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Articles

Highly Stereoselective Syntheses of *syn*- and *anti*-1,2-Amino Alcohols

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The reduction of N-protected amino ketones can be carried stereoselectively to produce either the *syn*- or *anti*-amino alcohol diastereomer. Carbamate-protected amino ketones can be reduced predictably and selectively to *anti*-amino alcohols with $LiAlH(O\text{-}t\text{-}Bu)_3$ in ethanol at −78 °C. *N*-Trityl-protected amino ketones can be reduced selectively to *syn*-amino alcohols with $LiAlH(O\text{-}t\text{-}Bu)_3$ in THF at −5 °C.

Introduction

1,2-Amino alcohols are important and versatile synthetic intermediates for the preparation of a wide variety of natural products, drugs, and metal-binding ligands.[1] Consequently, the development of synthetic methods for their preparation in a stereocontrolled manner has received significant attention for quite some time. In general, the hydroxyl group of the amino alcohol is installed either by the addition of an organometallic reagent to an amino aldehyde **1** (R^2 = H) or by the reduction of an amino ketone **1** ($R^2 \neq$ H) (Scheme 1).[2] Moreover, stereochemical control is good for either strategy when the amino group is a primary, secondary, or unhindered tertiary amine **1** (P, P′ = alkyl, H), which is the most common class of amine used in these reactions.[2] In contrast, syntheses of amino alcohols by reduction of N-protected amino ketones **1** (R^2 = alkyl, aryl, P = protecting group, P′ = alkyl, H) are much more problematic.

Two modes of stereocontrol determine which diastereomer is the major product from the reduction of a protected amino ketone. Chelation control, in which a Lewis acid or metal ion coordinates to the carbonyl oxygen and the amine nitrogen, enforces a syn-periplanar relationship between the amine and ketone groups and leads to the anti diastereomer (Figure 1a). Felkin−Anh control, in which a dihedral angle of about 90° between the amine and ketone groups maximizes stereoelectronic interactions in the transition state,[3] leads to the syn diastereomer (Figure 1b).

Carbamate groups are ubiquitous protecting groups for amines. Stereocontrol in the reduction of carbamate-protected amino ketones would appear to favor chelation

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(1) (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (b) Paleo, M. R.; Cabeza, I.; Sardina, F. J. *J. Org. Chem.* **2000**, *65*, 2108.

(2) Tramontini, M. *Synthesis* **1982**, 605 is a definitive review.

(3) (a) Cherest,, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, *18*, 2199. (b) Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, *18*, 2205. (c) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61. (d) For an excellent summary, see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994; pp 876−880.

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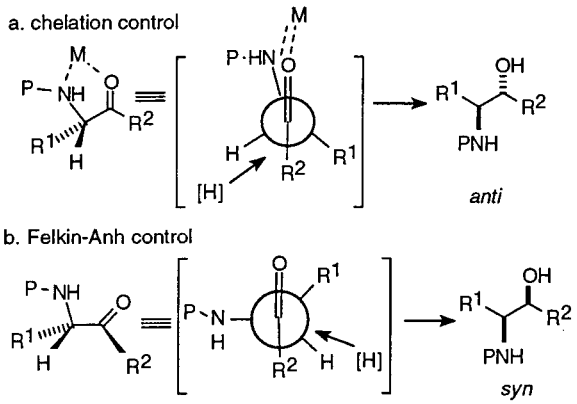
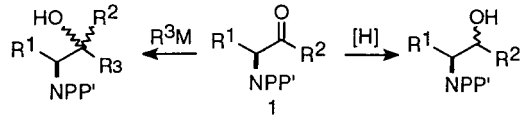


Figure 1.

Scheme 1



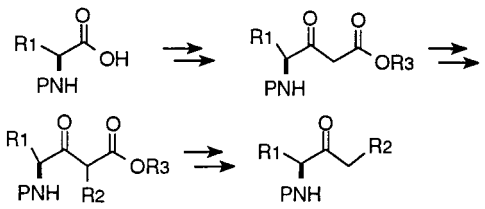
control since both the ketone oxygen and the carbamate nitrogen are sterically accessible for coordination to a Lewis acid. Thus, chelation stereocontrol in the reduction of carbamate-protected amino ketones provides a method for the stereoselective synthesis of anti carbamate-protected amino alcohols.

Examination of the literature reveals, however, that there is no reagent that reduces carbamate-protected amino ketones with predictable chelation control. In fact, contradictory results are the rule rather than the exception. For example, Benedetti et al. reported on the reduction of Boc-protected amino ketones with sodium borohydride in methanol, which had anti diastereoselectivities (chelation control) ranging from 3:1 to 32:1. There was no obvious correlation between the substrate structure and the diastereoselectivity. These and other experiments led the authors to conclude that the reduction is "not markedly affected by the reducing agent or solvent".[4]

In contrast, Koskinen studied stereoselectivity in the reductions of a series of Boc-protected unsaturated amino ketones. Anti-selectivity ranged from 6:1 to 1:4 for various reducing agents. In this case, sodium borohydride was found to give the syn isomer selectively (3:1) (Felkin–Anh control)! These authors concluded that "solvent effects and reagent size are very important" influences on the stereoselectivity.[5]

Good levels of chelation control in reductions of carbamate-protected amino ketones are often achieved by empiricle screening of a variety of reducing agents. For example, in the elegant synthesis of statine from leucine reported by Joullie, potassium borohydride gave a 10:1 anti diastereoselectivity for the reduction of a Cbz-protected γ-amino-β-keto ester and was clearly superior to other reductants examined.[6] More recently, Dondoni prepared a Boc-protected acetylenic amino ketone during a sphingosine synthesis and screened eight reducing agents before finding that L-Selectride gives a 19:1 ratio of the anti product.[7] (Normally, L-Selectride gives Felkin–Anh syn selectivity!)

Scheme 2



Many other studies where extensive screening of reducing agents is used to achieve stereocontrolled reduction[8] clearly highlight the need for a reliable, chelation controlled reduction of carbamate-protected amino ketones. Such a protocol must be anti selective, predictable, and structurally tolerant.

To achieve Felkin–Anh control in the reduction of protected amino ketones and thus produce *syn*-amino alcohols, the amine group must be modified to make it sterically bulky. This results in a steric preference for a Felkin–Anh transition state (Figure 1b) and minimizes effective chelation involving the amino nitrogen and the ketone oxygen. Reetz found that the *N*,*N*-dibenzylamine protecting group rendered the amine group sufficiently bulky to ensure Felkin–Anh control.[9] Other groups[10] including our own[11] utilized *N*,*N*-dibenzyl protection for effective stereocontrol in amino ketone reductions.

Despite these successes, we found that the installation of the *N*,*N*-dibenzyl protecting group is very problematic,[11b] and its hydrogenolytic removal is not compatible with unsaturated groups.[11a] In the course of a synthesis of sphingosines, we found that an *N*-trityl protecting group gave good Felkin–Anh control of an amino ketone reduction, and it was much easier to attach and remove.[12] That work provides the basis for a general amino ketone reduction protocol with Felkin–Anh stereocontrol if it is found to be general.

We had previously developed a very simple and direct method for preparing N-protected amino ketones with widely varying structures (Scheme 2). This methodolgy is very effective in the production of peptidomimetics[13] and sphingosines,[12] but it also is an excellent method for almost any amino ketone. Consequently, we undertook a study of the reductions of protected amino ketones in order to elucidate factors that contribute to effective stereocontrol and, hence, extend our amino ketone synthesis into a stereocontrolled synthesis of amino alcohols.

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(5) Koskinen, A. M. P.; Koskinen, P. M. *Tetrahedron Lett.* **1993**, *34*, 6765.
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(7) Dondoni, A.; Perrone, D.; Turturici, E. *J. Org. Chem.* **1999**, *64*, 5557.
(8) See, for example: (a) Tramontini, M. *Synthesis* **1982**, 605. (b) Nishida, A.; Sorimachi, H.; Iwaida, M.; Matsumizu, M.; Kawate, T.; Nakagawa, M. *Synth. Lett.* **1998**, 389. (c) Chung, S.-K.; Lee, J.-M. *Tetrahedron*: *Asymmetry* **1999**, *10*, 1441. (d) Rotella, D. P. *Tetrahedron Lett.* **1995**, *36*, 5453.
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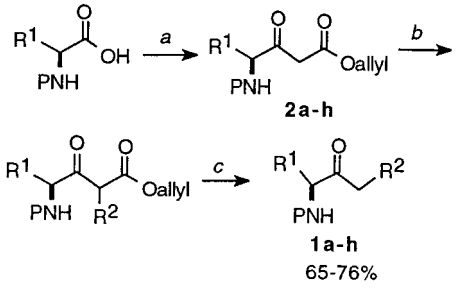
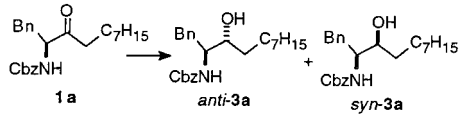
Scheme 3



1a. R^1= $CH_2C_6H_5$, R^2= n-heptyl, P=Cbz
1b. R^1= $CH_2C_6H_5$, R^2= $CH_2C_6H_5$, P=Boc
1c. R^1= CH_3, R^2= $(CH_2)_2C_6H_5$, P=Boc
1d. R^1= $(CH_2)_4NHCbz$, R^2= $CH_2C_6H_5$, P=Boc
1e. R^1= $CH_2CH(CH_3)_2$, R^2= $(CH_2)_2C_6H_5$, P=Cbz
1f. R^1= $CH_2C_6H_5$, R^2= n-heptyl, P=Fmoc
1g. R^1= $(CH_2)CO_2Me$, R^2= $CH_2CH{=}C(CH_3)_2$, P=Boc
1h. R^1=CH_2OBn, R^2=n-heptyl, P=Cbz

a. i. CDI *ii.* CH_3CO_2allyl/LDA. *b. i.* NaH *ii.* R^2OTf or R^2Br (for benzylic or allylic). *c.* $Pd(PPh_3)_4$, $NH_4{}^+HCO_2{}^-$

Table 1. The Reduction of 1a with Various Reducing Agents/Conditions



entry	reagent	conditions	yield (% crude)	anti/syn[a]
1	$NaBH_4$	EtOH, −78 °C	98	7:1
2	$LiBH_4$	EtOH, −78 °C	97	7:1
3	KBH_4	EtOH, −78 °C	98	7:1
4	$Me_4N^+BH_4^-$	EtOH, −78 °C	97	7:1
5	$NaBH_4/CeCl_3$	EtOH, −78 °C	97	7:1
6	$Zn(BH_4)_2$	THF, −78−0 °C	95	2:1
7	$Zn(BH_4)_2$	ether, −78−0 °C	94	1:2
8	L-Selectride	THF, −78 °C	91	1:9
9	N-Selectride	THF, −78 °C	93	1:9
10	$LiAl(O\text{-}t\text{-}Bu)_3H$	THF, −78- −20 °C	95	1:1
11	$LiAl(O\text{-}t\text{-}Bu)_3H$	EtOH, −78 °C	98	>95:5[b]

[a] The anti/syn ratio was determined on the crude product. [b] Only one diastereomer could be observed in the NMR spectrum of the crude product.

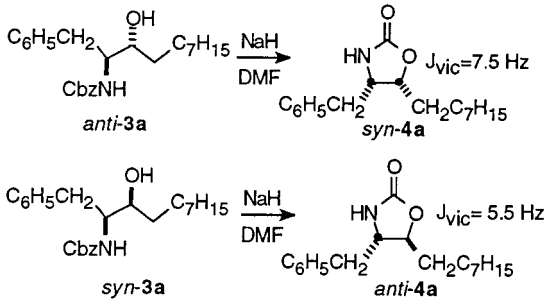
Results

***N*-Carbamate-Protected Amino Ketones.** A series of eight carbamate-protected amino ketones **1a**−**h** were prepared via *β*-keto esters **2a**−**h** (Scheme 3). Noteworthy is that the method is compatible with a variety of functional groups and carbamate protecting groups. Somewhat surprisingly, even the Fmoc group of **1f** appears to pose no problem even though strong bases are used during its preparation.

Chelation Control. To examine chelation control in the reductions of *N*-carbamate-protected amino ketones, compound **1a** was reduced to mixtures of *syn*- and *anti*-**3a** with a variety of reducing agents and conditions that have been reported in the literature. These data appear in Table 1.

The diastereomers produced from reductions of **1a** could be distinguished by both ^{1}H and ^{13}C NMR. For example, the benzylic protons of *syn*- and *anti*-**3a** appeared as distinct singlets in the ^{1}H NMR spectrum, and the carbinol carbons of *syn*- and *anti*-**3a** gave distinct

Scheme 4

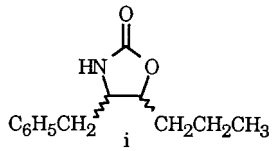


signals in the proton-decoupled ^{13}C NMR spectrum. These spectral differences could not be used to assign the stereochemistry, but they did indicate that a mixture of diastereomers was present. It was very important to be able to assign the stereochemistry of the reduction readily and unambiguously. Thus, *syn*- and *anti*-**3a** were separated chromatographically and converted to their cyclic oxazolidinone derivatives **4a** with sodium hydride in DMF. *anti*-**3a** cyclizes to *syn*-**4a** while *syn*-**3a** cyclizes to *anti*-**4a** (Scheme 4). Irradiation of the benzylic protons or the α-methylene protons allows the vicinal coupling constants between the methine protons of the oxazolidinone ring to be determined accurately. *syn*-**4a** had the larger coupling constant J_{vic} = 7.5 Hz, while *anti*-**4a** had a smaller coupling constant J_{vic} = 5.5 Hz. This agrees with previous studies that established that *syn*-oxazolidinones have larger vicinal coupling constants than the anti diastereomers.[14] Ab initio calculations on a truncated version of *syn*-**4a** and *anti*-**4a** show that the dihedral angle between the methine hydrogens is 25.5° in the most stable conformations of *syn*-**4a** and 137° in the most stable conformations of *anti*-**4a**.[15] These dihedral angles also predict that syn isomers of oxazolidinones have larger coupling constants (6.6 Hz calcd) than the anti isomers (4.9 Hz calcd).

These results led to several conclusions about the reduction. First, the reduction is very efficient for all the reducing agents as the crude yields are very high and the crude product was nearly pure in all cases. Only trace amounts of contaminants could be detected in the NMR of the crude products. The syn/anti ratios in Table 1 were determined on the crude products to avoid fractionation during purification. Second, borohydride reagents in alcohol solvents give chelation-controlled reduction, but the chelating atom is not the metal counterion. Identical results are found (Table 1, entries 1−5) irrespective of the metal (or none, Table 1, entry 4) present in solution. Third, solvent appears to play an important role in the diastereoselection. Our hypothesis is that hydroxylic solvents (EtOH and other alcohols) promote the exchange and/or disproportionation of ligands attached to boron so that the substrate can become bound to boron in a chelated fashion needed for effective chelation stereo-

(14) Harris, B. D.; Bhat, K. L.; Joullie, M. M. *Tetrahedron Lett.* **1987**, *28*, 2837.

(15) Calculations were carried out on *syn*- and *anti*-**i** at the HF 6-31G* level using the Titan suite of programs from Wavefunction. A solvation model was not included in the calculations.



control (vide infra). In non-hydroxylic solvents (Table 1, entries 6 and 7) diastereoselection is nearly absent.

In support of this mechanistic rationale is the observation that Selectride reagents, which do not have exchangeable ligands on boron and thus should not readily chelate, give the Felkin−Anh product. These results should be viewed with caution, however, as we, in this work, and others[5,7] have observed that relatively minor changes in the substrate structure can result in a switch to the anti product with Selectride reducing agents.

Since alkoxy ligands bound to aluminum are also readily exchangeable,[22] lithium tri-*tert*-butoxyaluminum hydride was tested. In THF, the diastereoselection was poor. This was presumably due to inefficient ligand exchange in the non-hydroxylic medium according to the mechanistic hypothesis derived for borohydride reduction. These considerations culminated in the experiment shown in entry 11, Table 1. If solid LiAl(O-*t*-Bu)$_3$H is added to −78 °C ethanol, very little hydrogen formation is observed upon dissolution, and smooth reduction of **1a** to *anti*-**3a** in very high yield is observed. Temperature control is critical since at −50 °C reaction between the aluminum hydride and ethanol begins to compete with the reduction.

As a further confirmation of the stereochemical assignments, amino ketone **1c** was reduced with sodium borohydride in ethanol to give a mixture of *syn*-**3c** and *anti*-**3c**. Both diastereomers could be detected in the ^{1}H NMR by distinct methyl doublets at δ 1.05 and 1.13 and in the ^{13}C NMR by separate signals for the carbinol carbons at δ 74.4 and 74.9. These diastereomers were not separable by silica gel chromatography. Only a single diasteromer was observed from the reduction of **1c** with LiAl(O-*t*-Bu)$_3$H, which had a methyl doublet at δ 1.05 and a carbinol carbon signal at δ 74.4. It was converted to oxazolidinone **4c**, which had a coupling constant of 7.5 Hz between the methine protons. Thus, **4c** is the syn diastereomer. This was further confirmed by X-ray analysis of a crystal of **4c** that showed the syn geometry. The syn stereochemistry of **4c** derives from the anti isomer of **3c**, which results from chelation controlled reduction of **1c** by LiAlH(O*t*Bu)$_3$.

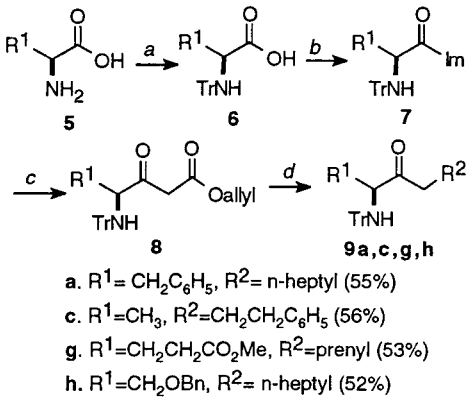
With these results in hand, amino ketones **1a**−**h** were reduced with LiAl(O-*t*-Bu)$_3$H in ethanol at −78 °C. For the entire series, the yields were very high and only one diastereomer could be detected by both ^{1}H and ^{13}C NMR in the crystalline crude products (Table 2). Recrystallization gave analytically pure products (75−80%); however, the NMR spectra of the crude material and the recrystallized products were virtually indistinguishable.

Amino alcohols **3b** and **3h** were also cyclized to oxazolidinones **4b**,**h**, which had methine coupling constants of 7.5 Hz demonstrating the anti geometry of **3b**,**h**. Cyclization of the remaining examples was problematic because of reactions of the side-chain protecting groups. Since only one diastereomer was observed in the NMR, it is reasonable to conclude that the geometry of these products is anti as well. Noteworthy is that the method appears to be insensitive to the nature of the carbamate group and tolerates a range of functionality in the R^1 and R^2 substituents in amino ketones **1a**−**h**. This generality suggests that many other functional groups should be tolerated as well.

Table 2. Reduction of Carbamate-Protected Amino Ketones 1a−h with LiAl(O-*t*-Bu)$_3$H in Ethanol at −78 °C

compd	yield (%) crude (recrystallized)	anti/syn
1a	97 (88)	>95:5
1b	96 (80)	>95:5
1c	97 (89)	>95:5
1d	97 (82)	>95:5
1e	97 (82)	>95:5
1f	95 (81)	>95:5
1g	96 (82)	>95:5
1h	99 (85)	>95:5

Scheme 5



Felkin−Anh Stereocontrol. We had used the trityl protecting group on nitrogen as an easily manipulated, bulky protecting group to achieve Felkin−Anh control of an amino ketone reduction during a sphingosine synthesis.[12] In that work, sodium borohydride was used as the reductant. We since had reason to question the stereochemical assignment[16] and hoped to establish a general protocol for achieving Felkin−Anh control in amino ketone reductions.

To that end, a series of four *N*-trityl amino ketones **9a**,**c**,**g**,**h** were prepared from amino acids **5** in good overall yields by the same general sequence used for carbamate-protected examples (Scheme 5). The bulky trityl group causes a significant increase in reaction time for conversion of the tritylated amino acid to the β-keto ester (3 h at −40 °C) compared to carbamate protecting groups (30 min at −78 °C).

Amino ketone **9c** was reduced with sodium borohydride in ethanol and with L-Selectride. The *syn*-amino alcohol **10c** was the major product (Felkin−Anh control), but only poor stereoselectivities of 1.5:1 and 1.6:1, respectively, were obtained. These reductions required 12 h at room temperature to be completed, which shows the rate-retarding effect of the trityl group. We reasoned that increased stereoselection would require a reducing agent that was bulkier and more reactive. We therefore examined LiAlH(O-*t*-Bu)$_3$ in THF (Table 3). High yields and

(16) NMR and optical rotation were used to determine the reduction diastereoselection. These methods may not be reliable for the accurate determination of diastereomeric excess in sphingosines. Li, C. Brigham Young University, personal communication.

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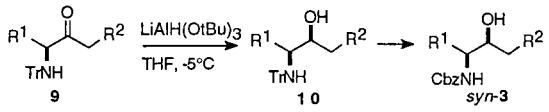
Table 3. Reductions of Amino Ketones 9a,c,g,h in THF at −5 °C



substrate	time (h)	yield[a] (%)	syn/anti[b]
9a	48	88 (76)	>18:1[c]
9c	8	91[d]	4:1
9g	60		mixture[e]
9h	60	90 (71)	12:1

[a] Yields are crude yields of the *syn*-**3**/*anti*-**3** mixture. Yields in parentheses are purified yields of *syn*-**3**. [b] The syn/anti ratio was determined by NMR of the crude product mixture. [c] Only one isomer was detected by NMR. [d] The mixture was not purified. [e] Products of both ketone and ester reduction were obtained.

good to excellent syn-selectivity was found for the reductions of **9a**,**c**,**h** with this reagent. The reaction time was lengthened considerably. Glutamate derivative **9g** gave a mixture of products. It appeared that reduction of the ester and some cyclization accompanied reduction of the ketone. This mixture was not pursued further.

The isomer distributions were determined by exchanging the trityl protecting group for a carbamate protecting group (Boc or Cbz) and cyclizing to the corresponding oxazolidinone. In these cases, the methine coupling constants indicated the *anti*-oxazolidinone was the major isomer; thus, amino alcohols **10a**,**c**,**h** were predominantly the syn stereoisomers. A simple recrystallization gave pure carbamate-protected *syn*-amino alcohols.

Discussion

Prior to this study, the reagent and conditions needed to produce *anti*-amino alcohols from carbamate-protected amino ketones were largely determined by trial and error. While chelation control is needed to ensure the proper stereochemical outcome, the literature provides no general guidelines on how to achieve it.

Several rationales have been proposed to account for the anti diastereoselectivity seen in the reductions of α-amino ketones. It is generally accepted that there must be some type of conformational control to keep the amino group coplanar (or nearly so) with the ketone (Figure 1a).[8a] It has been proposed that the aluminum or boron atom of the aluminum hydride or borohydride reductant is the control element in binding to both the amino nitrogen and the ketone oxygen.[17] Other workers have argued that the sodium or lithium (or other metal) counterion provides the conformational control by chelation to the nitrogen and oxygen.[18] Still others have suggested that hydrogen bonding between the NH proton of primary or secondary amines or the amide NH proton of N-acylated amines and the ketone oxygen provides the needed conformational bias.[19]

The data from Table 1 provide additional insight into the origins of diastereoselectivity in these reductions. In the first place, it appears that the metal ions examined do not bind sufficiently strongly to carbamate-protected amino ketones to produce chelation control. Identical stereoselection is found for borohydride regardless of the counterion. It is expected that lithium or zinc ions would provide increased conformational control and hence higher diastereoselectivity. This is not the case; thus, the counterion does not appear to be involved in the diastereoselection.

It also appears that hydrogen bonding between the NH proton and the carbonyl oxygen plays a minor role in controlling the conformation. In THF or ether where intramolecular H-bonding should be the greatest, only low diastereoselectivity is found. Much higher diastereoselectivity is found in ethanol, a solvent that should minimize intramolecular H-bonding by competetive H-bonding with the solvent. Moreover, in a given solvent at a given temperature the conformational control exerted by hydrogen bonding should remain relatively constant and should be relatively independent of the hydride donor. Consequently, one should at least observe the same major isomer irrespective of the reducing agent. Comparison of entries 6 and 8 of Table 1 shows this is not the case. These results cast serious doubt on intramolecular H-bonding to explain the diastereoselectivity.

There is also some earlier evidence suggesting that hydrogen bonding is not an important stereocontrol element in amino ketone reductions. Reductions of tertiary amino ketones generally give syn products because of Felkin−Ahn control by bulky tertiary amines. Reduction of protonated tertiary ammonium ketones by sodium borohydride in ethanol also gives the syn product. The ammonium ion NH proton should provide even greater hydrogen-bonding capability than an amide NH proton but fails to influence the diastereoselection significantly.[17b]

Our results suggest that chelation of the amino ketone to boron or aluminum is the key to stereochemical control. Both borohydride and aluminum hydride reagents can have multiple alkoxide ligands which can be exchanged to produce a chelated intermediate. The exchange/disproportionation of alkoxy ligands on borohydrides is rapid[20] and occurs by a dissociation/recombination mechanism.[21] Alkoxy ligands on aluminum hydrides also exchange rapidly[22] and by a dissociative process.[22,23] Thus it is possible for chelate formation to occur by dissociative ligand exchange for both boron and aluminum.

Boron[24] and aluminum[25] form only weak complexes with neutral species but much stronger complexes with anionic species. It is thus reasonable to postulate that the N-carbamate-protected amino ketone must be converted to an anion prior to complexation. The most likely anion is the deprotonated carbamate, which could bind through nitrogen to the boron or aluminum.[26] Chelate formation to the carbonyl oxygen follows (Scheme 6). This process is directly analogous to chelate formation to aluminum(III) in hydroxy ketones.[27] It is also related to the chelation of amino acids to aluminum.[25] Reduction of the chelated amino ketone occurs stereoselectivly to give the amino alcohol product. Although Scheme 6 is shown for borohydrides, a similar process is likely for aluminum hydride reagents with alkoxy ligands.

The results also show that the use of an alcohol as solvent increases the diastereoselectivity significantly for borohydride reducing agents. It is possible that small

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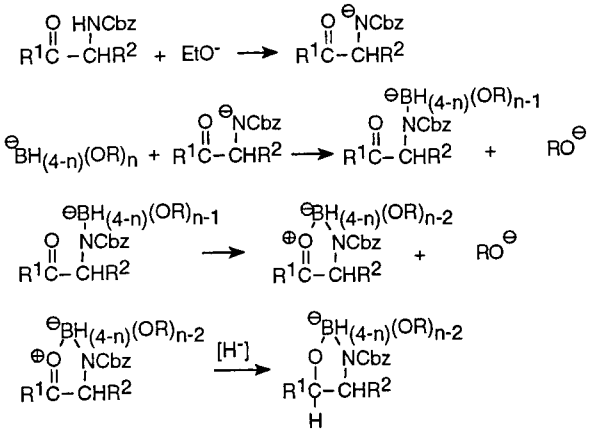
Scheme 6



amounts of alcohol are converted to ethoxide by reaction with borohydride and the ethoxide deprotonates the carbamate to initiate complex formation and ultimately chelate formation.

The choice of ethanol as a solvent for $LiAlH(OtBu)_3$ is unprecedented but effective. The ability of a hydroxylic solvent to increase diastereoselectivity was clear from the results with borohydride reductants. When it was found that no stereocontrol was observed for $LiAlH(O\text{-}t\text{-}Bu)_3$ in THF, it was logical to try an alcohol solvent. There was a good chance that the experiment would fail, since experience suggested that reaction with the solvent to produce hydrogen would be much faster than the reduction of the ketone, particularly at −78 °C. To our surprise and delight, $LiAlH(O\text{-}t\text{-}Bu)_3$ dissolves in ethanol at −78 °C without evidence of hydrogen evolution. Warming to −50 °C causes gas evolution to begin. Nevertheless, $LiAlH(O\text{-}t\text{-}Bu)_3$ is sufficiently reactive at −78 °C to reduce ketones, so that high yields of *anti*-amino alcohols are obtained. The reaction appears to be broadly applicable and thus provides a predictable and general means to achieve chelation control. This reagent−solvent combination might be useful in other situations where ligand exchange is needed prior to reduction.

This study also highlights the mixed blessing of the trityl protecting group as a stereocontrol element. To achieve Felkin−Anh stereocontrol, a large nitrogen protecting group is needed. Certainly the trityl group is large. Moreover, it is much more easily attached and removed than the *N*,*N*-dibenzyl protecting group, which is presently the only alternative for enforcing Felkin−Anh control. However, while the stereoselectivities shown in Table 3 are usable, they are not as high as expected on the basis of the bulk of the trityl group. In addition, the reaction rate dropped significantly. This lowered reactivity led to complications in the reduction of **9g** where reduction of the ester group competes with ketone reduction to produce product mixtures.

To understand the origins of these trends, we carried out a conformational search on amino ketones **9a**,**c**,**g**,**h**.[28] The conformers were ranked by energy and their structures compared. From these structures, it is clear that the trityl group not only blocks one face of the carbonyl group itself, but it also plays a dominant role in determining conformational preferences of the other groups in the molecule by forcing them toward the opposite face of the carbonyl group. In essence, it causes *both* faces of the carbonyl group to become sterically congested.

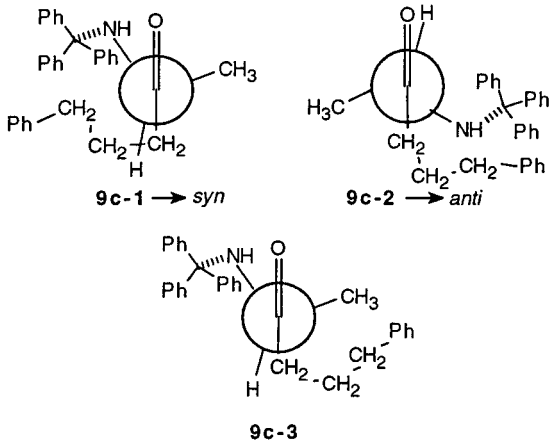


Figure 2.

In the normal depiction of the Felkin−Anh transition state, the large group is pictured as blocking one face of the carbonyl group, whereas the opposite face is pictured as relatively unencumbered. Stereoselection derives from the difference between the incoming nucleophile eclipsing a proton or the R^1group at the α−position (Figure 1b). The size difference between R^1 and the proton is the basis for the stereoselectivity. In addition, the size of R^2 does not exert a large influence on the stereoselectivity when the α′-carbon is unbranched.[29] It is usually assumed that R^1or R^2 (when the α-carbon is unbranched) can rotate out of the way of the approaching nucleophile.

In N-tritylated amino ketones, a much different picture emerges. In **9c**, which gives only modest stereoselectivity, only two low energy conformers **9c-1** and **9c-2** have accessible faces of the carbonyl group (Figure 2). The rest (e.g., **9c-3**) have the 3-phenylpropyl substituent wrapping away from the tritylamino group and blocking the opposite face of the ketone. Thus, **9c-1** and **9c-2** appear to be the reactive conformers and are similar in energy. As a result of their similarity, there are only small differences in the nucleophilic approach to the carbonyl face, and stereoselectivity is modest. However, since there are many other low energy conformers of the type **9c-3** (which are all within 1−2 kcal of **9c-1**), the concentration of the reactive conformers is low and the rate of reduction is relatively slow as well (8 h at −5 °C)

When the R^1 group is larger than methyl, steric congestion about the carbonyl group increases dramatically. For example, conformational analysis of **9a** shows that the lowest energy conformers (>10 within ∼1 kcal of each other) all have the tritylamino group forming a dihedral angle of about 47° with the carbonyl group (instead of 90°). One phenyl ring of the trityl group is parallel to the plane of the carbonyl and completely hides that face of the carbonyl group. In addition, the low lying

(28) Calculations were carried out using the Titan suite of programs from Wavefunction. Conformational searching used the MMFF (Merck) force field to identify the conformational minima which were then ranked according to their energies. The equilibrium geometries of the lowest several conformers were calculated by ab initio calculations at the 6-31G* level. It was found that the confomational energy *differences* between the low energy conformers were very similar for the two methods. A solvation model was not included in the calculations.

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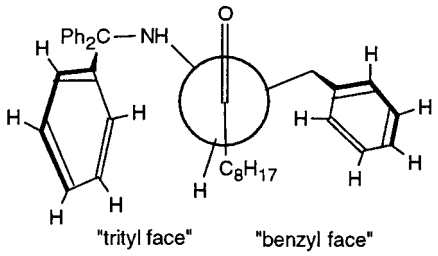

Figure 3.

conformers all have the α-benzyl group curving away from the trityl such that its phenyl ring partially blocks the opposite face of the carbonyl group. The octyl ketone substituent is largely in the extended conformation. This is depicted schematically in Figure 3. Thus, the "trityl face" of the carbonyl group is more sterically blocked than the "benzyl face", and reduction occurs from the "benzyl face" preferentially to give the syn isomer.

Even though the preferred product is syn, this is not typical Felkin−Anh stereoselection because the stereoselectivity does not arise from differences between two reactive conformers. Instead, the low-lying conformers are all similar. Stereoselection results from steric differences between the two faces of the carbonyl group. In the case of **9a**, the benzyl face is only partially blocked, and thus, there is good facial selectivity. However both faces are sterically congested to some degree and this results in a much slower rate of reduction (48 h).

Similar factors are operative in **9g** and **9h**. The low energy conformers are similar with respect to the dihedral angle between the tritylamino group and the carbonyl group. Thus, the choice is not between different Felkin−Anh conformers; rather, the choice is between the two faces of the carbonyl group. The trityl group provides steric congestion on one face and the α-substituent bends away from the trityl group and thus provides steric congestion to the other face. It is the relative steric crowding on each face which determines the stereoselectivity. Moreover, as both faces are fairly hindered, the overall reduction rate decreases significantly.

This analysis suggests that the trityl protecting group is actually too large for efficient Felkin−Anh control. Its large size restricts rotation about the bond between the carbonyl group and the α-carbon and restricts the conformational mobility of the remaining ketone substituents in the molecule forcing them to bend toward the carbonyl group. This results in steric crowding at both faces of the carbonyl group. Stereoselection is dependent on the relative crowding at each face, which may account for the unexpectedly low stereoselectivities found for **9h** and the competitive ester reduction in **9g** (Table 3).

We are evaluating other nitrogen protecting groups smaller than trityl that may give Felkin−Anh stereoselection, but with higher reactivity and stereoselectivity. In the meantime, the *N*-trityl protecting group can be used as an effective stereocontrol element to give *syn*-amino alcohols in high yields and with very good stereocontrol for substrates without other reducible groups. Much longer reaction times are required, however.

Experimental Section

Infrared spectra were taken as a KBr pellets, as solution in $CHCl_3$, or as neat liquids. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively. Unless otherwise indicated, $CDCl_3$ was used as the NMR solvent. Thin-layer chromatography was performed on silica gel 60 F_{254} plates from EM reagents and visualized by UV irradiation or by spraying $Ce(SO_4)_2$ solution and heating on a hot plate. Flash chromatography was performed using silica gel 60 (230−400 mesh). Tetrahydrofuran was distilled from benzophenone ketyl. Other solvents were HPLC grade and were used without further purification. Starting materials were purchased from Acros, Aldrich, or Novabiochem and used as received. Elemental analyses were performed by MHW Laboratories. N-Tritylated amino aicds were prepared from amino acids by a procedure modified slightly from the standard preparation.[30]

General Procedure for the Preparation Carbamic N-Protected α-Amino-*β*-keto Allyl Esters (2).[12a,13b] CDI (carbonyl-1,1′-diimidazole) (1.70 g, 10.5 mmol) was added at room temperature to a stirred solution of a carbamic N-protected α-amino acid (10 mmol) in dry THF (20 mL) under a N_2 atmosphere. The resulting solution was stirred for 1 h at the same temperature and used for the next step without further purification. Meanwhile, a solution of lithium enolate of allyl acetate was made from BuLi (2.5 M, 14 mL, 35 mmol, 3 equiv are required), diisopropylamine (4.9 mL, 35 mmol), and allyl acetate (3.8 mL, 35 mmol). The above imidazole solution was added dropwise to the pale yellow solution of lithium enolate at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred for 30 min and then quenched at −78 °C with 10% citric acid and extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with saturated bicarbonate (2 × 50 mL) and brine (50 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide the crude product, which could be purified by chromatography or recrystallization: yield (90−94%).

4(*S*)-Benzyloxycarbonylamino-3-oxo-5-phenylpentanoic Acid Allyl Ester (2a). Compound **2a** (3.50 g, 92%) was obtained as a colorless solid after purification on silica gel eluting with 90:10 hexanes/EtOAc. Pure material could be obtained by recrystallization from hexanes: mp 57 °C; $[\alpha]^{21}_D$ +30.4 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 1755, 1730, 1701, 1536, cm^{-1}; ^{1}H NMR δ 3.00 (dd, 1H, *J* = 7.4, 14.2 Hz), 3.15 (dd, 1H, *J* = 6.1, 14.1 Hz), 3.48 (d, 1H, *J* = 17.2 Hz), 3.52 (d, 1H, *J* = 16.2 Hz), 4.60 (d, 2H, *J* = 5.8 Hz), 4.62 (m, 1H), 5.04 (s, 2H), 5.27 (m, 3H), 5.87 (m, 1H), 7.12−7.32 (m, 10H); ^{13}C NMR δ 37.1, 46.9, 60.9, 66.1, 67.2, 118.9, 127.2, 128.1, 128.2, 128.6, 128.8, 129.3, 135.8, 155.8, 166.4, 201.2.

4(*S*)-*tert*-Butoxycarbonylamino-3-oxo-5-phenylpentanoic Acid Allyl Ester (2b). Compound **2b** (3.10 g, 89%) was obtained as a colorless oil after purification on silica gel eluting with 90:10 hexanes/EtOAc: $[\alpha]^{21}_D$ +10.5 (*c* 1.00, CH_2Cl_2); FTIR (neat) 1751, 1715, 1691, 1526 cm^{-1}; ^{1}H NMR δ 1.40 (s, 9H), 3.15 (dd, 1H, *J* = 5.9, 14.2 Hz), 2.99 (dd, 1H, *J* = 7.4, 14.2 Hz), 3.48 (d, 1H, *J* = 16.2 Hz), 3.54 (d, 1H, *J* = 16.1 Hz), 4.54 (m, 1H), 4.61 (d, 2H, *J* = 5.6 Hz), 5.00 (d, 1H, *J* = 7.0 Hz), 5.28 (m, 2H), 5.90 (m, 1H), 7.15−7.28 (m, 5H); ^{13}C NMR δ 28.3, 37.1, 46.8, 60.6, 66.1, 80.4, 118.9, 127.1, 128.8, 129.4, 131.7, 136.2, 155.3, 166.6, 201.7.

4(*S*)-*tert*-Butoxycarbonylamino-3-oxopentanoic Acid Allyl Ester (2c). Compound **2c** (2.43 g, 90%) as a colorless oil after purification on silica gel eluting with 90:10 hexanes/EtOAc: $[\alpha]^{21}_D$ −12.0 (*c* 1.00, CH_2Cl_2); FTIR (neat) 1755, 1735, 1701, 1526 cm^{-1}; ^{1}H NMR δ 1.36 (d, 3H, *J* = 7.2 Hz), 1.45 (s, 1H), 3.59 (d, 1H, *J* = 16.7 Hz), 3.63 (d, 1H, *J* = 17.3 Hz), 4.37 (m, 1H), 4.64 (d, 1H, *J* = 5.8 Hz), 5.29 (m, 3H), 5.90 (m, 1H); ^{13}C NMR δ 16.9, 28.3, 45.7, 55.4, 66.0, 80.0, 118.5, 131.5, 155.2, 166.6, 202.3.

8-Benzyloxycarbonylamino-4(*S*)-*tert*-butoxycarbonylamino-3-oxooctanoic Acid Allyl Ester (2d). Compound **2c** (4.06 g, 88%) was obtained as a colorless oil after purification on silica gel eluting with 85:15 hexanes/EtOAc: $[\alpha]^{21}_D$ −3.6 (*c* 1.00, CH_2Cl_2); FTIR (neat) 1756, 1716, 1526 cm^{-1}; ^{1}H NMR δ 1.42 (broad, 12H), 1.48 (m, 2H), 1.79 (m, 1H), 3.17 (m, 2H), 3.57 (s, 2H), 4.29 (m, 1H), 4.62 (d, 1H, *J* = 5.8 Hz), 5.09 (broad, 3H), 5.27 (m, 3H), 7.19−7.34 (m, 5H); ^{13}C NMR δ 22.3, 28.3, 29.4, 30.3, 40.4, 46.0, 59.6, 66.0, 66.6, 80.1, 118.8, 128.0, 128.5, 131.6, 136.7, 156.6, 166.6.

4(*S*)-Benzyloxycarbonylamino-6-methyl-3-oxoheptanoic Acid Allyl Ester (2e). Compound **2e** (3.10 g, 89%) was obtained as a colorless oil after purification on silica gel eluting with 90:10 hexanes/EtOAc: $[\alpha]^{22}_D$ −3.6 (*c* 1.00, CH_2Cl_2); FTIR (neat) 1761, 1731, 1531 cm^{-1}; ^1H NMR δ 0.89 (d, 3H, J = 5.8 Hz), 0.92 (d, 3H, J = 5.1 Hz), 1.42 (m, 1H), 1.60 (m, 2H), 3.53 (d, 1H, J = 16.2 Hz), 3.57 (d, 1H, J = 15.7 Hz), 4.40 (m, 1H), 4.57 (d, 2H, J = 5.7 Hz), 5.06 (s, 2H), 5.25 (m, 2H), 5.36 (d, 1H, J = 8.5 Hz), 5.84 (m, 1H), 7.18−7.34 (m, 5H); ^{13}C NMR δ 21.5, 23.2, 24.8, 39.8, 46.2, 58.7, 66.0, 67.1, 118.8, 128.0, 128.2, 128.5, 131.5, 136.2, 156.1, 166.5, 202.1.

4(*S*)-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-oxo-5-phenylpentanoic Acid Allyl Ester (2f). Compound **2f** (4.28 g, 91%) was obtained as a colorless solid after purification on silica gel eluting with 85:15 hexanes/EtOAc. Pure material could be obtained by recrystallization from EtOH: mp 103 °C; $[\alpha]^{20}_D$ −2.0 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 1745, 1720, 1686, 1541 cm^{-1}; ^1H NMR δ 3.00 (dd, 1H, J = 6.1, 14.1 Hz), 3.16 (dd, 1H, J = 7.2, 14.1 Hz), 3.45 (d, 1H, J = 16.1 Hz), 3.49 (d, 1H, J = 16.2 Hz), 4.15 (t, 1H, J = 6.6 Hz), 4.38 (d, 1H, J = 2.6 Hz), 4.41 (d, 1H, J = 3.4 Hz), 4.60 (d, 2H, J = 5.6 Hz), 4.65 (m, 1H), 5.26 (m, 3H), 5.88 (m, 1H), 7.12−7.77 (m, 13H); ^{13}C NMR δ 36.9, 46.8, 47.3, 60.9, 66.1, 67.0, 118.9, 120.0, 125.0, 127.2, 128.8, 129.3, 131.5, 135.9, 141.4, 143.7, 155.8, 166.3, 201.1.

4(*S*)-*tert*-Butoxycarbonylamino-3-oxoheptanedioic Acid 1-Allyl Ester 7-Methyl Ester (2g). Compound **2g** (3.00 g, 87%) was obtained as a colorless oil after purification on silica gel eluting with 90:10 hexanes/EtOAc: $[\alpha]^{20}_D$ −8.4 (*c* 1.00, CH_2Cl_2); FTIR (neat) 1751, 1726 cm^{-1}; ^1H NMR δ 1.44 (s, 9H), 1.86 (m, 1H), 2.18 (s, 1H), 2.41 (m, 2H), 3.65 (d, 2H, J = 10.1 Hz), 3.67 (s, 3H), 4.40 (m, 1H), 4.64 (d, 2H, J = 5.8 Hz), 5.29 (m, 3H), 5.90 (m, 1H); ^{13}C NMR δ 25.9, 28.3, 29.8, 46.1, 51.9, 59.1, 66.1, 80.4, 119.0, 131.6, 155.5, 166.6, 173.4, 201.5.

5-Benzyloxy-4*S*-*tert*-butoxycarbonylamino-3-oxopentanoic Acid Allyl Ester (2h). Compound **2h** (3.56 g, 87%) was obtained as a colorless oil after purification on silica gel eluting with 85:15 hexanes/EtOAc: $[\alpha]^{21}_D$ +6.1 (*c* 1.00, CH_2Cl_2); FTIR (neat) 1755, 1735, 1516 cm^{-1}; ^1H NMR δ 3.58 (s, 2H), 3.66 (dd, 1H, 4.1, 9.9 Hz), 3.91 (dd, 1H, 3.1, 9.6 Hz), 4.47 (s, 2H), 4.57 (d, 2H, J = 5.9 Hz), 4.58 (m, 1H), 5.10 (s, 2H), 5.25 (m, 2H), 5.83 (m, 2H); ^{13}C NMR δ 46.6, 60.3, 66.0, 67.2, 69.2, 73.5, 118.8, 127.7, 128.1, 128.2, 128.5, 131.6, 136.2, 137.1, 155.9, 166.2, 200.0.

General Procedure for the Preparation of the Carbamic N-Protected α-Amino Ketones (1). Method A. With an Alkyl Triflate as an Alkylating Agent. A solution of carbamic N-protected α-amino-*β*-keto allyl ester **2** (2.6 mmol) in dry THF (10 mL) was added dropwise to a stirred suspension of NaH (125 mg of 60% in oil, 3.1 mmol, 1.2 equiv) in dry THF (10 mL) at −20 °C under nitrogen. The mixture was stirred for 20 min. Then the alkyl triflate (2.86 mmol, 1.1 equiv) in 5 mL of THF was added. The resulting solution was allowed to warm to room temperature and stirred for 3 h. After being quenched with 10 mL 10% citric acid, the reaction mixture was then extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with saturated bicarbonate and brine, dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide a pale yellow oil. Without further purification, this oil was dissolved in THF (20 mL) and added dropwise to a stirred solution of palladium acetate (14.3 mg, 0.064 mmol), PPh_3 (33.8 mg, 0.13 mmol), formic acid (0.2 mL, 5 mmol), and Et_3N (0.9 mL, 6.5 mmol) in dry THF at room temperature under nitrogen. The mixture was stirred overnight. After the filtrate was concentrated, the residue was chromatographed on SiO_2 with hexanes−ethyl acetate (90:10) to afford the amino ketone in 65−78% yield.

Method B. With an Alkyl Bromide as an Alkylating Agent. A solution of carbamic N-protected α-amino-*β*-keto allyl ester 2 (2.60 mmol) in dry THF (10 mL) was added dropwise to a stirred suspension of NaH (125 mg of 60% in oil, 3.10 mmol, 1.2 equiv) in dry THF (10 mL) at −20 °C under nitrogen. The mixture was stirred for 20 min, and then the alkyl bromide (2.60 mmol) in 5 mL of THF and 10% NaI were added. The resulting solution was allowed to warm to room temperature and refluxed for 2 h in order to complete the reaction. After being quenched with 10 mL of 10% citric acid, the reaction mixture was extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with saturated bicarbonate and brine, dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide a pale yellow oil. Without further purification, this oil was dissolved in THF (20 mL) and added dropwise to a stirred solution of palladium acetate (14.3 mg, 0.064 mmol), PPh_3 (33.8 mg, 0.13 mmol), formic acid (0.2 mL, 5 mmol), and Et_3N (0.9 mL, 6.5 mmol) in dry THF at room temperature under nitrogen. The mixture was stirred overnight. After the filtrate was concentrated, the residue was chromatographed on SiO_2 with hexanes−ethyl acetate (90:10) to afford the ketone in 71−76% yield.

(1*S*-Benzyl-2-oxodecyl)carbamic acid benzyl ester (1a) was prepared by method A. Alkylation of 993 mg (2.60 mmol) of **2a** with 1.85 g (2.86 mmol, 1.1 equiv) of heptyl triflate afforded 770 mg (75%) of **1a** as a colorless solid after purification on silica gel eluting with 90:10 hexanes/EtOAc. Pure material could be obtained by recrystallization from hexanes: mp 52 °C; $[\alpha]^{21}_D$ +4.5 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 1716, 1692 cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 6.5 Hz), 1.23 (m, 10H), 1.49 (m, 2H), 2.36 (m, 2H), 3.03 (t, 2H, J = 6.8 Hz), 4.61 (q, 1H, J = 7.2 Hz), 5.07 (s, 2H), 5.42 (d, 1H, J = 7.9 Hz), 7.22−7.31 (m, 10H); ^{13}C NMR δ 14.1, 22.7, 23.3, 29.1, 29.3, 31.8, 38.0, 40.9, 60.4, 66.9, 76.4, 127.1, 128.1, 128.2, 128.6, 128.7, 129.3, 135.9, 155.7, 208.8. Anal. Calcd for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.54. Found: C, 75.95; H, 8.35; N, 3.64.

(1*S*-Benzyl-2-oxo-4-phenylbutyl)carbamic acid 2,2-dimethylpropyl ester (1b) was prepared by method B. Alkylation of 903 mg (2.60 mmol) of **2b** with 489 mg (2.86 mmol, 1.1 equiv) of benzyl bromide afforded 703 mg (76%) of **1b** as a colorless solid after purification on silica gel eluting with 90:10 hexanes/EtOAc. Pure material could be obtained by recrystallization from hexanes: mp 84 °C; $[\alpha]^{23}_D$ +3.4 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 1688, 1516 cm^{-1}; ^1H NMR δ 1.40 (s, 9H), 2.69 (m, 2H), 2.84 (m, 2H), 2.96 (t, 2H, J = 6.5 Hz), 4.51 (m, 1H), 5.08 (d, 1H, J = 7.3 Hz), 7.09−7.27 (m, 10H); ^{13}C NMR δ 28.3, 29.4, 37.9, 42.5, 60.2, 80.0, 126.3, 127.0, 128.4, 128.6, 128.7, 129.3, 136.2, 140.8, 155.2, 208.3. Anal. Calcd for $C_{22}H_{27}NO_3$: C, 75.76; H, 7.70; N, 3.96. Found: C, 75.44; H, 7.70; N, 3.99.

(1*S*-1-Methyl-2-oxo-5-phenylpentyl)carbamic acid 2,2-dimethylpropyl ester (1c) was prepared by method A. Alkylation of 705 mg (2.60 mmol) of **2c** with 727 mg (2.86 mmol, 1.1 equiv) of phenethyl triflate afforded 553 mg (73%) of **1c** as a colorless solid after purification on silica gel eluting with 90:10 hexanes/EtOAc. Pure material could be obtained by recrystallization from hexanes: mp 46 °C; $[\alpha]^{23}_D$ +1.1 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 3332, 2984, 1710, 1684, 1528, 1452, 1368, 1252 cm^{-1}; ^1H NMR δ 1.28 (d, 3H, J = 7.1 Hz), 1.43 (s, 9H), 1.94 (q, 2H, J = 7.4 Hz), 2.50 (m, 2H), 2.62 (t, 2H, J = 7.2 Hz), 4.27 (q, 1H, J = 7.1 Hz), 5.25 (broad, 1H), 7.14−7.27 (m, 5H); ^{13}C NMR δ 17.9, 25.0, 28.4, 35.1, 38.3, 55.2, 79.8, 126.1, 126.4, 141.4, 155.2, 209.5. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.22; H, 8.53; N, 4.88.

(5*S*-*tert*-Butoxycarbonylamino-6-oxo-8-phenyloctyl)-carbamic acid benzyl ester (1d) was prepared by method B. Alkylation of 1000 mg (2.10 mmol) of **2d** with 360 mg (2.1 mmol) of benzyl bromide afforded 718 mg (73%) of **1d** as a colorless solid after purification on silica gel eluting with 80:20 hexanes/EtOAc: mp 76 °C; $[\alpha]^{20}_D$ +13.4 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 1726, 1696, cm^{-1}; ^1H NMR δ 1.42 (broad, 13H), 1.72 (m, 2H), 2.85 (m, 4H), 3.13 (m, 2H), 4.25 (m, 1H), 4.80 (broad, 1H), 5.09 (s, 2H), 5.22 (d, 1H, J = 7.3 Hz), 7.19−7.34 (m, 10H); ^{13}C NMR δ 22.1, 28.3, 29.5, 30.9, 40.5, 41.2, 59.2, 66.6, 79.8, 126.2, 128.0, 128.3, 128.5, 136.7, 140.8, 155.6, 156.5, 208.4. Anal. Calcd for $C_{27}H_{36}N_2O_5$: C, 69.21; H, 7.74; N, 5.98. Found: C, 69.44; H, 7.60; N, 5.99.

(1*S*-Isobutyl-2-oxo-5-phenylpentyl-carbamic acid benzyl ester (1e) was prepared by method A. Alkylation of 972 mg (2.80 mmol) of **2e** with 711 mg (2.80 mmol) of phenethyl triflate afforded 700 mg (68%) of **1e** as a colorless oil after purification on silica gel eluting with 90:10 hexanes/EtOAc. $[\alpha]^{22}_D$ +9.2 (*c* 1.00, CH_2Cl_2); FTIR ($CHCl_3$) 1721 cm^{-1}; ^1H NMR δ 0.89 (d, 3H, J = 6.6 Hz), 0.95 (d, 3H, J = 6.2 Hz), 1.34 (m,

2H), 1.67 (m, 1H), 1.92 (m, 2H), 2.51 (m, 2H), 2.61 (t, 2H, J = 7.4 Hz), 4.38 (m, 1H), 5.09 (s, 2H), 5.28 (d, 1H, J = 8.0 Hz), 7.18−7.34 (m, 10H); ^{13}C NMR δ 21.7, 23.3, 24.9, 35.0, 38.9, 40.7, 58.3, 66.9, 126.0, 128.1, 128.5, 129.0, 141.4, 156.1, 209.6.

(1*S*-Benzyl-2-oxodecyl)carbamic acid 9*H*-fluoren-9-ylmethyl ester (1f) was prepared by method A. Alkylation of 1173 mg (2.50 mmol) of **2f** with 620 g (2.50 mmol) of heptyl triflate afforded 785 mg (65%) of **1f** as a colorless solid after purification on silica gel eluting with 85:15 hexanes/EtOAc. Pure material could be obtained by recrystallization from hexanes: mp 104 °C; $[\alpha]^{20}_D$ +35.0 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 1725, 1691 cm^{-1}; ^{1}H NMR δ 0.88 (t, 3H, J = 6.6 Hz), 1.23 (broad, 10H), 1.53 (m, 2H), 2.37 (m, 2H), 3.04 (m, 2H), 4.18 (m, 1H), 4.38 (m, 2H), 4.62 (m, 1H), 5.43 (d, 1H, J = 7.6 Hz), 7.12−7.77 (m, 13H); ^{13}C NMR δ 14.1, 22.7, 23.4, 29.1, 29.3, 31.7, 38.0, 40.9, 47.3, 60.4, 67.0, 120.1, 125.1, 127.1, 127.9, 128.7, 129.3, 136.0, 141.4, 143.9, 155.7, 208.8. Anal. Calcd for $C_{32}H_{37}NO_3$: C, 79.47; H, 7.71; N, 2.90. Found: C, 79.60; H, 7.63; N, 3.04.

4*S*-*tert*-Butoxycarbonylamino-9-methyl-5-oxodec-8-enoic acid methyl ester (1g) was prepared by method B. Alkylation of 1063 mg (3.1 mmol) of **2g** with 462 mg (3.1 mmol) of prenyl bromide afforded 720 mg (71%) of **1g** as a colorless oil after purification on silica gel eluting with 90:10 hexanes/EtOAc: $[\alpha]^{20}_D$ +29.7 (*c* 1.00, CH_2Cl_2); FTIR ($CHCl_3$) 3435, 3026, 2986, 2927, 1741, 1710, 1506, 1451, 1381, 1182 cm^{-1}; ^{1}H NMR δ 1.43 (s, 9H), 1.61 (s, 3H), 1.67 (s, 3H), 1.73 (m, 2H), 2.29 (m, 2H), 2.31 (m, 2H), 2.54 (m, 2H), 3.68 (s, 3H), 4.35 (m, 1H), 5.04 (t, 1H, J = 7.1 Hz), 5.25 (d, 1H, J = 8.0 Hz); ^{13}C NMR δ 17.7, 22.3, 25.6, 26.8, 28.3, 29.7, 39.8, 51.7, 58.6, 79.9, 122.4, 133.1, 155.5, 173.3, 208.5.

(1*S*-Benzyloxymethyl-2-oxodecyl)carbamic acid benzyl ester (1h) was prepared by method A. Alkylation of 1070 mg (2.60 mmol) of **2h** with 1.85 g (2.86 mmol, 1.1 equiv) of heptyl triflate afforded 818 mg (74%) of **1h** as a colorless oil after purification on silica gel eluting with 90:10 hexanes/EtOAc: $[\alpha]^{21}_D$ +5.01 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 1785, 1730, 1666 cm^{-1}; ^{1}H NMR δ 0.88 (t, 3H, J = 6.0 Hz), 1.24 (m, 10H), 1.53 (m, 2H), 2.45 (m, 2H), 3.69 (dd, 1H, 3.3, 9.8 Hz), 3.90 (dd, 1H, 4.0, 9.9 Hz), 4.45 (m, 3H), 5.10 (s, 2H), 5.80 (d, 1H, J = 7.9 Hz), 7.25−7.31 (m, 10H); ^{13}C NMR δ 14.1, 22.7, 23.4, 29.2, 29.5, 29.7, 31.8, 39.8, 60.3, 67.0, 69.7, 73.3, 127.4, 127.6, 128.1, 128.2, 128.3, 128.5, 128.6, 137.4, 156.0, 207.1. These data are consistent with literature data.[12b]

General Procedure for the Preparation of the Carbamic N-Protected *anti*-α-Amino Alcohols (3a−h). Method A. LiAlH(O-*t*-Bu)$_3$ (127 mg, 0.50 mmol) was dissolved in EtOH (3 mL) at −78 °C under nitrogen, and then a solution of the ketone **1a**−**h** (0.25 mmol) in EtOH (4 mL) was added dropwise. After 2 h, the solution was quenched with 10% citric acid (2 mL), extracted with ethyl acetate (2 × 50 mL), washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to provide a white solid that could be recrystallized from an appropriate solvent.

Method B. $NaBH_4$ (19 mg, 0.50 mmol) was dissolved in EtOH (3 mL) at −78 °C under nitrogen, and a solution of the ketone **1a** (0.25 mmol) in EtOH (4 mL) was added dropwise. After 2 h, the solution was quenched with 10% citric acid (2 mL), extracted with ethyl acetate (2 × 50 mL), washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to provide a white solid, which could be recrystallized from an appropriate solvent. Other borohydride reagents were used in place of sodium borohydride to generate the data in Table 1.

Method C. A Selectride solution in THF (1 M, 0.5 mL) was cooled at −78 °C under nitrogen, and then a solution of the ketone **1a** (100 mg, 0.25 mmol) in THF was added dropwise. After 2 h, the solution was quenched with 10% citric acid (2 mL), extracted with ethyl acetate (2 × 50 mL), washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), passed through a short pad of silica gel, and concentrated to provide the crude product, which coul be recrystallized from an appropriate solvent.

(1*S*-Benzyl-2*R*-hydroxydecyl)carbamic Acid Benzyl Ester (*anti*-3a). Reduction of **1a** (100 mg, 0.25 mmol) using method A afforded 98 mg (98%) of crude *anti*-**3a** as a colorless solid that could be purified by recrystallization from hexanes with 90% recovery: mp 142 °C; $[\alpha]^{23}_D$ −21.4 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 3324, 1692 cm^{-1}; ^{1}H NMR δ 0.86 (t, 3H, J = 6.5 Hz), 1.27 (m, 11H), 1.49 (m, 3H), 2.00 (s, 1H), 2.75 (dd, 1H, J = 4.6, 14.1 Hz), 2.92 (dd, 1H, J = 9.4, 14.1 Hz), 3.70 (m, 1H), 3.90 (m, 1H), 4.85 (d, 1H, J = 6.2 Hz), 5.00 (s, 1H), 7.20−7.31 (m, 10H); ^{13}C NMR δ 14.4, 23.0, 26.4, 29.6, 29.9, 30.0, 32.2, 33.9, 35.7, 57.4, 67.1, 74.3, 126.8, 128.3, 128.8, 128.9, 129.6, 136.8, 138.4, 156.9. Anal. Calcd for $C_{25}H_{35}NO_3$: C, 75.53; H, 8.87; N, 3.52. Found: C, 75.65; H, 8.80; N, 3.58.

(1*S*-Benzyl-2*R*-hydroxy-4-phenylbutyl)carbamic Acid 2,2-Dimethylpropyl Ester (*anti*-3b). Reduction of **1b** (90 mg, 0.25 mmol) using method A afforded 84 (93%) mg of crude *anti*-**3b** as a colorless solid that could be purified by recrystallization from ethyl acetate with 86% recovery: mp 163 °C; $[\alpha]^{23}_D$ −1.4 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 3360, 1688 cm^{-1}; ^{1}H NMR δ 1.35 (s, 9H), 1.83 (m, 2H), 2.68 (m, 2H), 2.91 (m, 2H), 3.72 (m, 1H), 3.84 (m, 1H), 4.60 (d, 1H, J = 8.1 Hz), 7.15−7.30 (m, 10H); ^{13}C NMR δ 28.3, 32.4, 35.2, 36.9, 57.1, 73.5, 79.8, 126.0, 126.4, 128.6, 129.3, 138.1, 142.0, 156.4. Anal. Calcd for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94. Found: C, 74.19; H, 8.03; N, 3.99.

(2*R*-Hydroxy-1*S*-methyl-5-phenylpentyl)carbamic Acid 2,2-Dimethylpropyl Ester (*anti*-3c). Reduction of **1c** (73 mg, 0.25 mmol) using method A afforded 71 mg (97%) of crude *anti*-**3c** as a colorless solid that could be purified by recrystallization from hexanes with 92% recovery: mp 79 °C; $[\alpha]^{23}_D$ −8.2 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 3356, 1684 cm^{-1}; ^{1}H NMR δ 1.05 (d, 3H, J = 6.9 Hz), 1.43 (s, 9H), 1.64 (m, 2H), 1.82 (m, 2H), 2.25 (s, 1H), 2.64 (t, 2H, J = 7.6 Hz), 3.64 (m, 2H), 4.77 (broad, 1H), 7.15−7.27 (m, 5H); ^{13}C NMR δ 14.5, 27.8, 28.5, 32.8, 35.8, 50.8, 74.4, 79.6, 125.8, 128.4, 128.5, 142.2, 155.9. Anal. Calcd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.28; N, 4.77. Found: C, 69.72; H, 9.15; N, 4.86.

(5*S*-*tert*-Butoxycarbonylamino-6*R*-hydroxy-8-phenyloctyl)carbamic Acid Benzyl Ester (*anti*-3d). Reduction of **1d** (130 mg, 0.28 mmol) using method A afforded 127 mg (97%) of crude *anti*-**3d** as a colorless solid that could be purified by recrystallization from EtOH with 85% recovery: mp 113 °C; $[\alpha]^{20}_D$ −15.8 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 3366, 1696 cm^{-1}; ^{1}H NMR δ 1.42 (broad, 15H), 1.70 (m, 2H), 2.48 (broad, 1H), 2.69 (m, 2H), 2.84 (m, 1H), 3.16 (m, 2H), 3.61 (m, 2H), 4.76 (broad, 1H), 4.89 (broad, 1H), 5.09 (s, 2H), 7.21−7.34 (m, 10H); ^{13}C NMR δ 23.1, 28.4, 29.1, 29.8, 32.4, 35.0, 40.7, 55.4, 66.7, 74.1, 79.7, 118.6, 125.9, 127.6, 128.0, 128.4, 136.6, 142.0, 156.6.

(2*R*-Hydroxy-1*S*-isobutyl-5-phenylpentyl)carbamic Acid Benzyl Ester (*anti*-3e). Reduction of **1e** (200 mg, 0.56 mmol) using method A afforded 159 mg (97%) of crude *anti*-**3e** as a colorless solid that could be purified by recrystallization from hexanes with 87% recovery: mp 108 °C; $[\alpha]^{20}_D$ −35.6 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 3325, 1696 cm^{-1}; ^{1}H NMR δ 0.90 (d, 6H, J = 6.4 Hz), 1.23 (m, 2H), 1.40 (m, 2H), 1.61 (m, 2H), 1.84 (m, 1H), 2.25 (broad, 1H), 2.63 (t, 2H, J = 7.7 Hz), 3.67 (m, 2H), 4.86 (d, 1H, J = 8.2 Hz), 5.08 (s, 2H), 7.14−7.33 (m, 10H); ^{13}C NMR δ 21.6, 23.7, 24.7, 27.8, 32.5, 35.8, 38.1, 54.0, 66.9, 74.6, 125.8, 128.1, 128,4, 128.5, 136.5, 142.2, 156.8. Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.61; H, 8.35; N, 3.89.

(1*S*-Benzyl-2*R*-hydroxydecyl)carbamic Acid 9*H*-Fluoren-9-ylmethyl Ester (*anti*-3f). Reduction of **1f** (100 mg, 0.20 mmol) using method A afforded 95 mg (95%) of crude *anti*-**3f** as a colorless solid that could be purified by recrystallization from EtOH with 85% recovery: mp 172 °C; $[\alpha]^{20}_D$ −20.8 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 3335, 1696 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.23 (t, 3H, J = 6.2 Hz), 1.62 (broad, 12H), 1.85 (m, 2H), 2.90 (m, 2H), 2.96 (m 1H), 3.42 (dd, 1H, J = 13.5, 2.3 Hz), 3.83 (m, 1H), 4.51 (m, 3H), 5.09 (d, 1H, J = 6.3 Hz), 7.55−8.30 (m, 13H); ^{13}C NMR (DMSO-d_6) δ 14.1, 22.2, 25.7, 29.3, 31.4, 32.1, 33.5, 35.9, 57.0, 57.6, 73.1, 73.5, 109.9, 120.2, 121.6, 125.9, 127.5, 128.2, 129.2, 135.5, 140.5, 157.1. Anal. Calcd for $C_{32}H_{39}NO_3$: C, 79.14; H, 8.09; N, 2.88. Found: C, 78.97; H, 7.95; N, 2.92.

4*S*-*tert*-Butoxycarbonylamino-5*R*-hydroxy-9-methyldec-8-enoic Acid Methyl Ester (*anti*-3g). Reduction of **1g** (100 mg, 0.30 mmol) using method A afforded 96 mg (96%) of crude

anti-**3g** as a colorless solid that could be purified by recrystallization from EtOH with 85% recovery: mp 68 °C; $[\alpha]^{20}_D$ −17.7 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 3366, 1756, 1691 cm^{-1}; ^1H NMR δ 1.44 (broad, 11H), 1.62 (s, 3H), 1.69 (s, 3H), 1.94 (m, 2H), 2.19 (m, 2H), 2.41 (t, 2H, J = 7.3 Hz), 3.60 (m, 1H), 3.68 (s, 3H), 4.80 (d, 1H, J = 8.8 Hz), 5.12 (t, 1H, J = 7.1 Hz); ^{13}C NMR δ 17.8, 24.6, 25.7, 28.4, 30.9, 33.5, 51.7, 54.9, 74.4, 79.6, 82.0, 123.8, 132.6, 156.2, 174.1.

(1*S*-Benzyloxymethyl-2*R*-hydroxydecyl)carbamic Acid Benzyl Ester (*anti*-3h). Reduction of (106 mg, 0.25 mmol) of **1h** using method A afforded 106 mg (99%) of crude *anti*-**3h** as a colorless solid that could be purified by recrystallization from ethyl aceate with 86% recovery: mp 142 °C; $[\alpha]^{23}_D$ −21.4 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 3335, 1700 cm^{-1}; ^1H NMR δ 0.88 (t, 3H, J = 6.8 Hz), 1.26 (broad, 12H), 1.44 (m, 2H), 2.70 (d, 1H, J = 8.4 Hz), 3.67 (m, 3H), 3.79 (m, 1H), 4.46 (d, 1H, 11.1 Hz), 4.52 (d, 1H, 12.3 Hz), 5.10 (s, 2H), 5.63 (d, 1H, J = 8.7 Hz), 7.25−7.35 (m, 10H); ^{13}C NMR δ 14.2, 22.7, 26.0, 29.3, 29.6, 29.7, 31.9, 34.7, 54.1, 66.9, 70.1, 73.7, 73.9, 127,9, 128.1, 128.2, 128.3, 128.4, 128.6, 136.6, 137.4, 156.2. Anal. Calcd for $C_{26}H_{37}NO_4$: C, 73.03; H, 8.72; N, 3.28. Found: C, 72.89; H, 8.59; N, 3.27.

General Procedure for the Preparation of Trityl N-Protected α-Amino Acid (6). This procedure is slightly modified from the literature method.[30] Chlorotrimethylsilane (1.27 mL, 10.0 mmol) was added at room temperature to a stirred suspension of an L-amino acid (10.0 mmol) in 18 mL of $CHCl_3$/MeCN (5:1). The reaction mixture was refluxed for 2 h and then cooled to 0 °C. Dropwise addition of triethylamine (2.79 mL, 20.0 mmol) was followed by a solution of trityl chloride (2.79 g, 10.0 mmol) in chloroform (10 mL). The resulting mixture was stirred for 1 h, and then methanol (2 mL) was added. After concentration, the pale yellow residue was partitioned between diethyl ether and water. The aqueous layer was extracted twice with diethyl ether (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give the crude *N*-trityl α-amino acid, which was used for the next step without further purification.

General Procedure for the Preparation of Trityl *N*-Tritylacylimidazoles (7) from *N*-Tritylamino Acids. CDI (carbonyl-1,1′-diimidazole) (1.70 g, 10.5 mmol) was added to a stirred solution of a trityl N-protected α-amino acid (10 mmol) in dry THF (20 mL) under a N_2 atmosphere at room temperature. The resulting solution was stirred overnight. After evaporation of the solvent, the residue was partitioned between water and methylene chloride. The aqueous layer was extracted twice with methylene chloride. The combined organic layers were dried ($MgSO_4$) and concentrated to give the crude *N*-tritylacylimidazole, which was used for the next step without further purification.

General Procedure for the Preparation of *N*-Trityl *γ*-Amino-*β*-keto Ester (8). A solution of lithium enolate of allyl acetate was made from BuLi (2.5 M, 8 mL, 20 mmol), diisopropylamine (2.8 mL, 20 mmol), and allyl acetate (2.2 mL, 20 mmol). The crude imidazole was dissolved in THF (20 mL) and added dropwise to this pale yellow solution of lithium enolate at −40 °C under N_2 atmosphere. The resulting mixture was stirred for 3 h at the same temperature and then quenched with water. The reaction mixture was extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with water and brine (50 mL), dried ($MgSO_4$), and concentrated to provide the crude product, which could be purified by chromatography. Overall yield 74−78%.

3-Oxo-5-phenyl-4*S*-(tritylamino)pentanoic Acid Allyl Ester (8a). Phenylalanine (1.65 g, 10 mmol) was treated with Me_3SiCl (1.086 g, 10 mmol), trityl chloride (2.78 g, 10 mmol), and Et_3N (2.79 mL, 20.0 mmol) to give the *N*-tritylamino acid. After workup (general procedure), the crude product was sequentially converted with CDI (2.79 mL, 20.0 mmol) and then with 2 equiv of lithium enolate of allyl acetate to afford 3.6 g (76% overall yield) of **8a** as a colorless solid after purification on silica gel eluting with 95:5 hexanes/EtOAc. Pure material could be obtained by recrystallization from hexanes with 84% recovery: mp 109 °C; $[\alpha]^{21}_D$ +47.2 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 1730, 1606 cm^{-1}; ^1H NMR δ 2.49 (d, 1H, J = 16.3 Hz), 2.61 (d, 1H, J = 16.3 Hz), 2.87 (t, 2H, J = 6.6 Hz), 3.05 (broad, 1H), 3.71 (m, 1H), 4.48 (d, 2H, J = 5.7 Hz), 5.21 (m, 2H), 5.79 (m, 1H), 7.10−7.40 (m, 20H); ^{13}C NMR δ 40.6, 46.8, 63.9, 65.4, 71.2, 117.4, 126.6, 126.9, 128.0, 128.9, 130.0, 131.7, 136.9, 146.0, 166.4, 205.6. Anal. Calcd for $C_{33}H_{31}NO_3$: C, 80.95; H, 6.38; N, 2.86. Found: C, 81.03; H, 6.15; N, 2.95.These data are consistent with the literature data for **8a**.[12e]

3-Oxo-4*S*-(tritylamino)pentanoic Acid Allyl Ester (8c). Alanine (0.89 g, 10 mmol) was treated with Me_3SiCl (1.086 g, 10 mmol), trityl chloride (2.78 g, 10 mmol), and Et_3N (2.79 mL, 20.0 mmol) to give *N*-tritylalanine. After workup (general procedure), the crude product was sequentially converted with CDI (2.79 mL, 20.0 mmol) and then with 2 equiv of lithium enolate of allyl acetate to afford 3.05 g (74% overall yield) of **8c** as a colorless oil after purification on silica gel eluting with 90:10 hexanes/EtOAc: $[\alpha]^{21}_D$ +29.3 (*c* 1.00, CH_2Cl_2); FTIR (neat) 1760, 1725, 1661, 1606 cm^{-1}; ^1H NMR δ 1.25 (d, 3H, J = 7 Hz), 2.66 (d, 1H, J = 16 Hz), 2.86 (broad, 1H), 2.96 (d, 1H, J = 16 Hz), 3.52 (q, 1H, J = 7.1 Hz), 4.51 (d, 2H, J = 4.4 Hz), 5.22 (m, 2H), 5.80 (m, 1H), 7.21−7.47 (m, 15H); ^{13}C NMR δ 20.1, 45.8, 58.3, 65.7, 71.5, 118.6, 128.0, 128.9, 131.8, 146.3, 206.3. These data match the literature data for **8c**.[13e]

3-Oxo-4*S*-(tritylamino)heptanedioic Acid 1-Allyl Ester 7-Methyl Ester (8g). Glu(OMe)OH (1.61 g, 10 mmol) was treated with Me_3SiCl (1.086 g, 10 mmol), trityl chloride (2.78 g, 10 mmol), and Et_3N (2.79 mL, 20.0 mmol) to give the *N*-trityl glutamate. After workup (general procedure), the crude product was sequentially converted with CDI (2.79 mL, 20.0 mmol) and then with 2 equiv of lithium enolate of allyl acetate to afford 3.7 g (78% overall yield) of **8g** as a colorless oil after purification on silica gel eluting with 90:10 hexanes/EtOAc: $[\alpha]^{21}_D$ +34.5 (*c* 1.00, CH_2Cl_2); FTIR (neat) 1755, 1730, 1661 cm^{-1}; ^1H NMR δ 1.88 (m, 1H), 2.25 (m, 2H), 2.62 (d, 1H, J = 16.1 Hz), 2.64 (m, 1H) 3.05 (d, 1H, J = 16.1 Hz), 3.09 (d, 1H, J = 9.2 Hz), 3.67 (s, 3H), 4.49 (d, 2H, J = 5.7 Hz), 5.23 (m, 2H), 5.80 (m, 1H), 7.20−7.40 (m, 15H); ^{13}C NMR δ 27.8, 28.9, 46.0, 51.6, 60.9, 65.7, 71.4, 118.5, 126.5, 126.7, 127.8, 128.0, 128.8, 131.6, 146.0, 166.1, 173.5, 204.3.

5-Benzyloxy-3-oxo-4*S*-(tritylamino)pentanoic Acid Allyl Ester (8h). Ser(OBn)OH (1.95 g, 10 mmol) was treated with Me_3SiCl (1.086 g, 10 mmol), trityl chloride (2.78 g, 10 mmol), and Et_3N (2.79 mL, 20.0 mmol) to give the *N*-tritylserine derivative. After workup (general procedure), the crude product was sequentially converted with CDI (2.79 mL, 20.0 mmol) and then with 2 equiv of lithium enolate of allyl acetate to afford 3.8 g (74% overall yield) of **8h** as a colorless solid after purification on silica gel eluting with 95:5 hexanes/EtOAc. Pure material could be obtained by recrystallization from hexanes: mp 125 °C; $[\alpha]^{21}_D$ +34.5 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 1755, 1730 cm^{-1}; ^1H NMR δ 2.75 (d, 1H, J = 16.6 Hz), 3.11 (t, 1H, J = 8.3 Hz), 3.20 (broad, 1H), 3.43 (d, 1H, J = 16.6 Hz), 3.70 (m, 2H), 4.38 (s, 2H), 4.52 (d, 2H, J = 5.6 Hz), 5.23 (m, 2H), 5.82 (m, 1H), 7.10−7.40 (m, 20H); ^{13}C NMR δ 47.9, 61.9, 65.5, 71.2, 72.6, 73.6, 118.3, 126.8, 127.7, 128.1, 128.9, 132.0, 137.6, 146.1, 166.6, 206.2. Anal. Calcd for $C_{34}H_{33}NO_4$: C, 78.59; H, 6.40; N, 2.70. Found: C, 78.37; H, 6.29; N, 2.73.

General Procedure for the Preparation of Trityl N-Protected α-Amino Ketones (9). Method A. With an Alkyl Triflate as an Alkylating Agent. A solution of allyl *N*-trityl *γ*-amino-*β*-keto ester **8** (5.0 mmol) in dry THF (20 mL) was added dropwise under nitrogen to a stirred suspension of NaH (240 mg of 60% in oil, 6.0 mmol, 1.2 equiv) in dry THF (10 mL) at −10 °C and allowed to warm to 0 °C. The mixture was stirred for 20 min, and then the alkyl triflate (5.5 mmol, 1.1 equiv) in 5 mL of THF was added. The resulting solution was allowed to warm to room temperature and stirred for 3 h. After being quenched with 10 mL of water, the reaction mixture was then extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with water and

(30) Barlos, K.; Papaioannou, D.; Theodoropoulos, D. *J. Org. Chem.* **1982**, *47*, 1324.

brine, dried ($MgSO_4$), and concentrated to provide a pale yellow oil. Without further purification, this oil was dissolved in THF (20 mL) and added dropwise to a stirred solution of tetrakis-(triphenylphosphine)palladium (578 mg, 0.5 mmol) and morpholine (4.3 mL, 50 mmol) in dry THF under nitrogen at room temperature. The mixture was stirred overnight. After the filtrate was concentrated the residue was chromatographed on SiO_2 with hexanes−ethyl acetate (95:5) to afford the amino ketone in 70−76% yield.

Method B. With an Alkyl Bromide as a Alkylating Agent. A solution of allyl *N*-trityl γ-amino-β-keto ester **8** (5.0 mmol) in dry THF (10 mL) was added dropwise to a stirred suspension of NaH (240 mg of 60% in oil, 6.0 mmol, 1.2 equiv) in dry THF (10 mL) at −20 °C under nitrogen. The mixture was stirred for 20 min, and then the alkyl bromide (5.5 mmol) in 5 mL of THF and 10% NaI were added. The resulting solution was allowed to warm to room temperature and refluxed for 2 h in order to complete the reaction. After the reaction was quenched with 10 mL of water, the mixture was extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with water and brine, dried ($MgSO_4$), and concentrated to provide a pale yellow oil. Without further purification, this oil was dissolved in THF (20 mL) and added dropwise to a stirred solution of tetrakis(triphenylphosphine)-palladium (578 mg, 0.5 mmol) and morpholine (4.3 mL, 50 mmol) in dry THF under nitrogen at room temperature. The mixture was stirred overnight. After the filtrate was concentrated, the residue was chromatographed on SiO_2 with hexanes−ethyl acetate (95:5) to afford the amino ketone in 68% yield.

1-Phenyl-2*S*-(tritylamino)undecan-3-one (9a). Alkylation of **8a** (2.44 g, 5 mmol) with heptyl triflate (1.36 g, 5.50 mmol, 1.1 equiv) using method A afforded 1.83 g (73%) of **9a** as a colorless oil after purification on silica gel eluting with 95:5 hexanes/EtOAc: $[\alpha]^{21}_D$ +58.0 (*c* 1.00, CH_2Cl_2); FTIR (neat) 1730, 1606 cm^{-1}; ^1H NMR δ 0.87 (t, 3H, J = 7 Hz), 1.19 (m, 12H), 1.48 (m, 2H), 2.79 (dd, 1H, J = 7.5, 13.3 Hz), 2.94 (dd, 1H, J = 6.1, 13.3 Hz), 3.16 (broad, 1H), 3.58 (t, 1H, J = 6.6 Hz), 7.15−7.42 (m, 20H); ^{13}C NMR δ 14.2, 22.5, 28.9, 29.2, 31.9, 41.7, 42.2, 63.6, 71.3, 126.5, 127.9, 128.5, 129.3, 129.8, 138.0, 146.7, 213.7.

6-Phenyl-2*S*-(tritylamino)hexan-3-one (9c). Alkylation of **8a** (2.00 g, 5.00 mmol) with 1.40 g (5.5 mmol, 1.1 equiv) of phenethyl triflate using method A afforded 1.60 g (76%) of **9c** as a colorless solid after purification on silica gel eluting with 95:5 hexanes/EtOAc. Pure material could be obtained by recrystallization from hexanes with 86% recovery: mp 113 °C; $[\alpha]^{21}_D$ +42.6 (*c* 1.00, CH_2Cl_2); FTIR (KBr) 1725, 1606 cm^{-1}; ^1H NMR δ 1.20 (d, 3H, J = 6.9 Hz), 1.46 (m, 3H), 2.02 (m, 1H), 2.35 (m, 2H), 3.21 (broad, 1H), 3.38 (m, 1H), 7.15−7.47 (m, 20H); ^{13}C NMR δ 20.8, 24.4, 35.0, 38.8, 57.5, 71.4, 125.9, 126.4, 127.8, 128.1, 128.3, 128.5, 129.0, 141.7, 146.6, 213.3. Anal. Calcd for $C_{31}H_{31}NO$: C, 85.87; H, 7.21; N, 3.23. Found: C, 85.91; H, 7.04; N, 3.23.

9-Methyl-5-oxo-4*S*-(tritylamino)dec-8-enoic Acid Methyl Ester (9g). Alkylation of **8g** (2.42 g, 5 mmol) of with 820 mg (5.50 mmol, 1.1 equiv) of prenyl bromide using method B afforded 1.59 g (68%) of **9g** as a colorless oil after purification on silica gel eluting with 95:5 hexanes/EtOAc: $[\alpha]^{21}_D$ +47.9 (*c* 1.00, CH_2Cl_2); FTIR (neat) 1750, 1716, 1611 cm^{-1}; ^1H NMR δ 1.52 (s, 3H), 1.55 (m, 1H), 1.60 (s, 3H), 1.81 (m, 2H), 2.15 (m, 2H), 2.58 (m, 2H), 3.19 (broad, 1H), 3.54 (m, 1H), 3.67 (s, 3H), 4.82 (t, 1H), 7.15−7.42 (m, 15H); ^{13}C NMR δ 17.6, 21.8, 25.6, 28.4, 29.0, 40.0, 51.6, 60.1, 71.5, 122.9, 126.5, 127.5, 127.9, 129.0, 132.3, 146.4, 173.8, 211.5.

1-Benzyloxy-2*S*-(tritylamino)undecan-3-one (9h). Alkylation of **8h** (2.67 g, 5 mmol) of with 1.36 g (5.50 mmol, 1.1 equiv) of heptyl triflate using method A afforded 1.90 g (70%) of **9h** as a colorless oil after purification on silica gel eluting with 95:5 hexanes/EtOAc: $[\alpha]^{21}_D$ +13.1 (*c* 1.00, CH_2Cl_2); FTIR (neat) 1727, 1611 cm^{-1}; ^1H NMR δ 0.87 (t, 3H, J = 6.9 Hz), 1.19 (m, 12H), 1.48 (m, 1H), 2.22 (m, 1H), 3.30 (m, 2H), 3.56 (dd, 1H, J = 4.6, 8.9 Hz), 3.77 (dd, 1H, J = 4.6, 7.6 Hz), 4.42 (s, 2H), 7.15−7.42 (m, 20H); ^{13}C NMR δ 14.1, 22.7, 29.0, 29.2, 31.8, 41.9, 61.3, 71.1, 73.3, 126.5, 127.8, 128.4, 129.0, 138.0, 146.5, 213.4.

General Procedure for the Preparation the Carbamic N-Protected *syn*-α-Amino Alcohols. $LiAlH(O\text{-}t\text{-}Bu)_3$ 127 mg (0.50 mmol) was dissolved in THF (4 mL) at −5 °C under nitrogen, and then a solution of the *N*-tritylamino ketone (0.25 mmol) in THF (3 mL) was added dropwise. The reaction was monitored by TLC (95:5 hexanes/EtOAc). After 8−60 h, the solution was quenched with water (2 mL), extracted with ethyl acetate (2 × 50 mL), washed with H_2O (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated to provide a pale yellow oil. Without further purification, the crude product was used to exchange the trityl with the appropriate carbamic protecting group. Treatment with aqueous HCl in acetone removed the trityl group and treatment of the residue with a carbamoylating agent and triethylamine gave the carbamate. The final product was then purified by chromatography.

(1*S*-Benzyl-2*S*-hydroxydecyl)carbamic Acid Benzyl Ester (*syn*-3a). Reduction of **9a** (100 mg, 0.20 mmol) afforded 69.5 mg (88%) of *syn*-**3a** as a colorless solid that could be purified by recrystallization from hexanes with 87% recovery: mp 141 °C; $[\alpha]^{23}_D$ −17.5 (*c* 1.00, Cl_2Cl_2); FTIR (KBr) 3328, 1692 cm^{-1}; ^1H NMR δ 0.86 (t, 3H, J = 6.5 Hz), 1.21 (m, 12H), 1.42 (m, 2H), 2.00 (s, 1H), 2.89 (d, 2H, J = 7.3 Hz), 3.56 (m, 1H), 3.90 (q, 1H, J = 7.7 Hz), 5.06 (s, 1H), 5.17 (d, 1H, J = 9.0 Hz), 7.20−7.31 (m, 10H); ^{13}C NMR δ 14.5, 23.1, 26.1, 29.6, 29.8, 29.9, 32.2, 34.9, 39.2, 56.4, 67.1, 71.9, 126,8, 128.3, 128.4, 128.9, 129.6, 137.0, 138.7, 156.9. Anal. Calcd for $C_{25}H_{35}NO_3$: C, 75.53; H, 8.87; N, 3.52. Found: C, 75.65; H, 8.80; N, 3.58.

(2*S*-Hydroxy-1*S*-methyl-5-phenylpentyl)carbamic Acid 2,2-Dimethylpropyl Ester (*syn*-3c). Reduction of **9c** 108 mg (0.25 mmol) afforded 67 mg (91%) of a mixture of both diastereomers *syn*-**3c** and *anti*-**3c** (4:1). The mixture was not purified further. Spectral characterization of the major isomer was obtained from the mixture: FTIR (KBr) 3365,1691 cm^{-1}; ^1H NMR δ 1.13 (d, 3H, J = 6.7 Hz), 1.43 (broad, 9H), 1.48 (m, 2H), 1.75 (m, 2H), 2.25 (s, 1H), 2.62 (m, 2H), 3.46 (m, 1H), 3.62 (m, 1H), 4.81 (d, 1H, J = 8.9 Hz), 7.15−7.27 (m, 5H); ^{13}C NMR δ 18.3, 27.4, 28.5, 33.9, 35.9, 50.5, 74.9, 79.4, 125.8, 128.4, 128.5, 142.3, 156.3. Anal. Calcd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.28; N, 4.77. Found: C, 69.42; H, 9.12; N, 4.76.

(1*S*-Benzyloxymethyl-2*S*-hydroxydecyl)carbamic Acid Benzyl Ester (*syn*-3h). Reduction of 133 mg (0.25 mmol) of **9h** afforded 96 mg (90%) of a mixture of *syn*-**3h** and *anti*-**3h** (12:1). Spectral characterization of the major isomer was obtained from the mixture. The major isomer *syn*-**3h** could be purified by recrystallization from ethyl acetate, 85%: FTIR (KBr) 3335, 1700 cm^{-1}; ^1H NMR δ 0.87 (t, 3H, J = 6.9 Hz), 1.25 (broad, 12H), 1.36 (m, 2H), 3.00 (broad, 1H), 3.71 (m, 3H), 3.89 (1H), 4.49 (s, 2H), 5.10 (s, 2H), 5.50 (d, 1H, J = 8.5 Hz), 7.22−7.34 (m, 10H); ^{13}C NMR δ 14.1, 22.7, 25.7, 26.0, 29.3, 29.5, 29.6, 31.9, 33.9, 53.6, 66.8, 70.0, 72.6, 73.7, 127,7, 127.8, 128.0, 128.2, 128.3, 128.6, 136.6, 137.5, 156.6. Anal. Calcd for $C_{26}H_{37}NO_4$: C, 73.03; H, 8.72; N, 3.28. Found: C, 73.20; H, 8.66; N, 3.28.

General Procedure for the Cyclization of the Carbamic N-Protected α-Amino Alcohols 3 to the Corresponding Oxazolidinones 4. Method A. Aqueous sodium hydroxide (8 M, 0.5 mL) was added to a stirred solution of the protected α-amino alcohol **3** (0.25 mmol) in 5 mL of methanol−THF (1:2). The mixture was stirred for 3−5 h at room temperature and then evaporated. The residue was dissolved in 10 mL of water and extracted twice with 10 mL of ethyl acetate, washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated to provide the crude product, which could be recrystallized from an appropriate solvent.

Method B. A solution of the protected α-amino alcohol 0.25 mmol in 2 mL of DMF was added to a suspension of NaH (18 mg, 0.75 mmol) in 3 mL of DMF. The mixture was stirred for 3−5 h at room temperature. The mixture was dissolved in 10 mL of water, extracted twice with 10 mL of ethyl acetate, washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated to provide the crude product, which could be purified by chromatography or by recrystallization from an appropriate solvent.

4*S*-Benzyl-5*R*-octyloxazolidin-2-one (*syn*-4a) was prepared by method A from 100 mg (0.25 mmol) of alcohol *anti*-**3a** to give *syn*-**4a** as a colorless oil that was purified by chromatography to afford 64 mg (89%): ^{1}H NMR δ 0.89 (t, 3H, J = 6.8 Hz), 1.28 (m, 11H), 1.60 (m, 2H), 1.83 (m, 1H), 2.66 (dd, 1H, J = 3.9, 13.5 Hz), 2.86 (dd, 1H, J = 10.1, 14.3 Hz), 3.94 (m, 1H), 4.65 (m, 1H), 4.90 (s, 1H), 7.17−7.34 (m, 5H); ^{13}C NMR δ 14.1, 22.7, 26.0, 29.0, 29.2, 29.4, 29.7, 32.0, 36.3, 56.9, 80.0, 127.2, 129.0, 129.1, 136.8, 158.7. Irradiation of the proton signals at 2.75 and 1.83 ppm causes the methine signals at 4.66 and 3.96 ppm, respectively, to collapse to doublets with J = 7.3 Hz.

4*S*-Benzyl-5*R*-phenethyloxazolidin-2-one (*syn*-4b) was prepared by method B from 90 mg (0.25 mmol) of alcohol *anti*-**3b** to give *syn*-**4b** as a colorless solid, which was purified by chromatography to afford 60 mg (86%): ^{1}H NMR δ 1.95 (m, 1H), 2.17 (m, 1H), 2.72 (m, 4H), 3.92 (m, 1H), 4.62 (m, 1H), 5.10 (s, 1H), 7.14−7.32 (m, 10H); ^{13}C NMR δ 31.4, 32.1, 36.4, 56.7, 78.8, 126.3, 127.2, 129.0, 129.1, 136.1, 140.6, 158.5. Irradiation of the proton signals at 2.21 and 1.83 ppm causes the methine signals at 4.65 and 3.94 ppm, respectively, to collapse to doublets with J = 7.4 Hz.

4*S*-Methyl-5*R*-(3-phenylpropyl)oxazolidin-2-one (*syn*-4c) was prepared by method B from 73 mg (0.25 mmol) of alcohol *anti*-**3c** to give *syn*-**4c** as a colorless solid, which was purified by chromatography to afford 50 mg (90%). A crystal was prepared in toluene for X-ray analysis: ^{1}H NMR δ 1.11 (d, 3H, J = 6.4 Hz), 1.74 (m, 4H), 2.67 (m, 2H), 3.87 (m, 1H), 4.55 (m, 1H), 6.22 (s, 1H), 7.15−7.32 (m, 5H); ^{13}C NMR δ 15.9, 27.6, 28.7, 35.5, 51.1, 80.0, 126.0, 128.4, 141.7, 159.7. Irradiation of the proton signals at 1.65 and 1.11 ppm causes the methine signals at 4.56 and 3.87 ppm, respectively, to collapse to doublets with J = 7.6 Hz.

4*S*-Benzyloxymethyl-5*R*-octyl-oxazolidin-2-one (*syn*-4h) was prepared by method A from 107 mg (0.25 mmol) of alcohol *anti*-**3h** to give *syn*-**4a** as a colorless oil that was purified by chromatography to afford 74 mg (86%): ^{1}H NMR δ 0.88 (t, 3H, J = 6.6 Hz), 1.26 (broad, 11H), 1.56 (m, 3H), 3.49 (m, 2H), 3.91 (m, 1H), 4.52 (s, 2H), 4.60 (m, 1H), 5.64 (s, 1H), 7.26−7.36 (m, 5H); ^{13}C NMR δ 14.1, 22.7, 26.1, 29.1, 29.2, 29.3, 29.4, 31.9, 55.0, 68.8, 73.8, 79.9, 127.8, 128.1, 128.7, 137.4, 159.1. Irradiation of the proton signals at 1.56 and 3.47 ppm causes the methine signals at 4.60 and 3.92 ppm, respectively, to collapse to doublets with J = 7.3 Hz.

4*S*-Bezyl-5*S*-octyl-oxazolidin-2-one (*anti*-4a) was prepared by method A from 100 mg (0.25 mmol) of alcohol *syn*-**3a** to give *anti*-**4a** as a colorless oil that was purified by chromatography to afford 60 mg (83%): ^{1}H NMR δ 0.88 (t, 3H, J = 6.8 Hz), 1.23 (m, 11H), 1.50 (m, 2H), 1.65 (m, 1H), 2.83 (d, 2H, J = 7.0 Hz), 3.64 (q, 1H, J = 6.5 Hz), 4.28 (m, 1H), 5.45 (s, 1H), 7.15−7.34 (m, 5H); ^{13}C NMR δ 14.1, 22.8, 26.0, 29.0, 29.2, 29.4, 29.7, 31.8, 36.3, 57.0, 80.1, 127.2, 129.0, 129.2, 136.8, 158.7. Irradiation of the proton signals at 1.59 and 2.83 ppm causes the methine signals at 4.28 and 3.68 ppm, respectively, to collapse to doublets with J = 5.5 Hz.

4*S*-Methyl-5*S*-(3-phenylpropyl)oxazolidin-2-one (*anti*-4c) was prepared by method B from 73 mg (0.25 mmol) of the alcohol mixture of *anti*-**3c** and *syn*-**3c** (4:1) to give a mixture of *syn*-**4c** and *anti*-**4c** in the same ratio as a colorless oil, which was purified by chromatography to afford 51 mg (94%). Spectral characterization of the major isomer was obtained from the mixture: ^{1}H NMR δ 1.22 (d, 3H, J = 6.2 Hz), 1.71 (m, 4H), 2.66 (m, 2H), 3.52 (m, 1H), 4.07 (m, 1H), 6.58 (broad, 1H), 7.15−7.32 (m, 5H); ^{13}C NMR δ 20.58, 25.6, 33.6, 35.4, 53.7, 84.1, 126.0, 128.4, 141.6, 159.5. Irradiation of the proton signals at 1.73 and 1.22 ppm causes the methine signals at 4.07 and 3.65 ppm, respectively, to collapse to doublets with J = 6.4 Hz.

4*S*-Benzyloxymethyl-5*S*-octyloxazolidin-2-one (*anti*-4h) was prepared by method A from 107 mg (0.25 mmol) of an alcohol mixture *syn*-**3h** and *anti*-**3h** (12:1) with NaOH in THF−methanol to give a mixture of *syn*-**4h** and *anti*-**4h** in the same ratio as a colorless oil that was purified by chromatography to afford 73 mg (91%). Spectral characterization of the major isomer was obtained from the mixture: ^{1}H NMR δ 0.88 (t, 3H, J = 6.8 Hz), 1.26 (broad, 11H), 1.65 (m, 3H), 3.44 (m, 2H), 3.61 (m, 1H), 4.25 (m, 1H), 4.53 (s, 2H), 6.1 (s, 1H), 7.26−7.36 (m, 5H); ^{13}C NMR δ 14.1, 22.7, 24.6, 29.2, 29.3, 29.4, 31.9, 34.9, 57.3, 71.9, 73.6, 79.6, 127.7, 128.0, 128.6, 137.4, 159.1. Irradiation of the proton signals at 3.44 and 1.67 ppm causes the methine signals at 3.65 and 4.25 ppm, respectively, to collapse to doublets with J = 5.2 Hz.

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Supporting Information Available: ^{13}C NMR spectra of **1e**,**g**, *anti*-**3d**, *anti*-**3g**, **8g**, and **9a**,**g**,**h,** complete X-ray data for **4c**, and space-filling structures of **9a**,**g**,**h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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