Practical Syntheses of Enantiomerically Enriched γ-Lactones and γ-Hydroxy Ketones by the Alkylation of Pseudoephedrine Amides with Epoxides and Their Derivatives

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Pseudoephedrine amide enolates are shown to undergo efficient alkylation reactions with epoxides as electrophiles. Reactions with monosubstituted epoxides are subject to stereochemical matching such that the pairing leading to the 1,3-syn diastereomer is a highly selective, synthetically useful process, while the pairing forming the 1,3-anti diastereomer is not. Reactions with the 1,1-disubstituted epoxide isobutylene oxide are also highly diastereoselective and synthetically useful, but ethylene oxide exhibits poor diastereoselectivity. As an alternative to the use of ethylene oxide, 2-(*tert*-butyldimethylsilyloxy)ethyl iodide is shown to undergo highly diastereoselective and efficient alkylation reactions with pseudoephedrine amide enolates. Interestingly, epoxides and alkyl halides are found to attack opposite π-faces of pseudoephedrine amide enolates. The products of each of these alkylation reactions are transformed efficiently into γ-lactones by acidic hydrolysis and into methyl ketones by the addition of methyllithium. The methodology described provides useful procedures for the synthesis of enantiomerically enriched γ-lactones and γ-hydroxy ketones.

Introduction

We have shown that pseudoephedrine amides undergo efficient and highly diastereoselective alkylation reactions with a range of alkyl halides. The alkylation products are readily transformed in a single operation into highly enantiomerically enriched carboxylic acids, aldehydes, ketones, or primary alcohols. Both enantiomers of the chiral auxiliary, pseudoephedrine, are available in quantity and are inexpensive. This, and desirable process features such as the crystallinity of many pseudoephedrine amides, contribute to the practicality of the methodology.[1] Recently, we have extended the methodology to the preparation of D- and L-α-amino acids by the alkylation of (+)- and (−)-pseudoephedrine glycinamide, respectively.[2] In this work, we explore the use of epoxides and epoxide-derived electrophiles in the alkylation reaction.

The importance of epoxides as electrophiles in organic chemistry has grown collaterally with advances in methodology for their synthesis in enantiomerically enriched form.[3] Despite their high reactivity, epoxides typically do not react with lithium enolates of simple monoketones and monoesters.[4] Lithium enolates of amides, by contrast, are known to react readily with epoxides, presumably due to their greater thermal stability (versus ester enolates) and nucleophilicity.[5] The stereochemical consequences of the latter alkylation reaction are of great interest in the context of the present study. Specific questions concern the diastereoselectivity of the reaction of amide enolates bearing an α-substituent with monosubstituted epoxides (1,3-syn versus 1,3-anti) and the degree of enolate π-diastereofacial selectivity possible with the use of a chiral auxiliary. Addressing the first issue, Sauriol-Lord and Grindley showed that the reaction of achiral α-substituted *N*,*N*-dialkylamide enolates with monosubstituted epoxides, a reaction known to favor addition to the less-substituted epoxide terminus,[5] was inherently syn selective.[6] The magnitude of the observed diastereoselectivity was not large, with syn/anti ratios typically between 1 and 9, and was dependent upon the size of the epoxide substituent and the *N*-alkyl groups, in both cases larger being better.[6] Figure 1 below provides a useful mnemonic device (if not a valid rationalization) that summarizes these findings. The second stereochemical issue germane to the present work concerns the extent of enolate π-facial selectivity possible by virtue of a chiral auxiliary. Important precedence in this regard comes from the work of Askin et al. in a study of the reaction of epoxides with chiral amide enolates derived from prolinol.[7] Prolinol amide enolates were first developed independently by Evans and Takacs,[8a] and Sonnett and Heath,[8b] in new methodology for the asymmetric alkylation of carboxylate derivatives, where it was established that these enolates react with alkyl halides

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(3) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (c) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. For reviews, see also: (d) Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 7, p 193. (e) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 8, p 247.

(4) Successful enolate−epoxide bond constructions typically employ stabilized enolates (e.g., malonate derivatives) at elevated reaction temperatures or, in the case of monoester and monoketone enolates, utilize Lewis-acidic additives: (a) Danishefsky, S.; Kitahara, T.; Tsai, M.; Dynak, J. *J. Org. Chem.* **1976**, *41*, 1669; and references therein. (b) Sturm, T.; Marlewski, A. E.; Rezenka, D. S.; Taylor, S. K. *J. Org. Chem.* **1989**, *54*, 2039. (c) Chini, M.; Crotti, P.; Favero, L.; Pineschi, M. *Tetrahedron Lett.* **1991**, *32*, 7583. (d) Smith, A. B., III; Pasternak, A.; Yokoyama, A.; Hirschmann, R. *Tetrahedron Lett.* **1994**, *35*, 8977.

(5) (a) Sucrow, W.; Slopianka, M.; Winkler, D. *Chem. Ber.* **1972**, *105*, 1621. (b) Sucrow, W.; Klein, U. *Chem. Ber.* **1975**, *108*, 48. (c) Hullot, P.; Cuvigny, T.; Larcheveque, M.; Normant, H. *Can. J. Chem.* **1977**, *55*, 266. (d) Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 1688. (e) Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1978**, *43*, 1947. (f) Takahata, H.; Wang, E.; Yamazaki, T. *Synth. Commun.* **1988**, *18*, 1159. (g) Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277. For the reaction of carboxylate enolates with epoxides, see: (h) Creger, P. L. *J. Org. Chem.* **1972**, *37*, 1907. For the reaction of chiral oxazoline anions with epoxides, see: (i) Meyers, A. I.; Mihelich, E. D. *J. Org. Chem.* **1975**, *40*, 1187. (j) Meyers, A. I.; Yamamoto, Y.; Mihelich, E. D.; Bell, R. A. *J. Org. Chem.* **1980**, *45*, 2792.

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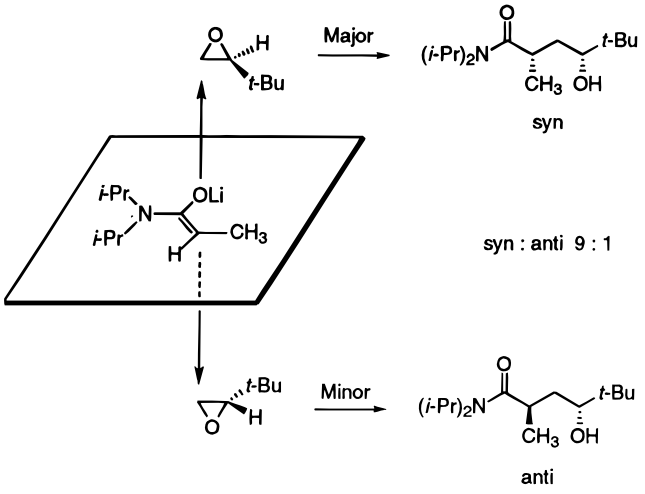


Figure 1. Stereochemical matching in the reaction of amide enolates with epoxides.[6]

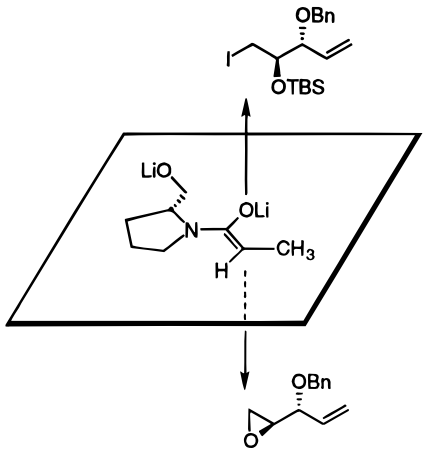


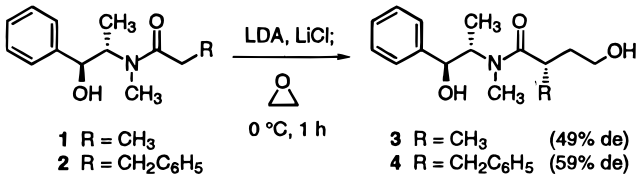
Figure 2. π-Facial selectivity in the reaction of prolinol amide enolates with alkyl halides and epoxides.[7,8]

with uniform and high π-facial selectivity. Askin et al. showed that these same enolates exhibit opposite π-facial selectivity in reactions with epoxides.[7] These differing stereochemical preferences can be summarized graphically, as shown in Figure 2. Detailed consideration of specific examples from the work of Askin et al. shows that in all cases, whether alkyl halides or epoxides were used as electrophiles, the inherent π-facial selectivity of the enolate (albeit different for the two classes of electrophiles) dominated the outcome of the reaction.[7] It is interesting to note that the epoxide additions were subject to stereochemical matching;[9] the reaction favoring the syn diastereomer was found to be the more highly diastereoselective.[7] This observation supports the notion that the reaction of amide enolates with monosubstituted epoxides is an inherently syn selective process.[6] These results impressively demonstrate that chiral auxiliaries can markedly influence the π-facial selectivity of enolate additions to epoxides. In results described herein, we establish that pseudoephedrine is a valuable chiral auxiliary for enolate additions to epoxides and epoxide-derived electrophiles. Our results corroborate and extend the precedents summarized above and provide practical new methodology for the synthesis of enantiomerically enriched γ-lactones and γ-hydroxy ketones.

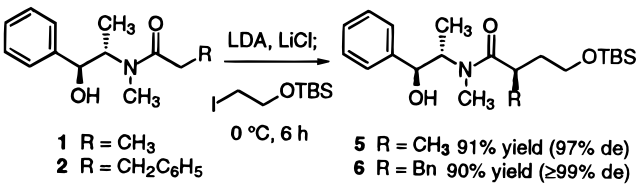
(7) Askin, D.; Volante, R. P.; Ryan, K. M.; Reamer, R. A.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 4245.
(8) (a) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233. (b) Sonnet, P. E.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3137.
(9) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

Results

Enolization of (*S*,*S*)-pseudoephedrine propionamide (**1**) or (*S*,*S*)-pseudoephedrine hydrocinnamide (**2**) with lithium *N*,*N*-diisopropylamide (2.1 equiv, −78 °C for 1 h, 0 °C for 15 min, 23 °C for 5 min) in tetrahydrofuran (THF) in the presence of anhydrous lithium chloride (6 equiv), as previously described,[1] followed by the addition of ethylene oxide (5 equiv) at 0 °C led to the efficient formation of a diastereomeric mixture of alkylation products, in either case (96−97% yield, 1 h reaction period). Accurate

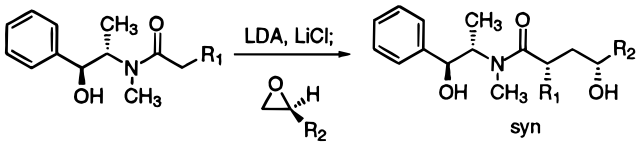


determination of diastereomeric excesses was conducted by acetylation of the crude reaction mixtures (acetic anhydride, (dimethylamino)pyridine (DMAP)) followed by capillary gas chromatographic analysis of the diacetates produced. As will be apparent from the discussion below, ethylene oxide represents a "worst-case" substrate; neither **1** nor **2** afforded synthetically useful levels of diastereoselectivity (for **1**: 49% de, for **2**: 59% de). The sense of asymmetric induction was established by acidic hydrolysis of the alkylation products to produce the corresponding γ-lactones (2 N aqueous sulfuric acid, dioxane, reflux, 89−90% yield), followed by comparison of the rotations of these products against literature values (lactone derived from alkylation/hydrolysis of **1**, observed: $[\alpha]^{20}_D = -10.2°$ ($c = 5.5$, ethanol), literature for (*S*)-(−)-2-methyl-γ-butyrolactone: $[\alpha]^{20}_D = -21.5°$ ($c = 5.5$, ethanol),[10] 48% ee; lactone derived from alkylation/hydrolysis of **2**, observed: $[\alpha]^{20}_D = +38.1°$ ($c = 5.0$, carbon tetrachloride), literature for (*S*)-(+)-2-phenylmethyl-γ-butyrolactone: $[\alpha]^{20}_D = +67.7°$ ($c = 5.0$, carbon tetrachloride),[11] 56% ee). Thus, the major diastereomer produced from **1** is **3**, while **2** produces **4**. In both cases the major product arises from the attack of ethylene oxide on the opposite enolate π-face as that attacked by simple alkyl halides, in accord with the observations of Askin et al. in their studies of amide enolates derived from prolinol.[7] The sense of π-facial attack by alkyl halides on enolates derived from **1** and **2** has been determined many times over[1] and was confirmed once again using the *tert*-butyldimethylsilyl ether of 2-iodoethanol as the alkyl halide; the diastereomers **5** and **6**, respectively, were formed in excellent yield and with high diastereoselectivity.



Desilylation of **5** and **6** with tetra *n*-butylammonium fluoride produced materials that were identical to the minor diastereomers formed in the respective ethylene

Table 1. Alkylation of Pseudoephedrine Amides with "Matched" Epoxides[a]



entry	R_1	R_2	temp (°C)	time (h)	isolated yield %	de %
1	CH_3	CH_3	−5	4	88	93
2	CH_3	C_6H_5	−5	7	82	90
3	CH_3	CH_2OTBS	−5	10	84	96
4	CH_3	CH_2OBn	−5	12	80	85
5	Bn	CH_3	−5	9	86	≥99
6	Bn	C_6H_5	−5	10	86	≥95
7	Bn	CH_2OTBS	−5	11	81	≥99
8	Bn	CH_2OBn	−5	12	87	≥95

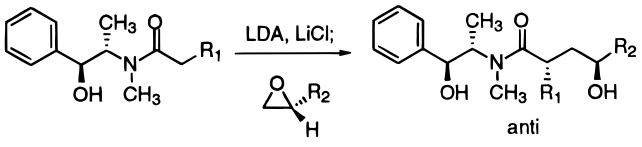
[a] 2 equiv of epoxide was used in each experiment.

oxide alkylations. For the synthesis of simple 2-hydroxyethyl alkylation products of this type, it is clear that 2-(*tert*-butyldimethylsilyloxy)ethyl iodide is the superior electrophile. It is shown below that the "inverse" selectivity found with ethylene oxide extends to monosubstituted and 1,1-disubstituted epoxides. It is also shown that substituted epoxides frequently afford higher and, often, synthetically useful levels of diastereoselectivity and can provide products not easily obtained using alkyl halides as electrophiles.

When chiral, enantiomerically enriched (≥89% ee, see Experimental Section) monosubstituted epoxides were used in the alkylation reaction it was found that the inherent π-facial selectivity of the pseudoephedrine amide enolate was the overriding feature in determining the stereochemical outcome of the reaction (Tables 1 and 2). Predictably, the stereochemistry of the epoxide was found to influence the reaction as well, giving rise to matched and mismatched combinations.[9] For monosubstituted epoxides, the matched combination is that which produces the 1,3-syn product (Table 1) while the mismatched combination leads to a modest predominance of the 1,3-anti products (Table 2). The stereochemistry of the products was determined by lactonization under acidic conditions (see below) followed by ^{1}H NMR analysis; cis and trans lactones were readily differentiated on the basis of coupling constants (see Experimental Section).[12] Inspection of Tables 1 and 2 reveals that matched alkylations are synthetically useful whereas mismatched alkylations are not. Although limited, the data suggests that larger α-substitutents ($R_1 = CH_2C_6H_5$ versus $R_1 = CH_3$) within the enolate lead to enhanced selectivity in the matched cases.

The diastereoselectivity of matched epoxide alkylations versus mismatched alkylations was such that the possibility of conducting kinetic resolutions with racemic monosubstituted epoxides as substrates was considered (for an earlier example using chiral oxazolidinone enolates, see reference 4d). As the data summarized in Table 3 reveal, the idea was sound, but did not provide a synthetically practical procedure. In all cases, the matched, (2*S*)-syn diastereomer predominated; however,

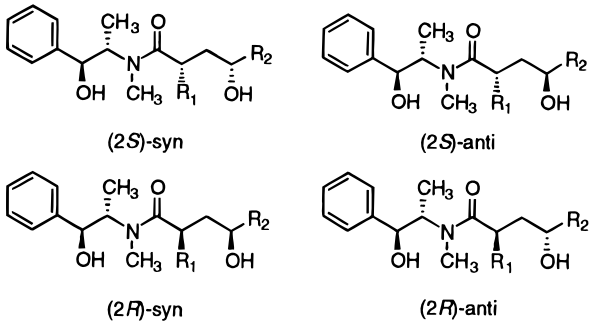
Table 2. Alkylation of Pseudoephedrine Amides with "Mismatched" Epoxides[a]



entry	R_1	R_2	temp (°C)	time (h)	isolated yield %	de %
1	CH_3	CH_3	−5	6	86	73
2	CH_3	C_6H_5	−5	10	73	25
3	CH_3	CH_2OTBS	0	21	78	12
4	CH_3	CH_2OBn	−5	13	78	38
5	Bn	CH_3	−5	10	79	45
6	Bn	C_6H_5	−5	15	72	46
7	Bn	CH_2OTBS	5	26	64	17
8	Bn	CH_2OBn	−5	12	80	36

[a] 2 equiv of epoxide was used, except in entry 3, where 1.5 equiv was employed.

Table 3. Alkylation of Pseudoephedrine Amides with Racemic Epoxides

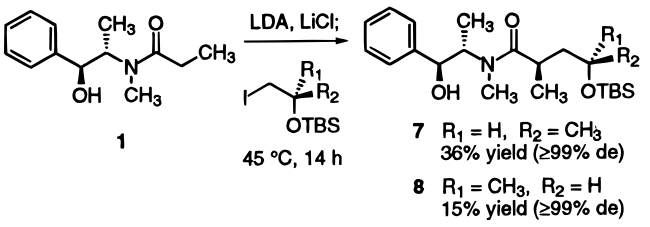


R_1	R_2	(±)-epoxide (equiv)	temp (°C)	isolated yield %	(2*S*)-syn	(2*S*)-anti	(2*R*)-syn	(2*R*)-anti
CH_3	CH_3	5.0	−5	81	72	18	6	4
CH_3	C_6H_5	10.0	−5	84	63	19	16	2
CH_3	CH_2OTBS	2.0	0	61	73	14	12	1
Bn	CH_3	5.0	−5	78	58	23	11	8
Bn	CH_2OTBS	2.0	0	55	62	25	13	0

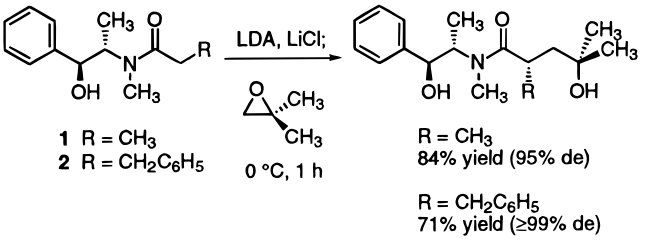
appreciable amounts of the (2*S*)-anti diastereomer arising from a mismatched reaction with the contaminating epoxide enantiomer were also formed, in addition to minor amounts of each of the (2*R*)-diastereomers. The data shows that, although the inherent π-facial selectivity of the pseudoephedrine amide enolate dominates the reaction, the rate ratio of matched to mismatched reactions with the respective epoxide enantiomers is only about 2.5−5, insufficient for a highly discriminating reaction.

As an alternative to the use of monosubstituted epoxides as electrophiles, alkylation reactions with the enantiomeric iodohydrin derivatives **7** and **8**[13] were examined (for the specific case of propylene oxide). Unfortunately, both iodides were exceedingly unreactive electrophiles, deactivated both by steric hindrance and β-oxygenation, and reacted sluggishly, inefficiently, but highly selectively with the enolate derived from **1**. When a racemic mixture of **7** and **8** was used in the alkylation reaction only the two 2*R*-isomers depicted were produced, in a 1:1 ratio. This demonstrates that the π-facial selectivity of the enolate exerts complete control in the alkylation reaction; there is no discernible rate discrimination between enantiomers **7** and **8**.

(10) Kaneko, T.; Wakabayashi, K.; Katsura, H. *Bull. Chem. Soc. Jpn.* **1962**, *35*, 1149.
(11) Helmchen, G.; Nill, G.; Flockerzi, D.; Youssef, M. S. K. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 63.
(12) Hussain, A. M. T.; Ollis, W. D.; Smith, C.; Stoddart, J. F. *J. Chem. Soc. Perkin Trans. 1* **1975**, 1480.
(13) Bajwa, J. S.; Anderson, R. C. *Tetrahedron Lett.* **1991**, *26*, 3021.



A single 1,1-disubstituted epoxide substrate, isobutylene oxide, was examined in the alkylation reaction and was found to undergo highly selective alkylations with enolates derived from both **1** and **2**. This is a useful



result, especially so given the almost certain failure of the corresponding alkylation reactions with iodohydrin derivatives of isobutylene oxide. In the only example of a 1,2-disubstituted epoxide studied to date, cyclohexene oxide was found to be completely inert toward enolates derived from **1** and **2** under a variety of conditions.

Heating of the alkylation products of Table 1 in aqueous dioxane at 95 °C in the presence of dilute sulfuric acid formed the corresponding trans-lactones (Table 4) in high yield and with high diastereomeric purity (the diastereomeric purity of the products was determined by ^{1}H NMR and capillary gas chromatographic analysis). In general, the benzyl-substituted substrates were observed to hydrolyze more slowly than the methyl-substituted substrates and, as a consequence, the *tert*-butyldimethylsilyloxy group was cleaved in the product of entry 5. Lactonization of the substrates of Table 2, by contrast, afforded the cis-lactones as the major products. The diastereomeric purity of these cis-lactones reflected the diastereomeric purity of the starting materials. For example, heating the product of entry 4, Table 2 (38% de) with dilute sulfuric acid afforded the corresponding cis-lactone with 36% de. Although they were not sufficiently diastereomerically enriched for preparative purposes, these cis-lactone products were important in corroborating stereochemical assignments. Lactonization of the products from alkylations with isobutylene oxide proceeded with detectable racemization in the case of the α-methyl substitutent, but not with the α-benzyl group (enantiomeric excesses were determined by reduction of the lactones with lithium aluminum hydride followed by selective Mosher esterification[15] of the primary hydroxyl groups and ^{1}H NMR analysis). It should be noted that whereas the trans-substituted lactones of Table 4 are available by alternative methods, including alkylation of enantiomerically pure 4-alkylbutyrolactones,[14] or even by

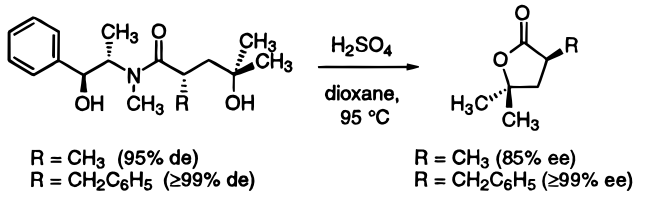
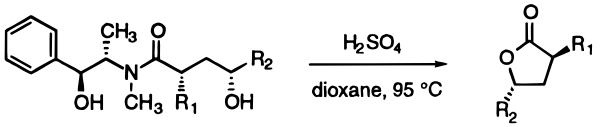


Table 4. Lactones by Acidic Hydrolysis of Pseudoephedrine Amides

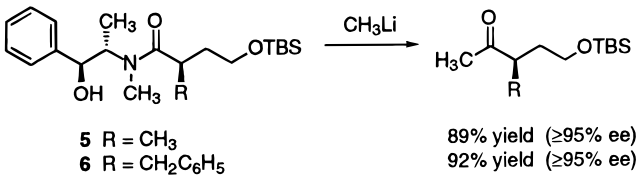


entry	R_1	R_2	time	$[H_2SO_4]$ (M)	isolated yield %	isolated de %
1	CH_3	CH_3	1 h	0.03	83	94[a]
2	CH_3	CH_2OTBS	20 min	0.05	90	≥99
3	CH_3	CH_2OBn	30 min	0.06	90	98
4	Bn	CH_3	2.5 h	0.43	92	≥99
5	Bn	CH_2OTBS	30 min	0.21	92[b]	≥99
6	Bn	CH_2OBn	1.5 h	0.17	94	≥99

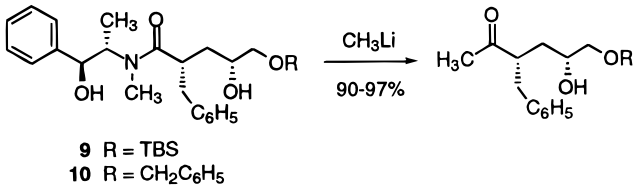
[a] Starting material was 94% de for entry 1, all others were ≥99% de. [b] Product was desilylated.

the alkylation of an achiral amide enolate with an enantiomerically pure epoxide followed by acid-induced hydrolysis/equilibration, the lactones derived from isobutylene oxide alkylations are not.

The addition of alkyllithium reagents to the alkylation products of this study afforded ketones in excellent yield and with high enantiomeric excess when diastereomerically pure starting materials were employed.[1] For example, addition of 2.5 equiv of methyllithium to the alkylation products **5** and **6** (≥99% de) in ether at −78 °C followed by warming to 0 °C afforded the corresponding methyl ketones as indicated in the equation below.



Addition of methyllithium to the diols **9** and **10** (≥99% de) was also successful, providing the corresponding ketones in 90−97% yield, without detectable epimerization of the α-substituent. The latter products existed as an equilibrating mixture of open-chain and epimeric closed forms.



Discussion and Conclusions

Alkyl halides and epoxides have been shown to attack opposite enolate π-faces in alkylation reactions with pseudoephedrine amide enolates. This represents the second example of such reversed selectivity, the first being that of prolinol amide enolates.[7] The correlation between the two systems is striking, and one is tempted to search for simple, unifying explanations for these observations. A moment's consideration of the complexity and variability of the solid state structures of lithium

(14) Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1979**, 3315.
(15) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

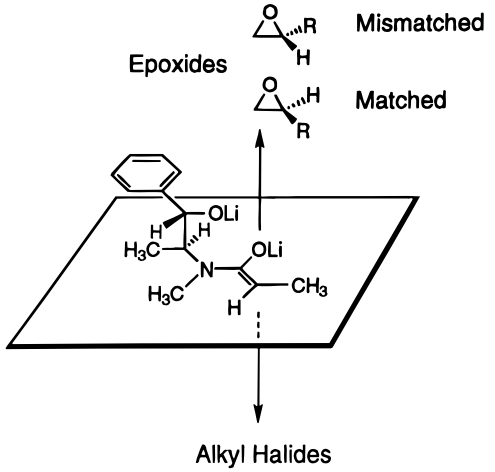


Figure 3. Selectivity in the reaction of pseudoephedrine amide enolates with epoxides and alkyl halides.

enolates,[16] a complexity only compounded in solution, and by the presence of lithium chloride (present study), should quickly discourage such efforts in the absence of further structural information. However, in simplistic terms, the proposal of Askin et al., that the lithium alkoxide of the chiral auxiliary directs the addition in the case of epoxides while providing a steric blockade in reactions with alkyl halides (see also reference 8), has some appeal.[7] Conformational analysis of both systems reveals that favorable structures can be invoked wherein the lithium alkoxide, and perhaps more importantly, the solvent molecules associated with this group, can reasonably occupy the space above the appropriate π-face of the *Z*-enolate. Figure 3 illustrates such a conformation for a pseudoephedrine amide enolate and provides a useful mnemonic for deriving the preferred reaction products with alkyl halides and epoxides (cf. Figure 2). Questions concerning the degree of aggregation of the respective transition states, their detailed structures (to include rotameric distributions, state of ionization, degree of pyramidalization of nitrogen, definition of trajectories, bond-breaking, and bond-formation) are completely unresolved and serve to illustrate how poorly understood even this "simple" organic reaction is.

In practical terms, the chemistry described herein provides useful methodology for the preparation of certain γ-lactones and γ-hydroxy ketones in enantiomerically enriched form. The alkylation reaction with ethylene oxide is insufficiently diastereoselective to be useful. The use of 2-(*tert*-butyldimethylsilyloxy)ethyl iodide as the electrophile, however, leads to a highly diastereoselective alkylation reaction, in accord with previous observations.[1] The alkylation of pseudoephedrine amide enolates with enantiomerically enriched, monosubstituted epoxides is an efficient method for the preparation of diastereomerically enriched 2,4-*syn*-2-alkyl-4-hydroxy amides, but not the corresponding anti products. These results reinforce the idea that the reaction of monosubstituted epoxides with monosubstituted amide enolates is inherently syn selective.[6] The alkylation of pseudoephedrine amide enolates with isobutylene oxide is also a highly diastereoselective process and provides access to products that are difficult to obtain by other means. The products of each of these alkylation reactions readily undergo lactonization with expulsion of the pseudoephedrine auxiliary upon heating with acid. They are also readily transformed into methyl ketones in high yield and with high enantio- or diastereoselectivity upon treatment with methyllithium. These results should serve to further expand the utility of pseudoephedrine as a useful chiral auxiliary in organic synthesis.

Experimental Section

General Methods. All reactions were performed in oven- or flame-dried glassware under an atmosphere of dry argon unless otherwise noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or cannula. Column (flash) chromatography was performed using 230−400 mesh silica gel. Analytical gas chromatography was performed with a 25 m × 0.25 mm ID Chirasil-Val III capillary column, under isothermal conditions, with a column head pressure of 17 psi. Proton and carbon nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded at 500 and 125 MHz, respectively. Infrared (IR) spectra were obtained as neat films unless otherwise specified.

Materials. Commercial reagents and solvents were used as received with the following exceptions. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane, benzene, *N,N*-diisopropylamine, and toluene were distilled from calcium hydride at atmospheric pressure. The molarities of alkyllithium solutions were established by titration with a standard solution of 2-butanol in xylenes using 1,10-phenanthroline as indicator.[17] Commercial anhydrous lithium chloride was rigorously dried at 110 °C and 0.1 mm Hg for 12 h and was stored under an atmosphere of dry nitrogen. (1*S*,2*S*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylpropionamide (**1**) and (1*S*,2*S*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylbenzenepropionamide (**2**) were prepared by *N*-acylation of (1*S*,2*S*)-(+)-pseudoephedrine with propionic anhydride or hydrocinnamoyl chloride, respectively, as previously described.[1] (*R*)- and (*S*)-2-(*tert*-butyldimethylsilyloxy)propyl iodide (**7** and **8** respectively), and 2-(*tert*-butyldimethylsilyloxy)ethyl iodide were prepared by silylation of the corresponding alcohols.[13] The following chiral epoxides were commercial products; their enantiomeric purity was determined by optical rotation: (*S*)-(−)-styrene oxide [$[\alpha]^{20}_D$ = −32.5° (neat); lit. $[\alpha]^{20}_D$ = −34.1° (neat),[18] 90% ee], (*R*)-(+)-styrene oxide [$[\alpha]^{20}_D$ = +34.3° (neat); lit. $[\alpha]^{20}_D$ = +34.1° (neat),[18] 99% ee], (*S*)-(−)-benzyl glycidyl ether [$[\alpha]^{20}_D$ = −14.6° (neat); lit. $[\alpha]^{20}_D$ = −15.3° (neat),[19] 95% ee], (*R*)-(+)-benzyl glycidyl ether [$[\alpha]^{20}_D$ = +14.9° (neat); lit. $[\alpha]^{20}_D$ = +15.0° (neat),[19] 99% ee]. The enantiomeric purity of commercial (*S*)-(−)-propylene oxide (97% ee) and (*R*)-(+)-propylene oxide (97% ee) was determined by conversion of each to the corresponding iodohydrin[13] followed by esterification with (*S*)-(−)-Mosher acid[15] and ^{1}H NMR and capillary GC analysis of the resulting Mosher ester derivatives. (*S*)-(−)-*tert*-butyldimethylsilyl glycidyl ether (89% ee) and (*R*)-(+)-*tert*-butyldimethylsilyl glycidyl ether (89% ee) were prepared from the respective glycidols according to the published procedures, and the enantiomeric purity of each reagent was determined by conversion of each to the corresponding iodohydrin[13] followed by esterification with (*S*)-(−)-Mosher acid[15] and ^{1}H NMR and capillary GC analysis of the resulting Mosher ester derivatives.

[1*S*(*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4-hydroxy-*N*,2-dimethylbutanamide (3). A dry 10-mL round-bottomed flask equipped with a magnetic stirring bar was

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charged with anhydrous lithium chloride (0.254 g, 6.00 mmol, 6.00 equiv), *N*,*N*-diisopropylamine (0.275 mL, 2.10 mmol, 2.10 equiv), and tetrahydrofuran (1.00 mL). The resulting suspension was cooled to −78 °C and *n*-butyllithium (2.40 M in hexanes, 0.921 mL, 2.21 mmol, 2.21 equiv) was added by syringe. The suspension was warmed to 0 °C for 10 min, then was cooled to −78 °C. A solution of (1*S*,2*S*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylpropionamide (**1**) (0.221 g, 1.00 mmol, 1 equiv) in tetrahydrofuran (2.00 mL) was added dropwise to the reaction flask by syringe. The transfer was quantitated with an additional portion of tetrahydrofuran (0.50 mL). Upon completion of the addition, the reaction mixture was stirred at −78 °C for 1 h, at 0 °C for 15 min, and at 23 °C for 5 min and finally was cooled to 0 °C. Ethylene oxide was condensed into a dry 5-mL round-bottomed flask at −78 °C. The condensed liquid (0.250 mL, 5.00 mmol, 5.00 equiv) was slowly transferred to the reaction vessel via a dry ice-jacketed syringe. After 1 h, saturated aqueous ammonium chloride solution (2 mL) was added, and the resulting biphasic mixture was partitioned between water (2.5 mL) and ethyl acetate (2.5 mL). The aqueous layer was separated and extracted further with three 2-mL portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and then were concentrated to give a viscous yellow oil. Purification of the oily residue by flash column chromatography (ethyl acetate) provided 2.57 g (97%) of **3** (an inseparable mixture of diastereomers) as a viscous, colorless oil. Capillary GC analysis of the corresponding *O*,*O*-diacetate, formed from the product diol by acetylation with excess acetic anhydride and DMAP, established a diastereomeric excess (de) of 49% for this product. Spectroscopic and analytical data for the diastereomeric mixture follow (assignments are secured unambiguously by the preparation of an authentic sample of the pure minor diastereomer, see below): ^{1}H NMR (C_6D_6) major diastereomer (**3**) (5:1 rotamer ratio, * denotes minor rotamer peaks): δ 7.37 (d, 2H, *J* = 7.5 Hz), 7.29* (d, 2H, *J* = 7.6 Hz), 7.14 (m, 3H), 7.09* (m, 3H), 5.23 (br s, 1H), 4.73 (br s, 1H), 4.43 (d, 1H, *J* = 7.4 Hz), 4.38* (d, 1H, *J* = 7.4 Hz), 4.16 (m, 1H), 3.87 (br s, 1H), 3.66 (m, 1H), 3.58 (m, 1H), 3.54* (m, 1H), 3.07* (m, 1H), 2.86* (s, 3H), 2.74 (m, 1H), 2.51 (s, 3H), 2.07 (m, 1H), 2.00* (m, 1H), 1.59* (m, 1H), 1.55 (m, 1H), 1.29* (d, 3H, *J* = 6.6 Hz), 0.99 (d, 3H, *J* = 6.8 Hz), 0.79 (d, 3H, *J* = 6.0 Hz), 0.78* (d, 3H, *J* = 6.3 Hz); minor diastereomer (2.5:1 rotamer ratio, * denotes minor rotamer peaks): δ 7.32* (d, 2H, *J* = 7.2 Hz), 7.26 (d, 2H, *J* = 7.3 Hz), 7.18 (m, 3H), 7.10* (m, 3H), 5.96 (br s, 1H), 5.30* (br s, 1H), 4.74 (br s, 1H), 4.63* (d, 1H, *J* = 9.3 Hz), 4.42 (d, 1H, *J* = 9.4 Hz), 4.06 (dq, 1H, *J* = 9.3, 6.7 Hz), 3.79 (dt, 1H, *J* = 8.9, 3.3 Hz), 3.63 (dt, 1H, *J* = 11.5, 4.9 Hz), 3.51* (m, 1H), 3.22 (m, 1H), 2.82 (s, 3H), 2.72* (m, 1H), 2.59* (s, 3H), 2.19 (m, 1H), 1.97* (m, 1H), 1.62 (m, 1H), 1.51* (m, 1H), 1.01 (d, 3H, *J* = 6.6 Hz), 1.00* (d, 3H, *J* = 6.0 Hz), 0.97* (d, 3H, *J* = 6.9 Hz), 0.58 (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (C_6D_6) major diastereomer (**3**): δ 178.46, 178.21*, 143.18, 142.90*, 128.58, 128.45, 127.67, 127.48, 127.35, 76.03, 75.33*, 60.54, 60.34*, 58.40*, 57.03, 37.69*, 37.36, 33.63, 33.02*, 31.12, 27.35*, 17.88, 15.51*, 14.34; minor diastereomer: δ 178.41*, 177.82, 143.41*, 142.93, 128.71, 128.52, 128.38, 127.53, 127.43, 127.13, 75.77*, 75.17, 60.58, 60.28*, 58.48, 37.62, 37.03*, 33.61*, 32.41, 27.02, 19.02, 17.45*, 15.72, 14.25*; IR 3378 (br, s, OH), 2966 (m), 2931 (m), 2872 (m), 1614 (s, C═O), 1455 (m), 1049 (m) cm^{-1}; HRMS (CI) calcd for $C_{15}H_{24}NO_3$ (MH^+) 266.1756, found 266.1757.

[1*S*(*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4-hydroxy-*N*-methyl-2-(phenylmethyl)butanamide (4). The alkylation of (1*S*,2*S*)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylbenzenepropionamide (**2**) (0.297 g, 1.00 mmol, 1 equiv) with ethylene oxide (0.250 mL, 5.00 mmol, 5.00 equiv) in tetrahydrofuran (0.400 M, 0 °C for 1 h) was carried out as described for **3**. Purification of the product by flash column chromatography (50% ethyl acetate in hexanes) provided 0.328 g (96%) of **4** (an inseparable mixture of diastereomers) as a highly viscous, colorless oil. Acetylation, as described above, and capillary GC analysis of the resulting *O*,*O*-diacetate established a diastereomeric excess (de) of 59% for this product. Spectroscopic and analytical data for the diastereomeric mixture follow (assignments are secured unambiguously by the preparation of an authentic sample of the pure minor diastereomer, see below): ^{1}H NMR (C_6D_6) major diastereomer (**4**) (20:1 rotamer ratio, * denotes minor rotamer peaks): δ 7.36 (d, 2H, *J* = 7.4 Hz), 7.20−7.10 (m, 3H), 7.10−7.05 (m, 4H), 6.99 (m, 1H), 5.04 (br s, 1H), 4.77 (br s, 1H), 4.29 (br d, 1H, *J* = 8.9 Hz), 3.74 (m, 1H), 3.59 (m, 1H), 3.07 (m, 1H), 3.02 (dd, 2H, *J* = 12.4, 10.4 Hz), 2.79* (s, 3H), 2.59 (dd, 1H, *J* = 12.2, 4.2 Hz), 2.33 (s, 3H), 2.21 (m, 1H), 1.65 (m, 1H), 0.79* (d, 3H, *J* = 6.7 Hz), 0.49 (d, 3H, *J* = 6.8 Hz); minor diastereomer (∼3:1 rotamer ratio, * denotes minor rotamer peaks): δ 7.29* (d, 2H, *J* = 7.5 Hz), 7.26 (d, 2H, *J* = 7.5 Hz), 7.22−7.04 (m, 10H), 7.01 (d, 2H, *J* = 7.2 Hz), 6.93 (t, 2H, *J* = 7.4 Hz), 6.89* (t, 2H, *J* = 7.2 Hz), 5.52 (br s, 1H), 4.61 (br s, 1H), 4.23 (d, 1H, *J* = 9.6 Hz), 3.94 (dq, 1H, *J* = 9.2, 6.8 Hz), 3.81 (dt, 1H, *J* = 11.8, 2.6 Hz), 3.68 (dt, 1H, *J* = 11.6, 4.6 Hz), 3.49 (m, 1H), 3.32* (m, 1H), 2.97 (dd, 1H, *J* = 12.6, 11.1 Hz), 2.74 (s, 3H), 2.56 (dd, 1H, *J* = 12.7, 4.4 Hz), 2.27* (s, 3H), 2.20 (m, 1H), 1.94* (m, 1H), 1.72 (m, 1H), 1.51* (m, 1H), 0.91* (d, 3H, *J* = 6.7 Hz), −0.03 (d, 3H, *J* = 6.6 Hz); ^{13}C NMR (C_6D_6) major diastereomer (**4**): δ 177.35, 176.50*, 142.83, 140.34, 129.76, 129.36, 128.65, 128.46, 128.38, 127.52, 126.37, 76.18, 75.40*, 60.87, 60.60*, 55.68, 42.22, 41.00*, 40.31, 39.70*, 36.49, 36.00*, 29.82, 15.30*, 14.05; minor diastereomer: δ 177.06*, 176.16, 143.37*, 142.85, 140.45, 140.22*, 129.45, 129.36, 128.71, 128.57, 127.44, 127.31, 127.04, 126.55, 126.34, 75.56*, 75.43, 60.63, 60.47*, 58.76, 42.01*, 41.40, 41.19, 39.76*, 37.47, 36.28*, 26.80, 23.80*, 14.81, 14.06*; IR 3378 (br, s, OH), 2966 (w), 2931 (m) 2872 (m), 1614 (s, C═O), 1496 (m), 1455 (s), 1414 (m), 1049 (s) cm^{-1}; HRMS (CI) calcd for $C_{21}H_{28}NO_3$ (MH^+) 342.2069, found 342.2064.

[1*S*(*R*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4-(*tert*-butyldimethylsilyloxy)-*N*,2-dimethylbutanamide (5). A dry 25-mL round-bottomed flask equipped with a magnetic stirring bar was charged with anhydrous lithium chloride (0.508 g, 12.0 mmol, 6.00 equiv), *N*,*N*-diisopropylamine (0.590 mL, 4.50 mmol, 2.25 equiv), and tetrahydrofuran (2.00 mL). The resulting suspension was cooled to −78 °C, and *n*-butyllithium (2.38 M in hexanes, 1.76 mL, 4.20 mmol, 2.10 equiv) was added by syringe. The suspension was warmed to 0 °C for 10 min and then was cooled to −78 °C. A solution of amide **1** (0.442 g, 2.00 mmol, 1 equiv) in tetrahydrofuran (4.50 mL) was transferred dropwise to the reaction flask by syringe. The transfer was then quantitated with an additional portion of tetrahydrofuran (0.50 mL). Upon completion of the addition, the reaction mixture was stirred at −78 °C for 1 h, at 0 °C for 15 min, and at 23 °C for 5 min and finally was cooled to 0 °C. 2-(*tert*-Butyldimethylsilyloxy)ethyl iodide (1.15 g, 4.00 mmol, 2.00 equiv) was added to the reaction flask by microliter syringe. After 5.5 h, saturated aqueous ammonium chloride solution (5 mL) was added and the resulting biphasic mixture was partitioned between water (3 mL) and ethyl acetate (5 mL). The aqueous layer was separated and extracted further with three 5-mL portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and then were concentrated. Purification of the residue by flash column chromatography (30% ethyl acetate in hexanes) provided 0.691 g (91%) of **5** as a highly viscous, colorless oil. Desilylation of **5**, as follows, produced a diol that was identical to the minor diastereomer formed by the alkylation of **1** with ethylene oxide. A solution of **5** (0.236 g, 0.621 mmol, 1 equiv) in tetrahydrofuran (2.00 mL) at 23 °C was treated with tetra-*n*-butylammonium fluoride (1.00 M in tetrahydrofuran, 0.745 mL, 0.745 mmol, 1.20 equiv). After 15 min, water (1 mL) was added and the solution was partitioned between water (2 mL) and ethyl acetate (5 mL). The aqueous layer was separated and extracted further with three 1-mL portions of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and then were concentrated. The resulting oil was purified by flash column chromatography (ethyl acetate) to furnish 0.153 g (93%) of the diol (spectroscopic data is included in the experimental procedure for **3**). Acetylation, as described above, followed by capillary GC analysis of the resulting *O*,*O*-diacetate, established a diastereomeric excess (de) of 97% for product **5**: ^{1}H NMR (∼3:1 rotamer ratio, * denotes minor rotamer peaks, C_6D_6) δ 7.34 (d, 2H, *J* = 7.2 Hz), 7.28* (d, 2H, *J* = 7.2 Hz), 7.16 (m, 3H), 7.08* (m, 3H),

4.55 (dd, 1H, J = 7.2, 7.1 Hz), 4.28* (dd, 1H, J = 5.9, 3.0 Hz), 4.03* (m, 1H), 3.68 (m, 1H), 3.46 (m, 1H), 3.37 (m, 1H), 3.11* (m, 1H), 2.81* (s, 3H), 2.78 (m, 1H), 2.48 (s, 3H), 2.44* (m, 1H), 1.91 (m, 1H), 1.62* (m, 1H), 1.46 (m, 1H), 1.09* (d, 3H, J = 6.8 Hz), 1.03 (d, 3H, J = 6.8 Hz), 0.99 (d, 3H, J = 6.9 Hz), 0.97* (s, 9H), 0.91 (s, 9H), 0.65* (d, 3H, J = 6.7 Hz), 0.09* (s, 3H), 0.08* (s, 3H), −0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (C_6D_6) δ 178.00, 176.72*, 143.79, 142.71*, 128.59, 128.31, 127.49, 127.37, 126.80, 76.38, 75.50*, 61.87*, 60.87, 58.90, 58.23*, 37.41, 32.73, 32.62*, 26.27* 26.09, 18.37*, 18.13, 17.30, 15.52*, 14.34, −5.03*, −5.15*, −5.30; IR 3377 (br, s, OH), 2954 (s), 2919 (s), 2860 (s), 1613 (s, C═O), 1472 (m), 1461 (m), 1443 (m), 1249 (s), 1090 (s), 838 (s) cm^{-1}; HRMS (CI) calcd for $C_{21}H_{38}NO_3Si$ (MH^+) 380.2621, found 380.2624.

[1*S*(*R*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4-(*tert*-butyldimethylsilyloxy)-*N*-ethyl-2-(phenylmethyl)-butanamide (6). The alkylation of **2** (1.19 g, 4.00 mmol, 1 equiv) with 2-(*tert*-butyldimethylsilyloxy)ethyl iodide (2.30 g, 8.00 mmol, 2.00 equiv) in tetrahydrofuran (8.00 mL, 0 °C for 6 h) was carried out as described above for compound **5**. The product was obtained as a viscous, light yellow oil (1.64 g, 90%) after purification by flash column chromatography (30% ethyl acetate in hexanes). Desilylation of **6**, as described for **5**, produced a diol (92%; spectroscopic data is included in the experimental procedure for **4**) that was identical to the minor diastereomer formed in the alkylation of **2** with ethylene oxide. Acetylation, as described above, followed by capillary GC analysis of the resulting *O*,*O*-diacetate established that product **6** had been formed with a diastereomeric excess (de) of ≥99%: ^{1}H NMR (3.5:1 rotamer ratio, * denotes minor rotamer peaks, C_6D_6) δ 7.23 (d, 2H, J = 7.2 Hz), 7.20* (m, 2H), 7.16−6.99 (m, 14H), 6.95 (m, 1H), 6.91* (m, 1H), 4.49 (br d, 1H, J = 6.8 Hz), 4.14* (dd, 1H, J = 9.2, 2.7 Hz), 3.99 (br s, 1H), 3.87* (dq, 1H, J = 9.8, 5.8 Hz), 3.75 (m, 1H), 3.41 (dt, 1H, J = 10.4, 5.1 Hz), 3.20 (dt, 1H, J = 10.0, 3.9 Hz), 3.15 (m, 1H), 3.07* (dd, 1H, J = 12.9, 10.4 Hz), 3.04 (dd, 1H, J = 12.9, 9.9 Hz), 2.72* (s, 3H), 2.67* (dd, 1H, J = 12.8, 4.8 Hz), 2.61 (dd, 1H, J = 12.9, 4.8 Hz), 2.45* (m, 1H), 2.28 (s, 3H), 1.91 (m, 1H), 1.66* (m, 1H), 1.61 (m, 1H), 0.96* (s, 9H), 0.93 (d, 3H, J = 7.0 Hz), 0.89 (s, 9H), 0.14* (d, 3H, J = 6.5 Hz), 0.10* (s, 3H), 0.09* (s, 3H), −0.04 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (C_6D_6) δ 176.87, 175.59*, 143.57, 142.82*, 140.68*, 140.47, 129.42, 128.63, 128.56, 127.43, 127.32, 126.84, 126.51, 126.32, 75.86, 75.42*, 62.22*, 60.65, 60.45, 58.71*, 41.21*, 40.98, 40.28*, 39.36, 36.88*, 36.58, 33.81, 26.88*, 26.30*, 26.06, 18.69*, 18.31, 14.87*, 14.18, −4.94*, −5.09*, −5.28; IR 3389 (br, s, OH), 2955 (s), 2931 (s), 2884 (s), 2861 (s), 1619 (s, C═O), 1455 (s), 1255 (m), 1084 (s), 838 (m) cm^{-1}; HRMS (FAB) calcd for $C_{27}H_{41}NO_3Si$ (M^+) 455.2857, found 455.2856.

[1*S*(2*S*,4*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4-hydroxy-*N*,2-dimethylpentanamide (Table 1, entry 1). A dry 10-mL round bottomed flask equipped with a magnetic stirring bar was charged with anhydrous lithium chloride (0.127 g, 3.00 mmol, 6.00 equiv), *N*,*N*-diisopropylamine (0.138 mL, 1.05 mmol, 2.10 equiv), and tetrahydrofuran (0.50 mL). The resulting suspension was cooled to −78 °C, and *n*-butyllithium (2.30 M in hexanes, 0.480 mL, 1.11 mmol, 2.21 equiv) was added by syringe. The suspension was warmed to 0 °C for 10 min and then was cooled to −78 °C. A solution of **1** (0.111 g, 0.500 mmol, 1 equiv) in tetrahydrofuran (1.80 mL) was transferred dropwise to the reaction flask by syringe. The transfer was quantitated with an additional portion of tetrahydrofuran (0.20 mL). Upon completion of the addition, the reaction mixture was stirred at −78 °C for 1 h, at 0 °C for 15 min, at 23 °C for 5 min, and finally was cooled to 0 °C. *(S)*-(−)-Propylene oxide (0.0581 g, 1.00 mmol, 2.00 equiv) was added to the reaction vessel by microliter syringe, and the resulting solution was stirred at −5 °C for 4 h. Saturated aqueous ammonium chloride solution (2 mL) was added, and the resulting biphasic mixture was partitioned between water (5 mL) and ethyl acetate (5 mL). The aqueous layer was separated and extracted further with three 5-mL portions of ethyl acetate and one 5-mL portion of dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and then were concentrated. Purification of the residue by flash column chromatography (75% ethyl acetate in hexanes) afforded 0.123 g (88%) of product as a white crystalline solid. Acetylation followed by capillary GC analysis of the resulting *O*,*O*-diacetate established a diastereomeric excess (de) of 93% for this product: mp 75−79 °C; ^{1}H NMR (~5:1 rotamer ratio, * denotes minor rotamer peaks, C_6D_6) δ 7.37 (d, 2H, J = 7.4 Hz), 7.26* (d, 2H, J = 7.4 Hz), 7.19−7.12 (m, 3H), 7.11−7.06* (m, 3H), 5.30 (br s, 1H), 4.75 (br s, 1H), 4.41 (d, 1H, J = 8.5 Hz), 4.35* (d, 1H, J = 8.4 Hz), 3.89 (m, 1H), 3.78* (m, 1H), 3.20* (m, 1H), 2.94 (m, 1H), 2.88* (s, 3H), 2.54 (s, 3H), 2.00 (ddd, 1H, J = 13.3, 10.4, 2.6 Hz), 1.39 (ddd, 1H, J = 13.5, 9.8, 3.8 Hz), 1.29* (d, 3H, J = 6.8 Hz), 1.21 (d, 3H, J = 5.6 Hz), 1.06* (d, 3H, J = 6.1 Hz), 0.99 (d, 3H, J = 6.9 Hz), 0.86* (d, 3H, J = 6.6 Hz), 0.78 (d, 3H, J = 6.5 Hz); ^{13}C NMR (C_6D_6) δ 178.37, 143.16, 128.44, 127.67, 127.37, 127.25, 76.13, 75.55*, 67.99*, 65.38, 58.50*, 57.12, 44.32*, 43.74, 34.50*, 33.13, 33.00*, 31.20, 27.40*, 24.55, 18.58*, 18.15, 15.98*, 14.41; IR 3378 (br, s, OH), 2964 (s), 2929 (m), 2871 (w), 1612 (s, C═O), 1451 (s), 1410 (m), 1376 (m), 1111 (m), 1082 (s), 1047 (m) cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{26}NO_3$ (MH^+) 280.1914, found 280.1913. Anal. Calcd for $C_{16}H_{25}NO_3 \cdot {}^1/_2H_2O$ (288.19): C, 66.62; H, 9.09; N, 4.86. Found: C, 66.58; H, 9.03; N, 4.88.

[1*S*(2*S*,4*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4-hydroxy-*N*,2-dimethyl-4-phenylbutanamide (Table 1, entry 2). The alkylation of **1** (0.111 g, 0.500 mmol, 1 equiv) with *(S)*-(−)-styrene oxide (0.120 g, 1.00 mmol, 2.00 equiv) in tetrahydrofuran (0.500 M, −5 °C for 7 h) was carried out as described above for entry 1 (Table 1). The product was obtained as a white crystalline solid (0.139 g, 82%) after recrystallization from benzene (3.00 mL). Acetylation and capillary GC analysis of the resulting *O*,*O*-diacetate established a diastereomeric excess (de) of 90% for this product: mp 122−126 °C; ^{1}H NMR (~4:1 rotamer ratio, * denotes minor rotamer peaks, $CDCl_3$) δ 7.36−7.26 (m, 10H), 7.26 −7.14* (m, 10H), 4.71 (dd, 1H, J = 9.2, 3.1 Hz), 4.56 (m and d, 2H, J = 7.7 Hz), 4.51* (d, 1H, J = 7.8 Hz), 4.04* (m, 1H), 3.70−3.11 (br s, 1H), 2.93 (m and s*, 1H and 3H), 2.82 (s, 3H), 2.15 (ddd, 1H, J = 13.8, 10.1, 3.1 Hz), 2.12* (m, 1H), 1.77* (m, 1H), 1.75 (ddd, 1H, J = 13.6, 9.2, 3.6 Hz), 1.21* (d, 3H, J = 6.8 Hz), 1.06 (d, 3H, J = 6.2 Hz), 1.03 (d, 3H, J = 6.9 Hz), 0.93* (d, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$) δ 178.88, 145.03, 142.28, 128.73, 128.36, 127.73, 127.20, 126.58, 125.66, 125.53, 76.44, 72.00*, 71.73, 58.55, 43.89*, 43.30, 33.13, 32.35, 18.50*, 17.79, 15.70*, 14.41; IR 3378 (br, s, OH), 2975 (m), 2929 (m), 2871 (m), 1612 (s, C═O), 1491 (m), 1451 (s), 1410 (m), 1111 (m), 1088 (m), 1047 (m), 1030 (m) cm^{-1}; HRMS (FAB) calcd for $C_{21}H_{28}NO_3$ (MH^+) 342.2070, found 342.2069. Anal. Calcd for $C_{21}H_{27}NO_3 \cdot H_2O$ (359.21): C, 70.15; H, 8.14; N, 3.90. Found: C, 70.45; H, 7.73; N, 3.94.

[1*S*(2*S*,4*R*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-5-(*tert*-butyldimethylsilyloxy)-4-hydroxy-*N*,2-dimethyl-pentanamide (Table 1, entry 3). The alkylation of **1** (0.221 g, 1.00 mmol, 1 equiv) with *(S)*-(−)-*tert*-butyldimethylsilyl glycidyl ether (0.377 g, 2.00 mmol, 2.00 equiv) in tetrahydrofuran (1.00 M, −5 °C for 10 h) was carried out as described above for entry 1 (Table 1). The product was obtained as a viscous, colorless oil (0.344 g, 84%) after purification by flash column chromatography (50% ethyl acetate in hexanes). Capillary GC analysis of the corresponding *O*,*O*,*O*-triacetate, prepared from the alkylated amide by sequential desilylation and acetylation (as described above for **5**), established a diastereomeric excess (de) of 96% for this product: ^{1}H NMR (4:1 rotamer ratio, * denotes minor rotamer peaks, C_6D_6) δ 7.33 (d, 2H, J = 7.3 Hz), 7.22* (d, 2H, J = 7.3 Hz), 7.17 (m, 3H), 7.07* (m, 3H), 4.49 (d, 1H, J = 7.3 Hz), 4.42 (br s, 1H), 4.28 (m, 1H), 3.78 (m, 1H), 3.53 (dd, 1H, J = 9.9, 4.1 Hz), 3.49* (dd, 1H, J = 9.9, 3.8 Hz), 3.39 (dd, 1H, J = 9.9, 6.6 Hz), 3.33* (dd, 1H, J = 9.9, 7.2 Hz), 3.10 (br s, 1H), 2.95 (m, 1H), 2.88* (s, 3H), 2.49 (s, 3H), 2.01 (ddd, 1H, J = 13.0, 10.7, 2.2 Hz), 1.45* (ddd, 1H, J = 13.7, 10.3, 3.6 Hz), 1.42 (ddd, 1H, J = 13.7, 10.3, 3.6 Hz), 1.34* (d, 3H, J = 6.8 Hz), 0.98 (d, 3H, J = 6.8 Hz), 0.90 (s and d, 9H and 3H, J = 6.8 Hz), 0.87* (s, 9H), 0.81* (d, 3H, J = 6.4 Hz), 0.03 (s, 6H), −0.04* (s, 6H); ^{13}C NMR (C_6D_6) δ 178.44, 143.65, 128.19, 127.40, 126.81, 76.48, 69.88, 68.02, 59.85, 37.89, 33.98, 33.05, 26.04, 18.35, 14.42, −5.27, −5.36; IR 3389 (br, s, OH), 2955 (s), 2931 (s), 2861 (s), 1614

(s, C═O), 1472 (s), 1461 (s), 1455 (s), 1255 (s), 1108 (s), 1085 (s) cm^{-1}; HRMS (FAB) calcd for $C_{22}H_{40}NO_4Si$ (MH^+) 410.2728, found 410.2727. Anal. Calcd for $C_{22}H_{39}NO_4Si·H_2O$ (427.28): C, 61.79; H, 9.67; N, 3.28. Found: C, 61.57; H, 9.26; N, 3.15.

[1*S*(2*S*,4*R*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-5-benzyloxy-4-hydroxy-*N*,2-dimethylpentanamide (Table 1, entry 4). The alkylation of **1** (0.221 g, 1.00 mmol, 1 equiv) with *(S)*-(−)-benzyl glycidyl ether (0.328 g, 2.00 mmol, 2.00 equiv) in tetrahydrofuran (1.00 M, −5 °C for 12 h) was carried out as described above for entry 1 (Table 1). The product was obtained as a highly viscous, colorless oil (0.310 g, 80%) after purification by flash column chromatography (2.5% methanol in dichloromethane). Acetylation followed by capillary GC analysis of the resulting *O*,*O*-diacetate established a diastereomeric excess (de) of 85% for this product: ^{1}H NMR (∼5:1 rotamer ratio, * denotes minor rotamer peaks, C_6D_6) δ 7.32 (d, 2H, *J* = 7.4 Hz), 7.24 (d, 2H, *J* = 7.5 Hz), 7.19−7.05 (m, 16H), 4.48 (br d, 1H, *J* = 7.9 Hz), 4.32 (br s, 1H), 4.24 (2d, 2H, *J* = 12.0 Hz), 4.19* (s, 2H), 4.09* (br d, 1H, *J* = 8.0 Hz), 3.93 (m, 1H), 3.88* (m, 1H), 3.27 (dd, 1H, *J* = 9.4, 3.6 Hz), 3.23* (dd, 1H, *J* = 9.4, 3.6 Hz), 3.17 (dd, 1H, *J* = 9.3, 7.4 Hz), 3.14* (dd, 1H, J = 9.4, 7.3 Hz), 2.94 (m, 1H), 2.84* (s, 3H), 2.73* (br s, 1H), 2.45 (s, 3H), 2.06* (m, 1H), 2.00 (ddd, 1H, *J* = 13.3, 10.8, 2.5 Hz), 1.42* (m, 1H), 1.37 (ddd, 1H, *J* = 13.5, 10.4, 3.4 Hz), 1.31* (d, 3H, *J* = 6.8 Hz), 0.97 (d, 3H, *J* = 6.9 Hz), 0.94 (s, 3H), 0.77* (d, 3H, *J* = 6.7 Hz); ^{13}C NMR (C_6D_6) δ 178.14, 177.87*, 143.22, 139.01, 138.87*, 128.56, 128.21, 127.71, 127.62, 127.52, 127.25, 75.91, 75.51, 75.34*, 73.33, 68.52*, 68.29, 58.54*, 57.42, 38.70*, 38.16, 32.79, 32.38*, 31.11, 27.46*, 18.89*, 18.29, 15.69*, 14.41; IR 3383 (br, s, OH), 2965 (m), 2934 (m), 2871 (m), 1611 (s, C═O), 1454 (s), 1105 (s), 1084 (s), 1047 (m), 1026 (m) cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{32}NO_4$ (MH^+) 386.2333, found 386.2331.

[1*S*(2*S*,4*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4-hydroxy-*N*-methyl-2-(phenylmethyl)pentanamide (Table 1, entry 5). The alkylation of **2** (0.149 g, 0.500 mmol, 1 equiv) with *(S)*-(−)-propylene oxide (0.0581 g, 1.00 mmol, 2.00 equiv) in tetrahydrofuran (0.500 M, −5 °C for 9 h) was carried out as described above for entry 1 (Table 1). The product was obtained as a white crystalline solid (0.152 g, 86%) after purification by flash column chromatography (ethyl acetate). Acetylation followed by capillary GC analysis of the resulting *O*,*O*-diacetate established a diastereomeric excess (de) of ≥99% for this product: mp 112−114 °C; ^{1}H NMR (∼15:1 rotamer ratio, * denotes minor rotamer peaks, C_6D_6) δ 7.35 (d, 2H, *J* = 7.3 Hz), 7.24−7.00 (2m, 7H), 6.97 (m, 1H), 5.02 (br s, 1H), 4.67 (br s, 1H), 4.27 (d, 1H, *J* = 9.3 Hz), 3.89 (m, 1H), 3.35 (m, 1H), 3.29 (m, 1H), 2.97 (dd, 1H, *J* = 12.9, 9.7 Hz), 2.78* (s, 3H), 2.57 (dd, 1H, *J* = 12.9, 5.6 Hz), 2.34 (s, 3H), 2.08 (ddd, 1H, *J* = 13.3, 11.0, 2.4 Hz), 1.48 (ddd, 1H, *J* = 13.5, 10.2, 3.5 Hz), 1.15 (d, 3H, *J* = 6.1 Hz), 0.88* (d, 3H, *J* = 6.2 Hz), 0.80* (d, 3H, *J* = 6.7 Hz), 0.54 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (C_6D_6) δ 177.30, 142.93, 140.40, 129.73, 129.37, 128.51, 128.45, 127.36, 126.42, 76.39, 65.42, 55.87, 42.58, 41.24, 40.44, 30.02, 24.52, 14.19; IR 3357 (br, s, OH), 2962 (m), 2930 (m), 1612 (s, C═O), 1494 (m), 1452 (s), 1126 (m), 1078 (m), 1046 (m), 1030 (m) cm^{-1}; HRMS (FAB) calcd for $C_{22}H_{30}NO_3$ (MH^+) 356.2227, found 356.2226.

[1*S*(2*S*,4*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4-hydroxy-*N*-methyl-4-phenyl-2-(phenylmethyl)butanamide (Table 1, entry 6). The alkylation of **2** (0.149 g, 0.500 mmol, 1 equiv) with *(S)*-(−)-styrene oxide (0.120 g, 1.00 mmol, 2.00 equiv) in tetrahydrofuran (1.00 M, −5 °C for 10 h) was carried out as described above for entry 1 (Table 1). The product was obtained as a white crystalline solid (0.178 g, 86%) after purification by flash column chromatography (2.5% methanol in dichloromethane). The diastereomeric excess (de) of the product was quantified by integration of the proton resonances (500 MHz ^{1}H NMR) corresponding to the methyl groups of the pseudoephedrine auxiliary (*N*-methyl and C-methyl) and was determined to be ≥95%. Recrystallization from benzene (2.00 mL) afforded very fine, white needles: mp 136−139 °C; ^{1}H NMR (∼18:1 rotamer ratio, * denotes minor rotamer peaks, $CDCl_3$) δ 7.38−7.03 (m, 15H), 4.73 (br s, 1H), 4.63 (dd, 1H, *J* = 9.8, 3.1 Hz), 4.35 (d, 1H, *J* = 9.1 Hz), 3.24 (m, 1H), 2.86 (m, 1H), 2.83* (s, 3H), 2.80 (dd, 1H, *J* = 13.0, 9.8 Hz), 2.64 (dd, 1H, *J* = 13.1, 5.5 Hz), 2.47 (s, 3H), 2.15 (ddd, 1H, *J* = 13.8, 10.7, 3.1 Hz), 1.82 (ddd, 1H, *J* = 13.6, 9.8, 3.6 Hz), 1.00* (d, 3H, *J* = 6.9 Hz), 0.64 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 177.09, 145.17, 141.65, 139.37, 129.08, 128.81, 128.23, 128.12, 128.08, 128.05, 127.62, 126.85, 126.80, 126.44, 126.10, 125.42, 75.73, 71.09, 54.91, 42.37, 40.81, 39.73, 29.70, 13.88; IR 3383 (br, s, OH), 2925 (m), 1613 (s, C═O), 1490 (s), 1450 (s), 1411 (m), 1048 (m), 1026 (m) cm^{-1}; HRMS (FAB) calcd for $C_{27}H_{32}NO_3$ (MH^+) 418.2384, found 418.2382. Anal. Calcd for $C_{27}H_{31}NO_3·{}^1/_2H_2O$ (426.24): C, 76.01; H, 7.57; N, 3.29. Found: C, 76.34; H, 7.69; N, 3.39.

[1*S*(2*S*,4*R*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-5-(*tert*-butyldimethylsilyloxy)-4-hydroxy-*N*-methyl-2-(phenylmethyl)pentanamide (9) (Table 1, entry 7). The alkylation of **2** (0.297 g, 1.00 mmol, 1 equiv) with *(S)*-(−)-*tert*-butyldimethylsilyl glycidyl ether (0.377 g, 2.00 mmol, 2.00 equiv) in tetrahydrofuran (1.00 M, −5 °C for 11 h) was carried out as described above for entry 1 (Table 1). The product **9** was obtained as a white crystalline solid (0.393 g, 81%) after purification by flash column chromatography (30% ethyl acetate in hexanes). Capillary GC analysis of the corresponding *O*,*O*,*O*-triacetate (prepared by desilylation/acetylation, as described above) established a diastereomeric excess (de) of ≥99% for **9**: mp 79−81 °C; ^{1}H NMR (10:1 rotamer ratio, * denotes minor rotamer peaks, C_6D_6) δ 7.35* (d, 2H, *J* = 7.3 Hz), 7.32 (d, 2H, *J* = 7.3 Hz), 7.16−7.12 (m, 6H), 7.07−7.03 (m 5H), 6.99* (m, 5H), 4.85 (br s, 1H), 4.34 (dd, 1H, *J* = 8.3, 4.2 Hz), 4.21 (br s, 1H), 4.14* (dd, 1H, *J* = 8.5, 3.0 Hz), 3.83 (m, 1H), 3.72* (m, 1H), 3.50 (dd, 1H, *J* = 10.0, 3.9 Hz), 3.39 (m, 1H,), 3.33 (dd, 1H, *J* = 9.9, 6.6 Hz), 3.17* (dd, 1H, *J* = 9.9, 6.6 Hz), 3.02 (dd, 1H, *J* = 12.8, 9.9 Hz), 2.84* (s, 3H), 2.63 (dd, 1H, *J* = 12.9, 5.4 Hz), 2.41 (s, 3H), 2.07 (ddd, 1H, *J* = 13.2, 11.1, 2.1 Hz), 2.02* (m, 1H), 1.59 (ddd, 1H, *J* = 13.5, 10.2, 3.5 Hz), 0.91 (s, 9H), 0.86* (d, 3H, *J* = 6.6 Hz), 0.82* (s, 9H), 0.60 (d, 3H, *J* = 6.6 Hz), 0.01 (s, 6H), −0.09* (s, 6H); ^{13}C NMR (C_6D_6) δ 177.37, 143.12, 140.26, 129.75, 129.35, 128.76, 128.63, 128.46, 127.43, 127.28, 126.44, 76.42, 69.69, 67.96, 41.06, 40.60, 36.85, 26.07, 25.98, 18.47, 14.17, −5.23, −5.34; IR 3381 (br, s, OH), 2956 (s), 2926 (s), 2855 (s), 1612 (s), 1451 (m), 1253 (m), 1122 (s), 1081 (s), 838 (s) cm^{-1}. Anal. Calcd for $C_{28}H_{43}NO_4Si$: C, 69.24; H, 8.93; N, 2.89. Found: C, 69.02; H, 8.90; N, 2.62.

[1*S*(2*S*,4*R*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-5-(benzyloxy)-4-hydroxy-*N*-methyl-2-(phenylmethyl)pentanamide (10) (Table 1, entry 8). The alkylation of **2** (0.297 g, 1.00 mmol, 1 equiv) with *(S)*-(−)-benzyl glycidyl ether (0.328 g, 2.00 mmol, 2.00 equiv) in tetrahydrofuran (1.00 M, −5 °C for 12 h) was carried out as described above for entry 1 (Table 1). The product **10** was obtained as a white solid (0.420 g, 87%) after purification by flash column chromatography (1% methanol, 29.7% ethyl acetate, 69.3% hexanes). Analysis by 500 MHz ^{1}H NMR, as described above (Table 1, entry 6), established a diastereomeric excess (de) of ≥95% for this product. A single recrystallization from toluene (20.0 mL) provided **10** as white needles: mp 126−128 °C; ^{1}H NMR (∼8:1 rotamer ratio, * denotes minor rotamer peaks, $CDCl_3$) δ 7.34−7.13 (m, 15H), 4.65 (br s, 1H), 4.52 (d, 1H, *J* = 12.0 Hz), 4.49 (d, 1H, *J* = 11.9 Hz), 4.47* (s, 2H), 4.41 (d, 1H, *J* = 8.9 Hz), 4.33* (d, 1H, *J* = 8.9 Hz), 3.78 (m, 1H), 3.62* (m, 1H), 3.46 (dd, 1H, *J* = 9.5, 3.1 Hz), 3.42* (dd, 1H, *J* = 9.5, 3.1 Hz), 3.32 (m, 1H), 3.28 (dd, 1H, *J* = 9.4, 7.5 Hz), 3.20* (dd, 1H, *J* = 9.4, 7.5 Hz), 3.10* (dd, 1H, *J* = 12.9, 9.9 Hz), 2.85 (dd, 1H, *J* = 12.9, 9.9 Hz), 2.84* (s, 3H), 2.69 (dd, 1H, *J* = 13.0, 5.3 Hz), 2.58 (s, 3H), 1.90 (ddd, 1H, *J* = 13.7, 11.1, 2.7 Hz), 1.83* (ddd, 1H, *J* = 13.7, 11.1, 2.7 Hz), 1.58 (ddd, 1H, *J* = 13.9, 10.6, 3.6 Hz), 1.50* (ddd, 1H, *J* = 13.9, 10.6, 3.6 Hz), 0.91* (d, 3H, *J* = 6.4 Hz), 0.68 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 177.66, 142.14, 139.75, 138.19, 129.50, 129.20, 128.85, 128.67, 128.62, 128.52, 128.07, 128.01, 127.26, 127.06, 126.59, 74.76, 73.51, 68.22, 56.80, 40.95, 40.37, 36.47, 31.22, 14.40; IR 3386 (br, s, OH), 2920 (m), 2858 (m), 1612 (s, C═O), 1493 (m), 1451 (s), 1415 (m), 1120 (s), 1079 (s), 1048 (m), 1027 (m) cm^{-1}. Anal. Calcd for $C_{29}H_{35}NO_4$: C, 75.45; H, 7.65; N, 3.04. Found: C, 75.36; H, 7.68; N, 2.84.

[1*S*(2*S*,4*R*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4-hydroxy-*N*,2-dimethylpentanamide (Table 2, entry 1).

The alkylation of **1** (0.111 g, 0.500 mmol, 1 equiv) with *(R)*-(+)-propylene oxide (0.0581 g, 1.00 mmol, 2.00 equiv) in tetrahydrofuran (0.500 M, −5 °C for 6 h) was carried out as described above for entry 1 (Table 1). The product was obtained as a viscous, colorless oil (0.121 g, 86%, an inseparable mixture of diastereomers) after purification by flash column chromatography (75% ethyl acetate in hexanes). Acetylation followed by capillary GC analysis of the resulting *O*,*O*-diacetates established a diastereomeric excess (de) of 73% for this product. Spectroscopic and analytical data for the diastereomeric mixture follow (assignments are secured unambiguously by the preparation of an authentic sample of the pure minor diastereomer, see the alkylation of **1** with **7**, described below): ^{1}H NMR (C_6D_6) major diastereomer (∼11:1 rotamer ratio, * denotes minor rotamer peaks): δ 7.38 (d, 2H, J = 7.4 Hz), 7.26* (d, 2H, J = 7.4 Hz), 7.20−7.11 (m, 4H), 7.09* (t, 1H, J = 7.1 Hz), 7.08 (t, 1H, J = 7.1 Hz), 5.00 (br s, 1H), 4.60 (br s, 1H), 4.49 (2d, 2H, J = 5.3 Hz), 3.57 (m, 1H), 2.84* (s, 3H), 2.69 (m, 1H), 2.54 (m, 1H), 2.41 (s, 3H), 2.03 (ddd, 1H, J = 13.9, 9.2, 9.0 Hz), 1.25 (ddd, 1H, J = 8.1, 4.8, 3.2 Hz), 1.05 (d, 3H, J = 6.1 Hz), 1.00* (d, 3H, J = 6.1 Hz), 0.99* (d, 3H, J = 6.6 Hz), 0.96 (d, 3H, J = 6.7 Hz), 0.85 (d, 3H, J = 6.5 Hz), 0.71* (d, 3H, J = 6.6 Hz); minor diastereomer (4:1 rotamer ratio, * denotes minor rotamer peaks): δ 7.36* (d, 2H, J = 7.6 Hz), 7.22 (d, 2H, J = 7.6 Hz), 7.20−7.12 (m, 3H), 7.10−7.04* (m, 3H), 5.61 (br s, 1H), 4.62* (d, 1H, J = 7.1 Hz), 4.51 (br s, 1H), 4.27 (d, 1H, J = 9.5 Hz), 4.13 (m, 1H), 4.03 (m, 1H), 3.61* (m, 1H), 3.34 (m, 1H), 2.81 (s, 3H), 2.78* (m, 1H), 2.53* (s, 3H), 2.38* (m, 1H), 2.14 (ddd, 1H, J = 13.2, 10.9, 2.3 Hz), 1.84* (ddd, 1H, J = 13.2, 10.9, 2.3 Hz), 1.37 (ddd, 1H, J = 13.3, 10.4, 2.9 Hz), 1.27* (ddd, 1H, J = 13.4, 10.0, 3.4 Hz), 1.21 (d, 3H, J = 6.2 Hz), 1.02 (d, 3H, J = 6.7 Hz), 0.98* (d, 3H, J = 6.7 Hz), 0.97* (d, 3H, J = 6.8 Hz), 0.59 (d, 3H, J = 6.6 Hz); ^{13}C NMR (C_6D_6) major diastereomer: δ 178.54, 143.06, 128.26, 127.57, 127.33, 127.20, 127.05, 75.87, 66.63, 57.33, 43.77, 34.18, 31.41, 24.19, 17.75, 14.02; minor diastereomer: δ 178.00, 177.20*, 143.30*, 142.25, 128.49, 128.34, 126.82, 75.09, 66.00*, 65.24, 60.00*, 58.01, 44.28, 44.21*, 33.70, 33.25*, 31.91, 27.62*, 26.80*, 23.55, 18.97, 15.55, 15.35*; IR 3376 (br, s, OH), 2965 (s), 2933 (m), 2881 (w), 1613 (s, C═O), 1455 (s), 1408 (m), 1087 (m), 1045 (m) cm^{-1}.

[1*S*(2*S*,4*R*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4-hydroxy-*N*,2-dimethyl-4-phenylbutanamide (Table 2, entry 2). The alkylation of **1** (0.111 g, 0.500 mmol, 1 equiv) with *(R)*-(+)-styrene oxide (0.120 g, 1.00 mmol, 2.00 equiv) in tetrahydrofuran (0.500 M, −5 °C for 10 h) was carried out as described above for entry 1 (Table 1). The product was obtained as a viscous, light yellow oil (0.124 g, 73%, an inseparable mixture of diastereomers) after purification by flash column chromatography (2.5% methanol in dichloromethane). Acetylation followed by capillary GC analysis of the resulting *O*,*O*-diacetates established a diastereomeric excess (de) of 25% for this product: ^{1}H NMR (∼2:1 rotamer ratio for each diastereomer, C_6D_6) δ 7.35 (d, 2H, J = 7.9 Hz), 7.32 (d, 2H, J = 7.9 Hz), 7.31 (d, 2H, J = 7.4 Hz), 7.28 (d, 2H, J = 7.9 Hz), 7.25−6.99 (m, 32H), 5.32 (br s, 1H), 5.01 (br d, 1H, J = 8.8 Hz), 4.70 (br s, 1H), 4.62 (dd and m, 2H, J = 8.1, 6.8 Hz), 4.59 (d,1H, J = 9.6 Hz), 4.47 (d, 1H, J = 8.2 Hz), 4.30 (br s, 1H), 4.24 (d, 1H, J = 9.6 Hz), 4.18 (d, 1H, J = 8.2 Hz), 4.14 (m, 1H), 4.00 (m, 1H), 3.44 (m, 1H), 3.26 (br s, 1H), 2.95 (m, 1H), 2.82 (s, 3H), 2.79 (s, 3H), 2.59 (s, 3H), 2.53−2.39 (m and ddd, 2H, J = 13.1, 8.8, 4.7 Hz), 2.47 (ddd, 1H, J = 13.2, 10.4, 2.8 Hz), 2.37 (s, 3H), 2.31 (s, 3H), 2.21 (ddd, 1H, J = 13.3, 10.4, 2.9 Hz), 1.73 (m, 1H), 1.63 (ddd, 1H, J = 13.1, 9.6, 4.3 Hz), 1.53 (m, 1H), 1.31 (d, 3H, J = 6.7 Hz), 1.01 (d, 3H, J = 6.9 Hz), 0.96 (d, 3H, J = 6.7 Hz), 0.89 (d, 3H, J = 6.9 Hz), 0.84 (d, 3H, J = 6.4 Hz), 0.64 (d, 3H, J = 6.6 Hz), 0.56 (d, 3H, J = 6.6 Hz); ^{13}C NMR (C_6D_6) δ 178.41, 178.36, 177.37, 175.31, 146.22, 145.85, 143.42, 143.14, 142.82, 142.69, 128.76, 128.53, 128.42, 128.38, 127.60, 127.55, 127.43, 127.38, 127.21, 127.05, 126.82, 126.60, 126.31, 126.15, 126.00, 76.02, 75.21, 73.09, 71.81, 58.20, 45.47, 44.25, 34.34, 32.48, 27.40, 26.87, 19.10, 17.88, 15.69, 14.32; IR 3378 (s, OH), 2974 (m), 2928 (m), 1612 (s, C═O), 1490 (m), 1451 (s), 1410 (m), 1110 (m), 1087 (m), 1047 (m), 1030 (m) cm^{-1}. Anal. Calcd for $C_{21}H_{27}NO_3 \cdot {}^1/_2H_2O$ (350.20): C, 71.96; H, 8.06; N, 4.00. Found: C, 71.71; H, 8.21; N, 3.61.

[1*S*(2*S*,4*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-5-(*tert*-butyldimethylsilyloxy)-4-hydroxy-*N*,2-dimethylpentanamide (Table 2, entry 3). The alkylation of **1** (0.221 g, 1.00 mmol, 1 equiv) with *(R)*-(+)-*tert*-butyldimethylsilyl glycidyl ether (0.283 g, 1.50 mmol, 1.50 equiv) in tetrahydrofuran (0.800 M, 0 °C for 21 h) was carried out as described above for entry 1 (Table 1). The product was obtained as a viscous, colorless oil (0.320 g, 78%, an inseparable mixture of diastereomers) after purification by flash column chromatography (50% ethyl acetate in hexanes). Capillary GC analysis of the corresponding *O*,*O*,*O*-triacetates (prepared by desilylation/acetylation, as described above) established a diastereomeric excess (de) of 12% for this product: ^{1}H NMR (∼1.5:1 rotamer ratio for each diastereomer, C_6D_6) δ 7.35 (d, 2H, J = 7.4 Hz), 7.34 (d, 2H, J = 7.4 Hz), 7.30 (d, 2H, J = 7.4 Hz), 7.22−7.15 (m, 11H), 7.12−7.06 (m, 3H), 4.60 (br s, 1H), 4.55 (br d, 1H, J = 5.9 Hz), 4.51 (br s, 1H), 4.31 (m, 1H), 4.22 (m, 1H), 4.12 (m, 1H), 4.00 (m, 1H), 3.75 (m, 1H), 3.65 (m, 1H), 3.63 (dd, 1H, J = 10.2, 4.4 Hz), 3.57−3.34 (m, 6H), 3.32 (dd, 1H, J = 10.2, 7.0 Hz), 3.21 (m, 1H), 3.05 (br s, 1H), 2.97 (m, 1H), 2.87 (m, 2H), 2.84 (s, 3H), 2.75 (ap q, 1H, J = 6.6 Hz), 2.53 (s, 3H), 2.49 (s, 3H), 2.42 (s, 3H), 2.24 (ddd, 1H, J = 12.8, 10.4, 2.3 Hz), 1.97 (m, 2H), 1.89 (m, 1H), 1.58 (ddd, 1H, J = 12.2, 9.3, 2.3 Hz), 1.51 (ddd, 1H, J = 14.0, 6.2, 2.8 Hz), 1.41 (ddd, 1H, J = 12.8, 11.0, 4.6 Hz), 1.37 (d, 3H, J = 6.8 Hz), 1.35 (ddd, 1H, J = 13.9, 11.6, 4.6 Hz), 1.10 (d, 3H, J = 6.9 Hz), 1.03 (d, 3H, J = 7.4 Hz), 0.99 (d, 3H, J = 6.8 Hz), 0.98 (d, 3H, J = 6.6 Hz), 0.95 (s, 9H), 0.93 (s, 9H), 0.91 (s, 9H), 0.89 (s, 9H), 0.84 (d, 3H, J = 6.7 Hz), 0.82 (d, 3H, J = 6.8 Hz), 0.77 (d, 3H, J = 6.5 Hz), 0.62 (d, 3H, J = 6.8 Hz), 0.06 (s, 6H), 0.04 (s, 6H), 0.00 (2 s, 6H), −0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (C_6D_6) δ 178.72, 178.26, 176.81, 143.73, 143.50, 142.95, 142.58, 128.70, 128.53, 128.31, 127.47, 127.37, 127.07, 126.93, 126.81, 76.32, 76.17, 75.55, 71.20, 70.99, 70.05, 69.79, 68.11, 67.99, 59.00, 58.36, 58.10, 38.30, 37.72, 33.98, 33.14, 32.88, 31.86, 27.45, 27.00, 26.15, 26.07, 19.29, 18.47, 18.27, 17.74, 16.22, 15.78, 14.26, −5.27; IR 3378 (br, m, OH), 2955 (s), 2931 (s), 2884 (m), 2861 (s), 1619 (s, C═O), 1472 (m), 1461 (m), 1455 (m), 1255 (s), 1114 (s), 1085 (s), 838 (s), 779 (s), 703 (s) cm^{-1}.

[1*S*(2*S*,4*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-5-(benzyloxy)-4-hydroxy-*N*,2-dimethylpentanamide (Table 2, entry 4). The alkylation of **1** (0.221 g, 1.00 mmol, 1 equiv) with *(R)*-(+)-benzyl glycidyl ether (0.328 g, 2.00 mmol, 2.00 equiv) in tetrahydrofuran (1.00 M, −5 °C for 13 h) was carried out as described above for entry 1 (Table 1). The product was obtained as a highly viscous, colorless oil (0.301 g, 78%, an inseparable mixture of diastereomers) after purification by flash column chromatography (2.5% methanol in dichloromethane). Acetylation followed by capillary GC analysis of the resulting *O*,*O*-diacetates established a diastereomeric excess (de) of 38% for this product: ^{1}H NMR (∼3:1 rotamer ratio for each diastereomer, C_6D_6) δ 7.37 (d, 2H, J = 7.4 Hz), 7.32−7.00 (m, 16H), 7.26 (d, 2H, J = 7.5 Hz), 4.60 (br s, 1H), 4.50 (2 d, 2H, J = 7.0 Hz), 4.38−4.13 (m, 2H), 4.30 (s, 2H), 4.25 (s, 2H), 3.77 (2 m, 2H), 3.24 (d, 2H, J = 5.0 Hz), 3.21 (d, 2H, J = 5.5 Hz), 2.88 (s, 3H), 2.85 (s, 3H), 2.71 (m, 1H), 2.51 (s, 3H), 2.41 (s, 3H), 2.04 (ddd, 1H, J = 14.3, 9.9, 7.5 Hz), 1.93 (m, 1H), 1.52 (m, 1H), 1.47 (ddd, 1H, J = 9.1, 6.1, 3.2 Hz), 1.34 (d, 3H, J = 6.6 Hz), 1.09 (d, 3H, J = 6.9 Hz), 1.01 (d, 3H, J = 6.9 Hz), 0.99 (d, 3H, J = 6.8 Hz), 0.95 (d, 3H, J = 6.1 Hz), 0.87 (d, 3H, J = 6.6 Hz), 0.78 (d, 3H, J = 6.9 Hz), 0.72 (d, 3H, J = 6.5 Hz); ^{13}C NMR (C_6D_6) δ 178.41, 177.60, 143.31, 138.67, 128.34, 127.56, 127.23, 126.84, 126.57, 76.16, 76.15, 75.14, 75.12, 73.24, 69.38, 69.00, 58.64, 57.80, 38.60, 37.92, 33.64, 33.00, 32.13, 21.80, 20.00, 17.48, 14.03; IR 3382 (br, s, OH), 2967 (m), 2928 (m), 2869 (m), 1614 (s, C═O), 1451 (m), 1106 (m), 1086 (m) cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{32}NO_4$ (MH^+) 386.2333, found 386.2331. Anal. Calcd for $C_{23}H_{31}NO_4 \cdot {}^1/_2H_2O$ (394.23): C, 70.01; H, 8.18; N 3.55. Found: C, 69.66; H, 8.16; N, 3.64.

[1*S*(2*S*,4*R*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4-hydroxy-*N*-methyl-2-(phenylmethyl)pentanamide (Table 2, entry 5). The alkylation of **2** (0.149 g, 0.500 mmol,

1 equiv) with *(R)*-(+)-propylene oxide (0.0581 g, 1.00 mmol, 2.00 equiv) in tetrahydrofuran (0.500 M, −5 °C for 10 h) was carried out as described above for entry 1 (Table 1). The product was obtained as a viscous, colorless oil (0.141 g, 79%, an inseparable mixture of diastereomers) after purification by flash column chromatography (50% ethyl acetate in hexanes). Acetylation followed by capillary GC analysis of the resulting *O,O*-diacetates established a diastereomeric excess (de) of 45% for this product: ^{1}H NMR (20:1 rotamer ratio for major diastereomer and 4:1 rotamer ratio for minor diastereomer, * denotes rotamer peaks, C_6D_6) δ 7.39 (d, 2H, J = 7.9 Hz), 7.32* (d, 2H, J = 7.9 Hz), 7.28* (d, 2H, J = 7.8 Hz), 7.22 (d, 2H, J = 7.8 Hz), 7.18−7.02 (m, 29 H), 6.98* (t, 1H, J = 7.8 Hz), 6.94 (t, 1H, J = 7.8 Hz), 6.87* (t, 1H, J = 7.8 Hz), 5.05 (br s, 1H), 4.61 (br s, 2H), 4.33 (d, 1H, J = 9.2 Hz), 4.14 (d, 1H, J = 9.0 Hz), 4.06 (m, 1H), 3.98 (dq, 1H, J = 9.5, 7.0 Hz), 3.60 (m, 2H), 3.35 (m, 2H), 3.01 (dd, 1H, J = 12.4, 10.7 Hz), 2.88 (m, 1H), 2.77 (s, 3H), 2.71* (s, 3H), 2.61 (dd, 1H, J = 12.9, 4.6 Hz), 2.53 (dd, 1H, J = 12.6, 4.6 Hz), 2.32* (s, 3H), 2.27 (s and m, 3H and 1H), 2.18 (ddd, 1H, J = 13.8, 10.0, 10.0 Hz), 1.89* (ddd, 1H, J = 13.4, 10.3, 3.1 Hz), 1.56 (ddd, 1H, J = 13.4, 10.3, 3.1 Hz), 1.37 (ddd, 1H, J = 13.8, 5.5, 2.7 Hz), 1.22 (d, 3H, J = 6.2 Hz), 1.08 (d, 3H, J = 6.3 Hz), 0.92* (d, 3H, J = 6.4 Hz), 0.77* (d, 3H, J = 6.8 Hz), 0.49 (d, 3H, J = 6.8 Hz), 0.05* (d, 3H, J = 6.4 Hz), −0.06 (d, 3H, J = 6.4 Hz); ^{13}C NMR (C_6D_6) δ 177.59, 175.98, 142.96, 142.73, 140.61, 140.30, 129.87, 129.46, 128.73, 128.60, 128.44, 127.57, 127.40, 127.05, 126.87, 126.46, 126.32, 76.10, 75.42, 68.04, 65.24, 58.50, 55.46, 44.41, 43.40, 43.30, 41.59, 40.73, 40.62, 29.64, 26.78, 24.50, 23.99, 14.85, 13.97; IR 3380 (br, s, OH), 2971 (m), 2928 (m), 1610 (s, C═O), 1492 (m), 1454 (s), 1411 (m), 1121 (m), 1083 (m), 1046 (m) cm^{-1}.

[1*S*(2*S*,4*R*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4-hydroxy-*N*-methyl-4-phenyl-2-(phenylmethyl)butanamide (Table 2, entry 6). The alkylation of **2** (0.149 g, 0.500 mmol, 1 equiv) with *(R)*-(+)-styrene oxide (0.120 g, 1.00 mmol, 2.00 equiv) in tetrahydrofuran (0.500 M, −5 °C for 15 h) was carried out as described above for entry 1 (Table 1). The product was obtained as a white solid (0.151 g, 72%, an inseparable mixture of diastereomers) after purification by flash column chromatography (2.5% methanol in dichloromethane). Analysis by 500 MHz ^{1}H NMR, as described above (Table 1, entry 6), established a diastereomeric excess (de) of 46% for this product. A single recrystallization of the product from benzene (2.00 mL) afforded a pure sample of the major diastereomer as white needles (mp 134−136 °C) allowing assignments to be made within the diastereomeric mixture, as follows: ^{1}H NMR ($CDCl_3$) major diastereomer (10:1 rotamer ratio, * denotes minor rotamer peaks): δ 7.24−7.02 (m, 15H), 4.63 (br s, 1H), 4.58 (dd, 1H, J = 9.5, 4.5 Hz), 4.31 (d, 1H, J = 9.1 Hz), 2.96 (m, 1H), 2.77 (m and dd, 1H and 1H, J = 13.1, 9.9 Hz), 2.74* (s, 3H), 2.62 (dd, 1H, J = 13.1, 5.6 Hz), 2.41 (s, 3H), 2.34 (ddd, 1H, J = 14.0, 9.5, 4.6 Hz), 1.78 (ddd, 1H, J = 14.0, 8.2, 3.9 Hz), 0.80* (d, 3H, J = 6.6 Hz), 0.58 (d, 3H, J = 6.1 Hz); minor diastereomer (∼2:1 rotamer ratio, * denotes minor rotamer peaks): δ 7.43−7.00 (m, 15H), 4.57 (m, 1H), 4.34 (d, 1H, J = 9.5 Hz), 3.99* (m, 1H), 3.62 (m, 1H), 3.19* (m, 1H), 2.82 (dd, 1H, J = 13.3, 9.9 Hz), 2.81 (s, 3H), 2.72 (dd, 1H, J = 13.3, 5.6 Hz), 2.54* (s, 3H), 2.18 (ddd, 1H, J = 14.0, 12.8, 2.5 Hz), 2.09* (ddd, 1H, J = 14.0, 11.5, 2.6 Hz), 1.79* (ddd, 1H, J = 14.0, 11.5, 2.5 Hz), 1.05 (m, 1H), 1.03 (d, 3H, J = 6.9 Hz), 0.43* (d, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) major diastereomer: δ 177.42, 176.75*, 144.32, 141.85, 141.20*, 139.37, 129.27, 129.05, 128.52, 128.32, 127.80, 127.69, 126.41, 127.00, 126.41, 126.00, 125.80, 76.21, 75.65*, 74.16, 73.20*, 56.15, 42.74, 42.31, 41.45*, 40.08, 39.20*, 30.34, 15.50*, 14.09; minor diastereomer: δ 175.46, 144.53, 144.50*, 142.20*, 141.53, 140.20*, 139.99, 129.24, 129.19, 128.43, 128.19, 127.13, 126.85, 126.75, 126.25, 126.14, 125.54, 125.34, 75.39*, 74.98, 71.65*, 70.68, 57.87, 53.50*, 44.10, 42.40*, 41.52*, 40.81, 40.49, 40.00*, 27.56*, 26.48, 15.25*, 14.53; IR 3381 (br, s, OH), 3057 (m), 3026 (m), 2976 (m), 2925 (m), 1610 (s, C═O), 1494 (s), 1453 (s), 1413 (s), 1119 (m), 1048 (m), 910 (m) cm^{-1}; HRMS (FAB) calcd for $C_{27}H_{32}NO_3$ (MH^+) 418.2384, found 418.2382. Anal. Calcd for $C_{27}H_{31}NO_3 \cdot H_2O$ (426.24): C, 76.01; H, 7.57; N, 3.29. Found: C, 76.07; H, 7.53; N, 3.32.

[1*S*(2*S*,4*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-5-(*tert*-butyldimethylsilyloxy)-4-hydroxy-*N*-methyl-2-(phenylmethyl)pentanamide (Table 2, entry 7). The alkylation of **2** (0.297 g, 1.00 mmol, 1 equiv) with *(R)*-(+)-*tert*-butyldimethylsilyl glycidyl ether (0.377 g, 2.00 mmol, 2.00 equiv) in tetrahydrofuran (0.400 M, 5 °C for 26 h) was carried out as described above for entry 1 (Table 1). The product was obtained as a viscous, colorless oil (0.312 g, 64%, an inseparable mixture of diastereomers) after purification by flash column chromatography (30% ethyl acetate in hexanes). Capillary GC analysis of the corresponding *O,O,O*-triacetates (prepared by desilylation/acetylation, as described above) established a diastereomeric excess (de) of 17% for this product: ^{1}H NMR (20:1 rotamer ratio for major diastereomer and 1.5:1 rotamer ratio for minor diastereomer, * denotes rotamer peaks, C_6D_6) δ 7.41* (d, 2H, J = 8.8 Hz), 7.36 (d, 2H, J = 8.8 Hz), 7.29* (d, 2H, J = 8.8 Hz), 7.24 (d, 2H, J = 8.8 Hz), 7.21−7.01 (m, 23H), 7.00 (t, 3H, J = 8.7 Hz), 6.95* (t, 3H, J = 8.6 Hz), 6.87* (t, 3H, J = 8.8 Hz), 4.95 (br s, 1H), 4.56* (br d, 1H, J = 5.8 Hz), 4.38 (d, 1H, J = 8.9 Hz), 4.19 (d, 1H, J = 9.5 Hz), 4.04 (m, 2H), 3.68 (m, 1H), 3.65 (m, 1H), 3.62 (dd, 1H, J = 10.3, 4.5 Hz), 3.53 (dd, 1H, J = 10.3, 5.6 Hz), 3.49 (dd, 1H, J = 9.7, 6.1 Hz), 3.44 (dd, 1H, J = 9.7, 5.5 Hz), 3.33* (m, 1H), 3.21* (dd, 1H, J = 7.2, 5.4 Hz), 3.11 (dd, 1H, J = 12.5, 10.8 Hz), 3.05 (m, 2H), 3.01 (dd, 1H, J = 13.2, 9.8 Hz), 2.81 (s, 3H), 2.77* (s, 3H), 2.64 (m, 2H), 2.36* (s, 3H), 2.29 (s, 3H), 2.17 (ddd, 1H, J = 13.6, 9.5, 4.4 Hz), 1.92* (ddd, 1H, J = 13.2, 11.1, 2.1 Hz), 1.74 (m, 2H), 1.44* (ddd, 1H, J = 13.5, 10.2, 3.5 Hz), 0.94 (2 s, 18H), 0.90* (s, 9H), 0.87* (s, 9H), 0.80* (d, 3H, J = 6.5 Hz), 0.53 (d, 3H, J = 6.6 Hz), 0.06 (2 s, 6H), 0.04 (2 s, 6H), 0.03* (d, 3H, J = 6.5 Hz), 0.00 (d, 3H, J = 6.5 Hz), −0.01* (2 s, 6H), −0.04* (s, 6H); ^{13}C NMR (C_6D_6) δ 177.54, 177.06*, 175.53, 143.62*, 143.05, 142.83, 140.53, 140.20, 140.05*, 129.82, 129.45, 129.41, 129.20, 128.71, 128.62, 128.59, 128.53, 128.44, 128.42, 127.62, 127.49, 127.28, 126.81, 126.58, 126.47, 126.33, 76.25, 75.72*, 75.63, 72.32, 69.81, 69.41*, 67.96, 67.89, 67.78, 58.54, 56.08, 42.76, 41.57, 41.02, 40.47, 40.35, 38.25, 37.32, 36.88*, 29.93, 26.71, 26.15, 26.09, 26.02*, 18.57, 18.46, 14.86, 14.24*, 13.99, −5.19, −5.27, −5.40*; IR 3378 (br, m, OH), 2938 (s), 2926 (s), 2858 (s), 1616 (s, C═O), 1452 (m), 1255 (m), 1125 (s), 1080 (s), 1051 (m), 837 (s), 775 (m), 701 (s) cm^{-1}.

[1*S*(2*S*,4*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-5-(benzyloxy)-4-hydroxy-*N*-methyl-2-(phenylmethyl)pentanamide (Table 2, entry 8). The alkylation of **2** (0.297 g, 1.00 mmol, 1 equiv) with *(R)*-(+)-benzyl glycidyl ether (0.328 g, 2.00 mmol, 2.00 equiv) in tetrahydrofuran (1.00 M, −5 °C for 12 h) was carried out as described above for entry 1 (Table 1). The product was obtained as a white crystalline solid (0.369 g, 80%) after purification by flash column chromatography (1% methanol, 29.7% ethyl acetate, 69.3% hexanes). Analysis by 500 MHz ^{1}H NMR, as described above (Table 1, entry 6), established a diastereomeric excess (de) of 36% for this product. A single recrystallization from toluene (20.0 mL) afforded a pure sample of the minor diastereomer as white needles (mp 153−155 °C) allowing spectroscopic assignments to be made within the diastereomeric mixture, as follows: ^{1}H NMR ($CDCl_3$) major diastereomer (∼15:1 rotamer ratio, * denotes minor rotamer peaks): δ 7.34−7.11 (m, 15H), 4.78 (br s, 1H), 4.52 (d, 2H, J = 6.8 Hz), 4.38 (d, 1H, J = 9.4 Hz), 3.90 (m, 1H), 3.43 (dd, 1H, J = 9.2, 5.8 Hz), 3.35 (m and dd, 1H and 1H, J = 9.4, 7.8 Hz), 3.15 (m, 1H), 2.93 (dd, 1H, J = 12.9, 9.9 Hz), 2.82* (s, 3H), 2.74 (dd, 1H, J = 12.8, 5.5 Hz), 2.58 (s, 3H), 2.11 (ddd, 1H, J = 14.0, 10.2, 3.9 Hz), 1.65 (ddd, 1H, J = 13.9, 9.9, 4.0 Hz), 0.92* (d, 3H, J = 6.9 Hz) 0.63 (d, 3H, J = 6.7 Hz); minor diastereomer (1.3:1 rotamer ratio, * denotes minor rotamer peaks): δ 7.34−7.11 (m, 30H), 4.52 (s, 2H), 4.51* (s, 2H), 4.48* (d, 1H, J = 7.4 Hz), 4.30 (d, 1H, J = 9.7 Hz), 4.19 (m, 1H), 3.92 (m, 1H), 3.87 (m, 1H), 3.55* (m, 1H), 3.51 (dd, 1H, J = 6.6, 3.3 Hz), 3.44* (m, 1H), 3.41 (dd, 1H, J = 10.3, 2.9 Hz), 3.36 (dd, 1H, J = 9.7, 6.6 Hz), 3.29 (m, 1H), 3.22* (dd, 1H, J = 9.1, 7.9 Hz), 2.91 (dd, 1H, J = 12.9, 10.5 Hz), 2.88* (dd, 1H, J = 13.2, 10.0 Hz), 2.78 (s, 3H), 2.72 (dd, 1H, J = 12.9, 4.7 Hz), 2.68* (dd, 1H, J = 12.6, 5.3 Hz), 2.58* (s, 3H), 2.00 (ddd, 1H, J = 13.4, 13.4, 2.2 Hz), 1.82* (ddd, 1H, J = 13.1, 13.1, 1.6 Hz), 1.70 (ddd, 1H, J = 13.6, 11.6, 3.6 Hz),

1.51* (ddd, 1H, J = 13.5, 10.8, 3.3 Hz), 0.94* (d, 3H, J = 6.5 Hz), 0.04 (d, 3H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) major diastereomer: δ 177.71, 140.89, 139.67, 138.04, 129.27, 128.90, 128.82, 128.53, 128.38, 128.05, 127.09, 126.63, 76.36, 74.65, 73.66, 70.93, 55.75, 42.69, 40.33, 36.83, 30.98, 14.25; minor diastereomer: δ 177.17*, 175.39, 142.32*, 141.88, 139.83, 139.45, 138.03, 129.06, 128.70, 128.47, 128.24, 127.78, 127.74, 127.52, 126.88, 126.54, 126.40, 126.33, 75.73, 74.78*, 74.13, 73.46*, 73.37, 68.17, 68.05*, 58.18, 41.02, 40.83*, 40.10*, 39.99, 37.61, 36.59*, 26.58, 14.82, 14.29*; IR 3381 (br, s, OH), 2915 (m), 2854 (m), 1605 (s, C═O), 1453 (s), 1124 (s), 1078 (s), 1048 (m), 1027 (m) cm^{-1}; HRMS (FAB) calcd for $C_{29}H_{36}NO_4$ (MH^+) 462.2646, found 462.2644. Anal. Calcd for $C_{29}H_{35}NO_4$: C, 75.45; H, 7.65; N, 3.04. Found: C, 75.00; H, 7.70; N, 2.80.

[1*S*(2*R*,4*R*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4-(*tert*-butyldimethylsilyloxy)-*N*,2-dimethylpentanamide. A dry 10-mL round-bottomed flask equipped with a magnetic stirring bar was charged with anhydrous lithium chloride (0.559 g, 13.2 mmol, 13.2 equiv), *N*,*N*-diisopropylamine (0.606 mL, 4.62 mmol, 4.62 equiv), and tetrahydrofuran (2.00 mL). The resulting suspension was cooled to −78 °C, and *n*-butyllithium (3.25 M in hexanes, 1.50 mL, 4.86 mmol, 4.86 equiv) was added by syringe. The suspension was warmed to 0 °C for 10 min and then was cooled to −78 °C. A solution of **1** (0.487 g, 2.20 mmol, 2.20 equiv) in tetrahydrofuran (1.70 mL) was transferred dropwise to the reaction flask by syringe. The transfer was quantitated with an additional portion of tetrahydrofuran (0.50 mL). Upon completion of the addition, the reaction mixture was stirred at −78 °C for 1 h, at 0 °C for 15 min, at 23 °C for 5 min, and finally was cooled to 0 °C. To the reaction vessel was added (*R*)-2-(*tert*-butyldimethylsilyloxy)propyl iodide (**7**, 0.300 g, 1.00 mmol, 1 equiv) by microliter syringe. The resulting mixture was warmed briefly to 23 °C and then was heated to 45 °C. After 14 h the suspension was cooled to 23 °C and subsequently was partitioned between water (5 mL) and ethyl acetate (5 mL). The aqueous layer was separated and extracted further with three 3-mL portions of ethyl acetate and one 5-mL portion of dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and then were concentrated. Purification of the residue by flash column chromatography (25% ethyl acetate in hexanes) afforded the product as a viscous, light yellow oil (0.140 g, 36%). Desilylation of the product, as described for **5**, produced a diol (92%; spectroscopic data is included in the procedure for the amide of Table 2, entry 1) that was identical to the minor diastereomer (2*R*-syn) formed in the alkylation of **1** with (*R*)-(+)-propylene oxide. Acetylation followed by capillary GC analysis of the resulting *O*,*O*-diacetate established a diastereomeric excess (de) of ≥99% for this product: ^{1}H NMR (10:1 rotamer ratio, * denotes minor rotamer peaks, C_6D_6) δ 7.37 (d, 2H, J = 7.4 Hz), 7.28* (d, 2H, J = 7.4 Hz), 7.19−7.16 (m, 3H), 7.10−7.00* (m, 3H), 4.77 (br s, 1H), 4.65 (br s, 1H), 4.53 (dd, 1H, J = 6.8 Hz), 3.78 (m, 1H), 2.81* (s, 3H), 2.76 (m, 1H), 2.56 (s, 3H), 2.09 (ddd, 1H, J = 13.2, 9.7, 3.2 Hz), 1.37 (ddd, 1H, J = 13.2, 8.9, 3.9 Hz), 1.27* (d, 3H, J = 6.1 Hz), 1.08 (d, 3H, J = 6.0 Hz), 1.05* (d, 3H, J = 6.9 Hz), 1.01* (s, 9H), 0.99 (d, 3H, J = 7.0 Hz), 0.96 (d, 3H, J = 7.0 Hz), 0.95 (s, 9H), 0.66* (d, 3H, J = 6.8 Hz), 0.18* (s, 3H), 0.16* (s, 3H), 0.02 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (C_6D_6) δ 177.73, 143.65, 128.40, 127.50, 126.98, 76.44, 75.65*, 68.88*, 67.62, 57.29, 44.59, 43.75*, 33.56, 31.64, 26.15, 24.63, 23.50*, 19.35*, 18.40, 18.20, 15.66*, 14.17, −3.80, −4.55; IR 3386 (br, m, OH), 2954 (s), 2933 (s), 2859 (s), 1619 (s, C═O), 1471 (m), 1461 (m), 1455 (m), 1255 (s), 1092 (m), 1050 (s) cm^{-1}.

[1*S*(2*R*,4*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4-(*tert*-butyldimethylsilyloxy)-*N*,2-dimethylpentanamide. The alkylation of **1** (0.487 g, 2.20 mmol, 2.20 equiv) with (*S*)-2-(*tert*-butyldimethylsilyloxy)propyl iodide (**8**) (0.300 g, 1.00 mmol, 1 equiv) in tetrahydrofuran (2.20 mL, 45 °C for 14 h) was carried out as described for the alkylation of **1** with **7**. The product was obtained as a viscous, colorless oil (0.0590 g, 15%) after purification by flash column chromatography (25% ethyl acetate in hexanes). Capillary GC analysis of the corresponding *O*,*O*-diacetate (prepared by desilylation/acetylation, as described above) established a diastereomeric excess (de) of ≥99% for this product: ^{1}H NMR (3:1 rotamer ratio, * denotes minor rotamer peaks, C_6D_6) δ 7.34 (d, 2H, J = 7.5 Hz), 7.24−7.02 (m, 8H), 4.56 (dd, 1H, J = 6.4 Hz), 4.30 (br s, 1H), 4.15* (m, 1H), 3.93* (m, 1H), 3.73 (m, 1H), 3.10* (m, 1H), 2.86* (s, 3H), 2.70 (m, 1H), 2.49 (s, 3H), 2.45* (m, 1H), 1.70 (ddd, 1H, J = 13.4, 8.2, 4.9 Hz), 1.56* (m, 1H), 1.35 (ddd, 1H, J = 13.3, 9.2, 4.6 Hz), 1.21* (d, 3H, J = 6.1 Hz), 1.19* (d, 3H, J = 6.7 Hz), 1.06 (d, 3H, J = 6.7 Hz), 1.01 (d, 3H, J = 6.8 Hz), 0.96 (d, 3H, J = 6.1 Hz), 0.95* (s, 9H), 0.94 (s, 9H), 0.69* (d, 3H, J = 6.7 Hz), 0.11* (s, 3H), 0.09* (s, 3H), 0.04 (s, 6H); ^{13}C NMR (C_6D_6) δ 178.28, 143.83, 128.63, 128.29, 127.35, 126.78, 76.47, 75.85*, 66.80*, 66.29, 59.47, 57.50*, 44.00, 33.20*, 32.89, 26.32*, 26.08, 24.18, 18.17, 17.55*, 16.68, 15.50*, 14.30, −4.15, −4.60; IR 3372 (br, m, OH), 2961 (s), 2928 (s), 2852 (m), 1619 (s), 1462 (m), 1256 (m), 1088 (m), 1045 (m) cm^{-1}.

[1*S*(2*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4-hydroxy-*N*,2,4-trimethylpentanamide. A dry 10-mL round-bottomed flask equipped with a magnetic stirring bar was charged with anhydrous lithium chloride (0.127 g, 3.00 mmol, 6.00 equiv), *N*,*N*-diisopropylamine (0.138 mL, 1.05 mmol, 2.10 equiv), and tetrahydrofuran (0.50 mL). The resulting suspension was cooled to −78 °C, and *n*-butyllithium (2.30 M in hexanes, 0.480 mL, 1.11 mmol, 2.21 equiv) was added by syringe. The suspension was warmed to 0 °C for 10 min and then was cooled to −78 °C. A solution of **1** (0.111 g, 0.500 mmol, 1 equiv) in tetrahydrofuran (0.80 mL) was transferred dropwise to the reaction flask by syringe. The transfer was quantitated with an additional portion of tetrahydrofuran (0.20 mL). Upon completion of the addition, the reaction mixture was stirred at −78 °C for 1 h, at 0 °C for 15 min, at 23 °C for 5 min, and finally was cooled to 0 °C. Isobutylene oxide (0.108 g, 1.50 mmol, 3.00 equiv) was added to the reaction vessel by microliter syringe, and the resulting solution was stirred at 0 °C for 4 h. Saturated aqueous ammonium chloride solution (2 mL) was added, and the resulting biphasic mixture was partitioned between water (5 mL) and ethyl acetate (5 mL). The aqueous layer was separated and extracted further with three 5-mL portions of ethyl acetate and one 5-mL portion of dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and then were concentrated. Purification of the residue by flash column chromatography (2.5% methanol in dichloromethane) afforded 0.123 g (84%) of product as a white crystalline solid. Acetylation, followed by capillary GC analysis of the resulting *O*,*O*-diacetate, established a diastereomeric excess (de) of 95% for this product: mp 89−92 °C; ^{1}H NMR (~10:1 rotamer ratio, * denotes minor rotamer peaks, C_6D_6) δ 7.35 (d, 2H, J = 7.5 Hz), 7.21−7.05 (m, 3H), 4.53 (br d, 1H, J = 6.5 Hz), 4.39 (br s, 1H), 4.08* (br s, 1H), 2.78* (s, 3H), 2.61 (m, 1H), 2.52* (m, 1H), 2.41 (dd, 1H, J = 13.9, 10.8 Hz), 2.37 (s, 3H), 2.00 (br s, 1H), 1.31* (d, 3H, J = 6.5 Hz), 1.18* (s, 3H), 1.13 (dd, 1H, J = 14.2, 2.1 Hz), 1.08 (s, 3H), 1.05* (s, 3H), 1.03 (s, 3H), 0.95 (d, 3H, J = 6.5 Hz), 0.88 (d, 3H, J = 6.8 Hz), 0.78* (d, 3H, J = 6.7 Hz); ^{13}C NMR (C_6D_6) δ 179.19, 143.47, 128.53, 128.30, 127.48, 127.16, 76.29, 70.17, 59.58, 47.65, 32.53, 32.50, 31.47, 28.72, 19.33, 15.61, 14.22; IR 3378 (br, s, OH), 2975 (s), 2929 (m), 2883 (w), 1618 (s, C═O), 1451 (m), 1410 (m), 1376 (m), 1134 (m), 1047 (m) cm^{-1}. Anal. Calcd for $C_{17}H_{27}NO_3$: C, 69.57; H, 9.28; N, 4.78. Found: C, 69.63; H, 9.25; N, 4.67.

[1*S*(2*S*),2*S*]-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-4-hydroxy-*N*,4-dimethyl-2-(phenylmethyl)pentanamide. The alkylation of **2** (0.149 g, 0.500 mmol, 1 equiv) with isobutylene oxide (0.108 g, 1.50 mmol, 3.00 equiv) in tetrahydrofuran (0.500 M, 0 °C for 4.5 h) was carried out as described for the alkylation of **1** with isobutylene oxide. The product was obtained as a white crystalline solid (0.131 g, 71%) after purification by flash column chromatography (2.5% methanol in dichloromethane). Acetylation followed by capillary GC analysis of the resulting *O*,*O*-diacetate established a diastereomeric excess (de) of ≥99% for this product: mp 96−99 °C; ^{1}H NMR (~25:1 rotamer ratio, * denotes minor rotamer peaks, C_6D_6) δ 7.45 (d, 2H, J = 7.4 Hz), 7.21−6.97 (m, 8H), 5.08 (m, 1H), 4.55 (br s, 1H), 4.40 (d, 1H, J = 9.2 Hz), 3.15 (br s, 1H), 3.11 (m, 1H), 2.97 (dd, 1H, J = 12.5, 10.0 Hz), 2.88* (s, 3H), 2.54 (d, 1H, J = 12.1 Hz), 2.52 (dd, 1H, J = 10.7, 8.0 Hz), 2.33 (s, 3H), 1.37 (dd, 1H, J = 13.9, 1.7 Hz), 1.18 (s, 3H), 1.12 (s, 3H), 0.98* (d, 3H, J = 7.0 Hz), 0.54 (d, 3H, J = 6.9 Hz); ^{13}C

NMR (C_6D_6) δ 178.02, 142.88, 140.08, 129.45, 128.76, 128.47, 128.41, 126.54, 76.26, 70.45, 55.94, 46.85, 41.37, 40.47, 31.77, 29.59, 28.44, 13.97; IR 3389 (br, s, OH), 2966 (m), 2931 (m), 2872 (w), 1614 (s, C═O), 1455 (m), 1132 (m), 1049 (m) cm^{-1}. Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.75; H, 8.46; N, 3.79. Found: C, 74.33; H, 8.64; N, 3.74.

Preparation of *trans*-γ-Butyrolactones by the Acidic Hydrolysis of Alkylated Pseudoephedrine Amides. The following provides a representative procedure:

(2*S*,4*R*)-*trans*-4-[(Benzyloxy)methyl]-2-methyl-γ-butyrolactone (Table 4, entry 3). An oven-dried test tube (16 × 125 mm) equipped with a magnetic stirring bar was charged with [1*S*(2*S*,4*R*),2*S*]-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-5-(benzyloxy)-4-hydroxy-*N*,2-dimethylpentanamide (Table 1, entry 4, ≥99% de, 0.136 g, 0.353 mmol, 1 equiv), aqueous sulfuric acid solution (2 N, 1.00 M, 0.706 mL, 0.706 mmol), and dioxane (3.00 mL). The solution was heated at 95 °C for 30 min. After cooling to 23 °C, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (2 mL) and ethyl acetate (2 mL). The aqueous layer was separated and extracted further with three 1-mL portions of ethyl acetate. The combined organic extracts were dried over anhydrous sodium sulfate and were concentrated. Purification of the residue by flash column chromatography (50% ethyl acetate in hexanes) provided 0.0719 g (90%) of the product as a viscous, colorless oil. The diasteromeric excess (de) of the product was quantified by capillary GC analysis and was found to be 98%: ^{1}H NMR (C_6D_6) δ 7.21−7.15 (m, 3H), 7.09 (m, 2H), 4.22 (d, 1H, J = 12.1 Hz), 4.17 (d, 1H, J = 12.1 Hz), 3.99 (m, 1H), 3.12 (dd, 1H, J = 10.4, 3.6 Hz), 2.96 (dd, 1H, J = 10.5, 3.9 Hz), 2.40 (m, 1H), 1.67 (ddd, 1H, J = 12.7, 9.3, 3.2 Hz), 1.17 (ddd, 1H, J = 12.7, 8.8, 8.8 Hz), 0.91 (d, 3H, J = 7.4 Hz); ^{13}C NMR (C_6D_6) δ 178.88, 138.40, 128.64, 127.81, 75.83, 73.50, 71.84, 33.89, 32.39, 16.03; IR 2972 (s), 2931 (s), 2869 (s), 1767 (s, C═O), 1451 (m), 1379 (m), 1364 (m), 1348 (m), 1198 (m), 1172 (s), 1100 (s), 1027 (s), 955 (m), 924 (m) cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{17}O_3$ (MH^+) 221.1178, found 221.1177.

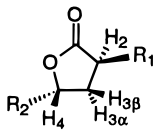
(2*S*,4*S*)-*trans*-2,4-Dimethyl-γ-butyrolactone (Table 4, entry 1). Hydrolysis of the alkylation product of Table 1 entry 1 (94% de) with 0.03 M sulfuric acid in dioxane (95 °C, 1 h) afforded the known[12] product lactone as a light yellow, volatile oil (83%). Analysis of this product by capillary GC established a diastereomeric excess (de) of 94%.

(2*S*,4*R*)-*trans*-2-Methyl-4-[(*tert*-butyldimethylsilyloxy)-methyl]-γ-butyrolactone (Table 4, entry 2). Hydrolysis of the alkylation product of Table 1 entry 3 (≥99% de) with 0.05 M sulfuric acid in dioxane (95 °C, 20 min) afforded the lactone product as a viscous, colorless oil (90%). Analysis of this product by capillary GC established a diastereomeric excess (de) of ≥99%: ^{1}H NMR (C_6D_6) δ 3.93 (ddd, 1H, J = 9.8, 6.7, 3.4 Hz), 3.42 (dd, 1H, J = 11.2, 3.5 Hz), 3.17 (dd, 1H, J = 11.1, 3.2 Hz), 2.49 (m, 1H), 1.82 (ddd, 1H, J = 12.5, 9.4, 2.9 Hz), 1.23 (dt, 1H, J = 12.3, 8.9 Hz), 0.98 (d, 3H, J = 7.3 Hz), 0.89 (s, 9H), −0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (C_6D_6) δ 178.85, 76.87, 65.19, 34.10, 32.05, 25.93, 18.37, 16.34, −5.45,−5.57; IR 2951 (s), 2931 (s), 2879 (m), 2858 (s), 1777 (s, C═O), 1472 (m), 1462 (m), 1255 (s), 1203 (s), 1172 (s), 1131 (s), 1069 (s), 1022 (s), 955 (m), 934 (m), 836 (s), 779 (s) cm^{-1}. Anal. Calcd for $C_{12}H_{24}O_3Si$: C, 58.98; H, 9.91. Found: C, 59.00; H, 10.03.

(2*S*,4*S*)-*trans*-4-Methyl-2-(phenylmethyl)-γ-butyrolactone (Table 4, entry 4). Hydrolysis of the alkylation product of Table 1 entry 5 (≥99% de) with 0.43 M sulfuric acid in dioxane (95 °C, 2.5 h) afforded the lactone product as a viscous, colorless oil (92%). Analysis of this product by capillary GC established a diastereomeric excess (de) of ≥99%: ^{1}H NMR (C_6D_6) δ 7.22−7.15 (m, 2H), 7.11 (m, 1H), 7.01 (d, 2H, J = 7.0 Hz), 3.90 (m, 1H), 3.05 (m, 1H), 2.54 (m, 2H), 1.48 (ddd, 1H, J = 12.8, 7.5, 7.5 Hz), 1.15 (ddd, 1H, J = 12.8, 8.4, 4.3 Hz), 0.79 (d, 3H, J = 6.4 Hz); ^{13}C NMR (C_6D_6) δ 177.25, 139.10, 129.20, 128.75, 126.77, 73.86, 40.85, 36.54, 33.91, 20.82; IR 2979 (w), 2934 (w), 1770 (s, C═O), 1155 (s) cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{14}O_2$ (M^+) 190.0994, found 190.0994.

(2*S*,4*R*)-*trans*-4-(Hydroxymethyl)-2-(phenylmethyl)-γ-butyrolactone (Table 4, entry 5). Hydrolysis of the alkylation product of Table 1 entry 7 (≥99% de) with 0.21 M sulfuric acid in dioxane (95 °C, 30 min) afforded the lactone product as a white crystalline solid (92%). Analysis of this product by capillary GC established a diastereomeric excess (de) of ≥99%: mp 79−80 °C (toluene); ^{1}H NMR (C_6D_6) δ 7.08 (m, 2H), 7.02 (m, 1H), 6.94 (d, 2H, J = 7.1 Hz), 3.79 (m, 1H), 3.32 (m, 1H), 3.00 (dd and m, 2H, J = 13.5, 4.6 Hz), 2.82 (ddt, 1H, J = 9.3, 9.3, 4.6 Hz), 2.45 (dd, 1H, J = 13.9, 9.3 Hz), 2.36 (br t, J = 6.0 Hz), 1.58 (ddd, 1H, J = 13.0, 9.5, 3.6 Hz), 1.38 (ddd, 1H, J = 13.0, 8.7, 8.7 Hz); ^{13}C NMR (C_6D_6) δ 178.41, 138.95, 129.20, 128.74, 126.74, 78.21, 64.31, 41.20, 36.96, 28.85; IR 3409 (s, OH), 1729 (s, C═O), 1218 (m), 1186 (m), 1154 (m), 1052 (m), 978 (m) cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.87; H, 6.84. Found: C, 69.73; H, 6.99.

Table 5. Coupling Constants for Trans-Lactone Derivatives of Alkylated Amides[a]



trans

entry	R_1	R_2	J (Hz) $H_2,H_{3\alpha}$	J (Hz) $H_2,H_{3\beta}$	J (Hz) $H_{3\alpha},H_4$	J (Hz) $H_{3\beta},H_4$	J (Hz) $H_{3\alpha},H_{3\beta}$
1	CH_3	C_6H_5[b]	7.0	9.0	7.5	5.5	12.8
2	CH_3	C_6H_5	8.0	8.6	8.1	4.6	12.9
3	CH_3	CH_2OTBS	8.9	9.4	8.9	2.9	12.5
4	CH_3	CH_2OBn	8.8	9.3	8.8	3.2	12.7
5	$CH_2C_6H_5$	CH_3	7.5	8.4	7.5	4.3	12.8
6	$CH_2C_6H_5$	C_6H_5	8.1	8.5	8.1	4.2	12.9
7	$CH_2C_6H_5$	CH_2OH	8.7	9.5	8.7	3.6	13.0
8	$CH_2C_6H_5$	CH_2OBn	9.0	9.4	9.0	3.3	12.8

[a] Spectroscopic data were measured in C_6D_6, except in entries 1 and 2, where $CDCl_3$ was used. [b] Literature values, see reference 12.

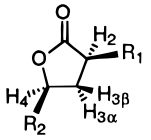
(2*S*,4*R*)-*trans*-4-[(Benzyloxy)methyl]-2-(phenylmethyl)-γ-butyrolactone (Table 4, entry 6). Hydrolysis of the alkylation product of Table 1 entry 8 (≥99% de) with 0.17 M sulfuric acid in dioxane (95 °C, 1.5 h) afforded the lactone product as a viscous, colorless oil (94%). Analysis of this product by capillary GC established a diastereomeric excess (de) of ≥99%: ^{1}H NMR (C_6D_6) δ 7.18−7.10 (m, 4H), 7.09−7.00 (m, 4H), 6.93 (d, 2H, J = 7.0 Hz), 4.16 (d, 1H, J = 12.1 Hz), 4.10 (d, 1H, J = 12.2 Hz), 3.85 (m, 1H), 3.08 (dd, 1H, J = 9.9, 3.4 Hz), 3.02 (dd, 1H, J = 13.9, 4.5 Hz), 2.86 (dd, 1H, J = 10.5, 3.8 Hz), 2.83 (dd, 1H, J = 9.3, 4.5 Hz), 2.47 (dd, 1H, J = 13.9, 9.3 Hz), 1.57 (ddd, 1H, J = 12.8, 9.4, 3.3 Hz), 1.41 (ddd, 1H, J = 12.8, 9.0, 9.0 Hz); ^{13}C NMR (C_6D_6) δ 177.68, 139.13, 138.36, 129.23, 128.75, 128.62, 127.72, 126.73, 76.22, 73.46, 71.82, 67.77, 40.97, 36.93, 29.66, 25.78; IR 2919 (w), 2861 (w), 1772 (s, C═O), 1455 (m), 1149 (m), 1114 (m) cm^{-1}. Anal. Calcd for $C_{19}H_{20}O_3$: C, 76.99; H, 6.81. Found: C, 76.60; H, 7.15.

Cis- and trans-isomers of 2,4-disubstituted γ-butyrolactones are easily distinguishable by the magnitude of their vicinal coupling constants (reference 12 and Tables 5 and 6). Key resonances are summarized in Tables 5 and 6.

(*S*)-2,4,4-Trimethyl-γ-butyrolactone. Hydrolysis of the product (95% de) from the alkylation of **1** with isobutylene oxide in 0.19 M aqueous sulfuric acid in dioxane (70 °C, 1 h) afforded (*S*)-2,4,4-trimethyl-γ-butyrolactone as a white, low-melting solid (94%). Reduction of the lactone with lithium aluminum hydride in ether at 0 °C and selective esterification of the primary hydroxyl groups of the resulting mixture of diols with (*S*)-(−)-Mosher acid[15] (with care to ensure complete conversion) provided the corresponding Mosher ester derivatives. An accurate evaluation of the diastereomeric ratio and, therefore, the enantiomeric excess (85% ee) for the starting lactone was provided by analysis of the Mosher esters by high resolution ^{1}H NMR spectroscopy. Lactone: mp 47−49 °C; lit.[20] mp for racemic lactone: 48−50 °C; ^{1}H NMR (CCl_4) δ 2.67−2.57 (m, 1H), 2.16 (dd, 1H, J = 11.7, 10.2 Hz), 1.58 (dd, 1H, J = 12.2, 11.7 Hz), 1.41 (s, 3H), 1.32 (s, 3H), 1.22 (d, 3H, J = 7.0

(20) Cannon, G. W.; Santilli, A. A.; Shenian, P. *J. Am. Chem. Soc.* **1959**, *81*, 1660.

Table 6. Coupling Constants for Cis-Lactone Derivatives of Alkylated Amides[a]



cis

entry	R_1	R_2	J (Hz) $H_2,H_{3\alpha}$	J (Hz) $H_2,H_{3\beta}$	J (Hz) $H_{3\alpha},H_4$	J (Hz) $H_{3\beta},H_4$	J (Hz) $H_{3\alpha},H_{3\beta}$
1	CH_3	C_6H_5[b]	8.1	12.9	5.8	10.8	12.4
2	CH_3	C_6H_5	8.2	11.9	5.5	10.9	11.6
3	CH_3	CH_2OTBS	9.2	11.9	6.3	10.2	12.5
4	CH_3	CH_2OBn	8.9	11.9	6.2	10.3	12.4
5	$CH_2C_6H_5$	CH_3	9.3	11.9	5.6	10.6	12.2
6	$CH_2C_6H_5$	C_6H_5	8.0	12.9	5.7	10.6	12.2
7	$CH_2C_6H_5$	CH_2OH	9.0	11.8	6.3	10.0	12.9
8	$CH_2C_6H_5$	CH_2OBn	9.0	11.6	6.3	10.1	12.6

[a] Spectroscopic data were measured in C_6D_6, except in entries 1 and 2, where $CDCl_3$ was used. [b] Literature values, see reference 12.

Hz); lit.[5a] δ 2.8−2.5 (m, 1H), 2.22 (dd, 1H, J = 12, 9 Hz), 1.63 (t, 1H, J = 12, 12 Hz), 1.44 (s, 3H), 1.35 (s, 3H), 1.23 (d, 3H).

(*S*)-4,4-Dimethyl-2-(phenylmethyl)-γ-butyrolactone. Hydrolysis of the product (≥99% de) from the alkylation of **2** with isobutylene oxide in 0.17 M aqueous sulfuric acid in dioxane (95 °C, 2 h) afforded (*S*)-4,4-dimethyl-2-(phenylmethyl)-γ-butyrolactone as a white crystalline solid (94%). High resolution ^{1}H NMR analysis of the corresponding Mosher ester derivative (prepared by reduction/esterification, as described above) established an enantiomeric excess (ee) of ≥99% for this product. Lactone: mp 78−79 °C; ^{1}H NMR (C_6D_6) δ 7.09 (m, 2H), 7.04 (m, 1H), 6.94 (d, 2H, J = 7.1 Hz), 3.17 (dd, 1H, J = 13.7, 4.1 Hz), 2.57 (m, 1H), 2.48 (dd, 1H, J = 13.7, 9.6 Hz), 1.36 (dd, 1H, J = 12.6, 8.7 Hz), 1.22 (dd, 1H, J = 11.6 Hz), 0.93 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (C_6D_6) δ 176.22, 139.46, 129.18, 128.75, 126.69, 80.63, 42.57, 40.62, 36.86, 28.71, 26.78; IR 2975 (s), 2930 (s), 1766 (s, C═O), 1604 (m), 1496 (s), 1455 (s), 1375 (s), 1265 (s), 1181 (s), 1129 (s) 955 (s) cm^{-1}.

Preparation of Methyl Ketones from Alkylated Pseudoephedrine Amides. Methyl ketones derived from alkylation products **5**, **6**, **9**, and **10** were prepared according to the procedure previously described.[1] Enantiomeric excesses of the ketones derived from products **5** and **6** were determined by the reduction of each ketone with lithium aluminum hydride in ether at 0 °C (producing a ∼1:1 mixture of diastereomeric alcohols). The diastereomeric mixture of alcohols was esterified with (*S*)-(−)-Mosher acid[15] (with care to ensure complete conversion), and the resulting Mosher esters were analyzed by high resolution ^{1}H NMR spectroscopy and capillary GC.

(*R*)-5-(*tert*-Butyldimethylsilyloxy)-3-methyl-2-pentanone. The reaction of **5** (≥99% de) with methyllithium (2.50 equiv, ether, −78 → 0 °C) provided the product ketone as a colorless oil (89%). Capillary GC and 500 MHz ^{1}H NMR analysis of the Mosher ester derivatives, prepared as described above, established an enantiomeric excess (ee) of ≥95% for this product. Ketone: ^{1}H NMR (C_6D_6) δ 3.46 (m, 2H), 2.47 (m, 1H), 1.85 (m, 1H), 1.79 (s, 3H), 1.36 (m, 1H), 0.95 (s, 9H), 0.88 (d, 3H, J = 7.1 Hz), 0.02 (s, 6H); ^{13}C NMR (C_6D_6) δ 209.90, 61.01, 43.65, 35.98, 27.71, 26.07, 18.40, 16.25, −5.38; IR 2953 (s), 2930 (s), 2883 (m), 2860 (s), 1715 (s, C═O), 1464 (m), 1360 (m), 1255 (s), 1098 (s), 836 (s), 778 (s) cm^{-1}. Anal. Calcd for $C_{12}H_{26}O_2Si$: C, 62.56; H, 11.38. Found: C, 62.77; H, 11.63.

(*R*)-5-(*tert*-Butyldimethylsilyloxy)-3-(phenylmethyl)-2-pentanone. The reaction of **6** (≥99% de) with methyllithium (2.50 equiv, ether, −78 → 0 °C) provided the product ketone as a colorless oil (92%). Capillary GC and 500 MHz ^{1}H NMR analysis of the corresponding Mosher ester derivatives, prepared as described above, established an enantiomeric excess (ee) of ≥95% for this product. Ketone: ^{1}H NMR (C_6D_6) δ 7.09 (m, 2H), 7.06 (m, 3H), 3.42 (m, 2H), 2.86 (m, 1H), 2.82 (dd, 1H, J = 12.9, 8.2 Hz), 2.49 (dd, 1H, J = 12.7, 6.0 Hz), 1.82 (m, 1H), 1.76 (s, 3H), 1.49 (m, 1H), 0.93 (s, 9H), −0.01 (2 s, 6H); ^{13}C NMR (C_6D_6) δ 209.37, 140.13, 129.21, 128.66, 126.46, 61.17, 53.25, 51.31, 38.25, 34.74, 29.91, 26.07, 18.41, −5.40; IR 2953 (s), 2930 (s), 2895 (m), 2860 (s), 1715 (s, C═O), 1255 (s), 1104 (s), 836 (s), 778 (s) cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{31}O_2Si$ (MH^+) 307.2094, found 307.2093.

(3*S*,5*R*)-6-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-3-(phenylmethyl)-2-hexanone. The reaction of **9** (≥99% de) with methyllithium (5.00 equiv, ether, −78 → 0 °C) provided the product ketone as a viscous, colorless oil (97%; an equilibrating mixture of open-chain and epimeric closed forms): ^{1}H NMR (C_6D_6) δ 7.12−6.94 (m, 15H), 4.22 (m, 1H), 4.10 (m, 1H), 3.64 (dd, 1H, J = 9.6, 4.5 Hz), 3.62 (m, 1H), 3.46 (dd, 1H, J = 10.6, 4.5 Hz), 3.39 (dd, 1H, J = 10.5, 4.3 Hz), 3.34 (dd, 1H, J = 10.5, 3.8 Hz), 3.23−3.19 (m, 2H), 2.90 (dd, 1H, J = 13.6, 5.5 Hz), 2.81 (dd, 1H, J = 13.6, 8.0 Hz), 2.73 (dd, 1H, J = 13.6, 9.5 Hz), 2.60 (br s, 1H), 2.53 (dd, 1H, J = 13.6, 7.2 Hz), 2.48 (m, 1H), 2.23 (m, 1H), 2.15 (m, 1H), 2.05 (ddd, 1H, J = 13.6, 12.5, 7.2 Hz), 1.96 (ddd, 1H, J = 11.6, 11.6, 9.1 Hz), 1.83 (s, 3H), 1.79 (ddd, 1H, J = 11.6, 8.4, 2.8 Hz), 1.76 (ddd, 1H, J = 13.3, 8.9, 2.8 Hz), 1.55 (s, 3H), 1.48 (ddd, 1H, J = 13.3, 6.0, 2.4 Hz), 1.41 (ddd, 1H, J = 13.8, 10.1, 3.6 Hz), 1.36 (s, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.86 (s, 9H), 0.00 (s, 3H), −0.01 (s, 3H), −0.02 (s, 3H), −0.04 (s, 3H), −0.05 (s, 6H); ^{13}C NMR (C_6D_6) δ 210.89, 141.67, 139.82, 129.21, 129.14, 128.69, 128.55, 126.52, 126.11, 105.03, 77.99, 77.18, 69.74, 67.91, 66.34, 65.51, 51.21, 50.23, 49.56, 39.12, 37.11, 36.35, 34.98, 33.26, 30.64, 29.44, 26.08, 26.01, 22.84, 18.46, −5.25; IR 3417 (m, OH), 2953 (s), 2928 (s), 2857 (s), 1713 (m, C═O), 1496 (m), 1472 (m), 1462 (m), 1455 (m), 1255 (s), 1146 (s), 1107 (s), 1014 (m), 928 (m), 838 (s) cm^{-1}.

(3*S*,5*R*)-6-(Benzyloxy)-5-hydroxy-3-(phenylmethyl)-2-hexanone. The reaction of **10** (≥99% de) with methyllithium (4.00 equiv, ether, −78 → 0 °C) afforded the product ketone as a viscous, colorless oil (90%; an equilibrating mixture of open-chain and epimeric closed forms): ^{1}H NMR (C_6D_6) δ 7.22−6.91 (m, 30H), 4.30 (m and d, 3H, J = 6.4 Hz), 4.16 (d, 1H, J = 12.3 Hz), 4.14 (d and m, 2H, J = 12.2 Hz), 3.71 (m, 1H), 3.38 (dd, 1H, J = 9.9, 3.1 Hz), 3.24 (d, 2H, J = 4.9 Hz), 3.18 (m, 1H), 3.06 (m, 2H), 2.96 (dd, 1H, 9.3, 7.5 Hz), 2.84 (dd, 1H, J = 13.7, 5.5 Hz), 2.78 (dd, 1H, J = 13.3, 8.2 Hz), 2.68 (dd, 1H, J = 13.6, 9.5 Hz), 2.50 (dd, 1H, J = 13.5, 6.9 Hz), 2.22−2.10 (m, 2H), 2.06 (ddd, 1H, J = 12.8, 9.1 Hz), 1.92 (ddd, 1H, J = 12.1, 9.0 Hz), 1.78 (s, 3H), 1.76 (ddd, 1H, J = 11.8, 8.3, 3.0 Hz), 1.72 (ddd, 1H, J = 13.5, 10.4, 2.9 Hz), 1.52 (s, 3H), 1.48 (ddd, 1H, J = 12.6, 10.4, 2.9 Hz), 1.37 (ddd, 1H, J = 13.7, 10.1, 3.6 Hz), 1.25 (s, 3H); ^{13}C NMR (C_6D_6) δ 210.71, 141.58, 140.90, 139.81, 139.22, 138.62, 129.16, 129.12, 128.62, 128.53, 128.40, 127.57, 127.48, 126.45, 126.06, 106.70, 104.92, 76.65, 75.69, 75.03, 73.44, 73.27, 72.84, 68.22, 50.85, 50.10, 49.31, 39.09, 36.98, 36.28, 35.24, 33.81, 30.65,30.48, 26.01, 23.07; IR 3422 (br, s, OH), 2918 (s), 2957 (s), 1709 (m, C═O), 1496 (m), 1454 (s), 1377 (m), 1260 (m), 1098 (br s), 1028 (m), 913 (m), 801 (m) cm^{-1}.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of compounds (39 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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