an aldol condensation product. In the presence of phosphorylating system, the phosphorus appears principally as inorganic phosphate, presumably by reaction with the water produced in the self-condensation of pyruvate.

Acknowledgment. We gratefully acknowledge the support of this investigation by the National Science Foundation.

Registry No. I, 10602-62-7; II, 10602-61-6; III, 84959-95-5; disodium 1-phenylvinyl phosphate, 76625-78-0; disodium 1-methylvinyl phosphate, 84959-92-2; disodium 1-furylvinyl phosphate, 84959-93-3; disodium 1-cyclohex-1-enyl phosphate, 84986-91-4; disodium 1,2-diphenylvinyl phosphate, 84959-94-4; acetophenone, 98-86-2; acetone, 67-64-1; 2-acetylfuran, 1192-62-7; cyclohexanone, 108-94-1; desoxybenzoin, 451-40-1; 2,2,6,6-tetramethylpiperidine, 768-66-1; diisopropylamine, 108-18-9; 2,6-dimethylpyridine, 108-48-5; 2,4,6-trimethylpyridine, 108-75-8; diisopropylmethylamine, 10342-97-9; *N*-*tert*-butylpiperidine, 14446-69-6; diisopropylethylamine, 7087-68-5; triethylamine, 121-44-8; diethylamine, 109-89-7; 1,5-diazabicyclo[4.3.0]non-5-ene, 3001-72-7; 1,52-diazabicyclo[5.4.0]undec-5-ene, 41015-70-7; 2-methylpyridine, 109-06-8; trichloromethane, 67-66-3; acetonitrile-d_3, 2206-26-0; dioxane, 123-91-1; *trans*-chalcone, 614-47-1; methyl dihydrogen phosphoric acid, 812-00-0; anilinium hydrogen 1-phenylvinyl phosphate, 70334-78-0; acetophenone anil, 1749-19-5; *O*-ethyl *N*-phenylacetimidate, 19655-72-2; anilinium hydrogen *N*-phenylphosphoramidate, 36097-59-3; anilinium hydrogen 1,2-diphenylvinyl phosphate, 84959-97-7; dimethyl 1,2-diphenylvinyl phosphate, 40731-57-5; dicyclohexylammonium 1-methylvinyl phosphate, 84959-99-9; dimethyl 1-methylvinyl phosphate, 4185-82-4; bis(trimethylsilyl) 1-methylvinyl phosphate, 57222-19-2; dicyclohexylammonium 1-furylvinyl phosphate, 84960-01-0; 2-(α-chloroacetyl)furan, 55984-17-3; dimethyl 1-furylvinyl phosphate, 66602-38-8; dicyclohexylammonium 1-cyclohex-1-enyl phosphate, 84960-03-2; (1-cyclohexen-1-yloxy)trimethylsilane, 6651-36-1; dihydrogen 2,4-dinitrophenyl phosphate, 2566-26-9; dimethyl 1-cyclohex-1-enyl phosphate, 3719-53-7.

Organoaluminum-Promoted Beckmann Rearrangement of Oxime Sulfonates

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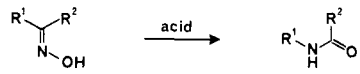
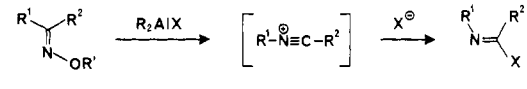
Abstract: The Beckmann rearrangement of oxime sulfonates with simultaneous nucleophilic trapping of the intermediary iminocarbocation by organoaluminum reagents is described. This process provides a new and highly efficient route to imino thioethers, imino selenoethers, imino nitriles, and α-alkylated amines starting from oxime sulfonates by the use of dialkylaluminum thiolates, selenolates, diethylaluminum chloride–trimethylsilyl cyanide, and trialkylaluminum–diisobutylaluminum hydride systems, respectively. The present organoaluminum-promoted Beckmann rearrangement of oxime sulfonates has been successfully applied to the synthesis of naturally occurring alkaloids, pumiliotoxin C and solenopsin A and B, in stereoselective fashion. Moreover, α,α-dialkylation of amines can be realized by the successive treatment of oxime sulfonates with trialkylaluminum followed by allylic or propargylic Grignard reagents in synthetically useful yields.

The Beckmann rearrangement is the skeletal rearrangement of ketoximes in the presence of certain acids, including Lewis acids, to give amides or lactams.[1] Since the first discovery of this



rearrangement by Beckmann in 1886,[2] successive investigations have largely clarified its scope, reaction mechanism, and the stereochemical configurations of the oximes employed. Accordingly, the Beckmann rearrangement has become an increasingly reliable synthetic tool in organic chemistry. The reaction has found broad application as a step in the manufacture of synthetic polyamides.[3] It is a preferred way to incorporate the nitrogen atom efficiently in both acyclic and alicyclic systems, thereby providing a powerful method for a variety of alkaloid syntheses.

The mechanism of the Beckmann rearrangement consists essentially of the formation of an electron-deficient nitrogen atom by the partial ionization of the oxygen–nitrogen bond of the oxime with a simultaneous intramolecular migration of the group anti to the departing hydroxy group, producing the iminocarbocation



which then reacts with water to give the corresponding amide. A careful examination of this reaction mechanism led us to consider that organoaluminum compounds might be employed as amphoteric reagents to induce the Beckmann rearrangement of oxime derivatives as well as to capture the intermediary iminocarbocation by the nucleophile which is originally attached to aluminum.[4] This proved to be the case. In this paper, we wish to disclose the organoaluminum-promoted Beckmann rearrangement of oxime derivatives, from which several new synthetic procedures have been developed as described in the following sections. Moreover, the synthetic utility of these new procedures has been clearly demonstrated by the synthesis of naturally occurring alkaloids, pumiliotoxin C and solenopsin A and B, in stereoselective fashion.

As oxime derivatives, oxime sulfonates can be used preferentially for the following reasons: (1) ready availability from oximes using *p*-toluenesulfonyl chloride or methanesulfonyl chloride in the presence of base in almost quantitative yields; (2) ease of handling because of their fine crystalline properties; (3) high enough reactivity to initiate the rearrangement by organoaluminum reagents.

(1) For reviews, see: (a) Blatt, A. H. *Chem. Rev.* **1933**, *12*, 215. (b) Jones, B. *Ibid.* **1944**, *35*, 335. (c) Moller, F. In "Methoden der Organischen Chemie"; Müller, E., Ed.; Thieme Verlag: Stuttgart, 1957; Vol. XI, Part 1, p 892. (d) Donaruma, I. G.; Heldt, W. Z. *Org. React. (N. Y.)* **1960**, *11*, 1. (e) Beckwith, A. L. J. In "The Chemistry of Amides"; Zabicky, J., Ed.; Interscience: New York, 1970; p 131. (f) McCarty, C. G. In "Chemistry of the Carbon-Nitrogen Double Bond"; Patai, S., Ed.; Wiley-Interscience: New York, 1970; p 408.

(2) Beckmann, E. *Ber.* **1886**, *19*, 988; **1887**, *20*, 1507.

(3) For reviews of polyamides, see: Moncrieff, R. W. "Man-made Fibres"; Wiley: New York, 1963; pp 335–355. "Nylon Plastics"; Kohan, M. I., Ed.; Wiley-Interscience: New York, 1973.

(4) For a review of aluminum reagents, see: Yamamoto, H.; Nozaki, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 169.

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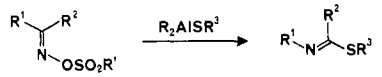
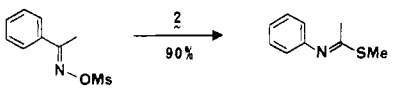
Synthesis of Imino Thioethers and Selenoethers. Imino thioethers are an important class of compounds as activated forms of amides for structural elaboration in alkaloid syntheses.[5] Classically, the preparation of imino thioethers has been effected in two steps from amides, i.e., conversion to thioamides with phosphorus pentasulfide followed by transformation to imino thioethers by Meerwein's reagent.[6] Several new methods have been reported recently, among which are (1) the reaction of ketenimines with thiols,[7] and (2) the transformation of thioketals into imino thioethers via thionium ions.[8] In addition to these previously known methodologies, we devised a more direct and general approach for the synthesis of imino thioethers from simple oximes by the use of dialkylaluminum thiolates.



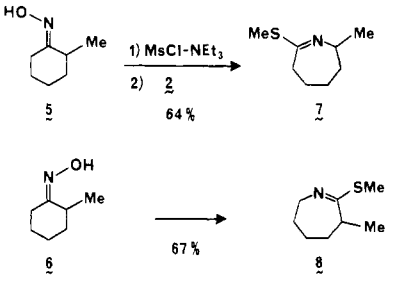
A series of dialkylaluminum thiolates were prepared in situ from (1) diisobutylaluminum hydride (DIBAH) and dimethyl disulfide, or from (2) trimethylaluminum and thiols.[9] Reaction of acetophenone oxime methanesulfonate (**1**) with diisobutylaluminum



methanethiolate (**2**) in methylene chloride proceeded smoothly under mild conditions (0 °C, 1 h) to furnish the desired imino thioether **3** in 90% yield. Structure **3** was characterized by an broad IR band at 1620 cm^{-1} ($\nu_{C=N}$) and ^1H absorpitons at δ 2.33 (SCH_3) and 1.93 ($N{=}CCH_3$). Notably, none of the substitution product **4** at the imino nitrogen was detected in this case. Structure **3** was further confirmed by the synthesis of the isomeric thiooxime derivative **4**. Thus, treatment of benzonitrile with

methyllithium followed by dimethyl disulfide produced **4**, which exhibited a sharp IR band at 1670 cm^{-1} ($\nu_{C=N}$) and ^1H absorptions at δ 2.70 (SCH_3) and 2.23 ($N{=}CCH_3$).

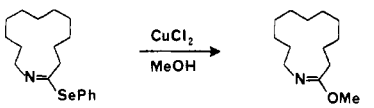
With the demonstration of the facility and effectiveness of this process, attention was directed toward the regioselectivity in the reaction of unsymmetrical ketoximes. The aluminum reagent **2** did react with methanesulfonates of the oximes **5** and **6** under sharp discrimination of the configuration of ketoximes. Thus, the anti oxime **5** was converted with methanesulfonyl choride–tri-



ethylamine into its mesylate which was treated with the reagent **2** to furnish the imino thioether **7** in 64% yield. In contrast, the isomeric syn oxime **6**[10] gave via the same reaction sequence the imino thioether **8** exclusively, in 67% yield. Obviously, the regioselectivity of the reaction follows the general rule of the Beckmann rearrangement, and preferential migration of the group anti to the oxime sulfonate was observed.

As revealed in Table I, most oxime sulfonates react readily with 1–2 equiv of organoaluminum thiolates at or below 0 °C (entry 16). Addition of organoaluminum thiolates at low temperature (−78 °C) is crucial (entries 6 and 9), since the reverse addition in some cases caused serious side reactions. The high regioselectivity of the reaction is apparent (entries 3, 7, 13–18). A synthetically more important feature of the new process is that introduction of various alkylthio as well as arylthio moieties (entries 11, 16, 17) could be easily attained. Indeed, preparation of these derivatives using other methods would be difficult by the methodological limitation. Furthermore, imino aryl thioethers were found to be more susceptible toward nucleophilic attack. This process, however, suffers from one limitation: reaction of cyclopentanone oxime *p*-toluenesulfonate (**9**) with the aluminum reagent **2** under standard conditions resulted in formation of unrearranged *N*-methylthioimine **18** in 47% yield (entry 1). Such anomalous behavior was observed only in the case of cyclopentanone oxime sulfonate (cf. entries 3 and 13).

The present aluminum method, in principle, is applicable to a synthesis of other heterosubstituted imino derivatives, since the preparations of various organoaluminum reagents of type R_2AlX are well established.[11] For instance, treatment of oxime sulfonates with organoaluminum selenolates[12] produced imino selenoethers as shown in Table II. To the best of our knowledge, the imino selenoethers cited in Table II were prepared for the first time.[13] The scope of the synthetic potential of this highly interesting functionality awaits further investigation. But, the high reactivity of imino selenoethers is evident from the following experiment. Addition of anhydrous cupric chloride (1 equiv) to a methanolic solution of imino selenoether **33** at 0 °C gave almost instantaneously the corresponding imino methyl ether **36** in 53% yield.



Synthesis of Imino Nitriles. Undoubtedly, α-amino acids are most widely distributed as proteins in both plant and animal kingdom, and a wide variety of synthetic approaches for these substances have been developed so far.[14] Among them, Strecker synthesis is well known and has a general applicability, although this method suffers from the severe disadvantages that a suitably optical resolution is always necessary to obtain the desired enantiomers from the racemic α-amino acids.[15] In contrast, imino nitriles are viewed as a masked form of α-amino acids, and the presence of an sp^2-prochiral center (a C=N bond) in them would serve a latent possibility to furnish optically active α-amino acids. Therefore, an efficient approach to imino nitriles would be expected.[16] The combination of diethylaluminum chloride with

(5) For a recent application of imino thioethers to the alkaloid synthesis, see: Aratani, M.; Dunkerton, L. V.; Fukuyama, T.; Kishi, Y.; Kakoi, H.; Sugiura, S.; Inoue, S. *J. Org. Chem.* **1975**, *40*, 2009. Fukuyama, T.; Dunkerton, L. V.; Aratani, M.; Kishi, Y. *Ibid.* **1975**, *40*, 2011.

(6) Walter, W.; Voss, J. In ref 1e, p 383.

(7) Barker, M. W.; Lauderdale, S. C.; West, J. R. *J. Org. Chem.* **1973**, *38*, 3951.

(8) Trost, B. M.; Vaultier, M.; Santiago, M. L. *J. Am. Chem. Soc.* **1980**, *102*, 7929.

(9) Davidson, N.; Brown, H. C. *J. Am. Chem. Soc.* **1942**, *64*, 316.

(10) Jung, M. E.; Blair, P. A.; Lowe, J. A. *Tetrahedron Lett.* **1976**, 1439.

(11) Mole, T.; Jeffery, E. A. "Organoaluminum Compounds"; Elsevier: Amsterdam, 1972.

(12) Kozikowski, A. P.; Ames, A. *J. Org. Chem.* **1978**, *43*, 2735.

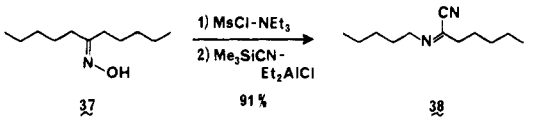
(13) Selenoamides have been synthesized previously from thioamides by the use of sodium hydrogen selenides. See: Hartmann, H. *Z. Chem.* **1971**, *11*, 60.

(14) For reviews, see: Greenstein, J. P.; Winitz, M. "Chemistry of the Amino Acids"; Wiley: New York, 1961; Vols. 1–3. Thompson, J. F.; Morris, C. J.; Smith, I. K. *Annu. Rev. Biochem.* **1969**, *38*, 137. "Amino-acids, Peptides, and Proteins", Specialist Periodical Reports; The Chemical Society: London, 1969 and succeeding years.

(15) For a review, see: Gilbert, E. E. "Sulphonation and Related Reactions"; Wiley-Interscience: New York, 1965; p 136.

(16) For recent syntheses of α-imino nitriles, see: Kimpe, N. D.; Verhé, R.; Buyck, L. D.; Chys, J.; Schamp, N. *Synthesis* **1978**, 895. Kimpe, N. D.; Verhé, R.; Buyck, L. D.; Chys, J.; Schamp, N. *Bull. Soc. Chim. Belg.* **1979**, *88*, 695. For a related study, see: Kimpe, N. D.; Verhé, R.; Buyck, L. D.; Hasma, H.; Schamp, N. *Tetrahedron* **1976**, *32*, 3063. Kimpe, N. D.; Verhé, R.; Buyck, L. D.; Chys, J.; Schamp, N. *Org. Prep. Proc. Int.* **1978**, *10*, 149. Kimpe, N. D.; Verhé, R.; Buyck, L. D.; Schamp, N. *Synthesis* **1979**, 741.

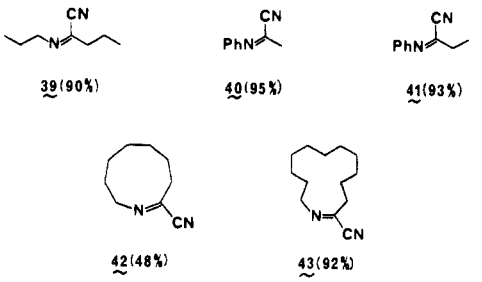
commercially available trimethylsilyl cyanide (Utimoto's method)[17] was utilized for our systems. For example, 6-undecanone oxime (**37**) (1 equiv) was converted in the usual manner to its mesylate,



37 **38**

which was treated successively with trimethylsilyl cyanide (1.1 equiv) and diethylaluminum chloride (1.1 equiv) at −78 °C. The mixture was stirred at −20 °C for 1 h to afford the imino nitrile **38** in 91% yield from **37**.

In a similar manner, a variety of oxime sulfonates were transformed to the corresponding imino nitriles which are listed below. Since several imino nitriles are acid labile, column

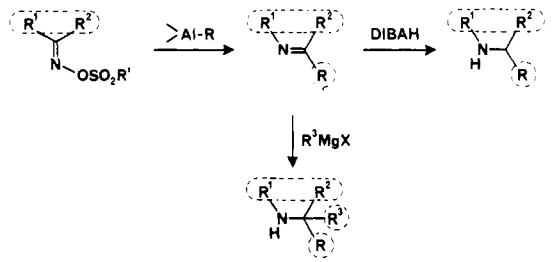


39 (90%) **40** (95%) **41** (93%)

42 (48%) **43** (92%)

chromatography on silanized silica gel can be employed to purify the products. The high regioselectivity is observed in the case of acetophenone and propiophenone oxime mesylates. It should be noted that other Lewis acids such as tin tetrachloride, boron trifluoride etherate, or trimethylsilyl trifluoromethanesulfonate failed to serve the desired imino nitriles in the presence of trimethylsilyl cyanide.

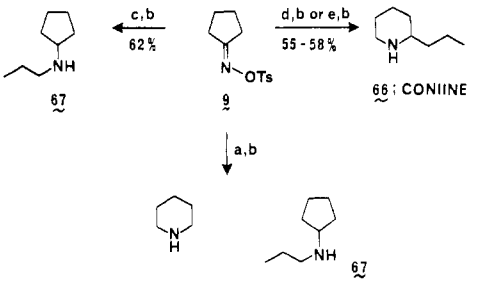
Synthesis of α-Alkylated Amines. α-Alkylation of amines has received a great deal of attention since a large range of biologically active alkaloids possess such structures.[18] Therefore, numerous approaches to α-alkylation of amines have been investigated.[19] Most of them reported so far, however, are not straightforward and require lengthy or complicated syntheses. A new and efficient approach to α-alkylated amines is now available based on the organoaluminum-promoted Beckmann rearrangement of oxime sulfonates. The reaction is summarized below. Reaction of oxime



sulfonates with several equivalents of alkylaluminum reagents in methylene chloride resulted in formation of imines, which were directly reduced with excess DIBAH to give the corresponding amines. Moreover, the intermediary imines were directly treated with Grignard reagents producing the α,α-dialkylated amines, which will be the subject in the last section. One of the characteristic features of the method is that it permits the introduction of two alkyl groups into a substrate with a simultaneous ring expansion operation. In other words, the carbon framework of a substrate can be elaborated with a regiospecific incorporation of a nitrogen functional group in one step.

This approach has a wide generality as illustrated in Table III. Oxime sulfonates of linear or cyclic structures are employable. Diethylaluminum alkynide (entries 5, 13, 16–18) can be successfully used for introduction of the alkynyl group to a substrate in preference to ethyl group. Thus, a new entry to propargylic amino derivatives is now available in a single operation. Halogenated hydrocarbons such as methylene chloride, chloroform, and 1,2-dichloroethane may be used as suitable solvent systems. Use of tetrahydrofuran (THF) gave little or no α-alkylated amines. Rigorous regioselectivity is seen for the rearrangement–alkylation site (entries 6–8, 14–20) as is observed in the synthesis of imino thioethers and selenoethers.

Since the first discovery of the successive Beckmann rearrangement–alkylation sequence by alkylaluminums, we had hoped to apply the reaction to the synthesis of physiologically active alkaloids such as pumiliotoxin C and solenopsin A and B. At the outset of these total syntheses, we studied the piperidine ring formation by Beckmann rearrangement in aprotic media and attempted the reaction of cyclopentanone oxime *p*-toluenesulfonate (**9**) with tri-*n*-propylaluminum to produce the simple piperidine

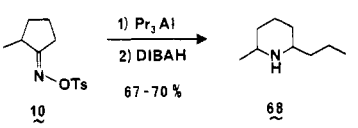


67 **9** **66**; CONIINE

67

alkaloid coniine (**66**).[20] Unfortunately, however, the original plan resulted in total failure. Thus, under standard conditions (method A in Table III), a mixture of the unrearranged amine **67** (23%) and piperidine was obtained in addition to a small amount of the desired **66** (4%). Moreover, using hexane as the solvent, amine **67** was produced exclusively in 62% yield. Surprisingly, switching the initial temperature from −78 to 40–80 °C enhances the normal rearranged product **66** at the expense of cyclopentylamine formation. These results are presumably ascribed to the rapid dissociation of dimeric tri-*n*-propylaluminum at high temperature, which would enhance the Lewis acidity of tri-*n*-propylaluminum toward the rearrangement of **9** as well as the nucleophilicity of the *n*-propyl group in $(n\text{-Pr})_3$Al at the intermediary imino carbocation.

In contrast with **9**, 2-alkylcyclopentanone oxime sulfonates undergo the rearrangement cleanly even in hexane solvent. For example, 2-methylcyclopentanone oxime tosylate (**10**) reacted with



10 **68**

tri-*n*-propylaluminum in either methylene chloride or hexane to furnish 2-methyl-6-*n*-propylpiperidine (**68**) in 67–70% yield. Thus, the rearrangement of five-membered ring systems appear to be highly dependent on the nature of the organoaluminum reagents in solution and the substrates.

With the modified recipe for the synthesis of α-alkylpiperidine systems in hand, a simple and highly efficient route to pumiliotoxin C is described in the following section.

Synthesis of Pumiliotoxin C. Pumiliotoxin C was originally isolated from the skin of neotropical frogs *Dendrobates pumilio* and *D. auratus*.[21] The complex stereochemical features and the

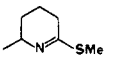
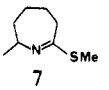
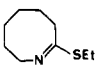
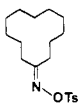
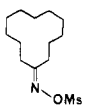
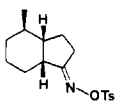
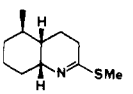
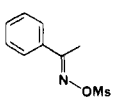
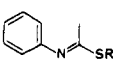
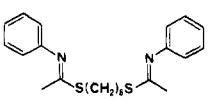
(17) Utimoto, K.; Obayashi, M.; Shishiyama, Y.; Inoue, M.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 3389.

(18) Glasby, J. S. "Encyclopedia of the Alkaloids"; Plenum Press: New York, 1975; Vols. 1–2.

(19) For example, see: Seebach, D.; Enders, D.; Renger, B. *Chem. Ber.* **1977**, *110*, 1852. Renger, B.; Kalinowski, H.-O.; Seebach, D. *Ibid.* **1977**, *110*, 1866. Seebach, D.; Enders, D.; Dach, R.; Pieter, R. *Ibid.* **1977**, *110*, 1879. Meyers, A. I.; Hoeve, W. T. *J. Am. Chem. Soc.* **1980**, *102*, 7125. Shono, T.; Matsumura, Y.; Tsubata, K. *Ibid.* **1981**, *103*, 1172.

(20) Chemnitius, F. *J. Prakt. Chem.* **1928**, *118*, 25.

Table I. Synthesis of Imino Thioethers[a]

entry	oxime sulfonate	reagent (equiv)	conditions[b] (°C, h)	product	R	yield[c] (%)
1	 **9**	*i*-Bu_2AlSMe (1.1)	0, 0.5 25, 2	 **18**		47
2		*i*-Bu_2AlSMe (3)	40, 0.1	 **19**		5
3	 **10**	*i*-Bu_2AlSMe (3)	40, 0.1	 **20**		46
4	 **11**	*i*-Bu_2AlSR (1.1)	0, 1		**21**, R = Me	58
5		Me_2AlSR (1.1)	0, 1		**22**, R = Et	62
6	 **12**	*i*-Bu_2AlSR (1.1)	0, 1		**21**, R = Me	52 (30)[e]
7	 **13**	*i*-Bu_2AlSMe (1.1)	0, 1	 **7**		66
8	 **14**	Me_2AlSEt (1.1)	0, 1	 **23**		90
9	 **15**	*i*-Bu_2AlSR (1.1)	0, 1		**24**, R = Me	97 (41)[e]
10		Me_2AlSR (1.1)	0, 1		**25**, R = Allyl	80
11		Me_2AlSR (1.1)	0, 1		**26**, R = Ph	82
12	 **16**	*i*-Bu_2AlSR (1.1)	0, 1		**24**, R = Me	95
13	 **17**	*i*-Bu_2AlSMe (3)	50, 0.1[d]	 **27**		70
14	 **1**	*i*-Bu_2AlSR (2)	0, 1		**3**, R = Me	90
15		Me_2AlSR (2)	0, 1		**28**, R = *t*-Bu	85
16		Me_2AlSR (2)	−78, 4		**29**, R = Ph	88
17		Me_2AlSR (2)	0, 0.5 25, 2		**30**, R = 	68
18		Me_2AlS $(CH_2)_6$ (0.5) Me_2AlS	0, 2	 **31**		46

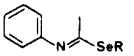
[a] Reaction performed on a 1-2 mmol scale. [b] In entries 2, 3, and 13, the aluminum reagent was added at 40-50 °C. [c] Isolated yield based on oxime sulfonate. [d] 1,2-Dichloroethane was used as solvent. [e] The oxime tosylates in CH_2Cl_2 were added at −78 °C to the aluminum thiolate.

paucity of this physiologically active alkaloid provide a considerable challenge to the synthetic chemists. Until recently, about ten independent syntheses of the toxin have been reported, but most of them suffer at least one disadvantage in the practical sense.[22]

(21) Daly, J. W.; Tokuyama, T.; Habemehl, G.; Karle, I. L.; Witkop, B. *Justus Liebigs Ann. Chem.* **1969**, *729*, 198. Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. L. *Helv. Chim. Acta* **1977**, *60*, 1128.

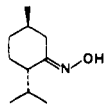
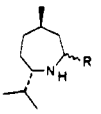
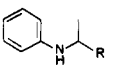
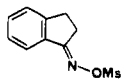
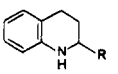
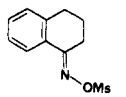
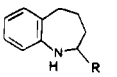
(22) For reviews, see: Inubushi, Y.; Ibuka, T. *Heterocycles* **1977**, *8*, 633, and references cited therein. See also: Overman, L. E.; Kessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179. For an enantioselective synthesis of pumiliotoxin C, see: Oppolzer, W.; Flaskamp, E. *Helv. Chim. Acta* **1977**, *60*, 204.

Table II. Synthesis of Imino Selenoethers

entry	oxime sulfonate	reagent[a] (equiv)	conditions[b] (°C, h)	product[c]	R	yield[d] (%)
1	16	Me_2AlSeR (2)	0, 1		**32**, R = Me	71
2		i-Bu_2AlSeR (1.1)	0, 0.5		**33**, R = Ph	57
3	1	Me_2AlSeR (2)	0, 1.5		**34**, R = Me	49
4		i-Bu_2AlSeR (1.1)	0, 0.5		**35**, R = Ph	61

[a] For preparation of the reagent, see Experimental Section. [b] The organoaluminum reagent was added at −78 °C, and the mixture was stirred under the conditions indicated. [c] Purified by a short-path column chromatography. [d] Isolated yield based on the starting oxime sulfonate.

Table III. Synthesis of α-Alkylated Amines

entry	starting material	method[a]	product	R	yield[b] (%)
1	11	A		**47**, Me	70
2		A		**48**, Et	47
3		A		**49**, n-Pr	64
4		A		**50**, i-Bu	52
5		B		**51**, C≡C-Bu	67
6	13	A		**52**, n-Pr[c]	48
7	 **44**	C		**53**, Me[c]	57[d]
8		D		**54**, H	82[d]
9	14	A		**55**, n-Pr	68
10	16	A		**56**, Me	60
11		E		**57**, H	73
12	15	A		**56**, Me	56
13		B		**58**, C≡C-Ph	71
14	1	A		**59**, Me	67
15		E		**60**, H	87
16		B		**61**, C≡C-Me	60
17		B		**62**, C≡C-Bu	83
18		B		**63**, C≡C-Ph	67
19	 **45**	E		**64**, H	80
20	 **46**	A		**65**, n-Pr	88

[a] For methods A-E, see Experimental Section. [b] Isolated yield based on oxime sulfonate, unless otherwise noted. [c] Obtained as a mixture of cis and trans isomers. [d] Overall yield from L-menthone oxime.

This fact prompted us to investigate the short and highly stereoselective synthesis of pumiliotoxin C, which should be easily adapted for the preparation of other pumiliotoxins.

Synthetic design was based on the strategy summarized in Scheme I. 4-Methyltetrahydroindenone (**69**) was envisaged as an ideal starting material for ease of large-scale preparation via the Stobbe condensation of 2-methylcyclohexanone.[23] The enone **69** could then be converted to cis-fused hexahydroindanone **70** by stereoselective hydrogenation[24] and elaborated via alkyl-

Scheme I

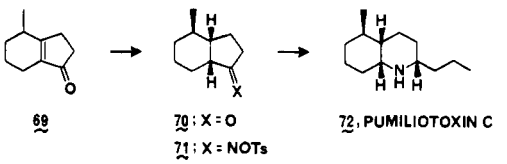


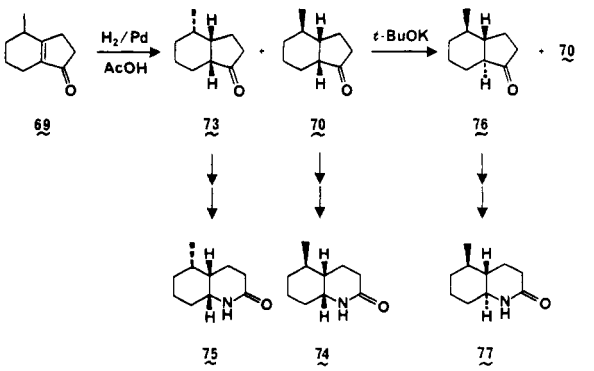
Table IV. Stereoselective Hydrogenation of 4-Methyltetrahydroindenone (**69**)[a]

run	solvent	additive	product ratio[b] (70/73)
1	EtOH		56:44
2	THF		79:21
3	HCOOH		75:25
4	CH_3COOH		73:27
5	CH_3CH_2COOH		87:13
6	$CH_3(CH_2)_7COOH$		76:24
7	THF	PhOH	85:15
8	THF	$(CH_3)_2CHCOOH$	88:12
9	THF	PhCOOH	90:10
10	THF	CH_3CH_2COOH	93:7
11	THF	CH_3CH_2COOH-Et_3N	94:6
12	hexane	CH_3CH_2COOH	90:10
13	acetone	CH_3CH_2COOH	93:7
14	ether	CH_3CH_2COOH	94:6
15	DME	CH_3CH_2COOH	94:6
16	dioxane	CH_3CH_2COOH	95:5

[a] The experiment was carried out over palladium black as catalyst in the presence or absence of additives. [d] Determined by GLC analysis.

aluminum-promoted Beckmann rearrangement of the oxime tosylate **71** to pumiliotoxin C (**72**). The stereochemical outcome in the present synthesis highly depends on the stereoselective hydrogenation of the enone **69** to establish the three chiral centers of the carbocyclic ring in **70**, and to utilize these centers to control the introduction of the chiral center at carbon 2 in pumiliotoxin C. Thus, we examined at the outset the hydrogenation conditions of **69**.

Attempted hydrogenation of the enone **69** in acetic acid over



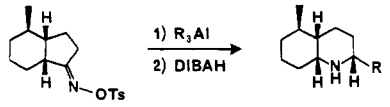
palladium black furnished a mixture of cis-fused indanones **70** and **73** in a ratio of 73:27. Both compounds were independently transformed into the corresponding lactams **74** and **75** by the

(23) El-Abbady, A. M.; El-Ashry, M.; Doss, S. H. *Can. J. Chem.* **1969**, *47*, 1483.

(24) We thank Professor S. Nishimura for helpful discussions for this hydrogenation reaction.

literature procedure.[25] Furthermore, the major isomer **70** was epimerized with potassium *tert*-butoxide to give a separable (3:2) equilibrium mixture of **70** and **76**, which gave the lactam **77** in a similar manner. The lactams **74** and **77** correspond to authentic samples in all respects.[25] In order to gain the desired ketone **70** selectively, the choice of the hydrogenation conditions is crucial. The degree of stereoselectivity of the reduction, **70**/**73**, was dependent on the catalyst and solvent used. Among the catalysts, platinum oxide gave similar selectivity to palladium black, but rhodium catalyst did not under comparable reduction conditions. Table IV shows the solvent effect over palladium black as hydrogenation catalyst. In carboxylic acid solvent the selectivity is lower. The use of propionic acid as catalyst in ethereal solvents gave marked selectivity (94/6–95/5).

Specifically, selective hydrogenation was realized with the greatest stereoselectivity (~95%) by using palladium black as catalyst in dioxane in the presence of catalytic propionic acid (12 mol %) at 20 °C for 12 h and 1 atm of H_2. Without isolation the ketone **70** was treated with hydroxylamine hydrochloride (1.5 equiv) and sodium acetate (2 equiv) in methanol at 20 °C for 5 h to furnish after one recrystallization from methanol–water the oxime **78** as white crystals in 84% overall yield from **69**. Treatment of the oxime **78** with *p*-toluenesulfonyl chloride (2 equiv) in pyridine at −20 °C for 1 h and at 0 °C for 5 h, followed by trituration with excess cold water, produced the oxime tosylate **71** in 90–95% yield. Finally, with tri-*n*-propylaluminum (3 equiv)

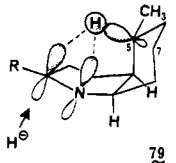


71 **72**; R = Pr (60%), PUMILIOTOXIN C
80; R = Me (57%)

the tosylate **71** was transformed into the imine **79** which was directly reduced with excess DIBAH (4 equiv) stereospecificially (99% pure by GC assay) from the exo side to give pumiliotoxin C (**72**) in 60% yield after column chromatography. The spectral and physical data of synthetic pumiliotoxin C and its hydrochloride were identical in all respects with those of an authentic sample.[22]

In a like manner, the synthesis of other pumiliotoxin analogues can be prepared without any difficulties. For example, reaction of **71** with trimethylaluminum–DIBAH afforded 2-methyl-*cis*-decahydroquinoline **80** in 57% yield in a stereoselective fashion.

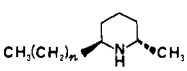
The remarkably high stereoselectivity in the DIBAH reduction of the imine **79** is presumably ascribed to the following steric as



79

well as electronic effects. The exo-side approach of the hydride ion toward the stable conformation of **79** is preferred in view of the steric screening effect of the imino group by the carbocyclic ring, especially its C-5 and C-7 axial hydrogens. Moreover, the electrostatic interaction between the C-5 axial hydrogen and the imino π bond are considered to be of importance, thereby facilitating the exo-side attack of the hydride ion.

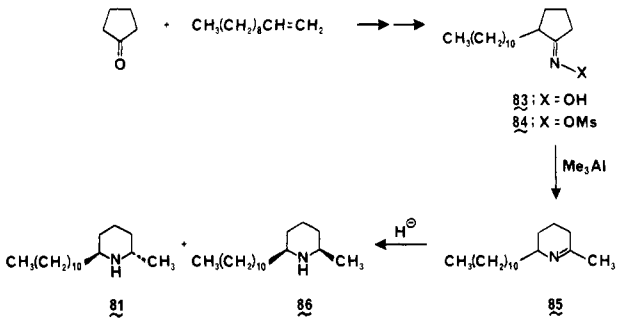
Synthesis of Solenopsin A and B. Solenopsin A (**81**) and B (**82**),



81; SOLENOPSIN A (n=10)
82; SOLENOPSIN B (n=12)

isolated from the red form of the fire ant, *Solenopsis saevissima*,[26] have gained interest because of their pronounced hemolytic, insecticidal, and antibiotic activity.[27] Therefore, synthetic investigations in several laboratories have been carried out to a great extent.[28] None of the procedures, however, are generally applicable for synthesizing the characteristic *trans*-2-alkyl-6-methylpiperidine structure in solenopsin A (**81**) and B (**82**), since specific introduction of an alkyl group to the desired trans form is not easy to achieve.[29,31] This fact, together with the occurrence of the same structural unit in other natural product such as *pseudo*-carpaine,[29] himbeline, himandravine,[30] lythranine, and lythranidine[31] led us to study the stereospecific route to solenopsin A and B, using the Beckmann rearrangement–alkylation sequence by alkylaluminum compounds.

Scheme II



Scheme II shows a simple route to solenopsin A. Reaction of excess cyclopentanone (10 equiv) with 1-undecene (1 equiv) in the presence of silver oxide (1 equiv) at 130 °C for 5 h produced, after isolation by the literature procedure, 2-undecylcyclopentanone,[32] which without purification was treated with hydroxylamine hydrochloride (2 equiv)–sodium acetate (3 equiv) in methanol at 25 °C for 5 h to give the pure anti oxime **83** in 73% overall yield from 1-undecene as a semisolid. The anti oxime **83** was converted to the corresponding mesylate **84** in 90–95% yield with methanesulfonyl chloride (1.1 equiv)–triethylamine (1.5 equiv) in methylene chloride at −20 °C for 40 min. The oxime tosylate of **83** can be prepared with *p*-toluenesulfonyl chloride (2 equiv) in pyridine in lower yield (35%) because of the difficulty in its trituration from excess cold water. Thus, the oxime mesylate **84** was employed for the rearrangement. Treatment of **84** in methylene chloride with 2 equiv of trimethylaluminum in toluene at −78 °C for 5 min and 25 °C for 1 h resulted in formation of imine **85** in 54% yield after workup with the sodium fluoride–water method. This rearrangement appeared to be sensitive to the reaction temperature, and at higher temperature (>40 °C) some decomposition of the product **85** was observed by TLC. Completion of the synthesis requires reduction of the C=N double bond of **85** with the correct configuration. Unfortunately, however, it was soon apparent from examination of the literature that the existing methodology was totally inadequate for the selective reduction of **85** into the trans 2,6-disubstituted piperidine structure, and up to 50% selectivity for the desired trans isomer was observed.[28] Thus, attempted reduction of **85** using usual aluminum- or borohydride-type reagents[33] in different solvent at low temperature afforded solenopsin A (**81**) and its cis isomer **86** in the range of 1/99 to 80/20 (by GC analysis) as illustrated in Table V (entries 1–10). Excellent stereoselectivity was attained in the

(25) Oppolzer, W.; Fehr, C.; Warneke, J. *Helv. Chim. Acta* **1977**, *60*, 48.
(26) MacConnell, J. G.; Blum, M. S.; Fales, H. M. *Tetrahedron* **1971**, *27*, 1129.
(27) Adroung, G. A.; Derbes, V. J.; Jung, R. C. *Science* **1959**, *130*, 449. Blum, M. S.; Walker, J. R.; Callahan, P. S.; Novak, A. F. *Ibid.* **1958**, *128*, 306.
(28) For previous syntheses of solenopsin A, see: Hill, R. K.; Yuri, T. *Tetrahedron* **1977**, *33*, 1569. Moriyama, Y.; Doan-Huynh, D.; Monneret, C.; Khuong-Huu, Q. *Tetraheron Lett.* **1977**, 852. Fuji, K.; Ichikawa, K.; Fujita, E. *Chem. Pharm. Bull.* **1979**, *27*, 3183. See also ref 25.
(29) Govindachari, T. R.; Pai, B. R.; Narasimhan, M. S. *J. Chem. Soc.* **1954**, 1847. Govindachari, T. R.; Nagarajan, K.; Viswanathan, N. *Tetrahedron Lett.* **1965**, 1907.
(30) Pinhey, J. T.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1961**, *14*, 106. Fridrichsons, J.; Mathieson, A. M. *Acta Crystallogr.* **1962**, *15*, 119.
(31) Fujita, E.; Fuji, K.; Bessho, K.; Sumi, A.; Nakamura, S. *Tetrahedron Lett.* **1967**, 4595.
(32) Hájek, M.; Málek, *J. Collect. Czech. Chem. Commun.* **1976**, *41*, 746.
(33) Hajos, A. "Complex Hydride"; Elsevier: Amsterdam, 1979.

Table V. Stereoselectivity in the Reduction of the Imine **85** with Hydride Reagents[a]

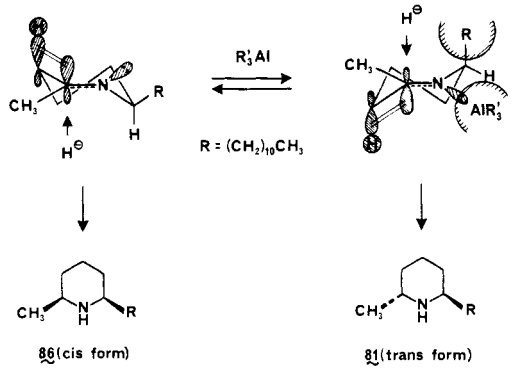
run	hydride reagent	solvent	product ratio[b] (86:81)
1	DIBAH (4 equiv)	CH_2Cl_2	99:<1
2	$LiAlH_4$ (7 equiv)-NaOMe (14 equiv)	THF	99:<1
3	$NaBH_3CN$ (3 equiv)-HCl	MeOH	98:2
4	$LiAlH_4$ (7 equiv)-$Ti(OPr^i)_4$ (7 equiv)	THF	90:10
5	*n*-BuLi (5 equiv)-DIBAH (5 equiv)	ether	83:17
6	$LiAlH_4$ (25 equiv)-LiCl (50 equiv)	THF	80:20
7	$LiAlH_4$ (7 equiv)-$NiCl_2$ (7 equiv)	THF	75:25
8	$LiAlH_4$ (5 equiv)-$TiCl_3$ (10 equiv)	THF	67:33
9	$LiAlH_4$ (25 equiv)	CH_2Cl_2 or THF	67:33
10	$LiAlH_4$ (25 equiv)	ether	20:80
11	$Mg(AlH_4)_2$ (25 equiv)	ether	33:67
12	$LiAlH_4$ (7 equiv)-$BF_3{\cdot}OEt_2$ (7 equiv)	ether	33:67
13	$LiAlH_4$ (7 equiv)-$TiCl_4$ (7 equiv)	THF	25:75
14	$LiAlH_4$ (7 equiv)-Me_3Al (7 equiv)	ether	13:87
15	$LiAlH_4$ (7 equiv)-Bu^i_3Al (7 equiv)	THF	6:94
16	$LiAlH_4$ (7 equiv)-Me_3Al (7 equiv)	DME	6:94
17	$LiAlH_4$ (7 equiv)-Me_3Al (7 equiv)	THF	5:95

[a] Unless specified, the experiment afforded **81** and **86** in >90% yield. For reduction conditions, see Experimental Section. [b] Determined by GLC analysis.

formation of the trans form **81** using lithium aluminum hydride ($LiAlH_4$) in ethereal solvents in the presence of an equimolar amount of trialkylaluminum at low temperature (entries 14–17), and finally solenopsin A (**81**) was obtained almost exclusively (~95% pure) by the use of $LiAlH_4$ (7 equiv)–Me_3Al (7 equiv) in THF at −78 to 0 °C (entry 17). The spectral data (^1H NMR and IR) of synthetic solenopsin A were in good agreement with the reported ones.[26]

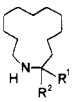
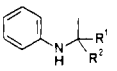
In a similar manner, solenopsin B (**82**) was prepared with high stereoselectivity (~95% by GLC assay) using the procedure which exactly paralleled that described above for synthesis of solenopsin A.

The observed high degree of stereoselectivity by the reduction of the imine with the $LiAlH_4$–trialkylaluminum system is of high synthetic value and deserves some comments for the stereochemical outcome, which is tentatively rationalized by the Houk theory[34] as well as the theory of charge-transfer stabilization of the transition state for nucleophilic addition to a carbonyl group.[35] Both theories would predict the strong preference for anti-periplanar and staggered attack of the hydride ion (H^-) with respect to the vicinal σ_{C-H} bond to the imino functional group. Thus, in the hydride reduction of the imine **85**, the underside approach of the hydride ion toward the imino π bond is preferred by the stabilization of the σ^*_+ orbital (low-lying vacant orbital of the imine) through electron delocalization from the σ_{C-H} bond into the σ^*_+ orbital, producing the cis isomer **86**. On the other hand,



in the presence of trialkylaluminum (R'_3Al) as Lewis acid, the alkyl group (R) of **85** would occupy the axial position because of the steric interaction between R and R'_3Al coordinated to the nitrogen lone-pair electrons ($A^{(1,2)}$ strain).[36] Such a conformational change facilitates the upperside approach of the hydride ion toward the imino π bond to furnish the desired trans isomer **81**.

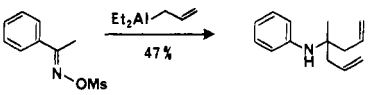
Table VI. Synthesis of α,α-Dialkylamines[a]

entry	oxime sulfonate	product	R^1	R^2	yield (%)
1	**9**		**89**, Me	allyl	51
2	**11**		**90**, Me	propargyl	55
3			**88**, Me	allyl	60
4			**91**, Pr	allyl	63
5	**16**		**92**, Me	propargyl	84
6			**93**, Me	allyl	84
7	**1**		**94**, Me	propargyl	61
8			**95**, $PhC{\equiv}C^b$	allyl	88
9			**96**, Me	allyl	54
10			**97**, Me	crotyl	56[c]
11			**98**, Me	propargyl	43
12			**99**, $CH_3(CH_2)_3C{\equiv}C^b$	allyl	74

[a] Unless otherwise stated, oxime sulfonate was treated with Me_3Al or Pr_3Al according to the method A, and the resulting ketimine was directly alkylated using R^2MgBr. For details, see Experimental Section. [b] Organoaluminum reagents of type $Et_2AlC{\equiv}CR$ were used. [c] A 3:4 mixture of α and γ isomers (R^2 = crotyl or 1-methyl-2-propenyl) was obtained.

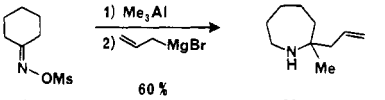
Synthesis of α,α-Dialkylated Amines. With the successful application of the newly developed Beckmann rearrangement–alkylation sequence to the synthesis of several alkaloids described above, we focus our interest toward the α,α-dialkylation process. In particular, the introduction of the functionalized alkyl groups enables further transformation of the produced amines to synthetically more important materials.

Reaction of acetophenone oxime mesylate (**1**) with excess al-



1 **87**

lyldiethylaluminum (4 equiv) in methylene chloride afforded α,α-diallylated amine **87** (47% yield) as the sole product. This information led us to investigate an efficient allylation of the ketimines derived from the Beckmann rearrangement of oxime sulfonates by organoaluminum reagents. As an allylation reagent, the Grignard reagent is employable for ease of preparation and handling. Thus, cyclohexanone oxime mesylate in methylene chloride was rearranged with trimethylaluminum (2 equiv) at 0 °C for 1 h to give the imine which was directly alkylated using allylmagnesium bromide (2 equiv) in ether to furnish 2-allyl-2-methylazacycloheptane (**88**) in 60% yield.



11 **88**

Other examples of the reaction are given in Table VI. Unsymmetrical allylic Grignard reagents such as crotylmagnesium bromide provide a mixture of α and γ isomers (entry 10). Successive introduction of alkynyl and allyl groups is also possible (entries 8 and 12). Notably, the propargyl group can be introduced in a regioselective fashion (entries 2, 5, 7, 11), providing an important precursor for the synthesis of various naturally occurring

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Table VII. Physical Properties and Analytical Data of Oxime Sulfonates

oxime sulfonate	mp (°C)	^{1}H NMR (δ)[a]
1	64-65	7.19-7.81 (5 H, m, aryl CH), 3.77 (3 H, s, CH_3SO_3), 2.40 (3 H, s, CH_3C=N)
9	75-77	7.02-7.82 (4 H, m, aryl CH), 2.41 (3 H, s, CH_3), 2.16-2.70 (4 H, m, CH_2C=N), 1.56-1.99 (4 H, m, CH_2CH_2)
10	b	7.10-7.88 (4 H, m, aryl CH), 2.43 (3 H, s, CH_3), 2.25-2.85 (3 H, m, CHC=N, CH_2C=N), 1.11 (3 H, d, J = 6.5 Hz, CH_3)
11	43-45	3.09 (3 H, s, CH_3), 2.13-2.72 (4 H, m, CH_2C=N), 1.40-1.97 (6 H, m, CH_2)
12	b	7.10-7.92 (4 H, m, aryl CH), 2.38 (3 H, s, CH_3), 1.38-1.93 (6 H, m, CH_2)
13	b	7.13-7.95 (4 H, m, aryl CH), 2.35 (3 H, s, CH_3), 1.03 (3 H, d, J = 6.5 Hz, CH_3)
14	38-40	3.00 (3 H, s, CH_3), 2.32-2.83 (4 H, m, CH_2C=N), 1.45-1.93 (8 H, m, CH_2)
15	85-87	7.13-7.93 (4 H, m, aryl CH), 2.40 (3 H, s, CH_3), 2.13-2.53 (4 H, m, CH_2C=N)
16	64-66	3.00 (3 H, s, CH_3), 2.27-2.65 (4 H, m, CH_2C=N), 1.22-2.01 (18 H, m, CH_2)
45	113-114	7.08-7.88 (4 H, m, aryl CH), 3.19 (3 H, s, CH_3), 3.06 (4 H, s, CH_2CH_2)
46	108-109	7.15-8.17 (4 H, m, aryl CH), 3.19 (3 H, s, CH_3), 2.67-3.08 (4 H, m, CH_2C=N, $PhCH_2$), 1.70-2.17 (2 H, m, CH_2)

[a] The ^{1}H NMR spectra were taken in CCl_4 solution for the oxime sulfonates **1**, **9**, **10**, **14**, and **16**, and in $CDCl_3$ solution for other compounds. [b] No melting point determination was performed owing to the thermal sensitivity of these compounds.

γ-keto amines such as anaferine,[37] anahygrine,[38] and norlobelanine.[39]

Experimental Section

General. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer. Mass spectra were obtained with a JEOL JMS-D300 mass machine. ^{1}H NMR spectra were measured on a JNM-PMX60 spectrometer. The chemical shifts are expressed in parts per million downfield from internal tetramethylsilane (δ = 0). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. Melting-point determinations were performed by using a Shimadzu MM-2 micro-melting-point determination apparatus and are uncorrected. Analytical gas–liquid phase chromatography (GLC) was performed on Hitachi Model 163 and 164 instruments equipped with a flame ionization detector using nitrogen as carrier gas. All experiments were carried out under an atmosphere of dry argon. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm, or silica gel 60 HF_{254} silanized, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel E. Merck Art. 9385, or silanized silica gel E. Merck Art. 7719. Microanalyses were accomplished at the Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University.

In experiments requiring dry solvents, ether, tetrahydrofuran (THF), dioxane, and 1,2-dimethoxyethane (DME) were distilled from sodium–benzophenone. Benzene, hexane, and toluene were dried over sodium metal. Methylene chloride was distilled from phosphorus pentoxide and stored over 4-Å molecular sieves. Pyridine and triethylamine were stored over potassium hydroxide pellets. Diisobutylaluminum hydride in hexane (1.0 M) was a commercial product. Other simple chemicals were purchased and used as such.

Preparation of Ketoximes. Aliphatic ketoximes were prepared by treatment of aliphatic ketones (1 equiv) with hydroxylamine hydrochloride (1.5 equiv) and sodium acetate (1.65 equiv) in methanol at 25 °C for several hours. On the other hand, aromatic ketoximes were syntheszied from aromatic ketones (1 equiv), hydroxylamine hydrochloride (1.5 equiv), and 50% potassium hydroxide (3 equiv) in methanol under reflux for 1–2 h. The crude products, thus obtained, were purified by recrystallization or by distillation.

General Method for Preparation of Oxime Tosylates. To a solution of the oxime (10 mmol) in pyridine (10 mL) at −20 °C was added *p*-toluenesulfonyl chloride (12 mmol) portionwise over a period of 5–10 min. The resulting mixture was stirred at ca. −20–0 °C for several hours. The reaction progress was monitored by analytical TLC. When the mixture was poured with stirring into ice and water, most oxime tosylates crystallized immediately. Filtration, washing several times with cold water, and recrystallization of the crude product afforded the pure oxime tosylate, which was stored in the freezer. In case of unstable oxime tosylates, the corresponding mesylates were prepared as described below.

General Method for Preparation of Oxime Mesylates. To a solution of the oxime (10 mmol) and triethylamine (15 mmol) in methylene chloride (50 mL) at −20 °C was added methanesulfonyl chloride (11 mmol) over a period of 5–10 min. Stirring for an additional 30 min at −20 °C completed the reaction. The reaction mixture was transferred to a separatory funnel with the aid of more methylene chloride. The mixture was first washed with cold 1 N hydrochloric acid, followed by saturated sodium bicarbonate solution and brine. Drying of the combined methylene chloride solution over sodium sulfate, followed by evaporative concentration, gave the crude product, which was pure enough for the organoaluminum-promoted Beckmann rearrangement. The crude oxime mesylates can be crystallized from ether–hexane or methylene chloride–hexane solvent at low temperature.

The physical properties and analytical data of oxime sulfonates are listed in Table VII. Because of the thermal and moisture sensitivity of these compounds, no elemental analyses were performed.

Preparation of Dialkylaluminum Thiolates. From Diisobutylaluminum Hydride (DIBAH) and Dimethyl Disulfide. Dimethyl disulfide (1 equiv) was added dropwise at 0 °C to a solution of DIBAH in hexane (2 equiv). The evolution of hydrogen gas was observed after a short while. The resulting solution was stirred at 0 °C for 30 min and used as a 1 M solution of diisobutylaluminum methanethiolate (**2**) in hexane without further purification.

From Trimethylaluminum and Thiols.[9] The thiol (1 equiv) was added drop by drop at −78 °C to a 1 M solution of trimethylaluminum in hexane (1 equiv). The hydrogen gas evolved slowly. The mixture was allowed to warm to 0 °C, stirred there for 30 min, and used as a 1 M solution of dimethylaluminum thiolate in hexane without any purification. The following aluminum thiolates were prepared by this method: Me_2AlSEt, $Me_2AlSCH_2CH{=}CH_2$, Me_2AlSBu^t, Me_2AlSPh, Me_2AlS(2-pyridyl). Bis(dimethylaluminum) 1,6-hexanedithiolate, $Me_2AlS(CH_2)_6SAlMe_2$, was prepared from 1,6-hexanedithiol (1 equiv) and trimethylaluminum (2 equiv) in a manner similar to that described above.

General Method for Preparation of Imino Thioethers. Imino thioethers were prepared by the reaction of oxime sulfonates with diisobutylaluminum methanethiolate (**2**) or dimethylaluminum thiolates in hexane–methylene chloride solvent. A typical procedure is illustrated by the transformation of acetophenone oxime mesylate (**1**) to the imino thioether **3**.

The physical properties and analytical data for the imino thioethers are given in Table VIII.

Imino Thioether 3. To a stirred solution of oxime mesylate **1** (231 mg, 1 mmol) in methylene chloride (10 mL) at −78 °C was added the aluminum thiolate **2** (1.1 mL, 1.1 mmol). After 5 min, the reaction mixture was warmed to 0 °C and stirred at this temperature for 1 h. The reaction was then quenched by successive treatment with sodium fluoride (185 mg, 4.4 mmol) and water (0.6 mL, 3.3 mmol). Vigorous stirring of the resulting suspension was continued at 0 °C for 20 min. The mixture was then filtered and the insoluble white precipitate was washed with methylene chloride. Concentration of the combined filtrates left a colorless oil, which was purified by short-path column chromatography on silica gel (ethyl acetate as eluant) to give the imino thioether **3** (149 mg, 90% yield) as a colorless oil: IR (liquid film) 2915 (w), 1622 (s), 1590 (m), 1476 (m), 1357 (w), 1215 (m), 1138 (s), 1065 (w), 1020 (w), 773 (m), 692 cm^{-1} (m); ^{1}H NMR (CCl_4) δ 6.40–7.43 (5 H, m, aryl CH), 2.33 (3 H, s, SCH_3), 1.95 (3 H, s, $=CCH_3$).

Anal. Calcd for $C_9H_{11}NS$: C, 65.41; H, 6.71; N, 8.48. Found: C, 65.33; H, 6.89; N, 8.37.

Acetophenone Thiomethoxyoxime (4). To an ethereal solution (6 mL) of benzonitrile (206 mg, 2 mmol) was added at 0 °C methyllithium (1.6

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Table VIII. Analytical Data of Imino Thioethers and Selenoethers

imino thioether[a] or selenoether	IR (cm^{-1})[b]	^1H NMR (δ)[c]
20		3.13–3.67 (1 H, m, NCH), 2.17 (3 H, s, SCH_3), 1.52 (3 H, d, J = 6.5 Hz, CH_3)
21	1627 (s), 1105 (m), 1055 (m), 780 (s), 750 (s)	3.55 (2 H, m, CH_2N), 2.38 (2 H, m, $CH_2C{=}N$), 2.14 (3 H, s, SCH_3), 1.28–1.92 (6 H, m, CH_2)
22	1630 (s), 1452 (s), 1373 (s), 1187 (s), 1139 (m), 790 (m)	3.57 (2 H, t, J = 5.5 Hz, CH_2N), 2.79 (2 H, q, J = 7.5 Hz, SCH_2), 2.34 (2 H, m, $CH_2C{=}N$), 1.24–1.98 (6 H, m, CH_2), 1.19 (3 H, t, J = 7.5 Hz, CH_3)
23	1630 (s), 1452 (m), 1373 (m), 1187 (m), 1139 (m), 790 (m)	3.57 (2 H, t, J = 5.6 Hz, CH_2N), 2.79 (2 H, q, J = 7 Hz, CH_2S), 2.37 (2 H, m, $CH_2C{=}N$), 1.20–1.93 (8 H, m, CH_2), 1.20 (3 H, t, J = 7 Hz CH_3)
24	1620 (s), 1452 (m), 1438 (m), 1341 (m), 780 (m), 756 (m)	3.09–3.58 (2 H, m, CH_2N), 2.17–2.63 (2 H, m, $CH_2C{=}N$), 2.19, 2.39 (3 H, two s (ratio 1:4), CH_3)
25	1630 (s), 1462 (m), 1448 (m), 990 (m), 920 (m)	5.55–6.26 (1 H, m, C=CH), 4.87–5.43 (2 H, m, $CH_2{=}C$), 3.55 (2 H, d, J = 7 Hz, CH_2S), 3.43 (2 H, m, CH_2N), 2.51 (2 H, m, $CH_2C{=}N$)[d]
26	1630 (s), 1433 (m), 741 (m)	7.02–7.55 (5 H, m, aryl CH), 3.41 (2 H, m, CH_2N), 2.13 (2 H, m, $CH_2C{=}N$)
27	1630 (s), 1450 (m), 1315 (m), 1087 (m), 1035 (m)	3.49 (1 H, br s, CHN), 2.20 (3 H, s, SCH_3)
28	1627 (s), 1600 (s), 1490 (m), 1477 (m), 1361 (m), 1132 (s)	6.47–7.35 (5 H, m, aryl CH), 1.89 (3 H, s, $CH_3C{=}N$), 1.55 (9 H, s, $(CH_3)_3C$)
29	1640 (s), 1599 (s), 1482 (m), 1440 (m), 1136 (m), 768 (s)	6.43–7.60 (10 H, m, aryl CH), 2.03 (3 H, s, CH_3)
30	1628 (s), 1593 (m), 1565 (m), 1445 (m), 1415 (m), 1137 (m), 1115 (s), 758 (s)	8.56 (1 H, m, aryl CH), 6.58–7.81 (8 H, m, aryl CH), 2.27 (3 H, CH_3)[d]
31	1615 (s), 1585 (m), 1125 (s), 765 (s)	6.45–7.33 (10 H, m, aryl CH), 2.95 (4 H, br t, CH_2S), 1.94 (6 H, s, CH_3), 1.22–1.85 (8 H, m, CH_2)
32	1635 (s), 1440 (m), 1370 (m), 1185 (m)	3.20 (2 H, m, CH_2N), 2.43 (2 H, m, $CH_2C{=}N$), 2.27 (3 H, s, $SeCH_3$)
33		7.04–7.73 (5 H, m, aryl CH), 3.37 (2 H, m, CH_2N), 2.20 (2 H, m, $CH_2C{=}N$)
34	1628 (s), 1587 (m), 1480 (m), 1208 (m), 1110 (s)	6.47–7.40 (5 H, m, aryl CH), 2.23 (6 H, br s, CH_3)[d]
35	1640 (s), 1593 (m), 1480 (m), 1435 (m), 1117 (s), 772 (s)	6.77–7.78 (10 H, m, aryl CH), 2.16 (3 H, s, CH_3)

[a] Elemental analysis. **21**: Calcd for $C_{17}H_{13}NS$: C, 58.69; H, 9.15; N, 9.78. Found: C, 58.40; H, 9.25; N, 9.95. **23**: Calcd for $C_8H_{17}NS$: C, 63.16; H, 9.93; N, 8.18. Found: C, 63.25; H, 10.03; N, 7.99. **24**: Calcd for $C_{13}H_{25}NS$: C, 68.66; H, 11.08. Found: C, 68.97; H, 11.21. **29**: Calcd for $C_{14}H_{13}NS$: C, 74.01; H, 5.72; N, 6.16. Found: C, 74.08; H, 5.75; N, 6.05. **32**: Calcd for $C_{13}H_{25}NSe$: C, 56.92; H, 9.19. Found: C, 57.29; H, 9.35. **34**: Calcd for $C_9H_{11}NSe$: C, 50.97; H, 5.19; N, 6.60. Found: C, 51.03; H, 5.18; N, 6.53. [b] Taken as the liquid film. [c] Unless otherwise stated, the ^1H NMR spectra were taken in CCl_4 solution. [d] Determined in $CDCl_3$ solution.

mL of a 1.3 M ethereal solution, 2.1 mmol). After 30 min, the reaction mixture was treated with dimethyl disulfide (0.18 mL, 2.5 mmol) at 0 °C. The whole mixture was stirred for 1 h at 0 °C and worked up by the addition of cold water. The organic layer was separated and the aqueous layer was extracted with ether. The combined extracts were dried over sodium sulfate and concentrated in vacuo to give **4** as a colorless oil after purification by column chromatography on silica gel (ether–hexane, 1:10): TLC, R_f 0.46 (ether–hexane, 1:10); IR (liquid film) 2910 (m), 1557 (w), 1490 (m), 1440 (m), 1360 (m), 1283 (m), 1022 (w), 755 (s), 718 (w), 685 cm^{-1} (s); ^1H NMR (CCl_4) δ 7.10–7.77 (5 H, m, aryl CH), 2.70 (3 H, s, SCH_3), 2.23 (3 H, s, $=CCH_3$).

Imino Thioether 7 from 2-Methylcyclohexanone *anti*-Oxime (5). The *anti*-oxime **5** (127 mg, 1 mmol) was converted, as described previously, into its mesylate, which without purification was treated with the aluminum thiolate **2** (1.1 mL, 1.1 mmol) at −78 °C for 5 min and at 0 °C for 1 h to give the imino thioether **7** in 64% yield after usual workup and purification by short-path column chromatography on silanized silica gel (ethyl acetate as eluant). **7**: bp 130–135 °C (bath temp (5 mmHg)); IR (liquid film) 2950 (s), 2915 (s), 2840 (s), 1623 (s), 1440 (m), 1368 (w), 1320 (m), 1135 (m), 1055 (m), 1000 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 3.37–3.63 (1 H, m, NCH), 2.22 (3 H, s, SCH_3), 1.30 (3 H, d, J = 6.5 Hz, C–CH_3).

Anal. Calcd for $C_8H_{15}NS$: C, 61.14; H, 9.55; N, 8.91. Found: C, 61.15; H, 9.41; N, 9.02.

Imino Thioether 8 from 2-Methylcyclohexanone *syn*-Oxime (6). The *syn*-oxime **6**[10] (127 mg, 1 mmol) was transformed into its mesylate, followed by the imino thioether **8** in 67% yield as a colorless oil as described for the preparation of **7**. **8**: IR (liquid film) 2955 (s), 2910 (s), 2845 (s), 1645 (s), 1615 (s), 1445 (m), 1375 (w), 1335 (w), 1172 (m), 1055 (m), 985 (m), 925 (w), 785 (s), 760 cm^{-1} (s); ^1H NMR (CCl_4) δ 3.45–3.83 (2 H, m, NCH_2), 2.08 (3 H, s, SCH_3), 1.16 (3 H, d, J = 6.5 Hz, C–CH_3).

Cyclopentanone Thiomethoxyoxime (18): IR (liquid film) 2955 (s), 2920 (s), 2860 (m), 1626 (m), 1413 (m), 1186 (m), 960 (w), 785 cm^{-1} (m); ^1H NMR (CCl_4) δ 2.63 (3 H, s, SCH_3), 1.58–2.57 (8 H, m, CH_2).

Preparation of Dialkylaluminum Selenolates. Diisobutylaluminum Benzeneselenolate (*i*-Bu_2AlSePh). Diphenyl diselenide (1 equiv) was added portionwise at 0 °C to a solution of DIBAH in hexane (2 equiv). The resulting mixture was stirred at 0 °C for 30 min and used as a 1 M solution of *i*-Bu_2AlSePh in hexane without further purification.

Dimethylaluminum Methaneselenolate (Me_2AlSeMe). This reagent was prepared by heating a 2 M toluene solution of trimethylaluminum with powdered selenium under reflux for 2 h according to the literature procedure.[12] The yellow-colored solution so generated is ready for use.

General Method for Preparation of Imino Selenoethers. Imino selenoethers were prepared by treatment of oxime sulfonates with *i*-Bu_2AlSePh or Me_2AlSeMe in a way similar to the preparation of the imino thioether **3**. Since most imino selenoethers are so labile, a short-path column chromatography on silanized silica gel would be recommended in order to suppress the decomposition during the purification. The physical properties and analytical data for the imino selenoethers are listed in Table VIII.

Reaction of Imino Selenoether 33 with Cupric Chloride. Cupric chloride (84 mg, 0.63 mmol) was added in one portion to a methanolic solution (3 mL) of the imino selenoether **33** (210 mg, 0.63 mmol) at 0 °C. The starting material **33** disappeared immediately with formation of the new product which after removal of methanol was purified by column chromatography on silica gel (*i*-$PrNH_2$–CH_2Cl_2, 1:30) to give the corresponding imino methyl ether **36** as a colorless oil: ^1H NMR ($CDCl_3$) δ 3.66 (3 H, s, OCH_3), 3.30 (2 H, m, NCH_2), 2.23 (2 H, m, $N{=}CCH_2$).

General Method for Preparation of Imino Nitriles. Imino nitriles were obtained by the reaction of oxime sulfonates with trimethylsilyl cyanide in the presence of diethylaluminum chloride at low temperature. The synthesis of imino nitrile **38** from 6-undecanone oxime (**37**) is representative.

Imino Nitrile 38. 6-Undecanone oxime (**37**) (195 mg, 1 mmol) was converted to its mesylate by the use of methanesulfonyl chloride (85 μL, 1.1 mmol) and triethylamine (0.21 mL, 1.5 mmol) as described previously. The crude mesylate thus obtained was dissolved in methylene chloride (10 mL), cooled to −78 °C, and treated successively with trimethylsilyl cyanide (0.15 mL, 1.1 mmol) and diethylaluminum chloride (1.1 mL of a 1 M hexane solution, 1.1 mmol) at this temperature. The reaction mixture was allowed to warm to −20 °C and stirred there for 1 h. The mixture was then poured onto ice-cold 10% NaOH (20 mL) and extracted with methylene chloride several times. Purification of the concentrated crude product by a short-path column chromatography on silanized silica gel (ether–hexane, 1:5) gave imino nitrile **38** (177 mg,

91% yield) as a colorless oil: IR (liquid film) 2960 (s), 2930 (s), 2860 (m), 2220 (w), 1639 (m), 1464 (m), 1380 (m), 1261 (w), 1170 cm^{-1} (m); ^1H NMR (CCl_4) δ 3.62 (2 H, t, NCH_2), 2.46 (2 H, t, N=CCH_2), 0.92 (6 H, br t, CH_3).

Anal. Calcd for $C_{12}H_{22}N_2$: C, 74.17; H, 11.41. Found: C, 74.02; H, 11.67.

Imino Nitrile 39: IR (liquid film) 2975 (s), 2945 (s), 2880 (m), 2230 (w), 1641 (m), 1470 (m), 1380 (s), 1352 (w), 1263 (w), 1190 (s), 1170 (m), 975 cm^{-1} (w); ^1H NMR (CCl_4) δ 3.60 (2 H, t, J = 6.5 Hz, NCH_2), 2.45 (2 H, t, J = 6.5 Hz, N=CCH_2), 1.35–1.97 (4 H, m, CCH_2C), 0.78–1.21 (6 H, m, CH_3).

The syntheses of other imino nitriles **40–43** starting from oxime mesylates were carried out in a manner similar to that described above. The physical properties and analytical data of these imino nitriles **40–43** are listed below.

40: IR (liquid film) 3052 (w), 2215 (w), 1660 (m), 1630 (s), 1595 (s), 1580 (w), 1482 (s), 1428 (m), 1370 (m), 1206 (s), 1190 (m), 826 (m), 770 (s), 692 cm^{-1} (s); ^1H NMR (CCl_4) δ 6.53–7.51 (5 H, m, aryl CH) 2.04 and 2.41 (3 H, two s (ratio, 17:83), CH_3).

Anal. Calcd for $C_9H_8N_2$: C, 74.98; H, 5.59. Found: C, 75.38; H, 5.93.

41: IR (liquid film) 3060 (m), 2980 (s), 2935 (s), 2875 (w), 2220 (w), 1635 (s), 1595 (m), 1482 (m), 1478 (m), 1374 (m), 1185 (s), 1133 (m), 1076 (w), 960 (w), 835 cm^{-1} (m); ^1H NMR (CCl_4) δ 6.80–7.72 (5 H, m, aryl CH), 2.65 (2 H, q, J = 7.6 Hz, CH_2), 1.28 (3 H, t, J = 7.6 Hz, CH_3).

42: IR (liquid film) 2930 (s), 2860 (m), 2240 (w), 1735 (s), 1627 (m), 1440 (m), 1370 (s), 1235 (s), 1163 (m), 1115 (w), 1042 cm^{-1} (m); ^1H NMR (CCl_4) δ 3.71 (2 H, t, J = 6.0 Hz, NCH_2), 2.23–2.77 (2 H, m, N=CCH_2), 1.07–2.07 (10 H, m, CCH_2C).

43: IR (liquid film) 2920 (s), 2850 (m), 2220 (w), 1635 (m), 1456 (m), 1442 (m), 1374 (w), 1184 cm^{-1} (w); ^1H NMR (CCl_4) δ 3.68 (2 H, br t, NCH_2), 2.53 (2 H, br t, N=CCH_2), 1.13–2.00 (18 H, m, CCH_2C).

Anal. Calcd for $C_{13}H_{22}N_2$: C, 75.68; H, 10.75; N, 13.57. Found: C, 75.61; H, 10.79; N, 13.60.

General Method for Preparation of α-Alkylated Amines. α-Alkylated amines except piperidine systems were conveniently prepared from oxime sulfonates by one of the following five methods.

Method A. Trialkylaluminum (4 mL of a 1 M hexane solution, 4 mmol) was added to a solution of the oxime sulfonate (2 mmol) in methylene chloride (10 mL) at −78 °C. After 5 min, the solution was warmed to 0 °C and stirred there for 1 h. DIBAH (3 mL, 3 mmol) was added at 0 °C, and the mixture was stirred at 0 °C for 1 h. The reaction was terminated by dilution with methylene chloride (20 mL) followed by sequential treatment with sodium fluoride (1.18 g, 28 mmol) and water (0.38 mL, 21 mmol). Vigorous stirring of the resulting suspension was continued at 0 °C for 30 min. Filtration, washing with methylene chloride, and removal of sovlent left a pale yellow liquid which was subjected to column chromatography on silica gel (i-$PrNH_2$–ether for aliphatic amines; ether–hexane for aromatic amines as eluant) to give the desired α-alkylated amine.

Method B. To an ethereal solution (6 mL) of the alkyne (2.2 mmol) was added at 0 °C n-butyllithium (1.3 mL of a 1.56 M hexane solution, 2 mmol). After 30 min, diethylaluminum chloride (2 mL of a 1 M hexane solution, 2 mmol) was added at 0 °C. The solution immediately turned to a white suspension, which was stired at 0 °C for 30 min, cooled to −78 °C, and treated with the oxime sulfonate (1 mmol) in methylene chloride (2 mL) at this temperature. The whole mixture was stirred at 0–25 °C for 1–3 h and reduced with DIBAH (1.5 mmol) at 0 °C for 1 h to give the α-alkynylamine after workup and purification procedures as described above.

Method C. To a solution of L-menthone oxime (**44**) (338 mg, 2 mmol) in toluene (10 mL) at 0 °C was added n-butyllithium (1.35 mL of a 1.56 M hexane solution, 2.1 mmol). After 20 min, methanesulfonyl chloride (0.16 mL, 2.1 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 10 min and at 20 °C for 30 min, cooled to −78 °C, and treated with trimethylaluminum (6 mL of a 1 M hexane solution, 6 mmol) at this temperature. Stirring was continued at −20 °C for 1 h and at 0 °C for 1 h to complete the rearrangement. The mixture was then reduced with DIBAH (3 mmol) at 0 °C for 1 h to furnish the amine **53** (192 mg, 57% yield) after purification by column chromatography on silica gel (i-$PrNH_2$–ether, 1:100): bp 170–176 °C (bath temp); IR (liquid film) 2955 (s), 2920 (s), 2875 (s), 1455 (m), 1376 (m), 1173 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 2.43, 2.93 (2 H, two m, NCH), 0.77–1.30 (12 H, m, CH_3).

Anal. Calcd for $C_{11}H_{23}N$: C, 78.12; H, 13.60; N, 8.28. Found: C, 78.10; H, 13.56; N, 8.34.

Method D. To an ethereal solution (10 mL) of L-menthone oxime (**44**) (338 mg, 2 mmol) at 0 °C was added n-butyllithium (2.1 mmol). After 20 min, p-toluenesulfonyl chloride (400 mg, 2.1 mmol) was added in one portion. The mixture was then stirred at 0 °C for 30 min, cooled to −78 °C, and treated with excess DIBAH (6 mmol) at −78 °C. The rearrangement–reduction sequence was complete at −78 °C for 30 min and at 0 °C for 1 h to afford the amine **54** (278 mg, 82% yield) as a colorless oil: TLC, R_f 0.47 (i-$PrNH_2$–ether–CH_2Cl_2, 1:10:10); IR (liquid film) 2940 (s), 2895 (s), 2850 (s), 1450 (m), 1375 (s), 1150 cm^{-1} (s); ^1H NMR ($CDCl_3$) 2.84 (2 H, t, J = 5.0 Hz, NCH_2), 2.42 (1 H, m, NCH), 2.09 (1 H, br s, NH), 0.73–1.07 (9 H, m, CH_3).

Anal. Calcd for $C_{10}H_{21}N$: C, 77.43; H, 13.54; N, 9.03. Found: C, 77.48; H, 13.56; N, 8.96.

Method E. Excess DIBAH (3.5 mmol) was added to a solution of the oxime sulfonate (1 mmol) in methylene chloride (5 mL) at −78 °C. After 5 min, the solution was warmed to 0 °C and stirred there for 1–5 h. The mixture was then worked up and purified in the usual way.

Physical properties and analytical data of α-alkylated amines are given in Table IX.

***N*-Propylcyclopentylamine (67).** Tri-n-propylaluminum (3 mL of a 1 M hexane solution, 3 mmol) was added to a suspension of cyclopentanone oxime tosylate (**9**) (253 mg, 1 mmol) in hexane (3 mL) at −78 °C. The resulting mixture was stirred at −78 °C for 5 min and at 0 °C for 1 h to give the clear solution which was reduced with DIBAH (1.5 mmol) at 0 °C for 1 h. Then the reaction was quenched by the NaF–H_2O method and the crude product was purified by column chromatography on silica gel (i-$PrNH_2$–ether, 1:30) to give **67** (79 mg, 62% yield) as a colorless oil: TLC, R_f 0.48 (i-$PrNH_2$–ether–CH_2Cl_2, 1:10:10); IR (liquid film) 3375 (w), 2950 (s), 2860 (s), 2800 (m), 1450 (m), 1347 (s), 1133 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 3.02 (1 H, m, NCH), 2.52 (2 H, t, J = 7.2 Hz, NCH_2), 0.91 (3 H, t, J = 7.0 Hz, CH_3). These spectral and TLC values were identical with those of the authentic sample prepared by reductive amination of cyclopentanone with n-propylamine in the presence of sodium cyanoborohydride.

(±)-Coniine (66). A solution of **9** (253 mg, 1 mmol) in methylene chloride (5 mL) was heated at 40 °C and to this was added tri-n-propylaluminum (1.5 mL of a 2 M toluene solution, 3 mmol) rapidly. The mixture was heated at 40 °C for 30 min and then cooled to 0 °C. DIBAH (1.5 mmol) was added at this temperature. After stirring for 1 h at 0 °C, the mixture was worked up and purified by column chromatography on silica gel (i-$PrNH_2$–ether, 1:30) affording (±)-coniine (**66**)[20] (74 mg, 58% yield) as a colorless oil: TLC, R_f 0.44 (i-$PrNH_2$–ether–CH_2Cl_2, 1:10:10); IR (liquid film) 3275 (w), 2915 (s), 2850 (s), 2800 (w), 1440 (m), 1380 (w), 1327 (m), 1314 (w), 1121 (m), 1095 (w), 1055 (w), 750 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 2.87–3.31 (1 H, m, NCH), 2.22–2.87 (2 H, m, NCH_2), 1.67 (1 H, s, NH), 0.90 (3 H, br t, CH_3). (±)-Coniine (**66**) was also prepared in 55% yield by the reaction of **9** (1 equiv) in 1,2-dichloroethane with (n-$Pr)_3Al$ (2 equiv) at 80 °C for 15 min followed by reduction with DIBAH (1.5 mmol) at 0 °C for 1 h.

2-Methyl-6-propylpiperidine (68). The title compound was obtained in 70% yield by sequential treatment of 2-methylcyclopentanone oxime tosylate (**10**) (1 equiv) in methylene chloride with (n-$Pr)_3Al$ (3 equiv) and DIBAH (1.5 equiv) as described for the synthesis of (±)-coniine (**66**). **68**: TLC, R_f 0.37 (i-$PrNH_2$–ether–CH_2Cl_2, 1:20:20); IR (liquid film) 3270 (w), 2940 (s), 2910 (s), 2840 (s), 2780 (m), 2700 (w), 1455 (m), 1435 (m), 1370 (m), 1325 (m), 1155 (w), 1125 (m), 1100 (w), 743 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 2.23–2.78 (2 H, m, NCH), 1.74 (1 H, s, NH), 1.05 (3 H, d, J = 6 Hz, $NCCH_3$), 0.98 (3 H, br t, CH_3).

Anal. Calcd for $C_9H_{19}N$: C, 76.53; H, 13.56; N, 9.92. Found: C, 76.68; H, 13.53; N, 9.80.

Amine **68** was also prepared in 67% yield using hexane solvent as described above.

Hydrogenation of Enone 69 over Palladium Black. A solution of **69**[23] (800 mg, 5.4 mmol) in glacial acetic acid (6.6 mL) was hydrogenated at 25 °C and 1 atm in the presence of palladium black (100 mg) until the absorption of hydrogen had ceased. The mixture was then filtered and neutralized with a saturated sodium carbonate solution. The crude product was extracted with ether several times. The combined extracts were dried over sodium sulfate and the solvent was evaporated to give a colorless oil which was subjected to GLC analysis (10% Apiezon Grease L on Neopak 1A, 2 m, 150 °C). The ratio of **70** (t_R 4.9 min)/**73** (t_R 6.0 min) is 73:27. Purification by silica gel chromatography (ether–hexane, 2:3 to 1:1) gave **70** (498 mg), **73** (130 mg), and their mixture (131 mg). The structures of **70** and **73** were determined by conversion to the corresponding lactams **74** and **75**, respectively.

Preparation of Lactam 74. A mixture of the ketone **70** (304 mg, 2 mmol), hydroxylamine hydrochloride (209 mg, 3 mmol), and sodium acetate (271 mg, 3.3 mmol) in methanol (5 mL) was stirred at 25 °C for 1 h. After removal of methanol, the residue was diluted with water and extracted with ether several times. The combined ether extracts were concentrated to give the crude oxime (329 mg), which was dissolved in THF (16 mL)–water (22 mL), and treated with sodium hydroxide (360 mg, 9 mmol) followed by p-toluenesulfonyl chloride (763 mg, 4 mmol)

Table IX. Analytical Data of α-Alkylated Amines

amine[a]	IR (cm^{-1})[b]	^1H NMR (δ)
47		2.14–3.12 (3 H, m, CHN, CH_2N), 2.22 (1 H, s, NH), 1.08 (3 H, d, J = 6.3 Hz, CH_3)
48	3305 (w), 1260 (m), 1095 (m), 805 (m)	2.23–3.06 (3 H, m, CHN, CH_2N), 1.80 (1 H, s, NH), 0.87 (3 H, br s, CH_3)
49	3350 (w), 1450 (m), 773 (s), 750 (s)	2.33–3.03 (3 H, m, CHN, CH_2N), 1.79 (1 H, s, NH), 0.88 (3 H, br s, CH_3)
50	3300 (w), 1461 (s), 1363 (m), 1160 (m)	2.38–3.02 (3 H, m, CHN, CH_2N), 0.88 (6 H, d, J = 6 Hz, CH_3)
51	3295 (w), 2230 (w), 1450 (s), 1340 (m), 1160 (m), 745 (s)	3.65 (1 H, m, C≡CCHN), 2.87 (2 H, m, CH_2N), 2.31 (1 H, s, NH), 0.90 (3 H, br t, CH_3)
52	3315 (w), 1450 (m), 770 (s)	2.33–2.96 (2 H, m, CHN), 1.01 (3 H, d, J = 6 Hz, CH_3), 0.90 (3 H, br s, CH_3)
55	3350 (w), 1450 (m), 775 (s), 750 (s)	2.28–2.96 (3 H, m, CHN, CH_2N), 0.89 (3 H, br t, CH_3)
56	3300 (w), 1455 (m), 1440 (m), 780 (s), 760 (s)	2.41–2.83 (3 H, m, CHN, CH_2N), 1.00 (3 H, d, J = 6 Hz, CH_3)
57	1455 (m), 1440 (m), 780 (s), 775 (s)	2.61 (4 H, br t, CH_2N), 1.18–1.70 (20 H, br s, CH_2), 0.97 (1 H, s, NH)
58	3325 (w), 1485 (m), 1450 (m), 1440 (m), 765 (s)	7.05–7.45 (5 H, m, aryl CH), 3.45 (1 H, m, CHN), 2.79 (2 H, m, CH_2N)
59	3390 (w), 1600 (s), 1500 (s), 1315 (m), 1255 (m), 1180 (m), 745 (m), 690 (m)	6.45–7.38 (5 H, m, aryl CH), 3.61 (1 H, heptet, J = 6 Hz, CHN), 3.28 (1 H, br s, NH), 1.18 (6 H, d, J = 6.5 Hz, CH_3)
60	3390 (w), 1600 (s), 1500 (s), 1320 (m), 1255 (m), 742 (s), 685 (m)	6.48–7.40 (5 H, m, aryl CH), 3.41 (1 H, br s, NH), 3.14 (2 H, q, J = 7 Hz, CH_2N), 1.22 (3 H, t, J = 7 Hz, CH_3)
61	3400 (w), 1605 (s), 1500 (s), 1310 (m), 1255 (m), 1180 (m), 750 (s), 690 (s)	6.33–7.28 (5 H, m, aryl CH), 3.78–4.30 (1 H, m, CHN), 3.38 (1 H, br s, NH), 1.78 (3 H, d, J = 1.8 Hz, CH_3C≡C), 1.42 (3 H, d, J = 7 Hz, CH_3)
62		6.37–7.21 (5 H, m, aryl CH), 4.08 (1 H, br q, CHN), 3.40 (1 H, s, NH), 2.10 (2 H, m, C≡CCH_2), 1.42 (3 H, d, J = 6.5 Hz, CH_3)
63	3390 (w), 1595 (s), 1490 (s), 1305 (m), 1240 (m), 1145 (m), 740 (s), 680 (s)	6.45–7.42 (10 H, m, aryl CH), 4.34 (1 H, q, J = 6.5 Hz, CHN), 3.53 (1 H, br s, NH), 1.55 (3 H, d, J = 6.5 Hz, CH_3)
64		6.15–7.37 (4 H, m, aryl CH), 3.55 (1 H, br s, NH), 3.18 (2 H, t, J = 5.4 Hz, CH_2N), 2.68 (2 H, t, J = 6 Hz, CH_2)
65	3350 (w), 1465 (s), 1245 (m), 748 (s)	6.40–7.10 (4 H, m, aryl CH), 3.23 (1 H, br s, NH), 2.72 (3 H, m, CHN, $PhCH_2$), 0.94 (3 H, br s, CH_3)

[a] Elemental analysis. **48**: Calcd for $C_8H_{17}N$: C, 75.60; H, 13.38. Found: C, 75.98; H, 13.79. **49**: Calcd for $C_9H_{19}N$: C, 76.61; H, 13.47; N, 9.92. Found: C, 76.75; H, 13.74; N, 9.51. **50**: Calcd for $C_{10}H_{21}N$: C, 77.43; H, 13.54; N, 9.03. Found: C, 77.53; H, 13.67; N, 8.80. **52**: Calcd for $C_{10}H_{21}N$: C, 77.43; H, 13.54; N, 9.03. Found: C, 77.40; H, 13.66; N, 8.93. **53**: Calcd for $C_{11}H_{23}N$: C, 78.12; H, 13.60; N, 8.28. Found: C, 78.10; H, 13.56; N, 8.34. **54**: Calcd for $C_{10}H_{21}N$: C, 77.43; H, 13.54; N, 9.03. Found: C, 77.48; H, 13.56; N, 8.96. **55**: Calcd for $C_{10}H_{21}N$: C, 77.43; H, 13.54; N, 9.03. Found: C, 77.36; H, 13.29; N, 10.34. **56**: Calcd for $C_{13}H_{27}N$: C, 79.20; H, 13.70; N, 7.10. Found: C, 79.04; H, 13.79; N, 7.15. **59**: Calcd for $C_9H_{13}N$: C, 80.02; H, 9.62; N, 10.36. Found: C, 79.71; H, 9.57; N, 10.70. **65**: Calcd for $C_{13}H_{19}N$: C, 82.55; H, 10.55; N, 7.40. Found: C, 82.36; H, 10.26; N, 7.36. [b] Liquid film. [c] The ^1H NMR spectra were taken in CCl_4 solution for amines **50**, **52**, **55**, **58**, **61**, **62**, **63**, and **65**, and in $CDCl_3$ solution for other compounds.

at 0 °C. The mixture was stirred at 25 °C for 15 h, concentrated, and shaken with saturated aqueous NaCl–CH_2Cl_2. The crude product was extracted with methylene chloride and chromatographed on silica gel (MeOH–AcOEt, 1:20) to give the lactam **74** (216 mg) as white crystals, mp 151–153 °C (recrystallized from ether–EtOAc) (lit.[25] mp 150–152 °C): ^1H NMR ($CDCl_3$) δ 6.83 (1 H, br s, OH), 3.60 (1 H, m, NCH), 2.07–2.53 (2 H, m, CH_2C=O), 0.93 (3 H, d, J = 5.4 Hz, CH_3).

Lactam 75. Ketone **73** (114 mg) was transformed to lactam **75** (80 mg) exactly as described above. **75**: mp 133–134 °C (recrystallized from ether); ^1H NMR ($CDCl_3$) δ 7.55 (1 H, br s, OH), 3.28 (1 H, m, NCH), 2.09–2.55 (2 H, m, CH_2C=O), 0.95 (3 H, d, J = 6 Hz, CH_3).

Lactam 77. Ketone **70** (193 mg, 1.27 mmol) was epimerized with potassium *tert*-butoxide (28 mg, 0.25 mmol) in *tert*-butyl alcohol (2.5 mL) at 50 °C for 2 h. The reaction mixture was then poured into water and extracted with ether to furnish after concentration the mixture of **70** and **76**, which was converted into the corresponding oximes using NH_2OH·HCl (132 mg, 1.9 mmol)–NaOAc (172 mg, 2 mmol) in methanol (3 mL) at 20 °C for 1 h. Usual workup and separation by column chromatography on silica gel (ether–hexane, 1:2) afforded the desired trans-fused perhydroindanone oxime (51 mg) as a minor product. This oxime was subjected to Beckmann rearrangement as described above, providing the trans-fused lactam **77** (35 mg) as colorless needles: mp 159–162 °C (recrystallized from acetone) [lit.[25] 161 °C (acetone)]; ^1H NMR ($CDCl_3$) δ 6.44 (1 H, br s, OH), 2.96 (1 H, m, NCH), 2.10–2.60 (2 H, m, CH_2C=O), 0.94 (3 H, d, J = 5.5 Hz, CH_3).

Selective Hydrogenation of 69 over Palladium Black. Ketone **69** (150 mg, 1 mmol) and a catalytic amount of palladium black (30 mg) were mixed in a solvent (1 mL) in the presence or absence of additives (5–20 mol %) and stirred at 25 °C under atmospheric pressure of hydrogen for 3–30 h. The catalyst was removed by filtration; the filtrate was neutralized with a saturated $NaHCO_3$ solution and extracted with ether three times. The combined ether extracts were concentrated to give the mixture of **70** and **73**, which was subjected to GLC analysis (10% Apiezon Grease L on Neopak 1A) under the standard condition as described previously. The degree of stereoselectivity of the hydrogenation, **70**/**73**, thus obtained is summarized in Table IV.

Preparation of Oxime 78. Enone **69** (5 g, 33 mmol) in dioxane (30 mL) was hydrogenated at 25 °C and 1 atm for 24 h in the presence of a catalytic amount of Pd black (1 g) and propionic acid (300 mg, 4 mmol). The mixture was passed through a Celite 545 pad and the pad was washed with methanol. The combined filtrates were concentrated and treated with H_2NOH·HCl (3.47 g, 50 mmol)–NaOAc (4.5 g, 55 mmol) in methanol (150 mL) at 25 °C for 5 h. Usual workup followed by recrystallization of the crude product from MeOH–H_2O gave pure oxime **78** (4.66 g, 84% yield) as white crystals: TLC, R_f 0.26 (ether–hexane, 1:1); mp 101–102 °C; ^1H NMR ($CDCl_3$) δ 9.15 (1 H, br s, OH), 2.26–2.86 (3 H, m, CHC=N and CH_2C=N), 0.94 (3 H, s, CH_3).

Preparation of Oxime Tosylate 71. *p*-Toluenesulfonyl chloride (2.29 g, 12 mmol) was added portionwise to a solution of oxime **78** (1 g, 6 mmol) in pyridine (15 mL) at −20 °C. The reaction mixture was stirred at −20 °C for 1 h and at 0 °C for 5 h. The mixture was then poured onto ice and water to furnish white solids which were filtered and washed thoroughly with ice water. This material was dissolved in methylene chloride, dried over Na_2SO_4, and concentrated to give almost pure oxime tosylate **71** (1.83 g, 95% yield) as white solids: mp 69–71 °C; ^1H NMR ($CDCl_3$) δ 7.18–8.00 (4 H, m, aryl CH), 2.33–2.90 (3 H, m, NCH and NCH_2), 2.43 (3 H, s, aryl CH_3), 0.88 (3 H, br s, CH_3).

(±)-Pumiliotoxin C (72). Tri-*n*-propylaluminum (1.8 mL of a 2 M toluene solution, 3.6 mmol) was added rapidly to a solution of the oxime tosylate **71** (384 mg, 1.2 mmol) in methylene chloride (12 mL) at 25 °C. The resulting mixture was stirred at 25 °C for 30 min and reduced with excess DIBAH (4.8 mL, 4.8 mmol) at 25 °C for 2 h. Usual workup by NaF–H_2O method and chromatography on silica gel (*i*-$PrNH_2$–ether–CH_2Cl_2, 1:30:30) produced (±)-pumiliotoxin C (**72**) (135 mg, 60% yield) as a colorless oil: TLC, R_f 0.48 (*i*-$PrNH_2$–ether–CH_2Cl_2, 1:30:30); GLC (10% Silicone SE-30 on Chromosorb W AW DMCS, 150 °C) t_R 2.9 min; IR (liquid film) 3310 (w), 2950 (s), 2915 (s), 2855 (s), 2795 (m), 2710 (w), 1462 (m), 1445 (m), 1376 (w), 1325 (w), 1313 (w), 1124 (w), 1097 (w), 1081 (w), 753 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 2.70–2.96 (1 H, m, C_{8a}-H), 2.28–2.74 (1 H, m, C_2-H), 0.93 (3 H, br t, CH_3), 0.85 (3

Table X. Analytical Data of α,α-Dialkylated Amines

amine[a]	IR (cm^{-1})[b]	^1H NMR (δ)[c]
89	3260 (w), 1635 (m), 1430 (m), 1365 (m), 995 (m), 910 (s)	5.39–6.12 (1 H, m, C=CH), 4.73–5.17 (2 H, m, CH_2=C), 2.65 (2 H, m, NCH_2), 2.02 (2 H, d, J = 7 Hz, C=CCH_2)
90	3310 (w), 2120 (w), 1615 (m), 1260 (m), 780 (s)	2.77 (2 H, m, NCH_2), 2.32 (2 H, m, C≡CCH_2), 1.86 (1 H, m, C≡CH), 1.15 (3 H, s, CH_3)
91	3340 (w), 1640 (m), 1465 (s), 1160 (m), 915 (s)	5.36–5.99 (1 H, m, C=CH), 4.70–5.12 (2 H, m, CH_2=C), 2.65 (2 H, m, NCH_2), 2.02 (2 H, d, J = 7 Hz, C=CCH_2), 0.89 (3 H, br t, CH_3)
92	3320 (w), 2125 (w), 1465 (m), 1440 (m), 1380 (m), 1145 (m)	2.66 (2 H, m, NCH_2), 2.17 (2 H, d, J = 2.4 Hz, C≡CCH_2), 1.82 (1 H, t, J = 2.4 Hz, C≡CH), 1.09 (3 H, s, CH_3)
93	1645 (m), 1465 (s), 1450 (s), 920 (s)	5.39–6.00 (1 H, m, C=CH), 4.72–5.13 (2 H, m, CH_2=C), 2.48 (2 H, m, NCH_2), 2.06 (2 H, d, J = 7 Hz, C=CCH_2), 0.94 (3 H, s, CH_3)
94	3320 (w), 2130 (w), 1460 (m), 1380 (w)	2.48 (2 H, m, NCH_2), 2.17 (2 H, m, C≡CCH_2), 1.86 (1 H, t, J = 2.4 Hz, C≡CH), 1.08 (3 H, s, CH_3)
95	3330 (w), 1645 (w), 1610 (w), 1460 (m), 1442 (m), 920 (m), 755 (s), 690 (m)	7.26 (5 H, m, aryl CH), 5.63–6.40 (1 H, m, C=CH), 4.88–5.33 (2 H, m, CH_2=C), 2.77 (2 H, m, NCH_2), 2.34 (2 H, d, J = 7 Hz, C=CCH_2)
96	3410 (w), 1625 (s), 1600 (s), 1490 (s), 915 (m), 740 (m), 690 (m)	6.44–7.29 (5 H, m, aryl CH), 5.46–5.99 (1 H, m, C=CH), 4.79–5.20 (2 H, m, C=CH_2), 3.23 (1 H, s, NH), 2.34 (2 H, d, J = 7 Hz, C=CCH_2), 1.27 (6 H, s, CH_3)
97		6.37–7.24 (5 H, m, aryl CH), 4.77–6.01 (m, C=CH and $CH=CH_2$), 3.24 (1 H, br s, NH), 1.24 (6 H, s, CH_3)
98	3300 (w), 2120 (w), 1600 (s), 1490 (s), 1180 (m), 745 (s), 690 (s)	6.48–7.23 (5 H, m, aryl CH), 3.44 (1 H, s, NH), 2.36 (2 H, d, J = 2.4 Hz, CH_2), 1.93 (1 H, t, J = 2.4 Hz, C≡CH), 1.35 (6 H, s, CH_3)
99	3420 (w), 1605 (s), 1500 (s), 1100 (m), 920 (m), 750 (m), 690 (m)	6.59–7.26 (5 H, m, aryl CH), 5.58–6.21 (1 H, m, CH=C), 4.87–5.32 (2 H, m, C=CH_2), 3.48 (1 H, s, NH), 2.49 (2 H, d, J = 7 Hz, C=CCH_2), 2.15 (2 H, br t, C≡CCH_2)

[a] Elemental analysis. **89**: Calcd for $C_9H_{17}N$: C, 77.63; H, 12.31. Found: C, 77.41; H, 12.49. **92**: Calcd for $C_{10}H_{17}N$: C, 79.41; H, 11.33. Found: C, 79.36; H, 11.73. **93**: Calcd for $C_{16}H_{31}N$: C, 80.94; H, 13.16; N, 5.90. Found: C, 80.91; H, 13.22; N, 5.87. **94**: Calcd for $C_{16}H_{29}N$: C, 81.63; H, 12.45; N, 5.95. Found: C, 81.63; H, 12.43; N, 5.95. **95**: Calcd for $C_{22}H_{33}N$: C, 85.39; H, 10.28; N, 4.33. Found: C, 85.74; H, 9.99; N, 4.26. **96**: Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found, C, 82.07; H, 9.89; N, 8.03. **98**: Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.08. Found: C, 83.42; H, 8.70; N, 7.88. **99**: Calcd for $C_{17}H_{23}N$: C, 84.59; H, 9.60; N, 5.80. Found: C, 84.55; H, 9.68; N, 5.77. [b] Liquid film. [c] Taken in CCl_4 solution.

H, d, J = 6.5 Hz, CH_3); mass m/z (%) 195 (M^+, 6), 152 (100). For the characterization of **72**, its hydrochloride was prepared and recrystallized from 2-propanol–ether to give colorless needles: mp 241–243 °C (lit.[22] 243–244 °C); IR (KBr) 3430 (w), 2540 (m), 1582 (s), 1470 (s), 1455 (m), 1445 (m), 1435 (m), 1380 (w), 1185 (w), 1123 (w), 973 (w), 955 (w), 750 (w), 658 cm^{-1} (w).

Preparation of Amine 80. A successive Beckmann rearrrangement–alkylation–reduction sequence of **71** (1 equiv) in methylene chloride was carried out using trimethylaluminum (3 equiv) and DIBAH (4 equiv) at 25 °C as described above to afford the amine **80** in 57% yield as a colorless oil: GLC (10% SE-30, 165 °C) t_R 1.36 min; ^1H NMR ($CDCl_3$) δ 2.62–3.32 (2 H, m, NCH), 1.01 (3 H, d, J = 6 Hz, CH_3), 0.97 (3 H, d, J = 6 Hz, CH_3); mass m/z (%) 167 (M^+, 22), 152 (44), 135 (24), 124 (100); mp of **80**·HCl 204–206 °C (*i*-PrOH–ether); IR (KBr) of **80**·HCl 1592 (s), 1482 (m), 1467 (m), 1386 (m), 1340 (w), 1310 (w), 1134 (w), 1073 (w), 1050 (m), 980 (w), 927 cm^{-1} (w).

2-Undecylcyclopentanone Oxime (83). A mixture of cyclopentanone (44.2 mL, 500 mmol) and 1-undecene (7.71 g, 50 mmol) in the presence of silver(I) oxide (6.20 g, 50 mmol) was heated at 130 °C for 5 h according to the literature procedure.[32] After workup, the crude 2-undecylcyclopentanone was treated with H_2NOH·HCl (5.22 g, 75 mmol)–NaOAc (8.20 g, 100 mmol) in methanol (40 mL) at 25 °C for 5 h to furnish pure *anti*-oxime **83** (9.25 g, 73% yield) as a semisolid: TLC, R_f 0.51 (ether–hexane, 1:2); ^1H NMR (CCl_4) δ 5.58 (1 H, s, OH), 2.20–2.63 (3 H, m, CHC=N and CH_2C=N), 0.89 (3 H, br t, CH_3).

2-Undecylcyclopentanone Oxime Mesylate (84). Oxime **83** was converted to the corresponding oxime mesylate **84** in 90–95% yield by the general method for preparation of oxime mesylates. **84**: ^1H NMR (CCl_4) δ 2.98 (3 H, s, SO_2CH_3), 2.40–2.84 (3 H, m, CHC=N, CH_2C=N), 0.89 (3 H, br t, CH_3).

Preparation of Imine 85. Trimethylaluminum (6.8 mL of a 2 M toluene solution, 13.6 mmol) was added dropwise to a solution of the oxime mesylate **84** (1.51 g, 4.54 mmol) in methylene chloride at −78 °C. After 5 min, the mixture was allowed to warm to 25 °C and stirred there for 1 h. Workup by the NaF–H_2O method and purification by column chromatography on silica gel (*i*-$PrNH_2$–ether, 1:200) gave imine **85** (0.65 g, 57% yield) as a light yellow oil: TLC, R_f 0.58 (*i*-$PrNH_2$–ether, 1:100); IR (liquid film) 2920 (s), 2850 (s), 1660 (m), 1460 (m), 1445 (w), 1370 cm^{-1} (w); ^1H NMR (CCl_4) δ 3.40–3.87 (1 H, m, NCH), 1.81 (3 H, d, J = 2.0 Hz, CH_3C=N), 0.89 (3 H, br t, CH_3).

Reduction of Imine 85. Unless otherwise stated, imine **85** (0.3–1 mmol) was added to hydride reagents at −78 °C under argon, and then additives were introduced. The reaction mixture was stirred at −78 °C for 30 min, at −45 °C for 1 h, at −20 °C for 1 h, and finally at 0 °C for 1 h. After workup by the NaF–H_2O method, the crude product was purified by column chromatography on silica gel (*i*-$PrNH_2$–ether, 1:200). From the first elution, the cis isomer **86** was obtained: TLC, R_f 0.37 (*i*-$PrNH_2$–ether, 1:100); GLC (Silicone OV-101, 210 °C) t_R 3.91 min; IR (liquid film) 3290 (w), 2950 (s), 2920 (s), 2850 (s), 1460 (m), 1440 (w), 1373 (w), 1320 (w), 1128 (w), 720 cm^{-1} (w); ^1H NMR ($CDCl_3$) 2.33–2.83 (2 H, m, NCH), 1.68 (1 H, s, NH), 1.06 (3 H, d, J = 6.3 Hz, CH_3C–N), 0.88 (3 H, br t, CH_3). From the later elution, the trans isomer **81** was collected: TLC, R_f 0.26 (*i*-$PrNH_2$–ether, 1:100); GLC (Silicone OV-101, 210 °C) t_R 4.31 min; IR (liquid film) 3265 (w), 2945 (s), 2915 (s), 2845 (s), 1455 (m), 1440 (m), 1370 (w), 1335 (w), 1140 (w), 1065 (w), 715 cm^{-1} (m). The ^1H NMR spectrum of **81** was superimposable on that of **86**. The spectral properties of **81** and **86** were identical with those of an authentic sample.[26]

Some results under different reduction conditions are summarized in Table VI. In the runs 2, 5, and 8, imine **85** was added to a mixture of hydride reagents and additives at −78 °C. In run 3 the imine was reduced at 25 °C for 20 h and worked up in the usual manner. The use of excess $LiAlH_4$ (7 equiv of $LiAlH_4$ to 4 equiv of Me_3Al) or excess Me_3Al (10 equiv of Me_3Al to 5 equiv of $LiAlH_4$) did not affect the ratio of **81** to **86**. A typical example is demonstrated by the reduction of the imine **85** with $LiAlH_4$–Me_3Al. To a suspension of $LiAlH_4$ (80 mg, 2.1 mmol) in THF (5 mL) at −78 °C were added sequentially imine **85** (75 mg, 0.3 mmol) in THF (1 mL) and Me_3Al (1.05 mL of a 2 M toluene solution, 2.1 mmol). The resulting mixture was stirred at −78 °C for 30 min, at −45 °C for 1 h, at −20 °C for 1 h, and finally at 0 °C for 1 h. After workup by NaF–H_2O method, the crude product was purified by column chromatography to give a mixture of **81** and **86** (74 mg, 97% yield) in a ratio of 95:5.

Solenopsin B (82). Solenopsin B (**82**) was prepared with high stereoselectivity (95% pure by GLC analysis) using procedures which exactly paralleled those described above for the synthesis of solenopsin A. The isomeric ratio of **82** to its cis form was determined by GLC analysis: (Silicone OV-101, 220 °C) t_R (**82**) 5.18 min; t_R (cis isomer) 4.65 min.

Preparation of α,α-Diallylamine 87. Allyldiethylaluminum was prepared by treatment of allylmagnesium bromide (5.4 mL of a 0.77 M ethereal solution, 4 mmol) with diethylaluminum chloride (4 mL, 4 mmol) at 0 °C for 30 min. To this was added at 0 °C a solution of acetophenone oxime mesylate (**1**) (213 mg, 1 mmol) in methylene chloride (2 mL). The resulting mixture was stirred at 0 °C for 30 min and worked up by the NaF–H_2O method. Column chromatography on silica gel (ether–hexane, 1:10) produced the α,α-diallylamine **87** (94 mg, 47% yield) as a colorless oil: TLC, R_f 0.52 (ether–hexane, 1:5); ^1H NMR (CCl_4) δ 6.42–7.28 (5 H, m, aryl CH), 5.45–6.22 (2 H, m, =CH—C), 4.78–5.30 (4 H, m, CH_2=C), 3.35 (1 H, br s, NH), 2.34 (4 H, d, J = 7.2 Hz, CH_2), 1.25 (3 H, s, CH_3).

General Method for Preparation of α,α-Dialkylated Amines. α,α-Dialkylated amines were prepared in good yields via the Beckmann re-

arrangement–alkylation sequence by alkylaluminum reagents followed by the introduction of the second alkyl groups to the resulting ketimines by allylic or propargylic Grignard reagents. The synthesis of 2-allyl-2-methylazacycloheptane (**88**) is illustrative. To a solution of cyclohexanone oxime mesylate (**11**) (191 mg, 1 mmol) in methylene chloride (5 mL) at −78 °C was added trimethylaluminum (1 mL of a 2 M toluene solution, 2 mmol). After 5 min, the reaction mixture was allowed to warm to 0 °C and stirred for 30 min. The solution was cooled to −78 °C and treated with allylmagnesium bromide (1.67 mL of a 1.2 M ethereal solution, 2 mmol) at −78 °C for 5 min and at 0 °C for 1 h. Then the mixture was poured onto a 10% NaOH solution (30 mL), shaken well, and centrifuged to remove the white gel. Extractive workup with methylene chloride, followed by column chromatography on silica gel (*i*-$PrNH_2$–ether, 1:50), furnished 2-allyl-2-methylazacycloheptane (**88**) (92 mg, 60% yield) as a colorless oil: TLC, R_f 0.57 (*i*-$PrNH_2$–ether–CH_2Cl_2, 1:20:20); ^1H NMR (CCl_4) δ 5.37–6.17 (1 H, m, CCH=C), 4.70–5.13 (2 H, m, C=CH_2), 2.43–2.80 (2 H, m, CH_2N), 2.03 (2 H, d, J = 7.5 Hz, C=CCH_2), 1.23–1.77 (8 H, br s, $(CH_2)_4$), 1.07 (1 H, br s, NH), 0.93 (3 H, s, CH_3).

Anal. Calcd for $C_{10}H_{19}N$: C, 78.37; H, 12.50. Found: C, 78.37; H, 12.21.

In case of α-propargylation, excess propargyl Grignard reagents (4 equiv) are required with prolonged reaction time (>4 h). Other examples of the reaction are listed in Table VI and the physical properties and analytical data for α,α-dialkylamines are given in Table X.

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Registry No. (*E*)-**1**, 85027-95-8; (*E*)-**1** oxime, 10341-75-0; **2**, 85027-96-9; (*E*)-**3**, 59073-50-6; (*E*)-**4**, 85027-97-0; (*E*)-(±)-**5**, 85027-98-1; (*Z*)-(±)-**6**, 85027-99-2; (±)-**7**, 85028-00-8; (±)-**8**, 85028-01-9; **9**, 10442-97-4; **9** oxime, 1192-28-5; (*E*)-(±)-**10**, 85028-02-0; (*E*)-(±)-**10** oxime, 85028-03-1; **11**, 80053-69-6; **11** oxime, 100-64-1; **12**, 17512-84-4; (*E*)-(±)-**13**, 85028-04-2; (*E*)-(±)-**13** oxime, 85027-98-1; **14**, 80053-71-0; **14** oxime, 2158-31-8; **15**, 80053-73-2; **15** oxime, 946-89-4; **16**, 80053-72-1; (*E*)-(±)-**17**, 85114-16-5; **18**, 85028-05-3; **19**, 19766-29-1; (±)-**20**, 85028-06-4; **21**, 39488-50-1; **22**, 85028-07-5; **23**, 85028-08-6; **24**, 85028-09-7; **25**, 85028-10-0; **26**, 85048-06-2; (±)-**27**, 85028-11-1; (*E*)-**28**, 85028-12-2; (*E*)-**29**, 85028-13-3; (*E*)-**30**, 85028-14-4; (*E,E*)-**31**, 85028-15-5; **32**, 85028-16-6; **33**, 85028-17-7; (*E*)-**34**, 85028-18-8; (*E*)-**35**, 85028-19-9; **36**, 29376-34-9; **37**, 32504-26-0; **38**, 85028-20-2; **39**, 85028-21-3; **40**, 23579-36-4; **41**, 85028-22-4; **42**, 85028-23-5; **43**, 85028-24-6; (*E*)-L-**44**, 37886-68-3; (*E*)-**45**, 85028-25-7; (*E*)-**45** oxime, 68253-35-0; (*E*)-**46**, 85028-26-8; (*E*)-**46** oxime, 68253-36-1; (±)-**47**, 85028-27-9; (±)-**48**, 85028-28-0; (±)-**49**, 85028-29-1; (±)-**50**, 85028-30-4; (±)-**51**, 85028-31-5; *cis*-(±)-**52**, 85048-07-3; *trans*-(±)-**52**, 85048-08-4; **53** (isomer 1), 85081-37-4; **53** (isomer 2), 85081-38-5; (2*S*-*trans*)-**54**, 85081-39-6; (±)-**55**, 85028-32-6; (±)-**56**, 85028-33-7; **57**, 295-03-4; (±)-**58**, 85048-09-5; **59**, 768-52-5; **60**, 103-69-5; (±)-**61**, 85028-34-8; (±)-**62**, 85048-10-8; (±)-**63**, 85028-35-9; **64**, 635-46-1; (±)-**65**, 85028-36-0; (±)-**66**, 3238-60-6; **67**, 39190-95-9; **68**, 68170-79-6; (±)-**69**, 80053-78-7; (±)-**70**, 62400-71-9; (*E*)-(±)-**70** oxime, 80053-79-8; (±)-**72**, 55785-29-0; (±)-**72**·HCl, 55785-30-3; (±)-**73**, 85028-37-1; (±)-**74**, 55950-19-1; (±)-**75**, 85081-40-9; (±)-**76**, 62400-72-0; (±)-**77**, 62446-08-6; (±)-**78**, 85028-38-2; (±)-**80**, 80053-67-4; (±)-**81**, 28720-60-7; (±)-**82**, 83019-10-7; *cis*-(±)-**82**, 83019-09-4; (*E*)-(±)-**83**, 83019-14-1; (*E*)-(±)-**84**, 83019-15-2; (±)-**85**, 83019-11-8; (±)-**86**, 63950-16-3; **87**, 85028-39-3; (±)-**88**, 85028-40-6; (±)-**89**, 85028-41-7; (±)-**90**, 85028-42-8; (±)-**91**, 85028-43-9; (±)-**92**, 85028-44-0; (±)-**93**, 85028-45-1; **94**, 85028-46-2; (±)-**95**, 85028-47-3; **96**, 85028-48-4; **97** (isomer 1), 85028-49-5; **97** (isomer 2), 85028-50-8; **98**, 85028-46-2; (±)-**99**, 85028-51-9; Me_2AlSEt, 81701-35-1; $Me_2AlSCH_2CH{=}CH_2$, 85028-52-0; Me_2AlSPh, 36896-63-6; Me_2AlSBu-*t*, 60699-27-6; Me_2AlS-2-pyridyl, 85028-53-1; $Me_2AlS(CH_2)_6SAlMe_2$, 85028-54-2; $Me_2AlSeMe$, 67132-62-1; *i*-$Bu_2AlSePh$, 85028-55-3; DIBAH, 1191-15-7; MeSSMe, 624-92-0; PhCN, 100-47-0; PhSeSePh, 1666-13-3; $CuCl_2$, 7447-39-4; Pr_3Al, 102-67-0; $Et_2AlCH_2CH{=}CH_2$, 18760-02-6; $H_2C{=}CHCH_2MgBr$, 1730-25-2; Et_2AlCl, 96-10-6; cyclopentanone, 120-92-3; 1-undecene, 821-95-4.

Molten Salt Catalysis. Selective Bond Cleavage Reactions for Some α,ω-Diphenylalkanes in $SbCl_3$ Melts

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Abstract: The chemistry of the α,ω-diphenylalkanes, $C_6H_5(CH_2)_nC_6H_5$ [n = 1–4], in highly purified anhydrous $SbCl_3$ and $SbCl_3$–10 mol % $AlCl_3$ melts has been investigated from 100 to 130 °C by in situ ^1H NMR spectroscopy and by quench and separation techniques. These substrates, which are often used to model the aliphatic chains that link aromatic and hydroaromatic clusters in coal, are found to undergo selective cleavage of the sp^2–sp^3 bond. For n = 1 and 2 products are formed via a transaralkylation reaction, while for n = 3 and 4 the cleavage results in the selective production of only benzene and either indan (n = 3) or tetralin (n = 4). Toluene is also reactive in $SbCl_3$–$AlCl_3$, and typical transalkylation chemistry is observed. The relative rates for reaction in the aprotic $SbCl_3$ melts are in the order $PhCH_2Ph \gg Ph(CH_2)_2Ph \sim Ph(CH_2)_3Ph \sim Ph(CH_2)_4Ph \gg PhCH_3$. These relative reactivities, the discovery that $SbCl_3$–10 mol % $AlCl_3$ is a much more active catalytic medium than $SbCl_3$ alone, and the product distributions can be explained by a mechanism in which the rate-determining step involves the generation of a benzylic cation as the key reactive intermediate by hydride abstraction by $SbCl_2^+$ in the melt. This research provides new insights into the mechanism by which an aprotic molten salt medium catalyzes bond cleavage reactions for the α,ω-diphenylalkanes at temperatures substantially below those required for thermolysis. In addition, the mechanism is discussed in relation to mechanisms proposed for the transalkylation reactions of alkylbenzenes, which normally employ strong protic acid catalysts.

Recent interest in molten salt catalysis has stemmed from reports that molten metal halides such as SbX_3 (X = Cl, Br, I),[1] BiX_3 (X = Cl, Br),[1] AsI_3,[1] ZnX_2 (X = Cl, Br),[2] ZnI_2,[3,4] and ZnX_2–CuX (X = Cl, I)[4], which are relatively weak Lewis acids (particularly those based on Sb, As, and Bi), are very active catalysts for hydrocracking coal. When used in massive amounts, these catalysts are not only efficient at depolymerizing and liquefying coal, but also distinguish themselves from conventional

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