position, where only the stable M(II) complexes result, reaction with a second M(III) complex ion has been postulated to account for the products and the stoichiometry.[5,7] Although a silver(II) tetraglycine complex should be stable under the conditions at which some of the decomposition experiments were carried out, none was detected either as intermediate or as product, indicating that $Ag^{III}G_4$ undergoes an intramolecular two-electron redox reaction. An Ag(II) ligand-radical was tentatively reported as an intermediate in the reduction of a Ag(III) tetraaza macrocycle[38] and Ag(II) can be an intermediate in redox reactions of Ag(III).[12] However, it is clear that in the present system Ag(II) intermediates either do not occur or they undergo self-redox very rapidly.

The circumstances under which the reaction of a deprotonated intermediate or a ligand-radical with a M(III) species affects the decomposition rate has been discussed by Kurtz et al.[7] It seems that the absence of a bimolecular step involving Ag(II) and Ag(III) is sufficient to account for the faster rate of decomposition in the Ag(III) system when both acid and base catalyses are unimportant. The decomposition rate rises sharply at pH 7 in the copper pH profile, owing to the presence of Cu(II) products, a feature that is absent in the $Ag^{III}G_4$ complex.

The lower stability of $Ag^{III}(H_{-2}G_3)$ relative to $Ag^{III}(H_{-3}G_4)^-$ at neutral pH is probably due to the reduction in CFSE that occurs when a strongly donating N^- group is replaced by COO^-. The redox potentials[1] of the corresponding Cu(III) complexes are 0.92 V (G_3) and 0.63 V (G_4). However, deprotonation of the amine group causes a marked increase in the ligand field stabilization of the triglycine complex, and $Ag^{III}(H_{-3}G_3)^-$ and $Ag^{III}(H_{-4}G_4)^{2-}$ have comparable stability.

The triglycine ligand is decarboxylated in a process that is base catalyzed. The products of ligand oxidation of triglycine and tetraglycine by Ag(III) appear to be the same as in the Cu(III) system. The decomposition products of the nickel(III) tetraglycine complex (Table IV) indicate that electron transfer to the metal occurs mainly through the terminal peptide group. The site of electron transfer in the triglycine and tetraglycine complexes of Cu(III) and Ag(III) is the peptide ligand trans to the amine group. In the absence of coordinating peptide groups, glycine is deaminated by Ag(II)[36] and Ag(III).

Registry No. G_3, 556-33-2; G_4, 637-84-3; $Ag(OH)_4^-$, 23172-26-1; Ag, 7440-22-4.

Dipole-Stabilized Carbanions: The α' Lithiation of Piperidides

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Abstract: The α' lithiations and subsequent electrophilic substitutions of two series of piperidides are reported. In the cases of 2,4,6-triisopropylbenzopiperidide (**5**) and 4-*tert*-butyl-2,4,6-triisopropylbenzopiperidide (**6**) lithiations and electrophilic substitutions give α'-substituted products, as shown in Table I, which cannot be cleaved. 2,2-Diethylbutanopiperidide (**19**), 4-phenyl-2,2-diethylbutanopiperidide (**20**), and *N,N*-diethyl-2,2-diethylbutanamide (**18**) undergo α' lithiation and electrophilic substitution as shown in Table II to give products that can be cleaved to the substituted amines. This sequence thus provides the (α-lithioalkyl)alkylamine synthetic equivalent from secondary amines. The addition of the α'-lithiated piperidides from **20** to aldehydes is shown to provide equatorial substitution with erythro and threo isomers of the amido alcohol **31** produced in a 1:1 ratio. Exclusive conversion to an equatorial threo amino ester **36t** is observed on treatment with strong acid. All four possible equatorial-axial and erythro-threo isomers of the amino alcohol **34** can be obtained by appropriate manipulations. The formation of the equatorially substituted products from **6** and **20** and of syn products from *N,N*-diethyl-2,4,6-triisopropylbenzamide (**4**) is noted to be consistent with oxygen-lithium complexation and dipole stabilization as important factors in α' lithiation.

The formation of a formally dipole-stabilized carbanion **1** by removal of the α' proton adjacent to nitrogen from a *N,N*-dialkyl amide is an interesting and useful reaction.[1] The synthetic value of the intermediate **1** in the conversion of an amine **2** to an electrophically substituted amine **3** is illustrated by Scheme I.[2-5] The possibilities of stabilization of **1** by complexation, by dipole stabilization, or by delocalization are shown by the contributors **a**, **b**, and **c**, respectively.[1] While the novel step in this approach is the α' metalation of the amide the utility of the sequence also depends on the facile preparation, electrophilic substitution, and hydrolysis of the amide. In this paper we give details of the methodology of the synthetic use of these species[1,3,6] and provide evidence that the formation of α'-lithiated amides is consistent with stabilization by complexation and dipole stabilization.

The methodology of Scheme I provides the (α-lithioalkyl)alkylamine synthetic equivalent and is representative of a strategy for amine elaboration which is frequently more efficient than classical approaches.[2] In addition to the carbon-oxygen double bond of amides,[3] carbon-nitrogen double bonds of formamidines[4] and nitrogen-oxygen double bonds of nitrosoamines[5] have been shown to be useful in providing activation for the formation of species analogous to **1**.

Results and Discussion

Sterically Hindered Aromatic Amides. The α' lithiations and subsequent electrophilic substitutions of *N,N*-dialkyl-2,4,6-triisopropylbenzamides have been reported from two laboratories.[6-8]

(1) For recent work see: Al-Aseer, M.; Beak, P.; Hay, D.; Kempf, D. J.; Mills, S.; Mills, S. G.; Smith, S. G. *J. Am. Chem. Soc.* **1983**, *105*, 2080. Meyers, A. I.; Rieker, W. F.; Fuentes, L. M. *Ibid.* **1983**, *105*, 2082. Bach, R. D.; Braden, M. L.; Wolber, G. J. *J. Org. Chem.* **1983**, *48*, 1509. Seebach, D.; Lohman, J. J.; Syfrig, M. D.; Yoshifuju, M. *Tetrahedron* **1983**, *39*, 1963.

(2) For a review of α-lithio amine synthetic equivalents see: Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.*, in press.

(3) Reitz, D. B.; Beak, P.; Tse, A. *J. Org. Chem.* **1981**, *46*, 4316.

(4) Meyers, A. I.; Hellring, S. *J. Org. Chem.* **1982**, *47*, 2229. Meyers, A. I.; Fuentes, L. M. *J. Am. Chem. Soc.* **1983**, *104*, 117. Meyers, A. I.; Jardmann, G. E. *Ibid* **1982**, *104*, 877 and references cited therein.

(5) Seebach, D.; Enders, D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 15. Wykypiel, W.; Seebach, D. *Tetrahedron Lett.* **1980**, *21*, 1927 and references cited therein.

(6) Rondon, N. G.; Houk, K. N.; Beak, P.; Zajdel, W. J.; Chandrasekhar, J.; Schleyer, P. V. R. *J. Org. Chem.* **1981**, *46*, 4108 and references cited therein.

0002-7863/84/1506-1010$01.50/0

Scheme I

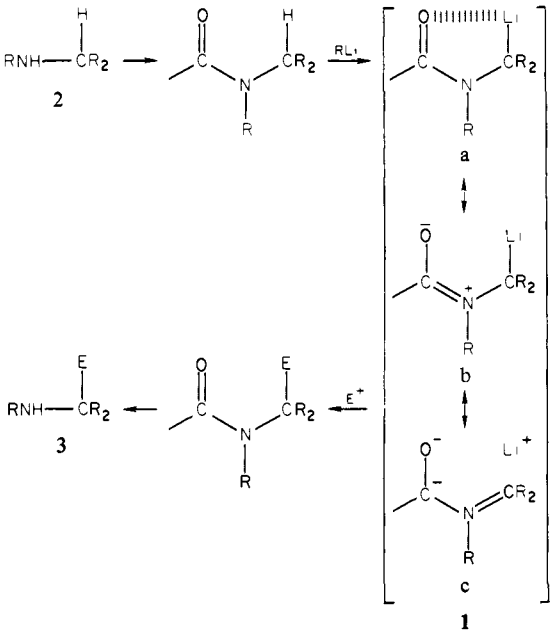
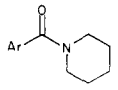
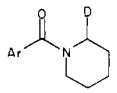
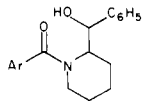
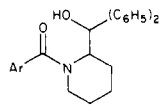
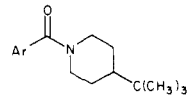
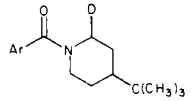
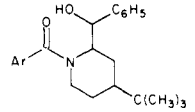
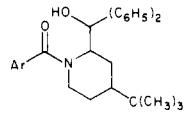
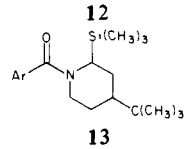


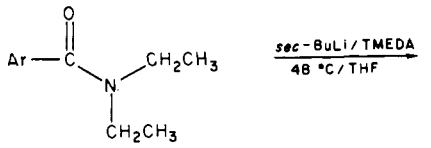
Table I. Lithiations and Electrophilic Substitutions of 2,4,6-Triisopropylbenzopiperidides[a]

reactant	electrophile	product	yield, %
 5	CH_3OD	 7	91 (82% *d*)
5	C_6H_5CHO	 8	30
5	$(C_6H_5)_2CO$	 9	30
 6	CH_3OD	 10	91 (85% *d*)
6	C_6H_5CHO	 11	61
6	$(C_6H_5)_2CO$	 12	50
6	$ClSi(CH_3)_3$	 13	30

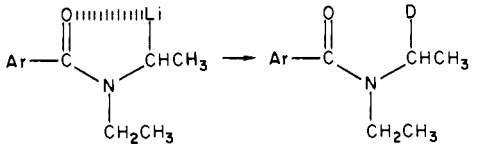
[a] Ar = 2,4,6-triisopropylphenyl.

The sterically hindered carbonyl group in this system is designed to favor lithiation over nucleophilic addition of the organolithium base to the carbonyl. Previous work establishes this lithiation is regiospecific for the alkyl group syn to the carbonyl oxygen.[7-10]

In a typical case, the lithiation and deuteration of *N,N*-diethyl-2,4,6-triisopropylbenzamide (**4**), syn substitution is established

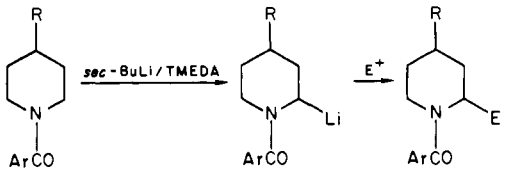


4, Ar = 2,4,6-triisopropylphenyl



by NMR spectroscopy. The methylene at δ 3.60 is seen to be deuterated after the sequence while the methylene at δ 3.15 is unaffected.[8,9] The slow exchange of the *N,N*-dialkyl groups in this sterically hindered environment on the laboratory time scale is also illustrated by this result.[11] The syn substitution, a result which is in contrast to calculations which suggest that a free carbanion anti to the carbonyl would be thermodynamically most stable, is attributed to lithium association with the carbonyl group.[1,6,8,9]

In our experience the positions adjacent to nitrogen on piperidine rings are the most difficult secondary sites for metalation. Since that ring also appears in a number of potential synthetic targets, we have carried out the lithiations and electrophilic substitutions on 2,4,6-triisopropylbenzopiperidide (**5**) and 4-*tert*-butyl-2,4,6-triisopropylbenzopiperidides (**6**). The results summarized in Table



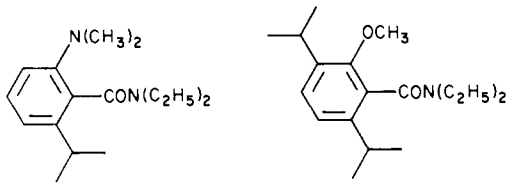
5, R = H; Ar = 2,4,6-triisopropylphenyl
6, R = $C(CH_3)_3$; Ar = 2,4,6-triisopropylphenyl

I show that substitution is possible and that the second and third steps of Scheme I can be achieved with this system.

However, a synthetically useful sequence requires that the amide bond be cleaved. Although we have prepared the amides **5** and **6** by reaction of the acid chloride and piperidine, we have been unable to cleave the amide bond of *N,N*-dialkyl-2,4,6-triisopropylbenzamides under a wide variety of acidic, basic, and reductive conditions. In one approach to surmount this problem, we synthesized and did achieve α' lithiation and deuteration of the amides **14**, **15**, and **16**. The possibility that the hydrolyses of these systems would be facilitated by protonation or demethylation of the ortho substituents, however, was not experimentally realized.[10]

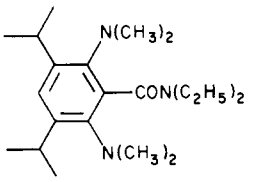
Sterically Hindered Aliphatic Amides. A predicament appears to underlie the choice of an amide which will be useful as an α-lithioalkylamine synthetic equivalent. The carbonyl group must be inert toward nucleophilic addition by the organometallic base required for α' lithiation; however, the carbonyl group of a precursor must be accessible in order to form the amide from the amine, and the amide itself must be subject to cleavage to afford

(7) Beak, P.; McKinnie, B. G.; Reitz, D. B. *Tetrahedron Lett.* **1977**, 1839. Beak, P.; Brubaker, G. R.; Farney, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 3621.
(8) Schlecker, R.; Seebach, D.; Lubosch, W. *Helv. Chim. Acta* **1978**, *61*, 512. Seebach, D.; Wykypiel, W.; Lubosch, W.; Kalinowski, H. *Ibid.* **1978**, *61*, 3100. Wykypiel, W.; Lohmann, J.; Seebach, D. *Ibid.* **1981**, *64*, 1337.
(9) For a review of dipole stabilized carbanions see: Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275.
(10) For details see: Zajdel, W. J. Ph.D. thesis, University of Illinois, 1982, available from Michigan Microfilms, Ann Arbor, MI.
(11) For related cases see: Staab, H. A.; Lauer, D. *Chem. Ber.* **1968**, *101*, 864.



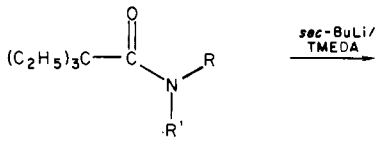
14

15

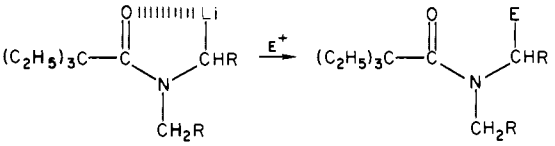


16

the substituted amine. We have found an appropriate balance of steric hinderance and accessibility is provided by the triethyl carbinyl group.[3,12] To illustrate the utility of this group, *N,N*-diethyl-*2,2*-diethylbutanamide (**18**), 2,2-diethylbutanopiperidide (**19**) and 4-phenyl-2,2-diethylbutanopiperidide (**20**) were synthesized by the condensation of the appropriate amine with 2,2-diethylbutanoyl chloride (**17**). Subsequent lithiation and sub-



18, R = R' = CH_2CH_3
19, RR' = $-(CH_2)_5-$
20, RR' = $-(CH_2)_2CHC_6H_5(CH_2)_2-$

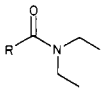
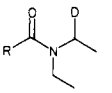
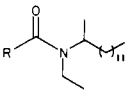
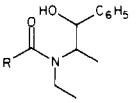
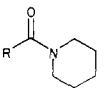
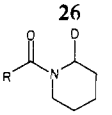
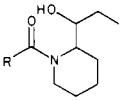
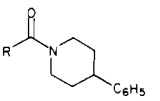
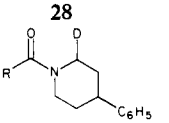
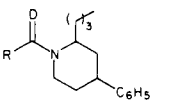
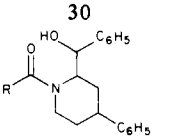


stitution provided the α'-substituted products in useful yields as shown in Table II. The metalations are carried out by treatment of the amide with *sec*-butyllithium/tetramethylethylenediamine in ether at −78 °C followed by warming to 0 °C for 1 h and addition of the electrophile. The substitution is considered to occur on the carbon syn to the carbonyl oxygen by analogy to **4** and other 2,4,6-triisopropylbenzamides.[7-10]

The exceptional steric bulk of the triethyl carbinyl group is pecedented by Brown's studies of F strain, implied in Newman's "rule of six", and has been discussed quantitatively by Dubois.[13,14] Seebach and co-workers have shown that triphenyl acetamides can undergo lithiation, electrophilic substitution, and reductive or alkylative cleavage.[8] Dubois and co-workers have reported that the carbonyl group of trialkyl acetic acid esters are sufficiently hindered that dealkylation occurs on treatment with *n*-propyllithium at 0 °C.[15]

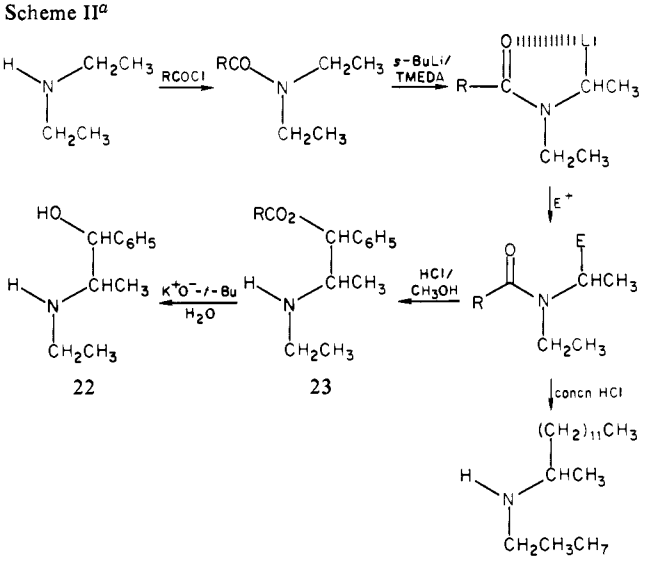
The products in Table II can be hydrolytically cleaved to the substituted amines. Thus these amides are the key intermediates

Table II. Lithiations and Electrophilic Substitutions of *N,N*-Dialkyl-2,2-diethylbutanamides

reactant[a]	electrophile	product[a]	yield, %
 **18**	CH_3OD	 **24**	91 (93% *d*)
18	n-$C_{12}H_{25}I$	 **25**	65[b]
18	C_6H_5CHO	 **26**	69[b]
 **19**	CH_3OD	 **27**	92 (92% *d*)
19	C_2H_5CHO	 **28**	65[c]
 **20**	CH_3OD	 **29**	87 (90% *d*)
20	n-C_4H_9I	 **30**	69
20	C_6H_5CHO	 **31**	78

[a] R = $(C_2H_5)_3C$. [b] Unpurified material used in a synthetic sequence.

Scheme II[a]



[a] R = $(C_2H_5)_3C$.

in a sequence which provides the (α-lithioalkyl)alkylamine synthetic equivalent. The sequence is illustrated in Scheme II for

(12) We are grateful to Dr. D. B. Reitz, who first realized the advantage of the triethyl system in the preparation of an α-lithiomethylamine synthetic equivalent.

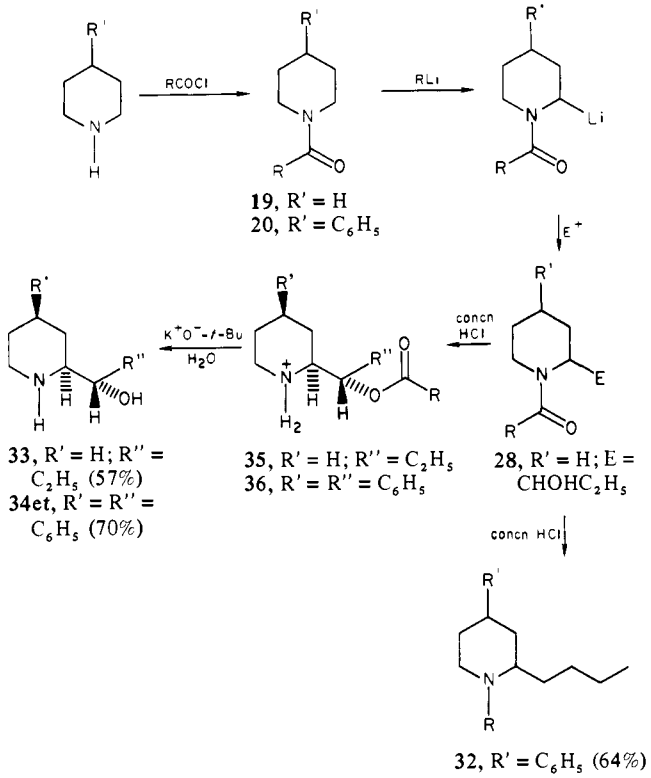
(13) Hine, J. "Structural Effects on Equilibria in Organic Chemistry"; Wiley: New York, 1975, pp 229–34. Newman, M. S., Ed. "Steric Effects in Organic Chemistry"; Wiley: New York, 1956; pp 201–248.

(14) Panaye, A.; MacPhee, J. A.; Dubois, J. E. *Tetrahedron Lett.* **1980**, *21*, 3485.

(15) Lion, C.; Dubois, J. E.; MacPhee, J. A.; Bonzougou, Y. *Tetrahedron* **1979**, *35*, 2077.

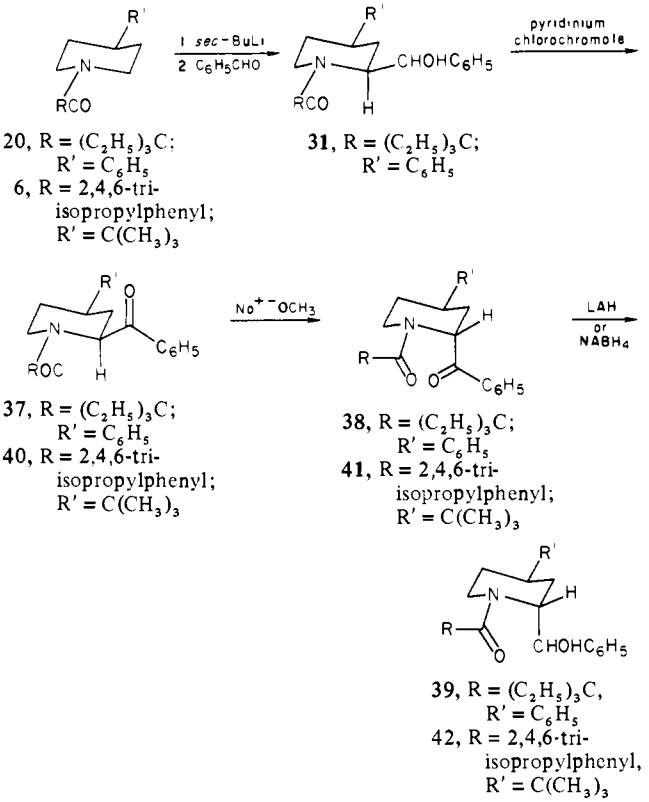
(16) In our experience *N,N*-diethyl-2,2-diethylbutanthiamide, *N,N*-dialkylpivalamides, trifluoroacetamides, 2,2-dimethylbutanamides, and trifluoromethanesulfonamides were not satisfactory due to nucleophilic addition to the carbonyl or, in cases where α' lithiation did occur, self-condensation.[10] With *N,N*-diethyl-2-ethyl-2-methylbutanamides, low yields of lithiation and deuteration could be obtained under conditions in which **10** reacted readily.

Scheme III[a]



[a] R = $(C_2H_5)_3C$.

Scheme IV



the conversion of diethylamine to 1-methyltridecylamine (**21**) and to 1-(hydroxybenzyl)ethylamine (**22**) in 45% and 40% overall yields, respectively. Treatment of the substituted amide with HCl is required for cleavage of the alkylated amide while the amido alcohol undergoes rearrangement upon treatment with acid to an amino ester **23** which can be cleaved with potassium *tert*-butoxide and water.[17,18] Similar sequences have been reported for amides of pyrrolidine[3] and isoquinoline.[19]

The piperidine rings of **19** and **20** can be substituted to give products **32**, **33**, and **34** as illustrated in Scheme III. The overall yields for the three steps to give α-(hydroxyalkyl)piperidines are high. In the case of **35** reductive cleavage with lithium aluminum hydride in 82% yield provides an alternative to the potassium *tert*-butoxide cleavage which proceeds in 96% yield. The requirement for strong acid and base or reductive conditions is a limitation of this approach. Nonetheless, the fact that such a sequence can be achieved in reasonable yields for this unactivated amide suggests this methodology should be useful for amine elaboration.[20]

The electrophilic substitutions outlined in Scheme III involve the formation of diasterioisomers. The alkoxyalkylation of the α'-litho derivative of **19** with propionaldehyde in this sequence is found to provide only the threo isomer **33**.[21] This stereospecificity, however, is not due to diastereoselectivity in the transition states for carbon–carbon bond formation. That reaction provides a 1:1 mixture of erythro and threo isomers **28** in 65% yield. Separation into the pure diastereoisomers was achieved by chromatography and treatment of either diasteriomer with the hydrochloric acid–methanol solution required to effect the nitrogen-to-oxygen migration of the acyl group exclusively provides the threo isomer **35**.

In order to fully elucidate the diastereoselectivity of the sequence, we have studied the substitution of 4-phenyl-2,2-diethylbutanopiperidide (**20**) to give ultimately 2-(α-hydroxybenzyl)-4-phenylpiperidine (**34**). Four different isomers of **34** are possible: equatorial–erythro, **34ee**, equatorial–threo, **34et**, axial–erythro, **34ae**, or axial–threo, **34at**. Through modifications in the sequence separable mixtures of the two equatorial or the two axial isomers or exclusively the equatorial–threo product can be obtained.

Metalation of 4-phenyl-2,2-diethylbutanopiperidide followed by treatment with benzaldehyde affords the amido alcohol **31** in 78% yield (Table II). The α-hydroxybenzyl moiety is assigned to the α-equatorial position based on the chemistry shown in Scheme IV. Oxidation of **31** to the amido ketone **37** with pyridinium chlorochromate proceeds in 90% yield. Equilibration of **37** to the thermodynamically more stable axially substituted amido ketone **38** occurs in 81% yield. Since the $A^{1,3}$ strain in *N*-acylpiperidines has been demonstrated to make the 2-equatorial-substituted amines less stable then the corresponding 2-axial isomers,[22] epimerization to the thermodynamically stable axially substituted amido ketones is expected only if the 2-substituent in **37** is equatorial. Hence **31** must also have equatorial substitution. A similar sequence has been carried out beginning with 4-*tert*-butyl-2,4,6-triisopropylbenzopiperidide (**6**) and has provided **41** as illustrated in Scheme IV.

Organolithiums have been reported to be configurationally stable at low temperatures and to react with retention of con-

(17) Evans, D. A.; McGee, L. R. *J. Am. Chem. Soc.* **1981**, *103*, 2876. Ruegger, A.; Kuhn, M.; Lichti, H.; Loosli, H.-R.; Huguenin, R.; Quigerez, C.; von Wartbur, A. *Helv. Chim. Acta.* **1976**, *59*, 1975. Pavlova, L. V.; Rachinskii, F. Y. *Russ. Chem. Rev. (Engl. Transl.)* **1968**, *37*, 587. The formation of ammonium salts to drive nitrogen-to-oxygen rearrangements is known.

(18) Gassman, P. G.; Hodgson, P.; Balchunis, R. *J. Am. Chem. Soc.* **1976**, *98*, 1275.

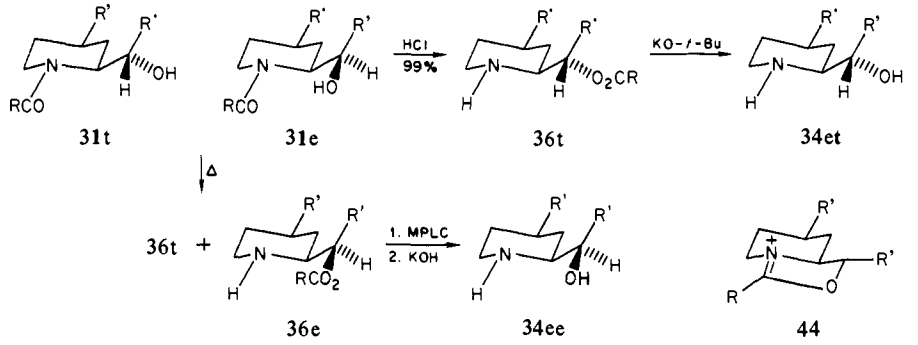
(19) Lohmann, J.; Seebach, D.; Syfrig, M. A.; Yoshifuji, M. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 128.

(20) Professor A. I. Meyers has noted in work with formamidines that unsubstituted, α'-lithio piperidine systems do not undergo alkylation readily, but that copper derivatives are reactive, private communication. We do not have information about this point in the amide systems.

(21) The erythro isomer is the alkaloid conhydrine. Hill, R. K.; *J. Am. Chem. Soc.* **1958**, *80*, 1609. Sicher, J.; Tichy, M. *Chem. Ind.* **1985**, 16.

(22) Johnson, F. *Chem. Rev.* **1968**, *68*, 375. Paulson, H.; Todt, K. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 899. Scott, J. W.; Durham, L. J.; DeJongh, H. A. P.; Burckhardt, V.; Johnson, W. S. Tetrahedron *Lett.* **1967**, 2381. Chow, Y. L.; Colon, C. J.; Tam, J. N. S. *Can. J. Chem.* **1968**, *46*, 2821. Fraser, R. R.; Grindley, T. B. *Tetrahedron Lett.* **1974**, 4169. Quick, J.; Modello, C.; Humora, M.; Brennan, T. *J. Org. Chem.* **1978**, *43*, 2705.

Scheme V[a]

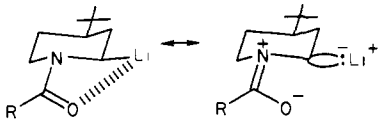


[a] R = $(C_2H_5)_3C$; R' = C_6H_5.

figuration with carbonyl compounds. Applequist and Chmurny have found norbornyllithiums to react with chloroformate esters with preferred retention.[23a] The exchange reactions of alkyllithiums with chiral *sec*-butylmercuric chlorides have been shown to proceed with retention of configuration by Curtin and Koehl.[23b] Recently, Still and Sreekumar have reported that chiral α-alkoxy organostannanes react with *n*-BuLi at −78 °C to afford configurationally stable organolithiums, which stereospecifically react with electrophiles.[23c]

If the organolithium intermediate derived from **20** is configurationally stable and reacts with retention of configuration with benzaldehyde at −78 °C, then the α′-lithio intermediate can be assigned the syn-equatorial stereochemistry shown for **43a**.[23,24] The alternate explanation of rapid equilibration of regioisomeric organolithiums with substitution controlled by transition-state energies is inconsistent with the probability that the transition state for the obtained equatorially substituted amide would be of higher energy than that leading to the more stable axial product.

The equatorial organolithium can be represented as a hybrid of the complex **43a** and the dipole-stabilized carbanion **43b**. The



43a 43b

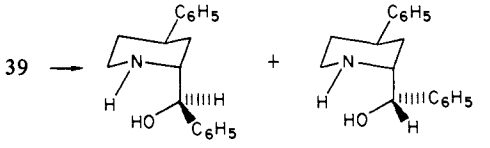
delocalized alternative would require that the carbanion be in a p orbital for effective overlap. This assignment and its comparison with calculations has been made.[6] Equatorial substitution of α′-organolithiums from piperidides appears general; Seebach et al. and we have observed only equatorial syn substitution in 2,4,6-triisopropylbenzopiperidides.[6,8]

The amido alcohol **31** produced by addition of **20** to benzaldehyde is assigned to be ca. a 1:1 mixture of equatorial erythro and threo isomers **31e** and **31t** on the basis of NMR spectroscopy. However, isomerization of the mixture with strong acid affords the equatorial threo amino ester **36t** in 99% yield as shown in Scheme V. Hydrolysis of the amino ester **36t** to the amino alcohol exclusively affords the equatorial threo isomer **34et** in 98% yield. The assignment of the diastereomer is made by comparison of the δ 4.34 chemical shift and 8-Hz coupling of the proton adjacent to oxygen in **34et** to the values of δ 4.30 and 8 Hz for the same proton in authentic *threo*-2-(α-hydroxybenzyl)piperidine.[25]

The equatorial erythro stereoisomer **34ee** can also be obtained. If the mixture of **31e** and **31t** is distilled under reduced pressure, partial isomerization occurs along with nitrogen-to-oxygen migration, but the threo and erythro isomers of **36** can be separated by medium-pressure liquid chromatography. The erythro isomer **36e** can be stereospecifically hydrolyzed to the diasterioisomeric substituted amino alcohol **34ee**. The benzylic proton of **34ee** is found to absorb at δ 4.52 as a doublet with a 5-Hz coupling constant which compares well to values of δ 4.55 and 5.5 Hz for the same proton in authentic *erythro*-2-(α-hydroxybenzyl)-piperidine.[25]

The formation of only the equatorial–threo amino ester **36et** from **31e** and **31t** in the acidic nitrogen-to-oxygen migration is interesting. In an independent experiment it was shown that the equilibration of the amino ester **31e** to **31t** does not occur by treatment with acid under conditions used to achieve nitrogen-to-oxygen migration. The stereospecificity of the cleavage sequence, therefore, must result from a reaction prior to or during the migration. The transformation could be achieved by the bicyclic iminium ion **44** which could provide the threo amido alcohol by a combination of displacement at carbon and nucleophilic addition at the iminium bond prior to the migration.

The axially substituted isomers of 4-phenyl-2-(α-hydroxybenzyl)piperidine can be obtained from the axially substituted benzoyl amide **38** as shown in Scheme IV. Reduction of **38** with $NaBH_4$ results in a 5:2 diasterisomeric mixture of axially substituted amido alcohols **39** as deduced from the NMR spectrum of the reaction mixture. Treatment of this mixture with acid effects the desired nitrogen-to-oxygen acyl migration, and the two diastereioisomeric amino esters obtained in a 2:5 ratio and a yield of 90% can be separated. These esters are readily hydrolyzed under basic conditions to yield the diasteriomerically pure but unassigned amino alcohols **34ax** and **34ay**.[26] A similar reduction



34ax 34ay

of **41** (Scheme IV) also provides a diasteriomeric mixture of axial amido alcohols **42**, which are different from the amido alcohols obtained by lithiation of **6** and addition to benzadehyde. This provides further support for the assignment of equatorial substitution to the amido alcohols formed in the addition. These results demonstrate that although four stereoisomers are possible from reaction of the α′-lithio derivative of **20** with an aldehyde, only the two equatorial isomers are formed initially and, ultimately, rearrangement and hydrolysis to only one, the equatorial threo amino alcohol isomer **34et**, can be achieved in high yield.

The present α′ lithiations of *N*,*N*-dialkyl-2,4,6-triisopropylbenzamides and *N*,*N*-dialkyl-2,2-diethylbutanamides provide evidence that metalation occurs to give an intermediate which has

(23) (a) Appelquist, D. E.; Chmurny, G. N. *J. Am. Chem. Soc.* **1967**, *89*, 875. (b) Curtin, D. Y.; Koehl, Jr., W. J. *J. Am. Chem. Soc.* **1962**, *84*, 1967. (c) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201.

(24) The energy barrier to inversion at the carbanion center has been calculated to be approximately 10 Kcal mol^{-1} for methyllithium and 2-methylbutyllithium. Koeppol, G. W.; Sagatys, D. S.; Miller, S. I. *J. Am. Chem. Soc.* **1967**, *89*, 3396. Rankel, G.; Dix, D. T.; Carlson, M. *Tetrahedron Lett.* **1968**, 579.

(25) Stork, G.; Jacobson, R. M.; Levitz, R. *Tetrahedron Lett.* **1979**, 771.

(26) If it is assumed that an intramolecular hydrogen bond exists between the alcohol and amine groups this would lead to a greater population with a 180° dihedrael angle between the benzyl and ring proton such that **34ax** would be the threo isomer.

a formal sp^3 carbon–lithium bond. Mechanistically, this is considered to reflect the importance of association between the carbonyl oxygen and lithium and the advantage of dipole stabilization of the formal carbanion.[1] Synthetically the metalations of the *N,N*-dialkyl-2,2-diethylbutanamides, in conjunction with their preparation from amines, electrophilic substitution of the α'-organolithio amide, and hydrolysis of the substituted product provide an α-lithioalkylamine synthetic equivalent.[2]

Experimental Section[27]

Materials. All solvents and starting materials from commercial sources were used without further purification, except as noted. Tetrahydrofuran (THF) and diethyl ether used for metalations were dried under nitrogen and distilled from sodium/benzophenone ketyl radical. *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) was dried by distillation under nitrogen from lithium aluminum hydride ($LiAlH_4$) and stored under nitrogen. All other amines were distilled under nitrogen from barium hydroxide.

All metalations were performed in oven-dried glassware which was assembled and cooled under a nitrogen atmosphere. The titer of commercially obtained *n*-butyllithium (*n*-BuLi) and *sec*-butyllithium (*sec*-BuLi) from Ventron and Aldrich were determined by the Watson–Eastham titration procedure.[28]

***N,N*-Diethyl-2,4,6-triisopropylbenzamide (4).** A solution of 7.0 g (28.2 mmol) of 2,4,6-triisoprypylbenzoic acid[29] in 25 mL of freshly distilled thionyl chloride was heated at reflux for 12 h. Removal of excess thionyl chloride by distillation left the white crystalline acid chloride which was dissolved in 20 mL of ether. To the ethereal solution was added 17.0 g (230 mmol) of diethylamine. After stirring for 3 h, the mixture was washed sequentially with 20 mL portions of aqueous 1 N HCl, 1 N NaOH, and saturated NaCl solutions. The ethereal layer was then dried with $MgSO_4$. Removal of solvent under vacuum gave 7.2 g of impure amide. Sublimation at 67 °C (0.05 torr) produced 6.9 g (82%) of a white crystalline solid: mp 70–72 °C; ^1H NMR ($CDCl_3$) δ 6.98 (s, 2 H, Ar H), 3.60 (q, 2 H, J = 7 Hz, syn NCH_2), 3.15 (q, 2 H, J = 7 Hz, anti NCH_2), 2.85 (m, 3 H, $CH(CH_3)_2$), 1.24 (m, 18 H, $CH(CH_3)_2$), 1.24 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.04 (t, 3 H, J = 7 Hz, CH_2CH_3); IR (mull) 1635 cm^{-1} (C=O); isotope ratio (70 eV), *m/e* (relative intensity) 302 (10.1), 303 (100, M^+), 304 (24.9), 305 (3.0).

Anal. ($C_{20}H_{33}NO$) C, H, N.

2,4,6-Triisopropylbenzopiperidide (5). In the same manner as above, **5** was prepared in 92% yield as a white crystalline solid: mp 82–84 °C; ^1H NMR ($CDCl_3$) δ 6.51 (s, 2 H, Ar H), 3.46 (m, 2 H, syn NCH_2), 2.92 (m, 2 H, anti-NCH_2), 2.57 (7, 3 H, $CH(CH_3)_2$), 1.48 (m, 6 H, $(CH_3)_2$), 1.11 (m, 18 H, $CH(CH_3)_2$); IR (mull) 1645 cm^{-1} (C=O); Isotope ratio (70 eV), *m/e* (relative intensity) 313 (1.54), 314 (5.89), 315 (100, M^+), 316 (26.66), 317 (3.66).

Anal. ($C_{21}H_{33}NO$) C, H, N.

4-*tert*-Butyl-2,4,6-triisopropylbenzopiperidide (6). In the same manner as above, **6** was prepared in 63% yield as a white crystalline solid after recrystallization from hexane: mp 75–77 °C; ^1H NMR ($CDCl_3$) δ 6.86 (s, 2 H, Ar H), 4.86 (d, 1 H, J = 13 Hz, syn/eq NCH), 3.47 (d, 1 H, J = 13 Hz, syn/ax NC*H*), 2.74 (m, 6 H, anti NCH_2, $CH(CH_3)_2$ and $CHC(CH_3)_3$), 1.60 (m, 4 H, CH_2), 1.15 (m, 18 H, $CH(CH_3)_2$), 0.83 (s, 9 H, $C(CH_3)_3$); IR (mull) 1645 cm^{-1} (C=O); isotope ratio (70 eV), *m/e* (relative intensity) 369 (6.8), 370 (9.2), 371 (100 M^+), 372 (29.7), 373 (4.5).

Anal. ($C_{25}H_{41}NO$) C, H, N.

Deutration of 4. A Typical Procedure. To a solution of 0.206 g (1.8 mmol) of TMEDA and 1.47 mL (1.20 M, 1.74 mmol) of *sec*-BuLi in 20 mL of THF under nitrogen at −78 °C, was added 0.429 g (1.41 mmol) of **4** in 10 mL of THF. After stirring for an additional 5 h, 1 mL of D_2O was added. The reaction mixture was warmed to ambient temperature and diluted with 100 mL of ether. The ethereal solution was washed sequentially with 30 mL portions of 1 N HCl and saturated NaCl solutions, then dried with $MgSO_4$. Removal of solvent under reduced pressure gave 0.442 g of impure amide. Sublimation at 37 °C (0.05 torr) produced 0.360 g (84%) of **4**: ^1H NMR ($CDCl_3$) δ 6.98 (s, 2 H, Ar H), 3.60 (q, 1 H, J = 7 Hz, syn NCHD), 3.15 (q, 2 H, J = 7 Hz, anti NCH_2), 2.85 (m, 3 H, $CH(CH_3)_2$), 1.24 (m, 18 H, $CH(CH_3)_2$), 1.24 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.04 (t, 3 H, J = 7 Hz, CH_2CH_3); isotope ratio (70 eV), *m/e* (relative intensity) 303 (13.0), 304 (100), 305 (26.8), 306 (1.1).

Deuterations of 5 and 6 were carried out in a similar manner and are described in the supplementary material.

2-(α-Hydroxybenzyl)-2,4,6-triisopropylbenzopiperidide (8). A Typical Procedure. In the same manner as above, **8** was prepared using 0.408 g (3.52 mmol) of TMEDA, 2.75 mL (1.28 M, 3.52 mmol) of *s*-BuLi, 0.887 g (2.82 mmol) of **5**, and 0.35 mL (3.45 mmol) of benzaldehyde. Recrystallization from heptane gave 0.349 g (30%) of **8** as a white crystalline solid: mp 184–187 °C; ^1H NMR ($CDCl_3$) δ 7.37 (m, 5 H, PhH), 6.83 (s, 1 H, Ar H), 6.73 (s, 1 H, Ar H), 5.23 (m, 1 H, NCH), 4.98 (d, 1 H, J = 8 Hz, C*H*(OH)Ph), 3.12 (m, 2 H, NCH_2), 2.78 (m, 3 H, $CH(CH_3)_2$), 1.85–1.30 (m, 6 H, $(CH_2)_3$), 1.17 (m, 18 H, $CH(CH_3)_2$); IR (mull) 3300 (OH), 1620 cm^{-1} (C=O); mass spectrum (70 eV), *m/e* (relative intensity) 421 (0.3, M^+), 315 (19), 314 (36), 232 (72), 231 (100), 230 (76), 212 (20), 105 (27), 43 (52).

Anal. ($C_{28}H_{39}NO_2$) C, H, N.

2-(Diphenylhydroxymethyl)-2,4,6-triisopropylbenzopiperidide (9) was prepared from **5** in 30% yield as a white crystalline solid: mp 218–220 °C; ^1H NMR ($CDCl_3$) δ 7.52 (m, 4 H, PhH), 7.11 (m, 6 H, PhH), 6.79 (s, 2 H, Ar H), 4.97 (m, 1 H, NCH), 3.20 (m, 2 H, NCH_2), 2.72 (m, 3 H, $CH(CH_3)_2$), 1.90–1.35 (m, 6 H, $(CH_2)_3$), 1.11 (m, 18 H, $CH(CH_3)_2$); IR (mull) 3400 (OH), 1610 cm^{-1} (C=O); mass spectrum (70 eV), *m/e* (relative intensity) 497 (0.02, M^+), 315 (6), 314 (6), 232 (17), 231 (100), 105 (9), 433 (13).

Anal. ($C_{34}H_{43}NO_2$) C, H, N.

2(e)-(α-Hydroxybenzyl)-4-*tert*-butyl-2,4,6-triisopropylbenzopiperidide (11) was prepared from **6** in 61% yield as a white crystalline solid: mp 173–175 °C; ^1H NMR ($CDCl_3$) δ 7.34–7.21 (m, 5 H, PhH), 6.90 (s, 2 H, Ar H), 5.07 (m, 1 H, CHO), 4.62 (m, 1 H, NCH), 3.00 (m, 1 H, $CHC(CH_3)_3$), 2.91 (m, 2 H, NCH_2), 2.70 (m, 3 H, $CH(CH_3)_2$), 1.45–1.90 (m, 4 H, CH_2), 1.23 (m, 18 H, $CH(CH_3)_2$), 0.79 (s, 9 H, $C(CH_3)_3$); IR (mull) 3280 (OH), 1590 (C=O), 1325, 1310, 1250, 1190, 1105, 1090, 940, 875, 790, 735, 695 cm^{-1}; mass spectrum (70 eV), *m/e* (relative intensity) 477 (0.1, M^+), 371 (3), 270 (9), 232 (19), 231 (100), 230 (4), 213 (4), 43 (10).

Anal. ($C_{32}H_{47}NO_2$) C, H, N.

2-(Diphenylhydroxymethyl)-4-*tert*-butyl-2,4,6-triisopropylbenzopiperidide (12) was prepared in 50% yield as a white crystalline solid: mp 218–219 °C; ^1H NMR ($CDCl_3$) δ 7.53 (m, 4 H, PhH), 7.14 (m, 6 H, PhH), 6.85 (s, 1 H, Ar H), 6.78 (s, 1 H, Ar H), 4.48 (m, 1 H, NCH), 3.40 (m, 1 H, $CHC(CH_3)_3$), 3.12 (m, 18 H, $CH(CH_3)2$), 0.73 (s, 9 H, C(9)CH_3)3); IR (mull) 3350 (OH), 1615 cm^{-1} (C=O); mass spectrum (70 eV), *m/e* (relative intensity) 553 (0.1, M^+), 371 (20), 370 (23), 232 (63), 231 (100), 213 (17), 171 (13), 105 (26), 41 (18).

Anal. ($C_{38}H_{51}NO_2$) C, H, N.

2-(Trimethylsilyl)-4-*tert*-butyl-2,4,6-triisopropylbenzopiperidide (13) was prepared from **6** in 30% yield as a white crystalline solid: mp 85–86 °C; ^1H NMR ($CDCl_3$) δ 6.97 (s, 2 H, Ar H), 4.80 (m, 1 H, NCH), 3.52 (d, 1 H, J = 12 Hz, eq NCH_2), 3.10–2.80 (m, 2 H, $CHC(CH_3)_3$ and ax NCH_2), 2.84 (m, 3 H, $CH(CH_3)_2$), 2.05–1.35 (m, 4 H, CH_2), 1.23 (m, 18 H, $CH(CH_3)_2$), 0.86 (s, 9 H, $C(CH_3)_3$), 0.19 (s, 9 H, $Si(CH_3)_3$); IR (mull) 1615 cm^{-1} (C=O); mass spectrum (70 eV), *m/e* (relative intensity) 443 (10, M^+), 428 (11), 400 (32), 386 (13), 304 (19), 303 (60), 231 (20), 231 (100), 230 (56), 73 (23), 42 (32).

Anal. ($C_{28}H_{49}NOSi$) C, H, N.

2,2-Diethylbutyroyl Chloride (17). The ester ethyl 2,2-diethylbutanoate was prepared in 81% yield as a colorless liquid from ethyl 2-ethylbutanoate, lithium diisopropylamide, and ethyl iodide:[6,7] bp 177–184 °C; ^1H NMR δ 4.12 (q, 2 H, J = 7 Hz, OCH_2), 1.58 (q, 6 H, J = 8 Hz, CCH_2), 1,24 (t, 3 H, J = 7 Hz, OCH_2CH_3), 0.78 (t, 9 H, J = 8 Hz, CH_3); IR (film) 1735 cm^{-1} (C=O). the ester was converted by treatment with potassium *tert*-butoxide with water in *tert*-butyl alcohol in 88% yield to 2,2-diethylbutyric acid, a white crystalline solid: mp 31–34 °C; ^1H NMR δ 10.0 (s, 1 H, OH), 1.57 (q, 6 H, J = 8 Hz, CH_2), 0.73 (t, 9 H, J = 8 Hz, CH_3); IR (mull) 1705 cm^{-1} (C=O). Reaction of the acid with thionyl chloride provided **17**, a colorless liquid, bp 172 °C, which was used without further purification.

***N,N*-Diethyl-2,2-diethylbutanamide (18).** To a solution of 5.0 g (47.1 mmol) of sodium carbonate in 80 mL of water and 4.0 g (54.8 mmol) of diethylamine in 100 mL of ether was added 4.0 g (24.7 mmol) of **17** in 25 mL of ether. After stirring for 4 h, the ethereal layer was removed and dried with $MgSO_4$ and the solvent was removed to leave 4.49 of impure amide. Distillation provided 4.39 g (89%) of **18** as a colorless oil: bp 75 °C (0.2 torr); ^1H NMR (CDCl) δ 3.44 (q, 4 H, J = 7 Hz, NCH_2), 1.68 (q, 6 H, J = 7 Hz, CH_2), 1.19 (k, 6 H, J = 7 Hz,

(27) Mass spectral data were obtained by C. Cook and associates on a Varian MAT CH-5 spectrometer. Isotopic ratio mass spectral data were obtained from oscillographic traces of the molecular or acylium ion regions by measurement of peak heights. Elemental analyses were performed by J. Nemeth and associates. Melting points and boiling points are uncorrected. The temperatures given for Kugelrohr distillations are those of the hot-air bath and are not necessarily accurate measures of the boiling points.

(28) Watson, S. C.; Eastham, J. F. *J. Organometal. Chem.* **1967**, *9*, 165.

(29) Fuson, R.; Hoxney, E. *J. Am. Chem. Soc.* **1940**, *62*, 2962. Beak, P.; Carter, L. G. *j. Org. Chem.* **1981**, *46*, 2363.

(30) Prepared in 77% yield by esterification of 2-ethyl butanoic acid with ethanol and sulfuric acid.

NCH_2CH_3), 0.88 (t, 9 H, J = 8 Hz, CH_3); IR (film) 1655 cm^{-1} (C=O); mass spectrum (70 eV), m/e (relative intensity) 199 (5, M^+), 129 (15), 127 (1), 102 (21), 100 (46), 99 (20), 72 (26)e, 57 (100), 41 (21); isotope ration (70 eV), m/e (relative intensity) 198 (2.6), 199 (100, M^+), 200 (14.5), 201 (1.3).

Anal. ($C_{12}H_{25}NO$) C, H, N.

2,2-Diethylbutanopiperidide (19). In the same manner as above, **19** was prepared in 90% yield as a colorless oil, bp 100 °C (0.9 torr); ^1H NMR ($CDCl_3$) δ 3.56 (m, 4 H, NCH_2), 1.63 (q, 6 H, J = 6 Hz, CCH_2), 1.55 (m, 6 H, $C(CH_2)_3$), 0.82 (t, 9 H, J = 6 H, CH_3); IR (film) 1655, 1640 cm^{-1} (C=O); mass spectrum (70 eV), m/e (relative intensity) 211 (3, M^+), 182 (11), 141 (28), 114 (30), 112 (45), 99 (12), 57 (100); isotope ration (70 eV), m/e (relative intensity) 213 (0.4), 212 (16.7), 211 (100, M^+), 210 (2.6).

Anal. ($C_{13}H_{25}NO$) C, H, N.

4-Phenyl-2,2-diethylbutanopiperidide (20). In the same manner as above, **20** was prepared in 99% yield as a white crystalline solid: mp 50–51 °C; ^1H NMR ($CDCl_3$) δ 7.45–6.90 (m, 5 H, PhH), 4.62 (d, 2 H, J = 13 Hz, syn NCH_2), 3.05–2.47 (m, 3 H, anti NCH_2 and CHPh), 2.05–0.60 (m, 4 H, CH_2), 1.66 (q, 6 H, J = 4 Hz, CH_2CH_3), 0.084 (t, 9 H, J = 6 Hz, CH_2CH_3); IR (mull) 1635 cm^{-1} (C=O); mass spectrum (70 eV), m/e (relative intensity) 287 (0.3, M^+), 259 (33), 231 (45), 230 (42), 216 (21), 188 (20), 91 (26), 85 (47), 71 (96), 57 (74), 43 (100); isotope ratio (70 eV), m/e (relative intensity) 289 (0.2), 288 (12.2), 287 (100, M^+), 286 (9.8).

Deuterations of 18, 19, and 20 are described in the supplementary material.

(1-Methyltridecyl)ethylamine (21). To a solution of 0.60 mL (0.90 mmol) of TMEDA and 5.5 mL (1.08 M, 5.94 mmol) of *sec*-BuLi in 40 mL of ether under nitrogen at −78 °C was added 1.00 g (5.0 mmol) of **18**. The solution was warmed to 0 °C for 1 h. After cooling to −78 °C, 3.0 mL of dodecyl bromide was added and the solution allowed to warm to ambient temperature, washed with 10 mL portions of 1 N HCl and saturated NaCl solutions, and dried with $MgSO_4$. Removal of solvent provided 1.2 g (65%) of *N*-(1-methyltridecyl)-*N*-ethyl-2,2-diethylbutyramide (**25**) as a colorless oil which was used without any further purification: ^1H NMR ($CDCl_3$) δ 3.49 (m, 3 H, NCH_2 and NCH), 1.70–1.30 (m, 28 H, CH_2), 1.20–0.80 (m, 18 H, CH_3).

The residue from the preceding reaction was added to 30 mL of water and 25 mL of concentrated HCl and heated at reflux for 72 h. The solution was cooled to ambient temperature, basified with NaOH, and extracted two times with 75-mL portions of ether. The ethereal solution was dried with $MgSO_4$ and the solvent removed to leave 0.69 g of oil. Distillation afforded 0.63 g (79%) of **21** as a colorless oil: ^1H NMR ($CDCl_3$) δ 3.67–3.00 (m, 3 H, NCH_2 and NCH), 2.45–2.31 (m, 22 H, CH_2), 1.30 (m, 9 H, CH_3); IR (film) 3470 cm^{-1} (NH); mass spectrum (70 eV), m/e (relative intensity) 241 (0.3, M^+), 226 (0.7), 198 (0.5), 116 (4), 85 (8), 72 (21), 71 (15), 58 (100).

Anal. ($C_{16}H_{35}N$) C, H, N.

2-(Ethylamino)-1-phenylpropyl 2,2-Diethylbutanoate (23) via 26. By a procedure similar to that above **18** was lithiated and allowed to react with 1 equiv of benzaldehyde to provide 4.0 g of impure product, which was purified by MPLC on silica using 1:5 (v/v) EtOAc–hexane as eluent to give 2.64 g (69%) of *N*-(1-(α-Hydroxybenzyl)ethyl)-*N*-ethyl-2,2-diethylbutanamide (**26**) as a colorless oil which was used without further purification: ^1H NMR ($CDCl_3$) δ 7.32 (m, 5 H, PhH), 4.11 (d, 1 H, J = 7 Hz, CHPh), 3.47 (m, 3 H, NCH_2 and NCH), 1.61 (q, 6 H, J = 6 Hz, CH_2), 1.21–0.85 (m, 15 H, CH_3).

The amido alcohol **26** was heated with concentrated HCl to give, after extractive workup, 0.58 g of impure ester. Recrystallization from 1:5 (v/v) EtOAc–hexane and sublimation at 165 °C (1.5 torr) gave 0.49 g (82%) of **23** as a white crystalline solid: mp 196–197 °C; ^1H NMR ($CDCl_3$) δ 7.44 (m, 5 H, PhH), 5.87 (d, 1 H, J = 10 Hz, CHPh), 4.00 (m, 1 H, NCH), 3.12 (m, 2 H, NCH_2), 1.75 (q, 6 H, J = 6 Hz, CH_2), 1.44 (m, 6 H, $NCHCH_3$ and NCH_2CH_3), 0.85 (t, 9 H, J = 6 Hz, CH_3); IR (mull) 3400 (NH), 1720 cm^{-1} (C=O); mass spectrum (10 eV), m/e (relative intensity) 305 (4, M^+), 163 (396), 162 (16), 161 (12), 134 (15), 99 (20), 73 (100), 44 (16).

Anal. ($C_{19}H_{31}NO_2$) C, H, N.

1-(α-Hydroxybenzyl)ethylethylamine (22). To a solution of 0.22 g (2.0 mmol) of potassium *tert*-butoxide and 0.01 mL (0.40 mmol) of water in 10 mL of *tert*-butyl alcohol was added 60 mg (0.20 mmol) of **23**. After heating at reflux for 48 h, the solution was diluted with 25 mL of CH_2Cl and 25 mL of water. The organic layer was separated and dried with $MgSO_4$, and the solvent was removed. Sublimation at 80 °C (0.5 torr) gave 28 mg (79%) of **22** as a white crystalline solid: mp 84–85 °C (lit.[31] 86 °C); ^1H NMR ($CDCl_3$) δ 7.29 (s, 5 H), 4.29 (d, 1 H, J = 8 Hz, CHPh), 3.80 (m, 1 H, NCH), 2.77 (q, 2 H, J = 7 Hz, NCH_2), 1.22 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.17 (d, 3 H, J = 7 Hz, $CHCH_3$); IR (mull) 3570 (OH), 3440 (NH), 1555 (NH), 1430 cm^{-1} (CN).

2-(1-Hydroxypropyl)-2,2-diethylbutanopiperidide (28). In the same manner as for **26**, **28** was prepared from **19** and proprionaldehyde. Purification by MPLC on silica using 3:7 (v/v) EtOAc–hexane provided clean separation of 3.06 g (32%) of **28a** and 3.15 g (33%) of **28b** representing a 65% yield of a 1:1 mixture of stereoisomers **28a**: ^1H NMR ($CDCl_3$) δ 4.51 (d, 1 H, J = 12 Hz, eq NCH_2), 4.11 (d, 1 H, J = 12 Hz, OH), 3.82 (m, 1 H, CHOH), 3.14 (m, 1 H, NCH), 2.78 (d, 1 H, J = 7 Hz, OH), 2.22–1.34 (m, 14 H, CH_2), 1.01 (5, 3 H, J = 7 Hz, $CH(OH)CH_2CH_3$), 0.88 (5, 9 H, J = 7 Hz, CH); IR (mull) 3360 (OH), 1595 cm^{-1} (C=O).

28b: ^1H NMR ($CDCl_3$) δ 4.57 (m, 1 H, eq NCH_2), 4.12 (m, 1 H, ax NCH_2), 3.78 (m, 2 H, CHOH and CHOH), 3.05 (m, 1 H, NCH), 2.30–1.60 (7, 8 H, CH_2), 1.55 (q, 6 H, J = 6 Hz, CCH_2), 1.04 (t, 3 H, J = 7 Hz, $CH(OH)CH_2CH_3$), 0.85 (t, 9 H, J = 6 Hz, CH_3); IR (mull) 3365 (OH), 1595 cm^{-1} (C=O). The mixture was used without further purification.

2-(1-Hydroxypropyl)piperidine (33). In the same manner as for **23**, **35** was prepared using 4.60 g (17.1 mmol) of a 1:1 mixture of **28a** and **28b**, 100 mL of methanol, and 50 mL of concentrated HCl heated at reflux for 12 h. Removal of solvent provided 4.58 g (99%) of *threo*-1-piperidin-2-ylpropyl 2,2-diethylbutanoate (**35**) as a colorless liquid: ^1H NMR ($CDCl_3$) δ 4.67 (m, 1 H, CHO), 3.07 (d, 1 H, J = 11 Hz, NCH), 2.80–2.35 (m, 3 H, NCH_2 and NH), 1.72–1.15 (m, 8 H, CH_2), 1.63 (q, 6 H, J = 7 Hz, CCH_2), 0.95–0.68 (m, 12 H, CH_3); IR (mull) 3300 (NH), 1725 (C=O), 1600 cm^{-1} (NH).

To a solution of 4.51 g (40.2 mmol) of potassium *tert*-butoxide and 0.22 mL (12.1 mmol) of water in 75 mL of diglyme was added 0.700 g (2.6 mmol) of **35**. After heating at reflux for 48 h, the solution was diluted with 100 mL of water and 125 mL of CH_2Cl_2. The organic layer was separated and dried with MgSO, and the solvent was removed. The impure amine was distilled at 55 °C (0.2 torr) and recrystallized from ether to afford 0.356 g (95%) of **33** as a white crystalline solid: mp 68–70 °C; ^1H NMR ($CDCl_3$) δ 3.07 (m, 1 H, CHO), 2.95 (s, 2 H, OH and NH), 2.75–2.12 (m, 3 H, NCH and NCH_2), 1.90–1.12 (m, 8 H, CH_2), 0.93 (t, 3 H, J = 6 Hz, CH_3); IR (mull) 3575 (OH), 3450 (NH), 1550 cm^{-1} (NH); mass spectrum (70 eV), m/e (relative intensity) 143 (4, M^+), 142 (3), 114 (60), 96 (30), 85 (89), 84 (100), 82 (37), 67 (39), 56 (100), 55 (73), 42 (54), 41 (61), 30 (99).

Anal. ($C_8H_{17}NO$) C, H, N.

2-(*n*-Butyl)-4-phenylpiperidine (32). In the same manner as for **25**, **30** was prepared using 3.2 mL (21.2 mmol) of TMEDA and 15.6 mL (1.35 M, 21.0 mmol) of *sec*-BuLi in 300 mL of ether, 5.0 g (17.4 mmol) of **19** in 30 mL of ether, and 3.5 mL of butyl iodide. Purification of the impure product by MPLC on silica with 3:7 (v/v) EtOAc–hexane gave 4.12 g (69%) of *N,N*-(2-(*n*-butyl)-4-phenylpentane-1,5-diyl)-2,2-diethylbutanamide (**30**) as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.19 (s, 5 H, PhH), 4.87 (m, 1 H, eq NCH_2), 4.28 (d, 1 H, J = 14 Hz, ax NCH_2), 3.07 (m, 2 H, NCH and CHPh), 1.66 (m, 12 H, CH_2), 1.30 (m, 4 H, CH_2), 0.86 (m, 12 H, CH_3); IR (mull) 1630 cm^{-1} (C=O).

In the same manner as for **21**, **32** was prepared using 1.0 g (2.9 mmol) of the amide, 30 mL of concentrated HCl, and 25 mL of water. Distillation afforded 0.59 g (93%) of **32** as a colorless liquid: bp 150 °C (0.2 mmHg); ^1H NMR ($CDCl_3$) δ 7.24 (m, 5 H, PhH), 3.45 (m, 2 H, NCH and NH), 2.87 (m, 3 H, NCH_2 and CHPh), 1.95–1.55 (m, 4 H, CH_2), 1.20 (m, 6 H, CH_2), 0.90 (t, 3 H, J = 7 Hz, CH_3); IR (mull) 3490 cm^{-1} (NH); mass spectrum (70 eV), m/e (relative intensity) 317 (1, M^+), 216 (2), 160 (100), 77 (3), 56 (15), 56 (80).

Anal. ($C_{15}H_{23}N$) C, H, N.

***threo*-α-(4-Phenylpiperidin-2(e)-yl)benzyl 2,2-Diethylbutanoate (36t).** In the same manner as for **26**, **31** was prepared using 3.1 mL (20.5 mmol) of TMEDA and 15.2 mL (1.35 *M*, 20.5 mmol) of *sec*-BuLi in 300 mL of ether, 5.0 g (17.4 mmol) of **20**, and 2.2 mL (2.22 mmol) of benzaldehyde. Purification by MPLC on silica using 3:7 (v/v) EtOAc–hexane gave 5.36 g (78%) of *N,N*-(2(e)-(α-hydroxybenzyl)-4-phenylpentane-1,5-diyl)-2,2-diethylbutanamide (**31**) as a 1:1 mixture of erythro and threo stereoisomers: ^1H NMR ($CDCl_3$) δ 7.36 (m, 5 H, PhH), 5.14 (m, 1 H, CHO), 4.52 (m, 1 H, NCH), 4.10 (m, 1 H, OH), 3.78 (m, 1 H, eq NCH_2), 3.11 (m, 11 H, ax NCH_2), 2.50–1.80 (m, 5 H, $(CH_2CH$Ph), 1.63 (m, 6 H, CH_2CH_3), 0.82 (t, 9 H, J = 7 Hz, CH_3); IR (mull) 3320 (OH), 1595 (C=O), 1450, 1420, 1365, 1240, 1137, 1104, 1035, 945, 868, 760, 700 cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 393 (4, M^+), 346 (12), 287 (100), 286 (100), 266 (14), 258 (45), 250 (44), 217 (59), 160 (100), 127 (100), 117 (100).

Anal. ($C_{26}H_{35}NO_2$) C, H, N.

In the same manner as for **23**, **36t** was prepared using 0.400 g (1.0 mmol) of the mixture of threo and erythro amides, 20 mL of methanol, and 10 mL of concentrated HCl. Recrystallization from ether gave 0.397 g (99%) of **36t** as a white crystalline solid: mp 78–79 °C; ^1H NMR

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($CDCl_3$) δ 7.38–6.90 (m, 10 H, PhH), 5.52 (d, 1 H, NCH, NCH_2, and CHPh), 1.80–1.30 (m, 4 H, CH_2), 1.50 (q, 6 H, J = 6 Hz, CH_2CH_3), 0.71 (t, 9 H, J = 6 Hz, CH_3); IR (mull) 3550 (NH), 1730 (C=O), 1600 (NH), 1440 cm^{-1} (CN); mass spectrum (70 eV), m/e (relative intensity) 393 (5, M^+), 250 (54), 161 (100), 160 (100), 146 (36), 144 (43), 130 (49), 129 (46), 117 (97), 115 (67).

Anal. ($C_{26}H_{35}NO_2$) C, H, N.

***threo*-2(e)-(α-Hydroxybenzyl)-4-phenylpiperidine (34et).** In the same manner for **22**, **34t** was prepared using 3.14 g (28.0 mmol) of potassium *tert*-butoxide, 0.1 mL (5.6 mmol) of water, and 1.1 g (2.80 mmol) of **36** in 25 mL of *tert*-butyl alocohol. Recrystallization from ether gave 0.73 g (98%) of **34t** as a white crystalline solid: mp 146–147 °C; ^1H NMR ($CDCl_3$) δ 7.21 (m, 10 H, PhH), 4.34 (d, 1 H, J = 8 Hz, CHO), 4.15 (s, 2 H, OH and NH), 2.85–2.18 (m, 4 H, NCH_2, NCH, and CHPh), 1.75–1.10 (m, 4 H, CH_2); IR (mull) 3260 (NH), 3100 (OH), 1610 cm^{-1} (NH); mass spectrum (70 eV), m/e (relative intensity) 267 (1, M^+), 249 (4), 161 (100), 160 (100), 115 (72), 107 (19), 104 (73), 91 (100), 77 (99).

Anal. ($C_{18}H_{21}NO$) C, H, N.

2(e)-Benzoyl-4-*tert*-butyl-2,4,6-triisopropylbenzopiperidide (40). To a solution of 56.3 mg (0.69 mmol) of sodium acetate and 0.745 g (3.45 mmol) of pyridinium chlorochromate in 20 mL of CH_2Cl_2 was added 0.396 g (0.83 mmol) of **11** and the solution was stirred at ambient temperature for 2 h. The reaction mixture was diluted with 100 mL of ether and filtered three times through celite. Removal of solvent left **40** as a yellowish oil: ^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H, PhH), 6.70 (s, 2 H, Ar H), 5.30 (m, 1 H, NCH), 3.52 (m, 2 H, NCH_2), 2.74 (m, 3 H, $CHCH_3$), 2.20–1.30 (m, 5 H, $CHC(CH_3)_3$ and CH_2), 1.24 (m, 18 H, $CHCH_3$), 0.84 (s, 9 H, CCH_3); IR (mull) 1680 (C=O), 1620 (C=O), 1300, 1225, 1095, 960, 875, 800, 695 cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 475 (2, M^+), 371 (16), 370 (52), 232 (99), 231 (100), 230 (54), 217 (30), 213 (25), 162 (48), 148 (26), 134 (32), 131 (61), 106 (58), 105 (100), 91 (43), 77 (100), 71 (100), 55 (62).

2(a)-Benzoyl-4-*tert*-butyl-2,4,6-triisopropylbenzopiperidide (41). To a solution of 0.70 g (30.4 mmol) of sodium in 50 mL of methanol was added the oil **40**. The solution was heated at reflux for 2 h, diluted with 100 mL of CH_2Cl_2, and washed with 75 mL of water. The organic layer was dried with $MgSO_4$ and the solvent was removed to give **41** as a yellowish oil: ^1H NMR ($CDCl_3$) δ 7.33 (m, 5 H, PhH), 6.80 (s, 2 H, Ar H), 6.35 (m, 1 H, NCH), 3.30 (m, 2 H, NCH_2), 2.74 (m, 3 H, $CHCH_3$), 1.75–1.40 (m, 5 H, $CHC(CH_3)_3$ and CH_2), 1.25 (m, 18 H, $CHCH_3$), 0.71 (s, 9 H, CCH_3); IR (mull) 1680 (C=O), 1620 (C=O), 1310, 1255, 1205, 1100, 1025, 880, 800, 695 cm^{-1}.

2(a)-(α-Hydroxybenzyl)-4-*tert*-butyl-2,4,6-triisopropylbenzopiperidide (42). To a solution of 0.348 g (9.2 mmol) of $LiAlH_4$ in 75 mL of ether was added the oil **41**. The mixture was heated at reflux for 10 h. After cooling to 0 °C, 30 mL of ethanol was added dropwise, followed by 100 mL of water. The organic layer was removed, washed three times with 100 mL portions of water, and dried with $MgSO_4$, and the solvent was removed. Recrystallization from ethanol/water gave 0.22 g (60%, from **11**) of **42** as a white crystalline solid: mp 202–204 °C; ^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H, PhH), 6.90 (d, 1 H, J = 2 Hz, Ar H), 6.78 (d, 1 H, J = 2 Hz, Ar H), 5.45 (m, 1 H, NCH), 4.95 (m, 1 H, CHO), 3.25 (m, 2 H, NCH_2), 2.73 (m, 3 H, $CHCH_3$), 2.20–1.20 (m, 5 H, CH_2 and $CHC(CH_3)_3$), 1.20 (m, 18 H, $CHCH_3$), 0.75 (s, 9 H, CCH_3); IR (mull) 3400 (OH), 1610 (C=O), 1255, 1145, 1085, 1050, 1020, 878, 795, 760, 700 cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 477 (2, M^+) 371 (54), 370 (100), 233 (80), 232 (100), 231 (100), 217 (58), 216 (58), 215 (55), 201 (40), 173 (50), 131 (53), 129 (53), 108 (75), 91 (77), 77 (86), 57 (76), 43 (100).

Anal. Calcd for $C_{32}H_{47}NO_2$: C, 80.45, H, 9.92; N, 2.93. Found: C, 80.18; H, 10.00; N, 2.80.

2(e)-Benzoyl-4-phenyl-2,2-diethylbutanopiperidide (37). To a solution of 80.0 mg (0.98 mmol) of sodium acetate and 0.85 g (3.9 mmol) of pyridinium chlorochromate in 15 mL of CH_2Cl_2 was added 1.0 g (2.54 mmol) of **31**. After the solution was allowed to stir at a consistent temperature for 2 h, the mixture was diluted with 100 mL of ether unfiltered through celite and removed in vacuo. Recrystallization of the residue from ether gave 0.90 g (90%) of **37** as a white crystalline solid: mp 137–138 °C; ^1H NMR ($CDCl_3$) δ 7.89 (m, 2 H, PhH), 7.36 (m, 3 H, PhH), 7.15 (s, 5 H, PhH), 5.17 (m, 1 H, NCH), 3.97 (m, 2 H, NCH_2), 2.78 (m, 1 H, CHPh), 2.33–1.70 (m, 4 H, CH_2), 1.14 (q, 6 H, J = 7 Hz, CCH_2), 0.78 (t, 9 H, J = 7 Hz, CH_3); IR (mull) 1680 (C=O), 1615 (C=O), 1455, 1375, 1260, 1030, 975, 855, 810, 697 cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 391 (3, M^+), 287 (100), 286 (100), 263 (29), 160 (100), 144 (93), 127 (100), 117 (51), 105 (100), 100 (100), 91 (94), 77 (100).

Anal. ($C_{26}H_{33}NO_2$) C, H, N.

2(a)-Benzoyl-4-phenyl-2,2-diethylbutanopiperidide (38). Treatment of 0.0360 g (0.92 mmol) of **37** in 20 mL of methanol with 0.90 g (16.7 mmol) of sodium methoxide at reflex for 2 h followed by extractive work gave a solid residue. Recrystallization from ether gave 0.292 g (81%) of **38** as a white crystalline solid: mp 104–105 °C; ^1H NMR ($CDCl_3$) δ 7.94 (m, 2 H, PhH), 7.45 (m, 3 H, PhH), 6.37 (m, 1 H, NCH), 4.33 (m, 1 H, eq NCH_2), 3.64 (m, 1 H, ax NCH_2), 2.90 (m, 1 H, CHPh), 2.33–1.70 (m, 4 H, CH_2), 1.70 (q, 6 H, J = 7 Hz, CH_2CH_3), 0.83 (t, 9 H, J = 7 Hz, CH_3); IR (mull) 1695 (C=O), 1627 (C=O), 1465, 1350, 1220, 1200, 1105, 1015, 970, 918, 803, 758, 996 cm^{-1}; mass spectrum (70 eV), m/e (relative intensity) 391 (6, M^+), 287 (100), 286 (100), 264 (20), 248 (11), 160 (100), 144 (49), 127 (100), 105 (84), 104 (74), 100 (99), 99 (100), 77 (87).

Anal. Calcd for $C_{26}H_{33}NO_2$: C, 79.77; H, 8.50; N, 3.58. Found: C, 79.38; H, 8.63; N, 3.54.

2(a)-(α-Hydroxybenzyl)-4-phenyl-2,2-diethylbutanopiperidide (39). To a solution of 1.8 g (47.6 mmol) of sodium borohydride in 65 mL of ethanol was added 1.60 g (4.08 mmol) of **38**. After stirring at ambient temperature for 0.5 h, the solution was diluted with water and worked up by extraction to afford 1.40 g (87%) of **39** as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.40 (m, 5 H, PhH), 5.20 (m, 1 H, NCH), 5.09 (m, 1 H, CHO), 3.68 (m, 1 H, eq NCH_2), 3.10 (m, 1 H, ax NCH_2), 2.53 (m, 1 H, CHPh), 1.90 (m, 4 H, CH_2), 1.60 (m, 6 H, CH_2CH_3), 0.87 (5, 9 H, J = 7 Hz, CH_3); IR (mull) 3365 (OH), 1595 (C=O), 1450, 1370, 1020, 997, 878, 765, 756, 698 cm^{-1}.

***erythro*-α-(4-Phenylpiperidin-2(e)-yl)benzyl 2,2-Diethylbutanoate (36e).** To a solution of 5.00 mL (33.1 mmol) of TMEDA and 24.5 mL (1.35 M, 33.1 mmol) of *sec*-BuLi in 500 mL of ether at −78 °C under nitrogen was added 8.0 g (27.8 mmol) of **20** in 75 mL of ether. After warming to 0 °C and stirring for 40 min, the solution was cooled to −78 °C and 3.5 mL (35.6 mmol) of benzaldehyde was added. The solution was warmed to ambient temperature and washed sequentially with 125-mL portions of 1 N HCl, 1 N NaOH, and saturated NaCl solutions. After drying with $MgSO_4$, the solvent was removed to leave 12.7 g of yellowish oil. Distillation at 120–130 °C (0.3 torr) afforded 9.1 g of thick yellow oil. Purification by MPLC on silica using 3:7 (v/v) EtOAc–hexane provided 1.76 of **36t** and 2.78 g of **36e**. Treatment with CH_3OH/HCl as described above provided a total yield of 4.14 g of **36t** and 2.78 g of **36e**. The overall yield was 69% (3:2 threo/erythro). The **36e** isomer was isolated as a colorless oil that could not be recrystallized: ^1H NMR ($CDCl_3$) δ 7.38–6.90 (m, 10 H, PhH), 5.63 (d, 1 H, J = 7 Hz, CHO), 3.20–2.20 (m, 4 H, NCH, NCH_2, and CHPh), 1.80–1.30 (m, 4 H, CH_2), 1.50 (q, 6 H, J = 6 Hz, CH_2CH_3), 0.71 (5, 9 H, J = 6 Hz, CH_3); IR (film) 1725 cm^{-1} (C=O); mass spectrum (70 eV), m/e (relative intensity) 393 (4, M^+), 265 (20), 264 (22), 250 (44), 161 (100), 160 (100), 144 (34), 130 (36), 129 (38), 117 (89), 115 (55).

Anal. ($C_{26}H_{35}NO_2$) C, H, N.

***erythro*-2(e)-(α-Hydroxybenzyl)-4-phenylpiperidine (34ee).** In the same manner as for **22**, **34ee** was prepared using 3.71 g (33.1 mmol) of potassium *tert*-butoxide, 0.1 mL (5.6 mmol) of water, and 1.30 g (3.31 mL) of **36e** in 25 mL of *tert*-butyl alcohol. Recrystallization from ether gave 0.80 g (90%) of **34e** as a white crystalline solid: mp 143–144 °C; ^1H NMR ($CDCl_3$) δ 7.20 (m, 10 H, PhH), 4.52 (d, 1 H, J = 5 Hz, CHO), 3.12–2.14 (m, 5 H, NCH, NCH_2, CHPh), 1.90–1.20 (m, 4 H, CH_2); IR (mull) 3290 (NH), 3100 (OH), 1610 (NH), 1260 (CO), 1120 cm^{-1} (OH); mass spectrum (70 eV), m/e (relative intensity) 267 (1, M^+), 266 (3), 161 (100), 160 (100), 144 (59), 117 (95), 115 (99), 104 (99), 91 (100), 79 (100).

Anal. ($C_{18}H_{21}NO$) C, H, N.

α-(4-Phenylpiperidin-2(a)-yl)benzyl 2,2-Diethylbutanoate (39). In the same manner as for **23** a diastereomeric mixture of **39** was prepared using 1.40 g (3.56 mmol) of **38**, 30 mL of methanol, and 15 mL of concentrated HCl. Purification by MPLC on silica using 3:7 (v/v) EtOAc–hexane gave 0.90 g of **39x** and 0.35 g of **39y**. The overall yield was 90% (2:5 threo/erythro).

One isomer, **39x**, was isolated as a colorless oil: ^1H NMR ($CDCl_3$) δ 7.50–7.00 (m, 10 H, PhH), 6.14 (d, 1 H, J = 10 Hz, CHO), 3.46 (m, 1 H, NCH), 3.34 (s, 1 H, NH), 3.00 (m, 3 H, NCH_2 and CHPh), 2.10–1.45 (m, 4 H, CH_2), 1.65 (q, 6 H, J = 6 Hz, CCH_2), 0.74 (t, 9 H, J = 6 Hz, CH_3); IR ($CDCl_3$) 3320 (NH), 1735 (C=O), 1605 cm^{-1} (NH); mass spectrum (70 eV), m/e (relative intensity) 393 (5, M^+), 249 (90), 160 (100), 159 (100), 145 (68), 143 (85), 129 (84), 128 (97), 116 (100), 114 (100), 103 (99), 90 (100).

Anal. ($C_{26}H_{35}NO$) C, H, N.

The other isomer **39y** was isolated as a white crystalline solid, mp 73–75 °C; ^1H NMR ($CDCl_3$) δ 7.40–7.00 (m, 10 H, PhH), 5.49 (d, 1 H, J = 7 Hz, CHO), 3.30–2.15 (m, 5 H, NCH, NCH_2, CHPh, and NH), 1.82–1.30 (m, 4 H, CH_2), 1.61 (q, 6 H, J = 7 Hz, CCH_2), 0.72 (t, 9 H, J = 7 Hz, CH_2CH_3); IR (mull) 3295 (NH), 1725 (C=O), 1600 cm^{-1} (NH); mass spectrum (70 eV), m/e (relative intensity) 393 (1, M^+), 250 (51), 161 (100), 160 (100), 146 (33), 144 (43), 130 (50), 117 (90), 104 (51), 91 (100).

Anal. ($C_{26}H_{35}NO$) C, H, N.

2(a)-(α-Hydroxybenzyl)-4-phenylpiperidine (34ay). In the same manner as for **22**, **34ay** was prepared using 0.67 g (6.0 mmol) of potassium *tert*-butoxide, 0.02 mL (0.92 mmol) of water, and 0.228 g (0.58 mmol) of **39ay** in 10 mL of *tert*-butyl alcohol. Recrystallization from ether gave 0.132 g (85%) of **34ay** as a white crystalline solid: mp 69-71 °C; ^{1}H NMR ($CDCl_3$) δ 7.38-6.90 (m, 10 H, PhH), 4.47 (d, 1 H, J = 8 Hz, CHO), 4.00 (br, 2 H, NH and OH), 3.05-2.65 (m, 2 H, NCH_2), 2.79 (m, 1 H, J = 8 Hz, NCH), 2.44 (m, 1 H, CHPh), 1.60 (m, 2 H, CH_2), 1.33 (m, 2 H, CH_2); IR (mull) 3400 (NH), 3200 (OH), 1650 (NH), 1310 cm^{-1} (CO); mass spectrum (70 eV), *m/e* (relative intensity) 267 (2, M^+), 231 (7), 161 (100), 160 (100), 144 (13), 117 (15), 104 (8), 91 (10).

Anal. ($C_{18}H_{21}NO$) C, H, N.

***threo*-2(a)-(α-Hydroxybenzyl)-4-phenylpiperidine (34ax).** In the same manner as for **22**, **34ax** was prepared using 1.57 g (14.0 mmol) of potassium *tert*-butoxide, 0.05 mL (2.3 mmol) of water, and 0.536 g (1.36 mmol) of **39x** in 10 mL of *tert*-butyl alcohol. Recrystallization from ether gave 0.303 g (83%) of **34ax** tentatively assigned the threo isomer,[26] as a white crystalline solid: mp 89-90 °C; ^{1}H NMR ($CDCl_3$) δ 7.35-6.95 (m, 10 H, PhH), 4.78 (d, 1 H, J = 11 Hz, CHO), 3.30 (br, 2 H, NH and OH), 3.10-2.75 (m, 4 H, NCH_2, CCH, and CHPh), 2.0-1.45 (m, 4 H, CH_2); IR (mull) 3280 (NH), 3200 (OH), 1615 (NH), 1280 cm^{-1} (CO); mass spectrum (70 eV), *m/e* (relative intensity) 267 (61, M^+), 231 (42), 230 (50), 161 (100), 160 (100), 144 (77), 132 (44), 117 (99), 104 (96), 91 (48).

Anal. ($C_{18}H_{21}NO$) C, H, N.

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Supplementary Material Available: Deuteration experiments and substituted benzamide syntheses (12 pages). Ordering information is given on any current masthead page.

Directional Hydrogen Bonding to sp^2- and sp^3-Hybridized Oxygen Atoms and Its Relevance to Ligand-Macromolecule Interactions

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Abstract: In order to analyze the directionality of hydrogen bonding to oxygen atoms the Cambridge Crystallographic Data File was searched for O···X (X = N, O) intermolecular contacts at less than 3 Å in structures containing ether, ketone, epoxide, enone, and ester groups. The results are represented as scatterplots. However, for further clarity, they are also represented as diffuse (probability) densities obtained by superposing spherical atomic electron density functions with a parameterizable temperature factor on each point in the scatterplot and contouring the maps at a height proportional to the number of data points. In all systems the largest concentration of hydrogen-bonded X groups lay in the direction commonly ascribed to lone pairs, but generally only one such X group per oxygen atom. In addition we obtained a tentative view that epoxides had a broader distribution of points for X than did ethers; in this respect the positions of the lone pairs in epoxides are more like those in ketones. The experimental plots that are described here may be used to map the stereochemistry of that part of the macromolecule (possibly of unknown structure) that binds to the ligand molecule.

There have been many attempts recently to understand the manner by which small molecules bind to macromolecules and how this binding can result in specific activity. The specificity of interactions between oxygen- and/or nitrogen-containing molecules in organic and biological systems suggest that hydrogen bonding and other directional constraints are important. Although there has been much interest in the geometry of the A-H···B system (A, B = oxygen, nitrogen, etc.), much less information is available on the angular distribution of proton donors around an acceptor, e.g., the H···O=C angle.[2] However, the constraints on this (and similar) systems are of vital importance to our understanding of the specificity of binding of ketones, epoxides, and related molecules to biological and other macromolecules.

Hydrogen bonding to epoxides has a second important function. The reactivity of epoxides is linked to their potency as alkylating

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