product ratio of **21**:**22** of 35:1 indicates that **4** is considerably more reactive toward lithiation than is **13**.



13

14, E = CH_3 (89%)
15, E = CHO (65%)
16, E = p-F-C_6H_4CHOH (31%, *anti*)
18, E = $(n\text{-}C_4H_9)_3Sn$ (100%)
22, E = $(CH_3)_3Si$ (94%)
17, R_1 = H, R_2 = p-F-C_6H_4 (23%, *syn*)
19, R_1, R_2 = CH_3, C_6H_5 (87% from 18)
20, R_1, R_2 = $(CH_2)_3$ (78% from 18)

2-Methyl-Substituted Boc-piperidine. The lithiation of *N*-Boc-2-methylpiperidine (**14**) with *s*-BuLi/TMEDA at C-6 and reaction with electrophiles provides the *trans*-2,6-disubstituted piperidines **23–27**. The reaction with aromatic aldehydes provides substitution product as a mixture of anti and syn isomers.[7] When the reaction with benzaldehyde is quenched at −78 °C, both isomers are obtained as benzylic alcohols. When the reaction mixture from reaction with *p*-methoxybenzaldehyde is allowed to warm −20 °C and maintained at that temperature for 30 min, the syn isomer selectively cyclizes to the bicyclic carbamate **25**. Cyclized and uncyclized



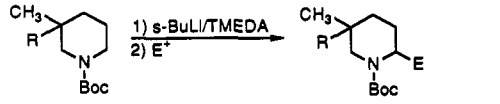
14

23, E = C_6H_4CHOH (*anti* 49%, *syn* 47%)
24, E = p-OCH_3-C_6H_4CHOH (*anti* 57%)
26, E = D (90%)
27, E = CHO (87%)
25, (41%)

products are easily separated by chromatography, and both carbamates are readily hydrolyzed by sodium hydroxide in ethanol to give the anti and syn amino alcohols. The reactions of the *N*-Boc-6-lithio-2-methylpiperidine to give methyl, trimethyltin, trimethylsilyl, phenylthio, and *p*-methoxyhydroxybenzyl-substituted compounds have been reported.[7b] The stereochemistry of *N*-Boc-2,6-dimethylpiperidine was determined by comparison of the benzamide to authentic samples of the *cis*- and *trans*-2,6-dimethylpiperidines.[8] The reaction of 2-lithio-6-methylpiperidine with dimethyl formamide (DMF) provides carboxaldehyde products as an 8/1 mixture of trans and cis isomers. The initially formed trans carboxaldehyde epimerizes during chromatography on silica gel which had been treated with Et_3N, and the trans/cis ratio changes to 1/5 after chromatography. By careful chromatography the two isomers can be separated (vide infra).

Attempted lithiation of the *N*-Boc-*trans*-6-deuterio-2-methylpiperidine (**26**) under standard lithiation condition (*s*-BuLi/TMEDA) followed by reaction with trimethylsilyl chloride did not provide any silylated product, and the deuterated material **26** was recovered. A competition experiment between equal amounts of **14** and **26** carried out under standard lithiation condition with 2.4 equiv of *s*-BuLi/1 equiv of TMEDA and 2.4 equiv of trimethylsilyl chloride as the electrophile provided silylated product only from the protio material **14**, and the d_1 material **26** was recovered almost quantitatively. This experiment establishes that the lithiation requires an equatorial proton and that there is a significant deuterium isotope effect in these lithiations of the Boc-piperidines.

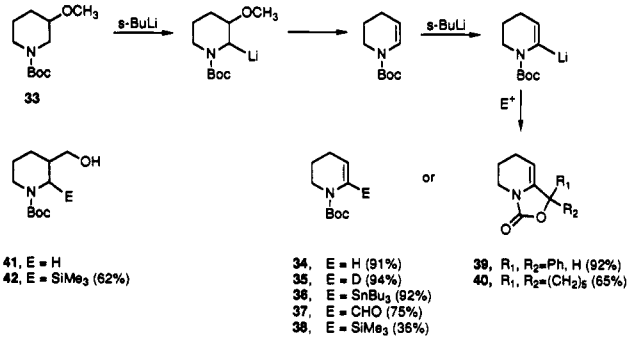
3-Substituted Boc-piperidines. Boc derivatives of 3-substituted piperidines were used to determine the regiochemistry and diastereoselectivity of lithiation substitution for unsymmetrical piperidines. The lithiation of *N*-Boc-3-methylpiperidine (**28**) with 1.2 equiv of *s*-BuLi in the presence of 1 equiv of TMEDA takes place at C-6, and reaction with DMF provides 44% of the substitution product **29** as a mixture of cis and trans isomers. When the electrophile is dimethyl sulfate the dimethylation product **30** is obtained in 34% yield as determined by GC. The stereochemistry of **30** was assigned to be trans based on coupling constants of the protons next to nitrogen but the compound was contaminated with **28**. Lithiation of *N*-Boc-3,3-dimethylpiperidine (**31**) followed by reaction with dimethyl sulfate provided *N*-Boc-2,5,5-trimethylpiperidine (**32**).



28, R = H
31, R = CH_3
29, R = H, E = CHO (44%)
30, R = H, E = CH_3 (34%)
32, R = CH_3, E = CH_3 (73%)

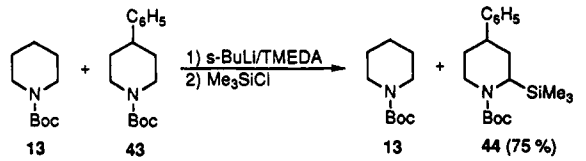
(8) (a) Hill, R. K.; Chan, T. H.; Joule, J. A. *Tetrahedron* **1965**, *21*, 2015. (b) For a previous application of the method to 2,5-disubstituted pyrrolidines see: Arseniyadis, S.; Huang, P. Q.; Piveteau, D.; Hussan, H. D. *Tetrahedron* **1988**, *21*, 2457.

N-Boc-3-methoxypiperidine (**33**) was prepared to test the effect of the methoxy functionality, a well-established lithiation director.[9] Reaction of **33** with 2.1 equiv of *s*-BuLi/TMEDA or 2.1 equiv of *s*-BuLi revealed that reaction occured rapidly at −78 °C at C-2; however, the methoxy group was eliminated to provide the Boc-tetrahydropyridine which undergoes further lithiation, as shown by the formation of the vinyl-substituted products **34–40**.[10]



N-Boc-3-(hydroxymethyl)piperidine (**41**) can be lithiated with 2 equiv of *s*-BuLi in the presence of 1 equiv of TMEDA, and reaction with trimethylsilyl chloride provides **42** the substitution product at C-2. However, reaction with dimethyl sulfate did not give the expected product.[11]

4-Substituted Boc-piperidines. The lithiations and substitution products of the 4-phenyl, 4-*tert*-butyl, 4-methyl, and 4-ethylene ketal substituted Boc-piperidines have been shown to give cis-2,4-disubstituted piperidine derivatives.[7b] Although 2-lithio-*N*-Boc-piperidine did not provide a methylation product on reaction with methyl iodide (vide supra), 2-lithio-*N*-Boc-4-phenylpiperidine reacted with methyl iodide to give 83% of *N*-Boc-*cis*-2-methyl-4-phenylpiperidine.[7b] This curious substituent effect has been observed previously in the lithiation–methylation of related piperidides.[2,9,12] A competition experiment between the Boc derivatives of piperidine and 4-phenylpiperidine established the latter to be lithiated more rapidly. When a mixture of equal amounts of *N*-Boc-piperidine (**13**) and *N*-Boc-4-phenylpiperidine (**43**) was treated with *s*-BuLi/TMEDA followed by trimethylsilyl chloride only the silylation product from **43** was obtained.



2,4-Disubstituted Boc-piperidines. The lithiations of *N*-Boc-2-methyl-4-phenylpiperidine (**45**) or *N*-Boc-2-methyl-4-*tert*-butylpiperidiene (**46**) occur at C-6 with *s*-BuLi/TMEDA, and the lithium reagent reacts with tributyltin chloride to provide the 2,4,6-trisubstituted Boc-piperidines **47** and **48**.[12] The corresponding reaction of **45** with trimethyltin chloride provides **49**, and a similar sequence with benzaldehyde was previously reported.[7b] The stereochemistry of the sequence was established by an X-ray crystal structure of **49** which shows the compound to exist in a twist-boat conformation as shown in Figure 1. Treatment of *N*-Boc-2-methyl-4-phenyl-6-(trimethylstannyl)piperidine (**49**) with *n*-BuLi in THF at −78 °C provides lithium reagent which reacts with dimethyl sulfate to give the trans 2,6-dimethylated compound **50**. This stereochemistry was established by conversion of **50** to **51** and ^{1}H NMR analyses. These results establish that the stereochemistry of dialkylation reactions of C-2 and C-6 of 4-substituted Boc-piperidines is trans[7] and that the configuration of the C–Li bond is retained in the sequences.

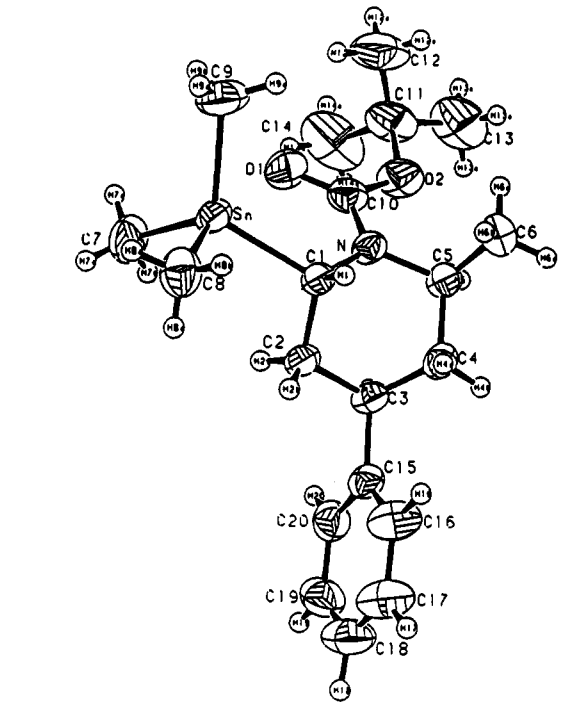
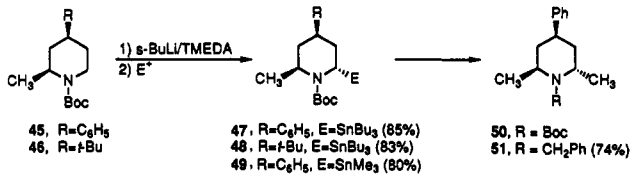


Figure 1. Twist-boat structure of *trans*-*N*-Boc-2-methyl-6-(trimethylstannyl)-4-phenylpiperidine (**49**).



Diastereoselective Syntheses of Substituted Piperidines. In order to illustrate the convenience of the lithiation–substitution sequence for diastereoselective syntheses, selected piperidines have been prepared.

D'Ambra and Bell reported recently syntheses of 4-phenyl-2-carboxanilides and piperidines by lithiations, electrophilic substitutions, and reductions from a Δ^3-piperidine derivative.[13] Lithiation of *N*-Boc-4-phenylpiperidine (**43**) with *s*-BuLi/TMEDA followed by phenyl isocyanate provided the 2,4-cis-disubstituted product **52** directly in 77% yield.

(9) (a) Bauer, W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 7191. (b) Wittig, G.; Pockels, U.; Droge, H. *Chem. Ber.* **1938**, *71*, 1903. (c) Klumpp, G. W.; Sinnige, M. J. *Tetrahedron Lett.* **1986**, *27*, 2247.

(10) Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1988**, *53*, 4437.

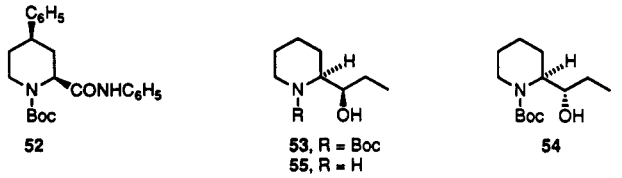
(11) We also prepared *N*-Boc-3-hydroxypiperidine, *N*-Boc-3-(benzoyloxy)piperidine, and *N*-Boc-3-[(benzoyloxy)methyl]piperidine and investigated lithiation reactions. The attempted lithiation of *N*-Boc-3-hydroxypiperidine with *s*-BuLi/TMEDA did not provide any substitution product even with trimethylsilyl chloride. The lithiations of the benzoyl esters of Boc-3-hydroxypiperidine and Boc-3-(hydroxymethyl)piperidine with *s*-BuLi/TMEDA gave ester hydrolysis products.

(12) Schlecker, R.; Seebach, D. *Helv. Chim. Acta* **1977**, *60*, 1459.

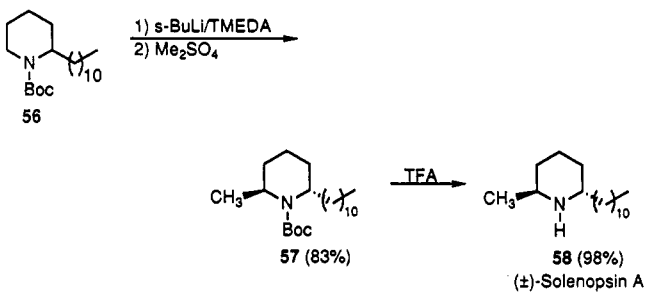
(13) D'Ambra, T. E.; Bell, M. R. *J. Org. Chem.* **1989**, *54*, 5632.

(14) (a) Hill, R. K. *J. Am. Chem. Soc.* **1958**, *80*, 1609. (b) Prasad, K. B.; Shaw, S. C. *Chem. Ber.* **1965**, *98*, 2822.

Under this methodology, (±)-α-conhydrine can be easily prepared. Conversion of *N*-Boc-piperidine (**13**) to *N*-Boc-piperidine-2-carboxaldehyde (**15**) followed by reaction with ethylmagnesium chloride provides the anti (38%) and syn (46%) products **53** and **54**, respectively. Separation by chromatography and hydrolysis of the anti isomer gives (±)-α-conhydrine (**55**) in 91% yield.[14]

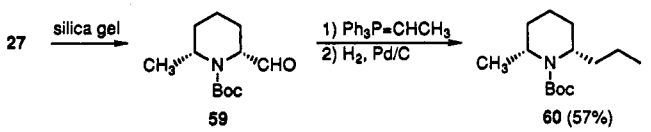


Many piperidine alkaloids have 2,6-disubstitution.[15] Solenopsin A, a synthetic targets of a number of syntheses, is representative of the trans series.[16] In the present synthesis, the reaction of **15** with decyltriphenylphosphonium ylide followed by catalytic hydrogenation provides 92% of *N*-Boc-2-undecylpiperidine (**56**). Lithiation



of **56** with *s*-BuLi/TMEDA, followed by dimethyl sulfate provides 83% of *N*-Boc-2-*trans*-methyl-6-undecylpiperidine (**57**). Hydrolysis of **57** gives (±)-solenopsin A (**58**) in an overall yield of 75% from **15**.

The alkaloid dihydropinidine is representative of the cis 2,6-disubstituted piperidines. The isomerization of **27** to give **59** followed by reaction of **59** with ethyltriphenylphosphonium ylide provides 62% of the olefin which is then reduced to give *N*-Boc-dihydropinidine (**60**) in an overall 57% yield.[17]

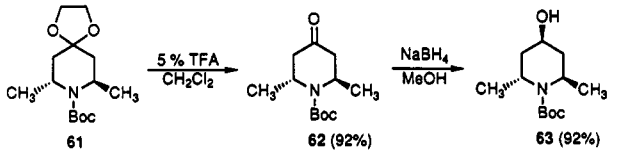


(15) (a) Baliah, V.; Jeyaraman, R.; Chandrasekaran, L. *Chem. Rev.* **1983**, *83*, 379. (b) Sibi, M. P.; Christensen, J. W. *Tetrahedron Lett.* **1990**, *31*, 5689. (c) Kurth, M. J.; Najdi, S. *Tetrahedron Lett.* **1990**, *31*, 3279. (d) Wasserman, H. H.; Rodriques, K.; Kucharczyk, R. *Tetrahedron Lett.* **1989**, *30*, 6077. (e) Yang, T.-K.; Lin, J.-H.; Teng, T.-F. *Heterocycles* **1990**, *31*, 1201.

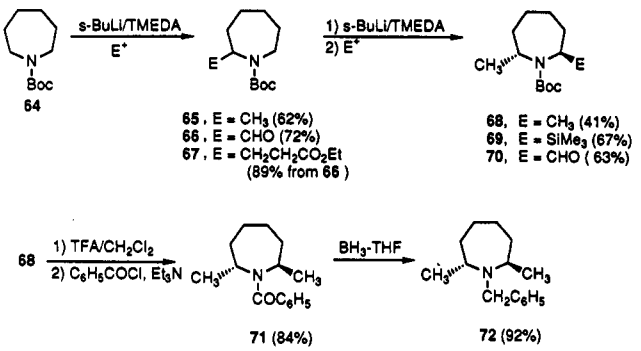
(16) (a) Wasserman, H. H.; Rusiecki, V. *Tetrahedron Lett.* **1988**, *29*, 4977. (b) MacConnell, J. G.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1971**, *26*, 1129. (c) Takahashi, K.; Kurita, H.; Ogura, K.; Iida, H. *J. Org. Chem.* **1985**, *50*, 4368. (d) Husson, H.-P.; Grierson, D. S.; Romero, J. R.; Bonin, M. *J. Org. Chem.* **1984**, *49*, 2392. (e) Nagasaka, T.; Hayashi, H.; Kumakawa, M.; Sakamoto, M.; Mizuno, M.; Hamaguchi, F. *Heterocycles* **1989**, *29*, 2157. (f) Husson, H.-P.; Grierson, D. S.; Royer, J.; Guerrier, L. *J. Org. Chem.* **1986**, *51*, 4475. (g) MacConnell, J. G.; Blum, M. S.; Fales, H. M. *Science* **1970**, *168*, 840. (h) Yamamoto, H.; Matsumura, Y.; Maruoka, K. *Tetrahedron Lett.* **1982**, *23*, 1929. (i) Kotsuki, H.; Kusumi, T.; Inoue, M.; Ushio, Y.; Ochi, M. *Tetrahedron. Lett.* **1991**, *32*, 4159. (j) Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1991**, *56*, 2506. (k) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100.

(17) Momose, T.; Toyooka, N.; Hira, Y. *Chem. Lett.* **1990**, 1319. Comins, D. L.; Weylarz, M. A. *J. Org. Chem.* **1991**, *56*, 2506. Royer, J.; Theodorakis, E.; Husson, H. D. *Synth. Commun.* **1991**, *21*, 521.

The preparation of *N*-Boc-7,9-dimethyl-1,4-dioxa-8-azaspiro[4,5]decane (**61**) was reported previously.[7b] Hydrolysis of the ketal with 5% trifluoroacetic acid in dichloromethane provides the ketone **62** which could be reduced by sodium borohydride to give **63** which shows two different methyl groups in both ^1H and ^{13}C NMR spectra.



Boc-perhydroazepines. The lithiation of *N*-Boc-perhydroazepine (**64**) with *s*-BuLi/TMEDA followed by reaction with electrophiles provides the 2-substituted products **65** and **66**. Reactions of the intermediate lithium reagent with trimethylsilyl chloride and tributyltin chloride has been previously reported.[7b] The aldehyde **66** was converted by reaction with the Horner–Emmons reagent to an α,β-unsaturated ester which was hydrogenated to provide the saturated ester **67**. Lithiation of *N*-Boc-2-methylperhydroazepine (**65**) with *s*-BuLi/TMEDA occurs at C-7, and reaction with dimethyl sulfate, trimethylsilyl chloride, or dimethyl formamide provides the trans 2,7-disubstituted Boc-perhydroazepines **68–70**. To assign the stereochemistry **68** was converted to **72** via **71**. The two benzylic protons show different chemical shifts consistent with trans stereochemistry of **68**, and the same stereochemistry is assigned to **69** and **70**.[8]



Boc-indoline and Boc-indole. We previously reported that lithiation of Boc-tetrahydroquinoline occurs on the aromatic ring at the 7 position.[7b] The reaction of Boc-indoline with *s*-BuLi takes a similar course to provide the substitution products **73** and **74**.[18a] Further lithiation of **74** with *s*-BuLi in the presence of TMEDA is at the benzylic position, and reaction of the anion with trimethylsilyl chloride provides substitution product **75**. Lithiation of Boc-indole with *s*-BuLi takes place at the α position, and the anion reacts with trimethylsilyl chloride and tributyltin chloride to provide 2-substitution products **76–77**, consistent with previous work.[18b,c]

Discussion

The advantages of the Boc group as an activator and director of lithiation are its applicability to carbanion formation at otherwise unactivated α′-positions and its

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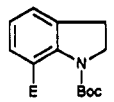
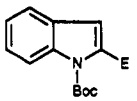


73, E=Si(CH$_3$)$_3$ (86%)
74, E=CH$_3$ (88%)
75, E=CH$_2$Si(CH$_3$)$_3$ (74%)

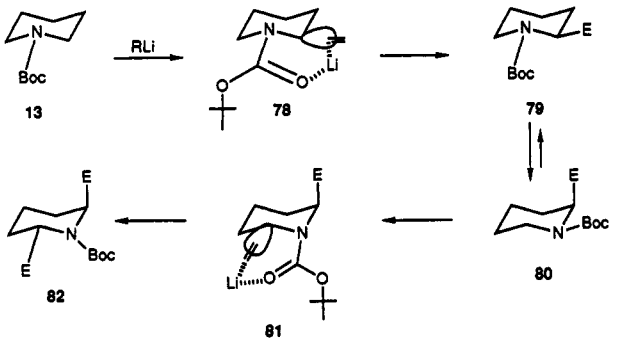


76, E=Si(CH$_3$)$_3$ (81%)
77, E=Sn(n-C$_4$H$_9$)$_3$ (97%)

convenience for addition and removal. Previous α′-lithiations of carbamates adjacent to nitrogen have been reported at a methyl group and for positions which have a substituent which contributes to stabilization of the carbanionic center.[19,20]

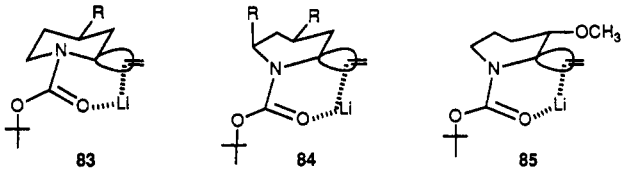
The stereochemical course of the majority of the Boc-piperidine lithiations we have investigated can be rationalized in terms of removal of an equatorial proton from a chairlike conformation to give the equatorially lithiated species which reacts with an electrophile with retention of configuration.[1,21] This sequence is illustrated for the conversion of **13** to **79** via **78**. The orthogonal disposition of the formally sp^3 carbanion with respect to the amide π bond is consistent with a transition structure and an organolithium intermediate in which association of the carbonyl group with the lithium is a stabilizing factor and this is an arrangement which is supported by calculations.[22]

Equatorially substituted 2-piperidides are well recognized to be less stable than their axially substituted isomers due to A^{1,3} strain so **79** would be expected to undergo conformational equilibration to **80**.[2,23] Subsequent equatorial lithiation and substitution of **80** then would proceed via **81** to provide the equatorially substituted product **82**. Thus, trans 2,6-disubstituted piperidines are provided by this sequence.



The formation of cis-2,6-disubstituted piperidines through equilibration, as illustrated by the conversion of **27** to **59** (vide supra), illustrates the flexibility and synthetic control possible with this methodology. It should be noted that use of the formamidine or nitroso group in analogous sequences for 4-substituted piperidines led to cis-2,6-disubstituted piperidines albeit with cis and trans 4-substituents respectively, and rationalizations for these reactions have been provided.[4,24,25]

The lithiation and substitution of 4-substituted Boc-piperidines can be considered to proceed via the equatorial lithiated intermediate **83** to give 2,4-cis-disubstituted products. Upon further lithiation and substitution of the 2,4-cis-disubstituted Boc-piperidines, however, the 6-substituent is introduced trans to the 2-substituent. In this case, conformational equilibration of the 2-substituent to the axial position would be inhibited by the requirement of simultaneously placing the 4-substituent in an axial position. We suggest that a twist-boat conformation, illustrated by **84**, is favored for the transition structure and the organolithium intermediate. This conformation allows the 2-substituent to be axial and the 4 substituent to be equatorial and maintains complexation of the lithium and orthogonality of the orbitals. Support for such a conformation may be found in the X-ray structure of **49** which shows a twist-boat conformation. A similar conformation shown as **85** may also be involved in the elimination of methoxide in the lithiation of **33** since an alternative chairlike conformation would lead to a trans double bond in the piperidine ring. In the lithiation and substitution of 2-methyl-*N*-Boc-pyrrolidine both cis and trans isomers are produced while the 2-methyl-*N*-Boc-perhydroazepine gives trans products. The low diastereoselectivities observed in reactions of these organolithium intermediates with aldehydes is consistent with observations with the corresponding formamidines except for recent cases reported by Sanner in which the pyrrolidine derivative showed 5:95 selectivity.[26]



In summary, the use of Boc-derivatives of cyclic amines in the sequence of α′-lithiation and electrophilic substitution can provide for the diastereoselective elaboration of pyrrolidines, piperidines, and perhydroazepines. The course of these reactions can be rationalized in terms of the dipole stabilization and complexation effects. The efficiency and convenience of this chemistry recommends the approach for syntheses of these and related systems.

Experimental Section

Analytical thin-layer chromatography (TLC) was performed on Merck silica gel plates with F-254 indicator. Visualization was accomplished by iodine or UV light (254 nm). Analytical capillary gas chromatography was performed on a Hewlett-Packard 5790 or 5890 gas chromatograph equipped with a programmable temperature control and flame ionization detector. Flash chromatography was performed by using silica gel (0.05–0.2 mm, Merck) and hexane/ethyl acetate mixtures as an eluent. Medium-pressure liquid chromatography (MPLC) was performed

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using various silica gel columns depending on the amount of material and the difficulty of separation. Title compounds for which analyses are not reported were judged to be >90% pure by their ^{1}H NMR which are provided as supplementary material.

Materials. All glassware was oven dried (120 °C) and cooled under a nitrogen atmosphere. All reagents were obtained from commercial sources and used without further purification, unless mentioned otherwise. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium and benzophenone under N_2 atmosphere. Ethyl acetate (EtOAc) was distilled from potassium carbonate. Commercial solutions of *n*-butyllithium (*n*-BuLi) in hexane, *sec*-butyllithium (*s*-BuLi) in cyclohexane, and *tert*-butyllithium (*t*-BuLi) in pentane were titrated prior to use with *N*-benzylbenzamide as the indicator. *N,N,N'N'*-Tetramethylethylenediamine (TMEDA) was distilled from calcium hydride and stored under a nitrogen atmosphere. All the organometallic reagents used were obtained commercially and stored in bottles at −10 °C. Yields are based on analytically pure material.

The following experimental procedures are selected as typical for use of this methodology. Data for compounds not described here is provided as supplementary material.

Preparation of *N*-Boc-2-methylpyrrolidine (5). A 0.5 M solution of **4** (580 mg, 3.39 mmol) in ether was cooled to −78 °C and treated with TMEDA (394 mg, 0.51 mL, 3.39 mmol), followed by *s*-BuLi (1.45 M, 2.80 mL, 4.06 mmol) dropwise. The mixture was stirred for 30 min at −78 °C and treated with a solution of dimethyl sulfate (854 mg, 0.64 mL, 6.77 mmol) in 1 mL of ether and then slowly warmed to room temperature. The mixture was diluted with 6 mL of water and extracted with ether (10 mL × 5). The combined extracts were dried over K_2CO_3 and concentrated to give a crude product as an oil which was distilled under reduced pressure to give 543 mg (87%) of **5** as a colorless oil: bp 81 °C/3 Torr; ^{1}H NMR ($CDCl_3$) δ 3.85 (br, 1 H), 3.35 (br, 2 H), 2.01–1.73 (m, 4 H), 1.46 (s, 9 H), 1.15 (d, *J* = 5.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.4, 78.6, 52.6, 46.0, 32.8, 28.4, 23.2, 20.4. Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.82; H, 10.37; N, 7.64.

Preparation of *N*-Boc-pyrrolidine-2-carboxaldehyde (7). A 0.5 M solution of **4** (315 mg, 1.83 mmol) in ether was cooled to −78 °C and treated with TMEDA (213 mg, 0.28 mL, 1.83 mmol), followed by *s*-BuLi (1.41 M, 1.56 mL, 2.20 mmol) dropwise. The mixture was stirred for 2 h at −78 °C and transferred to a solution of DMF (267 mg, 0.28 mL, 3.66 mmol) in 2 mL of ether at −78 °C. The mixture was slowly warmed to room temperature and quenched with 6 mL of saturated ammonium chloride solution, and then the organic layer was separated. The aqueous layer was extracted with ether (5 mL × 6), and the combined extracts were dried over K_2CO_3 and then concentrated to give 300 mg (82%) of **7** as an oil: ^{13}C NMR ($CDCl_3$) δ 200.20 (m), 154.56, 153.59, 80.17, 79.80, 64.70, 64.56, 46.54, 46.40, 28.05, 27.93, 27.62, 26.43, 24.32, 23.62. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 59.82; H, 8.86; N, 6.82.

Preparation of *N*-Boc-piperidine (13). A solution of di-*tert*-butyl dicarbonate (2.20 g, 10.08 mmol) in 10 mL of THF was cooled to 0 °C and treated with piperidine (1.29 g, 15.12 mmol) dropwise. The mixture was stirred for 10 min, warmed to room temperature, and then stirred for 30 min. The mixture was diluted with 10 mL of 10% sodium bicarbonate solution and extracted with ether (20 mL × 2). The extracts were washed with brine, and combined extracts were dried over K_2CO_3 and then concentrated to give a crude product as an oil which was distilled under reduced pressure to give 1.74 g (93%) of **13** as a colorless oil: bp 65 °C/1 Torr; ^{1}H NMR ($CDCl_3$) δ 3.20 (br, 4 H), 1.50–1.20 (br, 15 H); ^{13}C NMR ($CDCl_3$) δ 154.4, 78.6, 44.4, 28.1, 25.4, 24.1; IR (film) 1693 (s), 1148 (s), 1418 (s), 1239 (s), 1364 (s), 1024 (s), 1048 (m). Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.70; H, 10.19; N, 7.66.

Preparation of *N*-Boc-2-methylpiperidine (14). A 0.5 M solution of **13** (198 mg, 1.07 mmol) in ether was cooled to −78 °C and treated with TMEDA (162 mg, 1.39 mmol), followed by *s*-BuLi (1.38 M, 1.0 mL, 1.39 mmol) dropwise. The mixture was stirred for 3 h at −78 °C and then treated with dimethyl sulfate (202 mg, 1.60 mmol) in 1 mL of ether. The mixture was warmed to room temperature and then was diluted with 3 mL of water and extracted with ether (5 mL × 5). The combined extracts were dried over K_2CO_3 and then concentrated to give a crude product as a colorless oil. The product was purified by column chromatography on silica gel with 5% EtOAc/hexane (contains 0.5 g of Et_3N) as an eluent to give 190 mg (89%) of **14** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.36 (m, 1 H), 3.93 (dd, *J* = 12.4, 3.1 Hz, 1 H), 2.80 (td, *J* = 13.4, 2.9 Hz, 1 H), 1.66–146 (m, 5 H), 1.45 (s, 9 H), 1.42–1.34 (m, 1 H), 1.11 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.9, 78.8, 45.9, 38.5, 30.0, 28.4, 25.6, 18.6, 15.6; MS *m/z* (relative intensity) 199 (M^+, 9), 184 (7), 142 (9), 128 (100), 84 (53), 57 (72). Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.17; H, 10.56; N, 7.05.

Preparation of *N*-Boc-piperidine-2-carboxaldehyde (15). A 0.5 M solution of **13** (2.01 g, 10.86 mmol) in ether was cooled to −60 °C and treated with TMEDA (1.26 g, 1.64 mL, 10.86 mmol), followed by *s*-BuLi (1.20 M, 9.96 mL, 11.95 mmol) dropwise. The mixture was slowly warmed to −20 °C and stirred for 10 min and then cooled to −78 °C. The mixture was treated with a solution of DMF (1.19 g, 1.26 mL, 16.29 mmol) in 2 mL of ether via cannula, stirred for 10 min, and then quenched with 10 mL of saturated ammonium chloride solution. The mixture was warmed to room temperature, and the organic layer was separated. The aqueous layer was extracted with ether (10 mL × 6), and the combined extracts were dried over K_2CO_3. The organic layer was concentrated to give a crude product as an oil which was chromatographed on silica gel with 5% EtOAc/hexane (contains 0.5% of Et_3N) as an eluent to give 1.50 g (65%) of **15** as an oil. ^{1}H NMR ($CDCl_3$) δ 9.59 (s, 1 H), 4.61–4.50 (br d, 1 H), 2.90 (br, 1 H), 2.17 (m, 1 H), 1.72–1.52 (m, 3 H), 1.46 (s, 9 H), 1.41–1.16 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 201.1, 155.7, 80.1, 60.9, 42.8, 28.1, 24.5, 23.4, 20.7. Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 62.00; H, 8.99; N, 6.55.

Preparation of *N*-Boc-2-(tributylstannyl)piperidine (18). A solution of **13** (101 mg, 0.54 mmol) in 1.10 mL of ether was cooled to −78 °C and treated with TMEDA (139 mg, 1.20 mmol) and *s*-BuLi (1.50 M, 0.44 mL, 0.65 mmol). The mixture was slowly warmed to −20 °C, stirred for 1 h, and then cooled to −78 °C. The mixture was treated with tributyltin chloride (195 mg, 0.60 mmol) and allowed to warm to room temperature. The mixture was diluted with 3 mL of saturated potassium fluoride solution and stirred for 10 min and then extracted with ether (10 mL × 5). Combined extracts were dried over K_2CO_3 and then concentrated to give a crude product which was purified by chromatography on silica gel with 10% ether/hexane (contains 0.5% of Et_3N) as an eluent to give 260 mg (100%) of **18** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.40–4.20 (m, 1 H), 3.65–3.40 (m, 1 H), 3.20 (br, 1 H), 2.10–1.42 (m, 21 H), 1.30 (q, *J* = 7.1 Hz, 6 H), 0.88 (t, *J* = 7.2 Hz, 15 H); ^{13}C NMR ($CDCl_3$) δ 155.0, 79.0, 46.2, 43.4, 30.4, 29.1, 28.4, 27.6, 26.3, 24.3, 13.7, 10.9. Anal. Calcd for $C_{22}H_{45}NO_2Sn$: C, 55.71; H, 9.56; N, 2.95. Found: C, 55.88; H, 9.60; N, 2.86.

Generation of *N*-Boc-2-lithiopiperidine from *N*-Boc-2-(tributylstannyl)piperidine with *n*-BuLi and Reaction of the Lithium Reagent with Cyclohexanone To Give Spiro-[8-oxa-1-azabicyclo[4.3.0]nonane-7,1'-cyclohexan]-9-one (20). A 0.5 M solution of **18** in THF was cooled to −78 °C and treated with *n*-BuLi (1.85 M, 0.54 mL, 1.00 mmol) dropwise. The mixture was stirred for 1 h at −78 °C and then treated with a solution of cyclohexanone (134 mg, 0.14 mL, 1.36 mmol) in 0.5 mL of THF. The mixture was slowly warmed to room temperature and concentrated to give crude product as a yellow oil which was chromatographed on silica gel with 20% EtOAc/hexane as an eluent to give 145 mg (76%) of **20** as a mixture of anti and syn isomers: mp 95–96 °C; ^{13}C NMR ($CDCl_3$, mixture) δ 157.1, 80.9, 63.2, 41.2, 36.1, 30.6, 25.0, 24.7, 23.8, 22.6, 21.6, 21.4. Anal. Calcd for $C_{12}H_{19}NO_2$ (mixture): C, 68.87; H, 9.15; N, 6.69. Found: C, 68.86; H, 9.19; N, 6.70.

Preparation of *N*-Boc-2-methyl-6-(α-phenyl)piperidinemethanol (23). A 0.5 M solution of *N*-Boc-2-methylpiperidine (**14**) (168 mg, 0.84 mmol) in ether was cooled to −78 °C and treated with TMEDA (98 mg, 0.13 mL, 0.84 mmol), followed by *s*-BuLi (1.39 M, 0.67 mL, 0.96 mmol) dropwise. The mixture was slowly warmed to −30 °C, stirred for 1 h, and then cooled to −78 °C. The mixture was treated with benzaldehyde (90 mg, 86 μL, 0.84 mmol), stirred for 10 min at −78 °C, and then quenched with 4 mL of water. The mixture was warmed to room temperature and extracted with ether (5 mL × 6). The combined extracts were dried over K_2CO_3 and concentrated to give a crude

product as an oil which was chromatographed on silica gel with 5% EtOAc/hexane (contains 0.5% of Et_3N) as an eluent to give 126 mg (49%) of *anti*-**23** and 121 mg (47%) of *syn*-**23**. *anti*-**23**: ^1H NMR ($CDCl_3$) δ 7.41–7.21 (m, 5 H), 5.12 (d, J = 2.2 Hz, 1 H), 4.93 (br, 1 H), 4.15 (m, 1 H), 3.61 (m, 1 H), 1.76 (m, 1 H), 1.68–1.48 (m, 4 H), 1.45 (s, 9 H), 1.41–1.30 (m, 1 H), 1.19 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 156.2, 142.8, 127.9, 126.8, 126.3, 79.9, 74.2, 59.1, 49.7, 28.7, 28.4, 21.8, 18.2, 17.7. Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.78; H, 8.91; N, 4.59. Found: C, 70.92; H, 8.95; N, 4.38. *syn*-**23**: ^1H NMR ($CDCl_3$) δ 7.41–7.25 (m, 5 H), 4.97 (d, J = 5.5 Hz, 1 H), 4.71 (dd, J = 9.9, 6.2 Hz, 1 H), 4.07 (m, 2 H), 2.05 (m, 1 H), 1.68–1.54 (m, 4 H), 1.51 (s, 9 H), 1.32 (m, 1 H), 1.26 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 158.5, 143.3, 128.3, 127.6, 126.6, 80.5, 78.6, 57.7, 48.1, 28.4, 26.3, 21.8, 20.0, 13.6. Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.78; H, 8.91; N, 4.59. Found: C, 70.88; H, 8.95; N, 4.42.

Preparation of *N*-Boc-2-methyl-6-piperidinecarboxaldehyde (27). A 0.5 M solution of **14** (1.07 g, 5.34 mmol) in ether was cooled to −60 °C and treated with TMEDA (621 mg, 0.81 mL, 5.34 mmol), followed by *s*-BuLi (1.20 M, 4.90 mL, 5.88 mmol) dropwise. The mixture was slowly warmed to −20 °C, stirred for 30 min, and then cooled to −78 °C. The mixture was treated with DMF (586 mg, 0.62 mL, 8.02 mmol) in 2 mL of ether, stirred for 10 min, and then quenched with 10 mL of saturated ammonium chloride solution. The mixture was warmed to room temperature, and the organic layer was separated. The aqueous layer was extracted with ether (10 mL × 5), and the combined extracts were dried over K_2CO_3 then concentrated to give 1.05 g (87%) of a crude product as an oil as a mixture of cis and trans isomers which were separated by careful chromatography. *trans*-**27**: ^1H NMR ($CDCl_3$) δ 9.29 (d, J = 3.6 Hz, 1 H), 4.27 (br, 1 H), 3.63 (dt, J = 11.4, 3.7 Hz, 1 H), 1.75–1.36 (m, 6 H), 1.46 (s, 9 H), 1.13 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 196.0, 81.0, 59.0, 47.2, 29.1, 28.1, 28.0, 25.2, 16.3, 16.1. *cis*-**27** (**59**): ^1H NMR ($CDCl_3$) δ 9.61 (s, 1 H), 4.57 (d, J = 5.6 Hz, 1 H), 4.39 (m, 1 H), 2.32 (d, J = 13.0 Hz, 1 H), 1.69–1.18 (m, 5 H), 1.48 (s, 9 H), 1.07 (J = 7.0 Hz, 3 H). ^{13}C NMR ($CDCl_3$) δ 202.5, 155.0, 79.9, 58.8, 46.0, 29.2, 28.0, 22.4, 18.5, 14.9. Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.29; H, 9.41; N, 6.04. The initial cis/trans mixture of 1/8 could be isomerized by chromatography on silica gel in the presence of triethylamine to a 5/1 cis/trans mixture.

Preparation of spiro[8-oxa-1-azabicyclo[4,3,0]non-5-ene-7,1′-cyclohexan]-9-one (40). A 0.5 M solution of **33** (194 mg, 0.90 mmol) in THF was cooled to −78 °C and treated with *s*-BuLi (1.39 M, 1.43 mL, 1.98 mmol) dropwise. The mixture was stirred for 5 min and transferred to a cooled solution of cyclohexanone (91 mg, 96 μL, 1.08 mmol) in 1 mL of THF at −78 °C via cannula. The mixture was slowly warmed to room temperature and diluted with 4 mL of water. The mixture was extracted with ether (5 mL × 6), and the combined extracts were dried over K_2CO_3 and then concentrated to give a crude product as an oil which was chromatographed on silica gel with 10% EtOAc/hexane (contains 0.5% of Et_3N) as an eluent to give 41 mg of the *N*-Boc-1,4,5,6-tetrahydropyridine and 95 mg (65% based on the recovered material) of **40** as a white solid: ^1H NMR ($CDCl_3$) δ 4.55 (t, J = 4.0 Hz, 1 H), 3.49 (t, J = 5.7 Hz, 2 H), 2.08 (m, 2 H), 1.86–1.62 (m, 9 H), 1.52–1.47 (m, 2 H), 1.23 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 155.06, 142.30, 92.65, 83.51, 39.42, 36.55, 24.52, 21.46, 20.48, 20.26. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; N, 6.76. Found: C, 69.82; H, 8.41; N, 6.10.

Preparation of *cis*-*N*-Boc-2-methyl-4-*tert*-butylpiperidine (46). A 0.5 M solution of *N*-Boc-4-*tert*-butylpiperidine (308 mg, 1.28 mmol) in ether was cooled to −78 °C and treated with TMEDA (178 mg, 0.23 mL, 1.53 mmol), followed by *s*-BuLi (1.46 M, 1.05 mL, 1.53 mmol) dropwise. The mixture was slowly warmed to −30 °C, stirred for 1 h, and then cooled to −78 °C and treated with dimethyl sulfate (241 mg, 0.18 mL, 1.91 mmol) in 0.5 mL of ether. The mixture was slowly warmed to room temperature and diluted with 5 mL of water. The mixture was extracted with ether (5 mL × 6), and the combined extracts were dried over K_2CO_3 then concentrated to give a crude product as an oil which was chromatographed on silica gel with 5% EtOAc/hexane (contains 0.5% of Et_3N) as an eluent to give 230 mg (71%) of **46** as an oil: ^1H NMR ($CDCl_3$) δ 3.78 (m, 2 H), 2.88 (dq, J = 10.8, 5.9 Hz, 1 H), 1.80–1.60 (m, 2 H), 1.45 (s, 9 H), 1.28–1.20 (m, 1 H), 1.13 (d, J = 5.9 Hz, 3 H), 1.09–0.91 (m, 2 H), 0.83 (s, 9 H). Anal. Calcd for $C_{15}H_{29}NO_2$: C, 70.54; H, 11.45; N, 5.49. Found: C, 70.28; H, 11.33; N, 5.65.

Preparation of *N*-Boc-2-methyl-4-*tert*-butyl-6-(tributylstannyl)piperidine (48). A 0.3 M solution of **46** (91 mg, 0.36 mmol) in ether was cooled to −78 °C and treated with TMEDA (58 mg, 75 μL, 0.50 mmol), followed by *s*-BuLi (1.45 M, 0.34 mL, 0.50 mmol) dropwise. The mixture was slowly warmed to −20 °C, stirred for 1 h, and then cooled to −78 °C. The mixture was treated with a solution of tributyltin chloride (162 mg, 0.50 mmol) in 0.5 mL of ether and slowly warmed to room temperature. The mixture was diluted with 5 mL of saturated KF solution, stirred for 5 min, and then extracted with ether (5 mL × 6). The combined extracts were dried over K_2CO_3 and then concentrated to give a crude product as an oil which was purified on silica gel with 2% EtOAc/hexane (contains 0.5% of Et_3N) as an eluent to give 161 mg (83%) of **48** as a colorless oil: ^1H NMR ($CDCl_3$) δ 3.75 (m, 1 H), 2.73 (dd, J = 13.0, 5.6 Hz, 1 H), 1.89 (m, 1 H), 1.60–1.44 (m, 4 H), 1.41 (s, 9 H), 1.34–1.22 (m, 6 H), 1.07 (d, J = 6.1 Hz, 3 H), 0.91–0.75 (m, 30 H); ^{13}C NMR ($CDCl_3$) δ 156.7, 78.6, 51.8, 42.9, 35.3, 32.5, 30.5, 29.3, 28.5, 27.6, 27.1, 19.7, 13.9, 11.8, 8.7. Anal. Calcd for $C_{27}H_{55}NO_2Sn$: C, 59.56; H, 10.18; N, 2.57; Sn, 21.80. Found: C, 59.48; H, 10.26; N, 2.52; Sn, 21.79.

Preparation of *N*-Boc-4-phenyl-*N*′-phenyl-2-piperidinecarboxamide (52). A 0.3 M solution of the **43** (139 mg, 0.53 mmol) in ether was cooled to −78 °c and treated with TMEDA (62 mg, 80 μL, 0.53 mmol), followed by *s*-BuLi (1.45 M, 0.44 mL, 0.64 mmol) dropwise. The mixture was slowly warmed to −20 °C, stirred for 30 min, and then cooled to −78 °C. The mixture was treated with a solution of phenyl isocyanate (76 mg, 69 μL, 0.64 mmol) in 0.5 mL of ether and warmed to room temperature. The mixture was diluted with 5 mL of water and extracted with boiling ethyl acetate (5 mL × 6). The combined extracts were dried over K_2CO_3 and then concentrated to give a crude product as mixture of products and starting material as a white solid. The solid was washed with hexane and recrystallized from ethyl acetate to give 156 mg (77%) of **52** as a white solid: mp 225–226 °C; ^1H NMR ($CDCl_3$) δ 8.16 (br, 1 H), 7.52 (d, J = 8.1 Hz, 2 H), 7.34–7.21 (m, 7 H), 7.09 (t, J = 7.4 Hz, 1 H), 4.37 (t, J = 8.2 Hz, 1 H), 3.63 (m, 2 H), 2.77 (m, 1 H), 2.27–2.10 (m, 3 H), 1.75 (m, 1 H), 1.46 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 170.1, 156.6, 137.9, 128.9, 128.5, 126.5, 124.0, 119.5, 81.4, 58.5, 41.7, 37.8, 31.7, 30.9, 28.2. Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.60; H, 7.42; N, 7.37. Found: C, 72.37; H, 7.62; N, 7.35.

Preparation of *N*-Boc-2-(1-undecenyl)piperidine. A 0.5 M solution of undecyltriphenylphosphonium bromide (4.32 g, 8.93 mmol) in THF was cooled to −30 °C and treated with *n*-BuLi dropwise. The deep red solution was slowly warmed to 0 °C, stirred for 30 min, and then cooled to −78 °C. The ylide was treated with a solution of **15** (1.32 g, 6.18 mmol) in 2 mL of THF, and the mixture was slowly warmed to room temperature. The mixture was diluted with 10 mL of water, and the organic layer was separated. The aqueous layer was extracted with ether (10 mL × 5), and the combined extracts were dried over K_2CO_3 and then concentrated to give a crude product as an oil which was chromatographed on silica gel with 5% EtOAc/hexane (contains 0.5% of Et_3N) as an eluent to give 1.99 g (95%) of *N*-Boc-2-(1-undecenyl)piperidine as a colorless oil: ^1H NMR ($CDCl_3$) δ 5.66 (dd, J = 10.1, 8.5 Hz, 1 H), 5.46 (dt, J = 10.8, 6.7 Hz, 1 H), 5.01 (br, 1 H), 3.95 (dd, J = 13.3, 3.0 Hz, 1 H), 2.85 (td, J = 12.7, 2.3 Hz, 1 H), 2.09 (m, 2 H), 1.69–1.47 (m, 6 H), 1.44 (s, 9 H), 1.40–1.26 (m, 14 H), 0.87 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 154.56, 132.02, 126.71, 78.92, 47.89, 39.45, 31.79, 30.56, 29.58, 29.47, 292.28, 29.20, 28.38, 27.57, 25.56, 22.56, 19.43, 13.97. Anal. Calcd for $C_{21}H_{39}NO_2$: C, 74.72; H, 11.65; N, 4.15. Found: C, 74.70; H, 11.63; N, 4.17.

Preparation of *N*-Boc-2-undecylpiperidine (56). A solution of the *N*-Boc-2-(1-undecenyl)piperidine (697 mg, 2.07 mmol) in 3 mL of ethanol was stirred under H_2 pressure for 24 h, and then the mixture was filtered through Celite and concentrated to give a crude product which was chromatographed on silica gel with hexane (contains 0.5% of Et_3N) as an eluent to give 683 mg (97%) of **56** as a colorless oil: ^1H NMR ($CDCl_3$) δ 4.18 (br, 1 H), 3.96 (d, J = 11.9 Hz, 1 H), 2.73 (td, J = 13.5, 2.1 Hz, 1 H), 1.66–1.48 (m, 6 H), 1.45 (s, 9 H), 1.40–1.25 (m, 20 H), 0.88 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.06, 78.77, 50.27, 38.52, 31.84, 29.60, 29.56, 29.52, 29.27, 28.40, 26.28, 25.61, 22.61, 18.96, 14.03.

Anal. Calcd for $C_{21}H_{41}NO_2$: C, 74.28; H, 12.17; N, 4.13. Found: C, 74.16; H, 12.22; N, 4.18.

Preparation of *trans*-*N*-Boc-2-methyl-6-undecylpiperidine (57). A 0.3 M solution of **56** (151 mg, 0.45 mmol) in ether was cooled to −60 °C and treated with TMEDA (67 mg, 87 μL, 0.58 mmol), followed by *s*-BuLi (1.20 M, 0.48 mL, 0.58 mmol) dropwise. The mixture was slowly warmed to −20 °C, stirred for 30 min, and then cooled to −78 °C. The mixture was treated with a solution of dimethyl sulfate (112 mg, 84 mL, 0.89 mmol) in 0.5 mL of ether and slowly warmed to room temperature. The mixture was diluted with 5 mL of water and then extracted with ether (5 mL × 6). The combined extracts were dried over K_2CO_3 and concentrated to give a crude product as an oil which was chromatographed on silica gel with 5% EtOAc/hexane (contains 0.5% of Et_3N) as an eluent to give 132 mg (83%) of **57** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.92 (m, 1 H), 3.77 (m, 1 H), 1.87–1.74 (m, 2 H), 1.70–1.49 (m, 6 H), 1.46 (s, 9 H), 1.25 (s, 18 H), 1.23 (d, J = 7.0 Hz, 3 H), 0.88 (t, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.07, 78.46, 51.48, 46.77, 34.26, 31.78, 29.53, 28.40, 28.31, 27.01, 26.76, 23.06, 22.54, 20.69, 13.95, 13.60. Anal. Calcd for $C_{22}H_{43}NO_2$: C, 74.73; H, 12.26; N, 3.96. Found: C, 74.90; H, 12.31; N, 4.00.

Preparation of *trans*-2-Methyl-6-undecylpiperidine (58) (Solenopsin A). A solution of *trans*-*N*-Boc-2-methyl-6-undecylpiperidine (**57**) (65 mg, 0.18 mmol) in 1 mL of 15% trifluoroacetic acid in dichloromethane was stirred for 2 h at room temperature, and the reaction mixture was quenched with 4 mL of saturated $NaHCO_3$ solution. The mixture was extracted with ether (5 mL × 6), and the combined extracts were dried over K_2CO_3 and then concentrated to give 46 mg (98%) of *trans*-2-methyl-6-undecylpiperidine (**58**) as an oil: ^{1}H NMR ($CDCl_3$) δ 3.04 (m, 1 H), 2.86 (m, 1 H), 1.75 (br, 1 H), 1.64–1.35 (m, 6 H), 1.24 (s, 20 H), 1.06 (d, J = 6.5 Hz, 3 H), 0.86 (t, J = 6.9 Hz, 3 H) identical to an authentic sample of selenopsin A; ^{13}C NMR ($CDCl_3$) δ 50.75, 45.76, 33.89, 32.80, 31.83, 30.59, 29.69, 29.55, 29.27, 26.36, 22.59, 21.04, 19.42, 14.00. Anal. Calcd for $C_{17}H_{35}N$: C, 80.55; H, 13.92; N, 5.53. Found: C, 79.60; H, 14.02; N, 5.45.

Preparation of *cis*-*N*-Boc-2-methyl-6-(1-propenyl)piperidine. A suspension of ethyltriphenylphosphonium bromide (192 mg, 0.52 mmol) in 1.5 mL of THF was cooled to −40 °C and treated with *n*-BuLi (1.78 M, 0.29 mL, 0.52 mmol) dropwise. The mixture was stirred for 10 min, cooled to −78 °C, treated with the solution of **59** (107 mg, 0.47 mmol) in 1 mL of THF, and then slowly warmed to room temperature. The mixture was diluted with 5 mL of water and extracted with ether (5 mL × 6), and then the combined extracts with dried over K_2CO_3. The organic layer was concentrated to give a crude product as an oil which was chromatographed on neutral alumina to give 60 mg (62% based on recovered starting material) of *cis*-*N*-Boc-2-methyl-6-(1-propenyl)piperidine as an oil: ^{1}H NMR ($CDCl_3$) δ 5.69 (t, J = 10.6 Hz, 1 H), 5.44 (dq, J = 10.6, 6.8 Hz, 1 H), 4.96 (d, J = 8.2 Hz, 1 H), 4.33 (m, 1 H), 1.69 (d, J = 7.6 Hz, 3 H), 1.66–1.49 (m, 6 H), 1.45 (s, 9 H), 1.21 (d, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.1, 132.5, 124.3, 79.0, 47.4, 45.8, 30.5, 28.5, 20.7, 14.6, 12.8.

Preparation of *N*-Boc-dihydropinidine (60). A solution of the *cis*-piperidine (vide supra) (44 mg, 0.18 mmol) in 1.0 mL of ethanol was stirred under H_2 pressure over palladium–C catalyst overnight. The mixture was filtered through Celite and concentrated to give 42 mg of *N*-Boc-dihydropinidine **60** (96%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.29 (m, 1 H), 4.06 (m, 1 H), 1.70–1.20 (m, 10 H), 1.45 (s, 9 H), 1.15 (d, J = 7.0 Hz, 3 H), 0.91 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.27, 78.75, 50.00, 45.49, 37.23, 30.22, 28.43, 27.43, 20.64, 20.32, 14.14, 14.03.

Preparation of *trans*-*N*-Boc-7,9-dimethyl-1,4-dioxa-8-azaspiro[4.5]decane (61). A 0.5 M solution of the *N*-Boc-7-methyl-1,4-dioxa-8-azaspiro[4.5]decane (65 mg, 0.25 mmol) in ether was cooled to −78 °C and treated with TMEDA (35 mg, 0.30 mmol), followed by *s*-BuLi (1.40 M, 0.22 mL, 0.30 mmol) dropwise. The mixture was slowly warmed to −30 °C, stirred for 1 h, and then recooled to −78 °C. The mixture was treated with dimethyl sulfate (38 mg, 0.30 mmol) in 0.5 mL of ether and slowly warmed to room temperature. The mixture was diluted with 4 mL of water and extracted with ether (5 mL × 6). The combined extracts were dried over K_2CO_3 and then concentrated to give a crude product (70 mg) as an oil. The product was purified by column chromatography on silica gel to give 30 mg (44%) of **61** as an oil: ^{1}H NMR ($CDCl_3$) δ 4.11–4.00 (m, 2 H_{ax} on C_2 and C_6), 3.96–3.82 (m, 4 H), 2.19 (dd, J = 14.6, 5.4 Hz, 2 H_{ax} on C_3 and C_5), 1.81 (dd, J = 14.6, 2.9 Hz, 2 H_{eq} on C_3 and C_5), 1.45 (s, 9 H), 1.24 (d, J = 7.1 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 154.7, 106.3, 79.1, 63.7, 46.0, 39.1, 28.5, 20.9; MS m/z (relative intensity) 271 (M^+, 6), 256 (17), 215 (17), 200 (83), 156 (36), 126 (18), 113 (47), 87 (64), 70 (44), 57 (100).

Preparation of *trans*-*N*-Boc-2,6-dimethylpiperidin-4-one (62). A solution of **61** (77 mg, 0.28 mmol) in 1 mL of 5% trifluoroacetic acid in dichloromethane was stirred for 7 h at room temperature, and then the solvent was evaporated. The residue was dissolved in 4 mL of saturated $NaHCO_3$ solution and extracted with ether (5 mL × 6). The combined extracts were dried over K_2CO_3 and concentrated to give a crude product which was chromatographed on silica gel with 10% EtOAc/hexane (contains 0.5% of Et_3N) to give 59 mg (92%) of **62** as a white solid: ^{1}H NMR ($CDCl_3$) δ 4.38 (t, J = 6.6 Hz, 2 H), 2.58 (dd, J = 17.8, 6.5 Hz, 2 H), 2.37 (dd, J = 18.0, 1.6 Hz, 2 H), 1.49 (s, 9 H), 1.25 (d, J = 6.7 Hz, 6 H). There is about 10% of *N*-Boc-2-methyl piperidin-4-one which must be a contaminent of the starting material detectable in the ^{1}H NMR. ^{13}C NMR ($CDCl_3$) δ 207.9, 154.4, 79.8, 46.5, 44.2, 28.4, 22.7.

Preparation of *trans*-*N*-Boc-2,6-dimethylpiperidin-4-ol (63). A 0.2 M solution of **62** (23 mg, 0.10 mmol) in methanol was treated with sodium borohydride (8 mg, 0.20 mmol) and stirred for 10 min at room temperature, and then the solvent was evaporated. The residue was dissolved in 2 mL of saturated ammonium chloride solution and extracted with ether (5 mL × 6). The combined extracts were dried over K_2CO_3 and concentrated to give 23 mg (99%) of **63** as an oil: ^{1}H NMR ($CDCl_3$) δ 4.18 (m, 1 H), 3.89 (m, 1 H), 2.21 (dt, J = 13.7, 5.2 Hz, 1 H), 2.05 (ddd, J = 10.1, 7.2, 2.9 Hz, 1 H), 1.84 (ddd, J = 14.5, 9.6, 5.2 Hz, 1 H), 1.66–1.54 (m, 3 H), 1.45 (s, 9 H), 1.37 (d, J = 6.8 Hz, 3 H), 1.16 (d, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 155.1, 79.1, 62.9, 46.6, 46.4, 38.3, 37.0, 28.5, 22.5, 20.0. Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.67; H, 10.20; N, 6.17.

Preparation of *N*-Boc-perhydroazepine (64). A solution of di-*tert*-butyldicarbonate (12.20 g, 55.90 mmol) in 15 mL of THF was cooled to 0 °C and treated with a solution of perhydroazepine (5.82 g, 58.69 mmol) in 15 mL of THF. The mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was concentrated to give a crude product as an oil which was distilled under reduced pressure to give 9.0 g (81%) of **64** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.41–3.29 (m, 4 H), 1.67–1.65 (br, 4 H), 1.59–1.52 (br, 4 H), 1.46 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 155.5, 78.7, 46.8, 46.4, 28.4, 27.3, 26.7; MS m/z (relative intensity) 199 (M^+, 4), 143 (13), 128 (15), 98 (13), 70 (30), 57 (100). Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.11; H, 10.45; N, 7.02.

Preparation of *N*-Boc-2-methylperhydroazepine (65). A 0.5 M solution of **64** (1057 mg, 6.16 mmol) in ether was treated with TMEDA (616 mg, 0.8 mL, 5.3 mmol) followed by *sec*-butyllithium (1.4 m, 4.51 mL, 6.37 mmol) at −78 °C. The mixture was slowly warmed to −40 °C, stirred for 1 h, cooled to −78 °C, treated with dimethyl sulfate (803 mg, 0.6 mL, 6.37 mmol), and allowed to warm to room temperature. The mixture was diluted with 20 mL of water and extracted five times with 10 mL of ether. The combined extracts were dried over potassium carbonate and concentrated to give the crude product which was Kugelrohr distilled to give **65** (700 mg, 62%) as a colorless oil. ^{1}H NMR spectra showed a mixture of conformational isomers and are provided as supplementary material. Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.59; H, 11.04; N, 6.60.

Preparation of *N*-Boc-2-methylperhydroazepine-7-carboxaldehyde (70). A 0.5 M solution of **65** (75 mg, 0.36 mmol) in ether was cooled to −70 °C and treated with TMEDA (41 mg, 54 μL, 0.36 mmol), followed by *s*-BuLi (1.35 M, 0.34 mL, 0.46 mmol) dropwise. The mixture was slowly warmed to −30 °C, stirred for 2 h, and then cooled to −78 °C. The mixture was added to a cooled solution of DMF (34 mg, 36 μL, 0.46 mmol) in 0.5 mL of ether at −78 °C via cannula. The mixture was stirred for 10 min at −78 °C and then quenched with 4 mL of water. The mixture was warmed to room temperature and extracted with ether (5 mL × 6), and then the combined extracts were dried over K_2CO_3. The organic layer was concentrated to give a crude

product as an oil which was chromatographed on silica gel with 5% EtOAc/hexane (contains 0.5 M of Et_3N) as an eluent to give 39 mg (63%, based on the recovered starting material) of **70** as a white solid as a mixture of cis and trans mixture and 20 mg of the starting material: mp 85–89 °C; ^{13}C NMR ($CDCl_3$, mixture of both cis and trans isomers) δ 198.5, 155.4, 154.4, 81.4, 80.6, 61.5, 61.3, 51.4, 50.2, 36.2, 36.1, 28.6, 28.4, 28.2, 26.5, 25.9, 25.2, 24.7, 20.6, 20.2. Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.78; H, 9.65; N, 5.79.

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Supplementary Material Available: Experimental data for **4**, **6**, **8–10**, **16**, **17**, **19**, **21**, **24–26**, **28–39**, **41**, **43–45**, **47**, **49–51**, **53–55**, **66–69**, and **71–77** and analysis of the ^1H NMR spectra of **30** (46 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information. The X-ray data for **49** have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.