Alkylation Studies of *N*-Protected-5-substituted Morpholin-3-ones. A Stereoselective Approach to Novel Methylene Ether Dipeptide Isosteres

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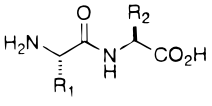
Received March 13, 1996[⊗]

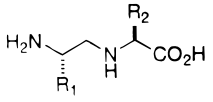
We have developed a versatile new synthesis of the Ψ[CH_2O] pseudopeptides from *N*-protected-5-substituted morpholin-3-ones. The morpholin-3-ones are prepared in two steps from the corresponding amino alcohols by treatment with ethyl chloroacetate, followed by protection of the amide. We found that direct alkylation of the protected morpholin-3-ones gives the expected alkylation product where the electrophile approaches from the face opposite to the existing side chain (derived from the amino alcohol). If an *S* amino alcohol is used, this procedure results in the formation of the (*S*,*R*) Ψ[CH_2O] dipeptide. Alternatively, the (*S*,*S*) Ψ[CH_2O] dipeptide can be obtained if the protected morpholin-3-one enolate is quenched with an aldehyde and the aldol product is dehydrated and reduced. We have explored an alkylation/deprotonation/kinetic protonation scheme which is also amenable to the preparation of (*S*,*S*) pseudodipetides. It is, of course, possible to obtain the corresponding (*R*,*R*) and (*S*,*R*) Ψ[CH_2O] dipeptides by simply selecting the appropriate amino alcohols and reaction conditions. Finally, we have established that this method is general and can be applied to the preparation of numerous Ψ[CH_2O] dipeptides which were previously unavailable by existing methods.

Introduction

The isosteric replacement of an amide bond in a small peptide can lead to a peptidomimetic which retains the ability to bind to its target receptor but has enhanced metabolic stability. This approach has been used to address numerous disease targets and offers the medicinal chemist attractive opportunities for converting peptide-based leads into useful therapeutics.[1] Although the reduced amide isostere Ψ[CH_2NH] (**1**) has been employed frequently in approaches to peptide mimics,[2] the methylene ether isostere Ψ[CH_2O] (**2**)[3] has not been fully exploited. This could be due, in part, to the fact that

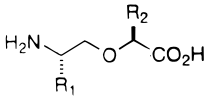


Dipeptide



1

Reduced Amide
Ψ[CH_2NH]



2

Methylene Ether
Ψ[CH_2O]

there are no general methods for the preparation of these pseudopeptides (Scheme 1). The most straightforward approach would depend upon a reaction between an amino alcohol derivative (**3**) and an α-hydroxy ester **4** to form the desired dipeptide isostere **2** (approach 1). This approach has been studied recently by Ho, who has shown that structures such as **3** typically form aziridines.[4] Ho has investigated aziridine ring opening with simple primary alkoxides to give mixtures of ethers, derived from a lack of regioselectivity in the aziridine ring opening reaction. An additional drawback to this approach is that even in the presence of a large excess of alkoxide, only moderate yields were obtained. Another approach which has been used to prepare Ψ[CH_2O] dipeptides is the displacement of α-halo esters **6** by protected amino alcohols **5** (approach 2).[5] Unfortunately, this scheme was only successful for the simplest α-halo esters or acids. In 1986, Nicolaides and co-workers reported that the Williamson ether route illustrated above could be carried out with greater success if the critical carbon−oxygen bond was formed intramolecularly from substrates such as **7** (approach 3).[6] Then in 1987, TenBrink further investigated this method and described the approach in greater detail.[7] It was shown that the intermediate morpholin-3-one **8** could be readily opened under acidic conditions to give the desired Ψ[CH_2O]

[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1996.

(1) The *Annual Reports in Medicinal Chemistry* has published several recent reviews on disease targets which have been addressed by peptidomimetics. Greenlee, W. J.; Siegl, P. K. S. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Acedemic Press: San Diego, 1992; Vol. 27, p 59 (ACE and Renin Inhibitors). Blackburn, B. K.; Gadek, T. R. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Acedemic Press: San Diego, 1993; Vol. 28, p 79 (Glycoprotein IIb/IIIa Antagonists). Thaisrivongs, S. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Acedemic Press: San Diego, 1994; Vol. 29, p 133 (HIV Protease Inhibitors). Bolton, G. L.; Sebolt-Leopold, J. S.; Hodges, J. C. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Acedemic Press: San Diego, 1994; Vol. 29, p 165 (Ras Farnesyltransferase Inhibitors) and references cited therein.

(2) Grahm, S. L.; deSolms, S. J.; Giuliani, E. A.; Kohl, N. E.; Mosser, S. D.; Oliff, A. I.; Pompliano, D. L.; Rands, E.; Breslin, M. J.; Deana, A. A.; Garsky, V. M.; Scholz, T. H.; Gibbs, J. B.; Smith, R. L. *J. Med. Chem.* **1994**, *37*, 725.

(3) Breton, P.; Monsigny, M.; Mayer, R. *Int. J. Pep. Protein Res.* **1990**, *35*, 346.

(4) Ho, M.; Chung, J. K. K.; Tang, N. *Tetrahedron Lett.* **1993**, *34*, 6513. Ho, M.; Uhrin, A.; Huang, M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 553.

(5) Ondetti, M.; Pluscec, J.; Weaver, E.; Williams, N.; Sabo, E.; Kocy, O. In *Proceedings of the Third American Peptide Symposium*; Meienhofer, J., Ed.; Ann Arbor, 1972; p 525.

(6) Nicolaides, E. D.; Tinney, F. J.; Kaltenbronn, J. S.; Repine, J. T.; DeJohn, D. A.; Lunney, E. A.; Roark, W. H.; Marriott, J. G.; Davis, R. E.; Voigtman, R. E. *J. Med. Chem.* **1986**, *29*, 959.

(7) TenBrink, R. E. *J. Org. Chem.* **1987**, *52*, 418.

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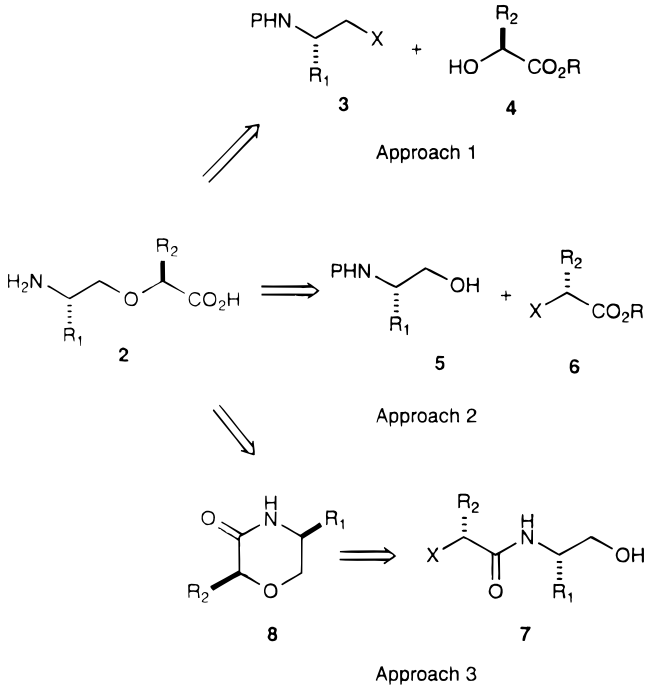
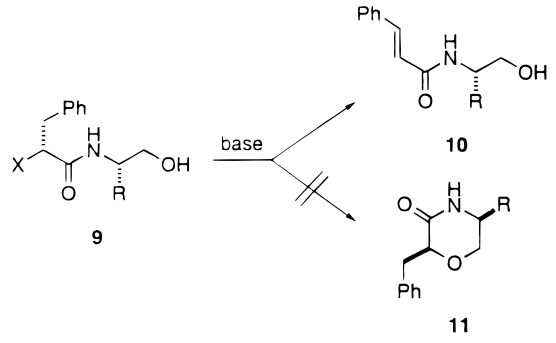
Scheme 1



dipeptide. However, this method provides a limited number of Ψ[CH_2O] dipeptides and relies on a synthetic approach where the side chain functionality is determined at an early stage in the synthesis. Additionally, this method cannot be used for most X-Ψ[CH_2O]-Phe dipeptides due to an undesired dehydrohalogenation which occurs during the formation of the important ether bond. Thus, substrates such as **9** give only products corresponding to **10**, and not the desired morpholin-3-one **11**. Since we required a more general route to these

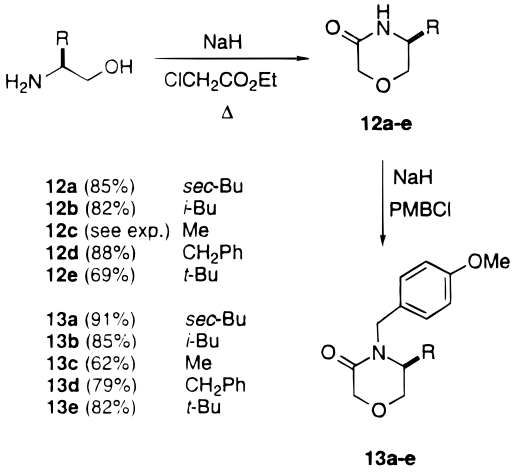


dipeptide isosteres and were specifically interested in preparing the phenylalanine derivatives, we investigated the possibility of introducing the side chain funtionality into the morpholin-3-ones *via* selective alkylation reactions.[8,9] We felt that this approach would give us access to previously unavailable Ψ[CH_2O] dipeptides and could be more amenable to preparing multiple pseudopeptide analogs. Additionally, it was hoped that this approach could provide all of the possible Ψ[CH_2O] dipeptide diasteromers.

Results and Discussion

Our method begins with the preparation of the 5-substituted morpholin-3-ones **12a**−**e** from commercially

Scheme 2



available amino alcohols and ethyl chloroacetate using the method of Clarke.[10] We initially explored the alkylation of **12a**, for we felt that if a selective alkylation were possible, this would be a preferred route to Ψ[CH_2O] dipeptides since 2, 5-disubstituted morpholin-3-ones are suitable precursors to these dipeptides. Additionally, we felt that this approach held promise given the successes of Williams[11] and others[12] in the selective alkylations of the related morpholin-2-ones. Our initial efforts to alkylate **12a** (2 equiv of LDA or LHMDS, $PhCH_2Br$) resulted in significant *N*-alkylation. We decided that we would simply block that position as the benzylamide and proceed. We subsequently discovered that the benzyl group could not be removed using reasonable methods and turned to *p*-methoxybenzyl (PMB), since it could be easily removed using ceric ammonium nitrate (CAN). Treatment of the 5-substituted morpholin-3-ones with sodium hydride, followed by the addition of *p*-methoxybenzyl chloride (PMBCl), resulted in the preparation of the *N*-protected morpholin-3-ones **13a**−**e** (Scheme 2). With these substrates in hand, it was our hope that selective alkylations would occur, giving us easy access to Ψ[CH_2O]dipeptides.

The alkylation of 5-*sec*-butylmorpholin-3-one **13a** (derived from (*S*) isoleucinol) proceeded smoothly using LDA as the base in THF. We initially chose to study benzyl bromide as our electrophile since we were interested in the preparation of pseudopeptides where the second residue corresponded to phenylalanine. The alkylation proceeded in 84% yield with good diastereospecificity (8:1) to yield the 2-benzyl-5-*sec*-butyl-4-(4-methoxybenzyl)-3-morpholinone (**14a**) (Scheme 3, Table 1). The PMB group could be easily removed by treatment of **14a** with ceric ammonium nitrate (CAN) to give the expected N-H morpholin-3-one **15**.

In an effort to firmly establish the stereochemistry of the alkylation product, we decided to study the alkylation of **13a** with methyl iodide. We used the same alkylation conditions to prepare the 2-methyl-substituted morpholinones **23** and **24**, as an inseparable 3:1 mixture. The mixture was deprotected using CAN to give a 3:1 mixture

(8) Norman, B. H.; Kroin, J. S. *Tetrahedron Lett.* **1995**, *36*, 4151.
(9) Anthony, N. J.; Gomez, R. P.; Holtz, W. J.; Murphy, J. S.; Ball, R. G.; Lee, T. *Tetrahedron Lett.* **1995**, *36*, 3821.

(10) Clarke, F. H. *J. Org. Chem.* **1962**, *27*, 3251.
(11) Williams, R. M.; Im, M. N. *Tetrahedron Lett.* **1988**, *29*, 6075. Williams, R. M.; Im, M. N. *J. Am. Chem Soc.* **1991**, *113*, 9276.
(12) Dellaria, J. F.; Santarsiero, B. D. *Tetrahedron Lett.* **1988**, *29*, 6079. Dellaria, J. F. *J. Org.Chem.* **1989**, *54*, 3916. Ornstein, P. L. *J. Org. Chem.* **1989**, *54*, 2251. Baker, W. R.; Condon, S. L.; Spanton, S. *Tetrahedron Lett.* **1992**, *33*, 1573. Baker, W. R.; Condon, S. L. *Tetrahedron Lett.* **1992**, *33*, 1577.

Scheme 3

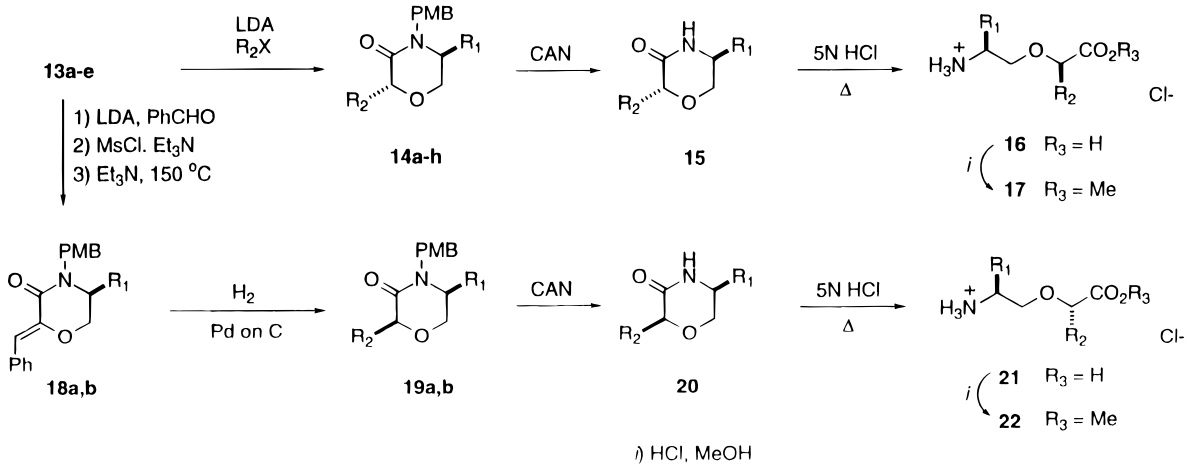
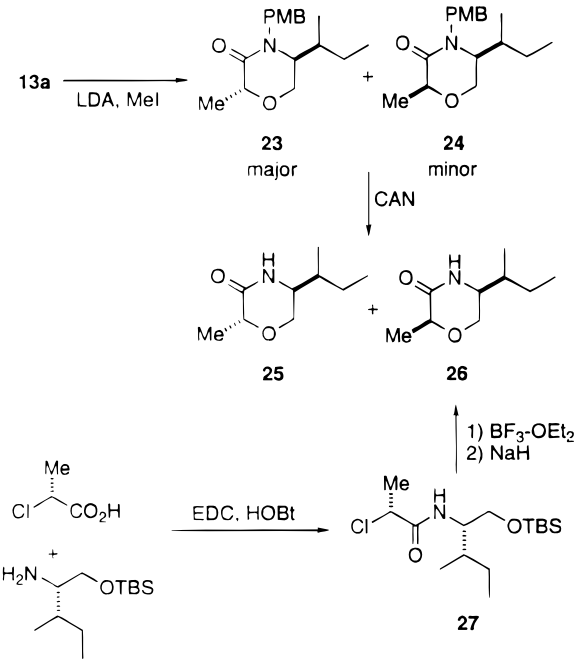


Table 1. Stereoselective Morpholin-3-one Alkylations and Preparation of Ψ[CH_2O] Dipeptides

substrate	R_1	R_2	product	yield[a]	selectivity[b]
13a	*s*-Bu	$PhCH_2$	**14a**	84	8:1
13a	*s*-Bu	$ChxCH_2$	**14b**	65	7:1
13a	*s*-Bu	$PhCH_2CH_2$	**14c**	66	3:1
13a	*s*-Bu	$CH_2{=}CHCH_2$	**14d**	85	6:1
13a	*s*-Bu	$CH_3(CH_2)_5$	**14e**	75	6:1
13c	CH_3	$PhCH_2$	**14f**	85	3:1
13d	CH_2Ph	$PhCH_2$	**14g**	73	5:1
13e	*t*-Bu	$PhCH_2$	**14h**	88	>20:1
14a	*s*-Bu	$PhCH_2$	**15**	76	
15	*s*-Bu	$PhCH_2$	**16**	100	
16	*s*-Bu	$PhCH_2$	**17**	100	
13a	*s*-Bu	PhCH=	**18a**	62[c]	
13b	*i*-Bu	PhCH=	**18b**	68[c]	
18a	*s*-Bu	$PhCH_2$	**19a**	97	8:1
18b	*i*-Bu	$PhCH_2$	**19b**	98	10:1
19a	*s*-Bu	$PhCH_2$	**20**	81	
20	*s*-Bu	$PhCH_2$	**21**	100	
21	*s*-Bu	$PhCH_2$	**22**	100	

[a] Isolated yields are reported. [b] Selectivities were determined on crude reaction mixtures using NMR integration techniques and are reported only for reactions where the new chiral center was formed. Single diastereomers were purified, and subsequent chemistry did not compromise stereochemical integrity. [c] Yields are for three steps (from **13a** or **13b**).

Scheme 4



of N-H morpholin-3-ones **25** and **26**, which could be separated by flash chromatography. An independent synthesis of the expected minor isomer **26** was accomplished *via* the intramolecular Williamson ether synthesis, as described by TenBrink (Scheme 4).[7] These two materials were identical by ^{1}H NMR. This study shows that the 5-substituent is responsible for directing the alkylation to the opposite face.

To show the generality of this reaction, we decided to study alkylations of various substituted protected morpholin-3-ones with several alkyl halides. The first set of experiments which we performed to address this issue focused on alkylation of **13a** with several electrophiles. Scheme 3 and Table 1 show that **13a** can be alkylated in good to excellent yields, giving selectivity ratios for the desired products (**14a**−**e**) of 3:1 to 8:1. It should be pointed out that alkylation occurred in all of the cases which we tried, which included activated (benzyl bromide and allyl bromide) as well as unactivated (cyclohexylmethyl bromide and phenethyl bromide) alkyl halides.

We also sought to show that facial selectivity could be achieved using substituted morphlin-3-ones derived from alanol (**13c**), phenylalanol (**13d**), and *tert*-leucinol (**13e**). Along with isoleucinol (**13a**), we felt that this represented a diverse collection of branched and unbranched substrates. Each of these substrates was subjected to standard alkylation conditions (LDA, −78 °C), using benzyl bromide as the electrophile (Scheme 3, Table 1). The selectivity ratios for the preparation of the products (**14a**,**f**−**h**) followed an expected trend. The poorest selectivity was observed for the alkylation of **13c** (3:1), which has the smallest and least branched substituent at the 5-position (methyl). Accordingly, the greatest selectivity was observed for the alkylation of **13e** (>20:1), the largest and most branched (*tert*-butyl) of the substrates which we studied. This result supports our belief that this side chain directs the stereochemistry of the alkylation.

Although we initially assumed that the electrophile would approach the enolate from the face opposite to the side chain functionality, it occurred to us that the large *p*-methoxybenzyl protecting group may be lying significantly under the morpholinone ring, due to $A_{1,2}$ strain. This effect could negatively impact our selectivity ratios. We knew that the protecting group had an influence on the conformation of the morpholin-3-ones by directing the side chain to a pseudoaxial conformation with concom-

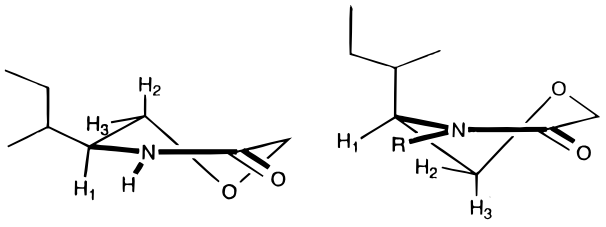


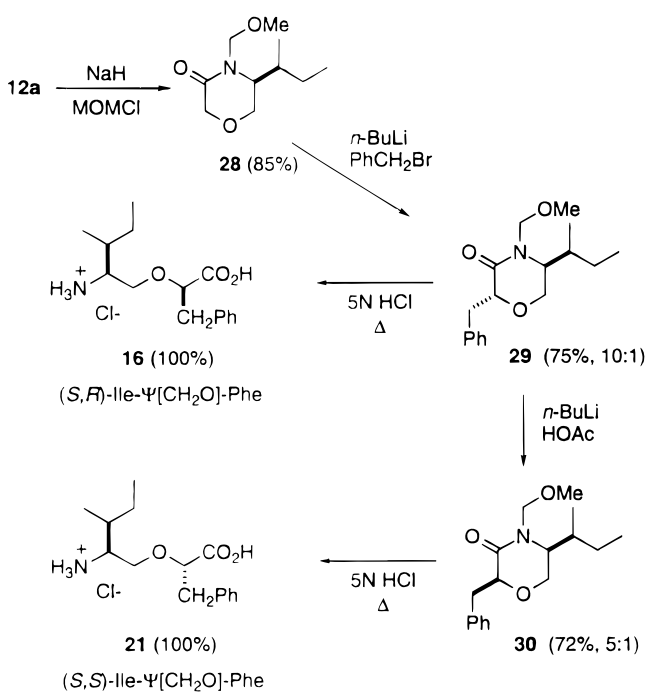
Figure 1. Conformational analysis of **12a** and **13a**.

mitant relief of $A_{1,2}$ strain. This was evident from NMR data obtained on the unprotected morpholin-3-one **12a** and the protected analog **13a** (Figure 1). For **12a**, the vicinal coupling constants $J_{1,2}$ and $J_{1,3}$ were 7.4 and 4.0 Hz, respectively. For **13a**, however, the vicinal coupling constants $J_{1,2}$ and $J_{1,3}$ were 2.5 and 3.6 Hz, respectiviely. This is consistant with a chairlike conformation of **12a**, where the side chain is in a pseudoequatorial conformation. Additionally, these coupling constants support a conformation of **13a** where the *sec*-butyl group occupies a pseudoaxial position, thus relieving $A_{1,2}$ strain and blocking this face of the molecule. This is consistent with the findings of Anthony and co-workers[9] in a closely related system.

Although this alkylation approach was applicable to the stereospecific synthesis of (2*R*,5*S*)-substituted morpholin-3-ones, we had hoped to be able to prepare the (2*S*,5*S*) analogs as well, since these would be precursors to (*S*,*S*) Ψ[CH_2O] dipeptide isosteres. Our initial efforts to invert the stereochemistry at the 2-position *via* deprotonation/kinetic protonation using LDA were unsuccessful. We therefore turned to an aldol approach to the (2*S*,5*S*)-morpholin-3-ones where the diasteroselectivity could be derived from a catalytic hydrogenation of the dehydrated aldol product. This approach is shown in Scheme 3. The lithium enolates of **13a** and **13b** were quenched with benzaldehyde to provide the aldol products, as diastereomeric mixtures. These materials could be dehydrated by initial preparation of the mesylate, followed by heating in DMF at 150 °C in the presence of triethylamine. This sequence provided benzylidenemorpholinones **18a** and **18b** as single olefin isomers[13] (*Z*) in good yield. Finally, catalytic hydrogenation gave the expected (2*S*,5*S*)-morpholin-3-ones **19a** and **19b** in near quantitative yield with 8:1 and 10:1 selectivities, respectively.

Preparation of the Ψ[CH_2O] dipeptide isosteres was accomplished *via* deprotection of the (2*R*,5*S*) and the (2*S*,5*S*) morpholin-3-ones **14a** and **19a** using CAN to give the corresponding N-H morpholinones **15** and **20**.[14] Acid hydrolysis (5 N HCl, 2 h) provided the Ψ[CH_2O] dipeptides **16** and **21** cleanly, with no loss of stereochemical integrity. We found that if methanol were added to the acidic reaction mixture before concentration, the corresponding methyl esters **17** and **22** could be isolated (Scheme 3, Table 1).

Scheme 5



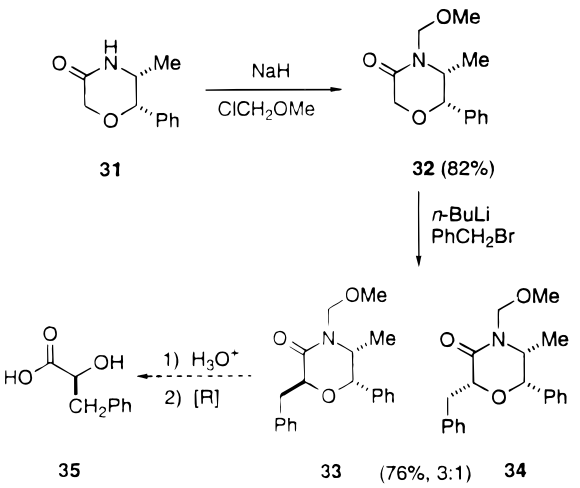
Although our observed diastereoselectivities with the PMB group were good, we were concerned that this large protecting group could be hindering an opportunity to obtain even higher facial selectivities in the alkylation reactions. Additionally, it occurred to us that it may be beneficial to use an acid labile amide protecting group which could be removed under the lactam hydrolysis conditions (5 N HCl, reflux). We felt that the much smaller methoxymethyl (MOM) protecting group could be used to achieve both of these goals. The MOM-protected *sec*-butyl morpholin-3-one **28** was prepared in excellent yield by treatment of **12a** with sodium hydride, followed by quenching with methoxymethyl chloride (MOMCl). Although **28** could be efficiently deprotonated with LDA, we found it more convenient to use *n*-BuLi. We should point out that the PMB-protected morpholinones could also be deprotonated with *n*-BuLi. These reactions were carried out at −78 °C, and products derived from addition to the amide carbonyl were not detected. The facial selectivity observed using the MOM protection was only slightly improved (10:1 compared to 8:1 with PMB)[15] for alkylation with benzyl bromide, forming **29** in good yield (Scheme 5). An unexpected benefit of MOM protection is that the kinetic protonation approach to stereochemical inversion of **29** was much more efficient than in the PMB-protected products such as **14a**. This precludes the need for the aldol approach to the 2*S* isomer. The diastereoselectivity for this reaction was diminished, relative to the direct alkylation, producing **30** as a 5:1 mixture of isomers. As expected, **29** was converted to (*S*,*R*)-Ile-Ψ[CH_2O]-Phe (**16**) in quantitative yield, with concommitant removal of the MOM group and lactam hydrolysis. In a similar fashion, (*S*,*S*)-Ile-Ψ[CH_2O]-Phe (**21**) was prepared from **30**, with no loss of stereochemical purity.

(13) The heteronuclear coupling between the C-3 carbonyl and the olefinic proton in **18a** is dependent upon the stereochemistry with a value of 7 Hz or greater signifying an *E* configuration (between the C and H). Less than 7 Hz is indicative of a *Z* orientation. The coupling was measured using a gated ^{13}C spectrum in which the proton was decoupled using low power. The observed coupling constant $J_{CH} = \sim 3$ Hz, indicating a *Z* orientation between the C-3 carbonyl and the olefinic proton. Therefore, we have assigned the olefin as *Z*.

(14) The stereochemistries of **15** and **20** have been established by NOE studies.

(15) The selectivities in these reactions are not base dependent. **29** was formed with 10:1 selectivity using LDA or *n*-BuLi.

Scheme 6



Although we had shown that the facial selectivity in the alkylation reactions was related to the size of the 5-substituent, we were interested in learning if substitution at the 6-position could have any effect on diastereoselectivity in these reactions. Morpholinone **31** was prepared from (1*S*,2*R*)-(+)-norephedrine using the usual conditions, and this material was protected as the MOM amide **32**. On the basis of our model of these *N*-substituted morpholin-3-ones, which indicates that the 5-substituent occupies a pseudoaxial conformation, we did not expect much enhancement of facial selectivity for alkylation of these substrates. For **32**, if the 5-substituent were pseudoaxial, then the 6-substituent would be pseudoequatorial and subsequently have little effect on the facial selectivity. The NMR coupling constants are consistent with this conformation, and as expected, no enhancement of stereoselectivity was observed (Scheme 6). In fact, the 3:1 selectivity favoring **33** is nearly identical to the selectivity observed for the alkylation of **13c**, indicating that the additional equatorial phenyl group in **32** has absolutely no effect on selectivity. We had hoped that the alkylation products such as **33** could be converted to optically pure α-hydroxy acids **35** *via* lactam hydrolysis/reductive hydrogenolysis. One drawback to this approach to α-hydroxy acids is that the carbon−oxygen bond is cleaved during the hydrogenolysis reaction. This necessarily precludes recycling of the norephedrine group by destoying a chiral center, thus preventing norephedrine from being a true chiral auxiliary. This approach, however, could be acceptable if the alkylation selectivities can be improved, since optically pure norephedrines are relatively inexpensive. We are presently exploring this approach to optically pure α-hydroxy acids.

In conclusion, we have shown that *N*-protected-5-substituted morpholin-3-ones can be alkylated with good to excellent selectivity to give 2-substituted products. The facial selectivity in these reactions is derived from the 5-substituent, where the electrophile prefers to approach the enolate from the face opposite the side chain. We have also shown that the epimeric 2-isomer can be obtained *via* an aldol reaction, followed by dehydration and catalytic hydrogenation. Alternatively, this isomer can also be prepared utilizing a kinetic protonation of the alkylation product enolate, under appropriate conditions. These materials were shown to be suitable precursors to novel methylene ether dipeptide isosteres. It should be emphasized that this method is amenable to the preparation of all four possible Ψ[CH_2O] dipeptides by the appropriate selection of amino alcohol enantiomer and reaction conditions. Furthermore, this approach is useful for the preparation of Ψ[CH_2O] dipeptides which were previously unavailable using existing methods, namely, the X-Ψ[CH_2O]-Phe dipeptides. Another important advantage to this new method is the fact that the side chain functionality is chosen at a later stage in the synthesis, thus being more amenable to SAR studies of potential Ψ[CH_2O] dipeptide enzyme inhibitors.

Experimental Section

Melting points are uncorrected. NMR spectra were performed at the indicated field strengths in the indicated solvents. Anhydrous solvents were purchased from Aldrich, stored over 3A molecular sieves, and transferred *via* syringe or canula. E. Merck silica gel 60 was used for flash chromatography. All reaction were performed under a nitrogen atmosphere. All yields are isolated yields of diastereomerically pure products unless otherwise noted. Selectivities were determined using NMR integration techniques.

(*S*)-5-*sec*-Butylmorpholin-3-one (12a). A solution containing 1.00 g (8.53 mmol) of (*S*)-isoleucinol in 100 mL of THF was stirred at 25 °C under a nitrogen atmosphere. To this solution was added 375 mg of sodium hydride (9.38 mmol, 60% in mineral oil). The reaction mixture was stirred at 25 °C for 30 min, at which time hydrogen evolution had ceased. To this solution was added 0.90 mL of ethyl chloroacetate (8.53 mmol), dropwise, over 5 min. The reaction mixture was stirred for 30 min at 25 °C and then 3 h at reflux. The resulting light brown solution was cooled to 25 °C and poured into 100 mL of 1 N HCl. The mixture was extracted with ethyl acetate (3 × 100 mL). The resulting organic extracts were dried over sodium sulfate and concentrated *in vacuo* to give a crude beige solid. This material was recrystallized from 50% ethyl acetate−isooctane to give 1.14 g (85%) of **12a** as a white crystalline solid (mp 112−114 °C): $[\alpha]^{25}_D = +14.9$ (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 3H, J = 7.2 Hz), 0.93 (d, 3H, J = 6.8 Hz), 1.21 (m, 1H), 1.42−1.65 (m, 2H), 3.43 (m, 1H), 3.58 (dd, 1H, J = 11.7 and 7.4 Hz), 3.87 (dd, 1H, J = 11.7 and 4.0 Hz), 4.07 (d, 1H, J = 16.6 Hz), 4.17 (d, 1H, J = 16.6 Hz), 6.70 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.4, 14.4, 25.2, 37.2, 55.4, 65.4, 67.6, 169.9; IR (KBr) 3220, 2965, 1668 cm^{-1}; MS (FD^+) m/z 157 $(M)^+$.

12b−e were prepared according to the procedure for **12a**.

(*S*)-5-Isobutylmorpholin-3-one (12b) (82%) (mp 70−71 °C): $[\alpha]^{25}_D = -3.2$ (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (d, 3H, J = 9.9 Hz), 0.99 (d, 3H, J = 5.8 Hz), 1.40 (m, 1H), 1.46 (m, 1H), 1.72 (m, 1H), 3.45 (dd, 1H, J = 11.5 and 7.2 Hz), 3.66 (m, 1H), 3.94 (dd, 1H, J = 11.5 and 3.5 Hz), 4.14 (d, 1H, J = 16.7 Hz), 4.23 (d, 1H, J = 16.7 Hz), 7.05 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.3, 22.7, 24.1, 41.8, 49.6, 67.6, 68.1, 169.4; IR (KBr) 3202, 2958, 2872, 1674, 1119 cm^{-1}; MS (FD^+) m/z 158 $(M + 1)^+$. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.93; H, 9.90; N, 8.77.

(*S*)-5-Methylmorpholin-3-one (12c). Due to the aqueous solubility of **12c**, the conditions described above did not result in the isolation of **12c**. Instead of applying the aqueous workup conditions, we simply concentrated the reaction mixture, dissolved the crude material in DMF, and carried out the introduction of the *p*-methoxybenzyl protecting group as described below.

(*S*)-5-Benzylmorpholin-3-one (12d) (88%) (mp 86−87 °C): $[\alpha]^{25}_D = +3.8$ (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.78 (dd, 1H, J = 13.3 and 8.4 Hz), 2.92 (dd, 1H, J = 13.3 and 6.0 Hz), 3.60 (dd, 1H, J = 11.7 and 6.4 Hz), 3.80 (m, 1H), 3.93 (dd, 1H, J = 11.7 and 2.5 Hz), 4.15 (s, 2H), 6.41 (bs, 1H), 7.20−7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 39.4, 52.8, 67.4, 67.8, 127.2, 129.0, 129.2, 136.0, 169.0; IR (KBr) 3189, 2970, 1677, 1121 cm^{-1}; MS (FD^+) m/z 191 $(M)^+$. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.90; H, 6.75; N, 7.26.

(*S*)-5-*tert*-Butylmorpholin-3-one (12e) (69%) (mp 114−115 °C): $[\alpha]^{25}_D = +14.7$ (*c* 1.0, CH_3OH); ^1H NMR ($CDCl_3$, 300

MHz) δ 0.96 (s, 9H), 2.80 (m, 1H), 3.61 (dd, 1H, J = 11.9 and 7.8 Hz), 3.92 (dd, 1H, J = 11.9 and 4.2 Hz), 4.06 (d, 1H, J = 16.6 Hz), d, 1H, J = 16.6 Hz), 6.38 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.9, 33.2, 60.1, 64.8, 67.5, 170.0; IR (KBr) 3203, 2970, 1674, 1127 cm^{-1}; MS (FD$^+$) m/z 157 (M)$^+$. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 61.33; H, 9.41; N, 8.85.

(*S*)-5-*sec*-Butyl-4-(4-methoxybenzyl)morpholin-3-one (13a). A solution containing 1.00 g of the morpholin-3-one **12a** (6.36 mmol) in 50 mL of DMF was stirred at 25 °C under a nitrogen atmosphere as 305 mg (7.63 mmol, 60% in mineral oil) of sodium hydride was added. The reaction was stirred at 25 °C for 30 min, after which 1.03 mL (7.63 mmol) of *p*-methoxybenzyl chloride was added dropwise over 5 min. The resulting solution was stirred at 25 °C for 4 h and then poured into 1 N HCl. The mixture was extracted with ethyl acetate (3 × 100 mL), and the combined extracts were washed twice with brine, dried over sodium sulfate, and concentrated *in vacuo* to give a brown oil. This crude material was purified by flash chromatography on a silica gel column using 50% ethyl acetate−hexane as the eluent. The major fraction was collected and concentrated *in vacuo* to give 1.61 g (91%) of **13a** as a clear oil: $[\alpha]^{25}_D = -83.4$ (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, 3H, J = 7.4 Hz), 1.00 (d, 3H, J = 7.0 Hz), 1.32 (m, 2H), 1.96 (m, 1H), 3.15 (m, 1H), 3.61 (dd, 1H, J = 12.1 and 3.6 Hz), 3.83 (s, 3H), 3.85 (d, 1H, J = 14.7 Hz), 3.95 (dd, 1H, J = 12.1 and 2.5 Hz), 4.20 (d, 1H, J = 16.7 Hz), 4.28 (d, 1H, J = 16.7 Hz), 5.50 (d, 1H, J = 14.7 Hz), 6.89 (d, 2H, J = 8.4 Hz), 7.21 (d 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.4, 14.4, 26.6, 35.2, 45.3, 55.3, 56.2, 64.5, 67.7, 114.1, 128.6, 159.1, 167.9; IR ($CHCl_3$) 3010, 2967, 1640, 1513, 1247 cm^{-1}; MS (FD$^+$) m/z 277 (M)$^+$. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.18; H, 8.35; N, 4.95.

13b−e were prepared according to the procedure for **13a**.

(*S*)-5-Isobutyl-4-(4-methoxybenzyl)morpholin-3-one (13b) (85%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (d, 3H, J = 6.4 Hz), 1.00 (d, 3H, J = 6.5 Hz), 1.45 (m, 1H), 1.62 (m, 1H), 1.90 (m, 1H), 3.15 (m, 1H), 3.61 (m, 1H), 3.78 (d, 1H, J = 14.7 Hz), 3.85 (s, 3H), 3.88 (d, 1H, J = 14.7 Hz), 4.23 (d, 1H, J = 16.7 Hz), 4.33 (d, 1H, J = 16.7 Hz), 5.46 (d, 1H, J = 14.7 Hz), 6.91 (d, 2H, J = 8.6 Hz), 7.24 (d, 2H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 23.8, 25.1, 38.8, 45.9, 52.1, 55.3, 66.3, 67.9, 114.1, 128.8, 129.6, 159.2, 166.8; IR ($CHCl_3$) 3010, 2962, 1641, 1513, 1247 cm^{-1}; MS (FD$^+$) m/z 277 (M)$^+$. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.23; H, 8.45; N, 5.03.

(*S*)-5-Methyl-4-(4-methoxybenzyl)morpholin-3-one (13c) (62%, 2 steps): $[\alpha]^{25}_D = -112.5$ (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (d, 3H, J = 6.5 Hz), 3.35 (m, 1H), 3.67 (dd, 1H, J = 11.7 and 3.0 Hz), 3.75 (dd, 1H, J = 11.7 and 3.2 Hz), 3.84 (s, 3H), 3.92 (d, 1H, J = 14.8 Hz), 4.24 (d, 1H, J = 16.6 Hz), 4.33 (d, 1H, J = 16.6 Hz), 5.37 (d, 1H, J = 14.8 Hz), 6.90 (d, 2H, J = 8.5 Hz), 7.23 (d, 2H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.7, 45.7, 49.6, 55.3, 68.1, 69.5, 114.1, 128.7, 129.5, 159.1, 166.9; IR ($CHCl_3$) 3010, 2980, 1643, 1513 cm^{-1}; MS (FD$^+$) m/z 235 (M)$^+$.

(*S*)-5-Benzyl-4-(4-methoxybenzyl)morpholin-3-one (23d) (79%): $[\alpha]^{25}_D = -54.8$ (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.99 (dd, 1H, J = 13.3 and 10.3 Hz), 3.12 (dd, 1H, J = 13.3 and 4.0 Hz), 3.32 (m, 1H), 3.47 (dd, 1H, J = 11.7 and 1.6 Hz), 3.74 (d, 1H, J = 11.7 Hz), 3.85 (s, 3H), 3.90 (d, 1H, J = 14.8 Hz), 4.26 (d, 1H, J = 16.7 Hz), 4.40 (d, 1H, J = 16.7 Hz), 5.48 (d, 1H, J = 14.8 Hz), 6.92 (d, 2H, J = 8.3 Hz), 7.17 (d, 2H, J = 7.4 Hz), 7.29−7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.6, 46.6, 55.3, 55.6, 65.6, 68.0, 114.2, 126.8, 128.6, 128.8, 129.3, 129.7, 137.5, 159.3, 166.9; IR ($CHCl_3$) 3013, 2935, 1644, 1513, 1248 cm^{-1}; MS (FD$^+$) m/z 311 (M)$^+$.

(*S*)-5-*tert*-Butyl-4-(4-methoxybenzyl)morpholin-3-one (13e) (82%): $[\alpha]^{25}_D = -77.4$ (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (s, 9H,), 2.89 (d, 1H, J = 1.5 Hz), 3.42 (dd, 1H, J = 12.0 and 2.7 Hz), 3.84 (s, 3H), 3.87 (d, 1H, J = 14.7 Hz), 4.14 (d, 1H, J = 12.0 Hz), 4.26 (d, 1H, J = 17.2 Hz), 4.33 (d, 1H, J = 17.2 Hz), 5.77 (d, 1H, J = 14.7 Hz), 6.90 (d, 2H, J = 8.5 Hz), 7.21 (d, 2H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.9, 36.7, 49.8, 55.3, 61.6, 66.5, 67.0, 114.1, 128.8, 129.6, 159.1, 168.5; IR ($CHCl_3$) 3010, 2967, 1639, 1513, 1249 cm^{-1}; MS (FD$^+$) m/z 277 (M)$^+$. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.00; H, 8.56; N, 4.81.

(2*R*,5*S*)-2-Benzyl-5-*sec*-butyl-4-(4-methoxybenzyl)morpholin-3-one (14a). LDA was prepared at 0 °C from 0.697 mL (4.98 mmol) of diisopropylamine and 3.11 mL (4.98 mmol) of *n*-butyllithium (1.6 M in hexane) in 10 mL of THF under a nitrogen atmosphere. The solution of LDA was then cooled to −78 °C, and 1.15 g (4.15 mmol) of the *N*-protected morpholin-3-one **13a** in tetrahydrofuran (5 mL) was added dropwise. The bright yellow solution was stirred at −78 °C for 30 min, after which 0.592 mL (4.98 mmol) of benzyl bromide was added. The reaction mixture was allowed to warm to 25 °C and stirred for an additional 2 h. The reaction mixture was poured into 1 N HCl and extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo* to give a crude oil, which was purified by flash chromatography on a silica gel column using 3:1 hexane−ethyl acetate as the eluent. The major fractions were combined and concentrated *in vacuo* to give 1.29 g (84%, 8:1 selectivity) of **14a** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83 (t, 3H, J = 7.4 Hz), 0.88 (d, 3H, J = 7.0 Hz), 1.17 (m, 2H), 1.86 (m, 1H), 3.19 (m, 2H), 3.33 (dd, 1H, J = 14.2 and 3.5 Hz), 3.60−3.85 (m, 3H), 3.79 (s, 3H), 4.41 (dd, 1H, J = 7.7 and 3.5 Hz), 5.53 (d, 1H, J = 14.8 Hz), 6.79 (d, 2H, J = 8.5 Hz), 6.94 (d, 2H, J = 8.5 Hz), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.3, 13.5, 26.3, 34.4, 37.9, 44.8, 55.2, 56.4, 61.9, 77.7, 114.0, 126.5, 128.2, 128.4, 129.2, 130.0, 138.0, 158.9, 169.8; IR ($CHCl_3$) 3031, 2967, 1640, 1513, 1248 cm^{-1}; MS (FD$^+$) m/z 367 (M)$^+$. Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.46; H, 7.95; N, 3.91.

(2*R*,5*S*)-5-*sec*-Butyl-2-(cyclohexylmethyl)-4-(4-methoxybenzyl)-morpholin-3-one (14b). 14b was prepared according to the procedure for **14a**, by quenching the enolate of **13a** with cyclohexylmethyl bromide. **14b** (65%, 7:1 selectivity): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80−1.10 (m, 8H), 1.10−1.38 (m, 5H), 1.40−1.60 (m, 1H), 1.60−1.77 (m, 5H), 1.78−2.10 (m, 3H) 3.25 (m, 1H), 3.43−4.18 (m, 3H), 3.80 (s, 3H), 4.21 (dd, 1H, J = 9.2 and 3.0 Hz), 5.50 (d, 1H, J = 14.7 Hz), 6.86 (d, 2H, J = 8.5 Hz), 7.15 (d, 2H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.62, 14.16, 27.26, 27.43, 27.53, 27.65, 33.12, 35.18, 35.37, 35.99, 39.75, 46.26, 55.69, 58.25, 61.50, 75.52, 115.12, 129.83, 130.38, 160.69, 173.62; IR ($CHCl_3$) 2926, 1632, 1513, 1248, 1036 cm^{-1}; MS (FD$^+$) m/z 373 (M)$^+$. Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.96; H, 9.45; N, 3.75. Found: C, 74.24; H, 9.46; N, 3.96.

(2*R*,5*S*)-5-*sec*-Butyl-4-(4-methoxybenzyl)-2-(2-phenylethyl)morpholin-3-one (14c). 14c was prepared according to the procedure for **14a**, by quenching the enolate of **13a** with 2-phenylethyl bromide. **14c** (66%, 3:1 selectivity): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80−1.10 (m, 6H), 1.18−1.40 (m, 2H), 1.92 (m, 1H), 2.10 (m, 1H), 2.35 (m, 1H), 2.78 (m, 2H), 3.30 (m, 1H), 3.48−4.10 (m, 3H), 3.79 (s, 3H), 4.11 (dd, 1H, J = 9.2 and 3.0 Hz), 5.52 (d, 1H, J = 14.9 Hz), 6.85 (d, 2H, J = 8.1 Hz), 7.14−7.45 (m, 7H); IR ($CHCl_3$) 3033, 2968, 1639, 1513, 1248 cm^{-1}; MS (FD$^+$) m/z 381 (M)$^+$. Anal. Calcd for $C_{24}H_{31}NO_3$: C, 75.55; H, 8.19; N, 3.67. Found: C, 75.31; H, 8.12; N, 3.74.

(2*R*,5*S*)-2-Allyl-5-*sec*-butyl-4-(4-methoxybenzyl)morpholin-3-one (14d). 14d was prepared according to the procedure for **14a**, by quenching the enolate of **13a** with allyl bromide. **14d** (85%, 6:1 selectivity): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80−1.10 (m, 6H), 1.16−1.38 (m, 2H), 1.90 (m, 1H), 2.63 (m, 1H), 2.7−2.9 (m, 1H), 3.29 (m, 1H), 3.63−4.05 (m, 3H), 3.80 (s, 3H), 4.20 (dd, 1H, J = 8.3 and 3.6 Hz), 5.10−5.25 (m, 2H), 5.52 (d, 1H, J = 14.8 Hz), 5.90 (m, 1H) 6.86 (d, 2H, J = 8.6 Hz), 7.16 (d, 2H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.60, 13.93, 27.33, 35.78, 37.26, 46.18, 55.69, 58.20, 62.37, 77.51, 115.10, 118.07, 129.62, 130.45, 135.47, 160.07, 172.33; IR ($CHCl_3$) 3011, 2969, 1640, 1513, 1464, 1247, 1176, 1036 cm^{-1}; MS (FD$^+$) m/z 317 (M)$^+$. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.58; N, 4.41. Found: C, 71.79; H, 8.68; N, 4.20.

(2*R*,5*S*)-5-*sec*-Butyl-2-*n*-hexyl-4-(4-methoxybenzyl)morpholin-3-one (14e). 14e was prepared according to the procedure for **14a**, by quenching the enolate of **13a** with *n*-hexyl iodide. **14e** (75%, 6:1 selectivity): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80−1.10 (m, 9H), 1.16−1.60 (m, 10H), 1.61−

2.10 (m, 3H), 3.26 (m, 1H), 3.63−4.05 (m, 3H), 3.80 (s, 3H), 4.10 (dd, 1H, J = 8.9 and 3.3 Hz), 5.52 (d, 1H, J = 14.9 Hz), 6.86 (d, 2H, J = 8.5 Hz),7.16 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.62, 13.97, 14.42, 23.63, 26.56, 27.36, 30.12, 32.64, 32.94, 35.84, 46.12, 55.69, 58.24, 62.03, 77.73, 115.10, 129.80, 130.40, 160.69, 173.25; IR ($CHCl_3$) 3009, 2964, 2931, 1635, 1513, 1464, 1248, 1176, 1036 cm^{-1}; MS (FD$^+$) m/z 361 (M)$^+$. Anal. Calcd for $C_{22}H_{35}NO_3$: C, 73.08; H, 9.76; N, 3.88. Found: C, 72.87; H, 9.72; N, 3.80.

(2*R*,5*S*)-2-Benzyl-4-(4-methoxybenzyl)-5-methylmorpholin-3-one (14f). 14f was prepared according to the procedure for **14a**, by quenching the enolate of **13c** with benzyl bromide. **14f** (85%, 3:1 selectivity): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10 (d, 3H, J = 6.1 Hz), 3.19 (m, 1H), 3.22−3.46 (m, 2H), 3.63 (s, 1H), 3.79 (s, 3H), 3.83 (m, 1H), 3.86 (d, 1H, J = 14.8 Hz), 4.45 (dd, 1H, J = 7.7 and 3.5 Hz), 5.36 (d, 1H, J = 14.8 Hz), 6.79 (d, 2H, J = 8.5 Hz), 6.90 (d, 2H, J = 8.5 Hz), 7.20−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.9, 37.9, 45.1, 49.8, 55.3, 67.7, 78.0, 114.0, 126.4, 128.0, 128.2, 129.0, 130.0, 137.9, 158.9, 168.8; IR ($CHCl_3$) 3010, 2965, 1642, 1513, 1454, 1175 cm^{-1}; MS (FD$^+$) m/z 325 (M)$^+$.

(2*R*,5*S*)-2,5-Dibenzyl-4-(4-methoxybenzyl)morpholin-3-one (14g). 14g was prepared according to the procedure for **14a**, by quenching the enolate of **13d** with benzyl bromide. **14g** (73%, 5:1 selectivity): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.81 (dd, 1H, J = 13.2 and 10.3 Hz), 3.06 (dd, 1H, J = 13.3 and 4.1 Hz), 3.26 (m, 3H), 3.47 (m, 2H), 3.82 (s, 3H), 3.83 (d, 1H, J = 14.8 Hz), 4.55 (dd, 1H, J = 7.4 and 4.2 Hz), 5.48 (d, 1H, J = 14.8 Hz), 6.85 (d, 2H, J = 8.5 Hz), 7.05 (m, 3H), 7.18−7.40 (m, 9H); IR ($CHCl_3$) 3005, 1642, 1513, 1248 cm^{-1}; MS (FD$^+$) m/z 401 (M)$^+$.

(2*R*,5*S*)-2-Benzyl-5-*tert*-butyl-4-(4-methoxybenzyl)morpholin-3-one (14h). 14h was prepared according to the procedure for **14a**, by quenching the enolate of **13e** with benzyl bromide. **14h** (88%, >20:1 selectivity): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.07 (s, 9H), 2.76 (d, 1H, J = 1.2 Hz), 3.25 (m, 3H), 3.79 (s, 3H), 3.85 (m, 2H), 4.51 (dd, 1H, J = 6.3 and 4.4 Hz), 5.75 (d, 1H, J = 14.7 Hz), 6.81 (d, 2H, J = 8.5 Hz), 7.02 (d, 2H, J = 8.5 Hz), 7.30 (m, 5H); IR ($CHCl_3$) 2962, 1639, 1513, 1249, 1130 cm^{-1}; MS (FD$^+$) m/z 367 (M)$^+$.

(2*R*,5*S*)-2-Benzyl-5-*sec*-butylmorpholin-3-one (15). A solution of 1.00 g (2.72 mmol) of **14a** in 25 mL of 50% acetonitrile−water was stirred at 25 °C as 2.98 g (5.44 mmol) of ceric ammonium nitrate (CAN) was added. The reaction mixture was stirred at 25 °C for 3 h and poured into 1 N HCl. The mixture was extracted with ethyl acetate (3 × 50 mL). The organic extracts were dried over sodium sulfate, concentrated *in vacuo*, and purified by flash chromatography on a silica gel column using 50% ethyl acetate−hexane as the eluent. The major fractions were combined and concentrated *in vacuo* to give 510 mg (76%) of (2*R*,5*S*)-2-benzyl-5-*sec*-butylmorpholin-3-one (**15**) as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (d, 3H, J = 6.8 Hz), 0.91 (t, 3H, J = 7.2 Hz), 1.21 (m, 1H), 1.45 (m, 2H), 3.01 (dd, 1H, J = 14.4 and 8.6 Hz), 3.34 (dd, 1H, J = 14.8 and 3.1 Hz), 3.43 (m, 2H), 3.95 (m, 1H), 4.26 (dd, 1H, J = 8.6 and 3.1 Hz), 6.44 (bs, 1H), 7.18−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.2, 14.1, 25.0, 36.9, 37.7, 56.0, 65.5, 78.2, 126.5, 128.2, 129.6, 138.0, 171.0; IR ($CHCl_3$) 3395, 3011, 2971, 1666, 1455, 1120 cm^{-1}; MS (FD$^+$) m/z 247 (M)$^+$.

(*S*,*R*)-Isoleucine-Ψ[CH$_2$O]-phenylalanine·HCl (16). A suspension of 500 mg (2.02 mmol) of morpholin-3-one **15** in 15 mL of 5 N HCl was heated to reflux for 2 h, cooled to 25 °C, and concentrated *in vacuo* to give 635 mg (99%) of **16** as a white amorphous solid: ^{1}H NMR (CD_3OD, 300 MHz) δ 0.89 (m, 6H), 1.19 (m, 1H), 1.44 (m, 1H), 1.70 (m, 1H), 2.97 (dd, 1H, J = 14.1 and 8.0 Hz), 3.13 (m, 1H), 3.16 (dd, 1H, J = 14.1 and 4.3 Hz), 3.58 (m, 2H), 4.22 (dd, 1H, 8.0 and 4.3 Hz), 7.2−7.35 (m, 5H). If the reaction is diluted with 150 mL of methanol prior to concentration, the corresponding methyl ester **17** is isolated instead in quantitative yield.

(*S*,*R*)-Isoleucine-Ψ[CH$_2$O]-phenylalanine methyl ester·HCl (17). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (m, 6H), 1.19 (m, 1H), 1.45 (m, 1H), 1.72 (m, 1H), 2.99 (dd, 1H, J = 14.1 and 7.8 Hz), 3.10 (dd, 1H, J = 14.1 and 4.7 Hz), 3.14 (m, 1H), 3.57 (d, 2H, J = 5.6 Hz), 3.70 (s, 3H), 4.27 (dd, 1H, J = 7.8 and 4.7 Hz), 7.18−7.35 (m, 5H); IR ($CHCl_3$) 3028, 2991, 1745, 1113 cm^{-1}; MS (FD$^+$) m/z 280 (M + 1)$^+$.

(2*Z*,5*S*)-2-Benzylidene-5-*sec*-butyl-4-(4-methoxybenzyl)morpholin-3-one (18a). LDA was prepared at 0 °C from 1.36 mL (9.71 mmol) of diisopropylamine and 6.06 mL (9.71 mmol) of *n*-butyllithium (1.6 M in hexane) in 30 mL of THF under a nitrogen atmosphere. The solution of LDA was then cooled to −78 °C, and 2.00 g (8.09 mmol) of the *N*-protected morpholin-3-one **13a** in tetrahydrofuran (10 mL) was added dropwise. The bright yellow solution was stirred at −78 °C for 30 min, after which 0.99 mL (9.71 mmol) of benzaldehyde was added. The reaction was allowed to warm to 25 °C and stirred an additional 1 h. The reaction mixture was poured into 1 N HCl and extracted with ethyl acetate (3 × 50 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo* to give the crude aldol product, as a mixture of four diastereomers, which was used without further purification. This material was dissolved in 20 mL of methylene chloride and cooled to 0 °C. To the reaction mixture was added 1.69 mL (12.1 mmol) of triethylamine, followed by 0.94 mL (12.1 mmol) of methanesulfonyl chloride, dropwise, with stirring, at 0 °C. The cooling bath was removed, and the reaction mixture was allowed to warm to 25 °C, after which the reaction mixture was washed with 1 N HCl (2×), brine (2×), and a saturated sodium bicarbonate solution (2×). The organic phase was dried over sodium sulfate and concentrated *in vacuo* to give the mesylate, which was dissolved in 50 mL of DMF. To this solution was added 1.69 mL (12.1 mmol) of triethylamine, and the reaction mixture was heated to 150 °C for 20 min, cooled to 25 °C, and poured into 100 mL of water. The mixture was diluted with 150 mL of ethyl acetate, and the organic phase washed with 1 N HCl (2×), brine (2×), and a saturated sodium bicarbonate solution (2×). The solution was dried over sodium sulfate and concentrated *in vacuo* to give the crude dehydrated aldol product. This material was purified by flash chromatography on a silica gel column using 50% ethyl acetate−hexane as the eluent. The major fractions were combined and concentrated *in vacuo* to give 1.85 g (62% from **13a**) of **18a** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (t, 3H, J = 7.4 Hz), 0.99 (d, 3H, J = 7.0 Hz), 1.35 (m, 1H), 1.43 (m, 1H), 1.94 (m, 1H), 3.19 (m, 1H), 3.78 (s, 3H), 3.84 (d, 1H, J = 14.8 Hz), 3.92 (dd, 1H, J = 12.1 and 3.6 Hz), 4.30 (d, 1H, J = 12.1 Hz), 5.59, 1H, J = 14.8 Hz), 6.87 (d, 2H, J = 8.5 Hz), 6.90 (s, 1H), 7.20−7.26 (m, 1H), 7.24 (d, 2H, J = 8.5 Hz), 7.35 (t, 2H, J = 7.6 Hz), 7.73 (d, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.0, 15.2, 26.6, 36.0, 48.2, 55.3, 57.2, 64.9, 112.6, 114.2, 127.5, 128.3, 128.8, 129.7, 129.9, 134.7, 144.2, 159.2, 160.6; IR ($CHCl_3$) 2964, 2934, 1662, 1616, 1512, 1246 cm^{-1}; MS (FD$^+$) m/z 365 (M)$^+$.

(2*Z*,5*S*)-2-Benzylidene-5-isobutyl-4-(4-methoxybenzyl)-morpholin-3-one (18b). 18b was prepared according to the procedure for **18a**, by quenching the enolate of **13b** with benzaldehyde, and following the dehydration procedure as described. **18b** (68% from **13b**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.93 (d, 3H, J = 6.4 Hz), 1.02 (d, 3H, J = 6.5 Hz), 1.47 (m, 1H), 1.66 (m, 1H), 1.88 (m, 1H), 3.35 (m, 1H), 3.85 (s, 3H), 3.88 (d, 1H, J = 14.6 Hz), 3.99 (d, 1H J = 12.1 Hz), 4.19 (d, 1H, J = 12.1 Hz), 5.51 (1H, J = 14.6 Hz), 6.92 (d, 2H, J = 8.5 Hz), 6.93 (s, 1H), 7.25−7.29 (m, 1H), 7.28 (d, 2H, J = 8.5 Hz), 7.39 (t, 2H, J = 7.6 Hz), 7.77 (d, 2H, J = 7.6 Hz); IR ($CHCl_3$) 3009, 2963, 1660, 1613, 1512, 1248 cm^{-1}; MS (FD$^+$) m/z 366 (M + 1)$^+$.

(2*S*,5*S*)-2-Benzyl-5-*sec*-butyl-4-(4-methoxybenzyl)morpholin-3-one (19a). To a solution of 100 mg (0.274 mmol) of the olefin **18a** in 20 mL of methanol was added 20 mg of palladium on carbon (10%) catalyst in a 500 mL Parr bottle. The reaction was run at 20 psi of hydrogen on a Parr shaker for 12 h, after which the catalyst was removed by filtration over a pad of Celite. The solution was concentrated *in vacuo* to give the reduced product. This material was purified by flash chromatography on a silica gel column using 50% ethyl acetate−hexane as the eluent. The major fractions were combined and concentrated *in vacuo* to give 97 mg (97%, 8:1 selectivity) of **19a** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (m, 6H), 1.28 (m, 2H), 1.81 (m, 1H), 3.03 (m, 1H), 3.08 (dd, 1H, J = 14.0 and 8.5 Hz), 3.44 (dd, 1H, J = 14.8 and 2.9

Hz), 3.50 (dd, 1H, J = 14.8 and 3.2 Hz), 3.84 (s, 3H), 3.86 (d, 1H, J = 12.3 Hz), 3.99 (d, 1H, J = 12.3 Hz), 4.37 (dd, 1H, J = 8.5 and 2.9 Hz), 5.45 (d, 1H, J = 14.6 Hz), 6.90 (d, 2H, J = 8.5 Hz), 7.22 (d, 2H, J = 8.5 Hz), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.2, 14.9, 26.6, 35.4, 38.4, 46.6, 55.2, 57.3, 63.9, 78.7, 114.1, 126.4, 128.1, 129.0, 129.6, 129.8, 138.1, 159.1, 169.4; IR (neat) 2964, 1647, 1512, 1247 cm^{-1}; MS (FD$^+$) m/z 367 (M)$^+$. Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 74.93; H, 8.02; N, 3.91.

(2*S*,5*S*)-2-Benzyl-5-isobutyl-4-(4-methoxybenzyl)morpholin-3-one (19b). 19b was prepared according to the procedure for **19a**. **19b** (98%, 10:1 selectivity): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.76 (d, 3H, J = 6.5 Hz), 0.82 (d, 3H, J = 6.6 Hz), 0.99 (m, 1H), 1.28 (m, 1H), 1.44 (m, 1H), 2.97 (d, 1H, J = 10.5 Hz), 3.17 (dd, 1H, J = 14.0 and 6.4 Hz), 3.26 (dd, 1H, J = 14.0 and 3.9 Hz), 3.50 (d, 1H, J = 12.0 Hz), 3.67 (d, 1H, J = 14.6 Hz), 3.75 (d, 1H, J = 12.0 Hz), 3.79 (s, 3H), 4.35 (dd, 1H, J = 6.4 and 3.9 Hz), 5.30 (d, 1H, J = 14.6 Hz), 6.83 (d, 2H, J = 8.5 Hz), 7.17 (d, 2H, J = 8.5 Hz), 7.22−7.35 (m, 5H); IR ($CHCl_3$) 2960, 1641, 1512, 1247, 1176 cm^{-1}; MS (FD$^+$) m/z 367 (M)$^+$.

(2*S*,5*S*)-2-Benzyl-5-*sec*-butylmorpholin-3-one (20). 20 was prepared from **19a** using the procedure for the preparation of **15**. **20** (81%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (m, 6H), 1.09 (m, 1H), 1.25−1.40 (m, 2H), 3.08 (m, 1H), 3.15 (dd, 1H, J = 14.3 and 7.5 Hz), 3.26 (dd, 1H, J = 14.3 and 3.6 Hz), 3.72 (dd, 1H, J = 12.1 and 3.3 Hz), 3.91 (d, 1H, J = 12.1 Hz), 4.39 (dd, 1H, J = 7.5 and 3.6 Hz), 6.85 (bs, 1H), 7.30 (m, 5H); IR ($CHCl_3$) 3404, 3010, 2970, 1666 cm^{-1}; MS (FD$^+$) m/z 247 (M)$^+$. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.56; H, 8.72; N, 5.51.

(*S*,*S*)-Isoleucine-Ψ[CH_2O]-phenylalanine·HCl (21). 21 was prepared according to the procedure for **16**. **21:** ^{1}H NMR (CD_3OD, 300 MHz) δ 0.76 (d, 3H, J = 6.9 Hz), 0.89 (t, 3H, J = 7.3 Hz), 1.15 (m, 1H), 1.46 (m, 1H), 1.69 (m, 1H), 2.95 (dd, 1H, J = 14.0 and 8.7 Hz), 3.14 (m, 2H), 3.53 (dd, 1H, J = 10.6 and 5.8 Hz), 3.68 (dd, 1H, J = 10.6 and 3.3 Hz), 4.18 (dd, 1H, J = 8.6 and 4.0 Hz), 7.21 (m, 5H).

(*S*,*S*)-Isoleucine-Ψ[CH_2O]-phenylalanine methyl ester·HCl (22). 22 was prepared according to the procedure for **17**. **22:** $[\alpha]^{25}_D$ = −33.3 (*c* 1.0, CH_3OH); ^{1}H NMR (CD_3OD, 300 MHz) δ 0.82 (d, 3H, J = 6.9 Hz), 0.95 (t, 3H, J = 7.3 Hz), 1.20 (m, 1H), 1.52 (m, 1H), 1.74 (m, 1H), 3.00 (dd, 1H, J = 14.0 and 8.6 Hz), 3.18 (m, 1H), 3.31 (m, 1H), 3.57 (dd, 1H, J = 10.6 and 5.9 Hz), 3.73 (dd, 1H, J = 10.6 and 3.1 Hz), 3.77 (s, 3H), 4.27 (dd, 1H, J = 8.6 and 4.4 Hz) 7.28 (m, 5H); ^{13}C NMR (CD_3OD, 75 MHz) δ 9.1, 12.2, 24.5, 34.0, 37.5, 50.5, 54.8, 66.3, 79.5, 125.2, 127.0, 128.5, 135.5, 174.1; IR ($CHCl_3$) 3032, 2972, 1743, 1116 cm^{-1}; MS (FD$^+$) m/z 280 (M + 1)$^+$.

(2*R*,5*S*)-5-*sec*-Butyl-4-(4-methoxybenzyl)-2-methylmorpholin-3-one (23). 23 and **24** were prepared as an inseparable 3:1 according to the procedure for **14a**. **23** (77%): ^{1}H NMR ($CDCl_3$, 300 MHz) (major diastereomer, **23**) δ 0.90−0.95 (m, 6H), 1.29 (m, 2H), 1.53 (d, 3H, J = 6.8 Hz), 1.92 (m, 1H), 3.30 (m, 1H), 3.71 (dd, 1H, J = 12.2 and 6.2 Hz), 3.82 (s, 3H), 3.86 (m, 2H), 4.28 (q, 1H, J = 6.8 Hz), 5.52 (d, 1H, J = 15.1 Hz), 6.89 (d, 2H, J = 8.4 Hz), 7.19 (d, 2H, 8.4 Hz); IR ($CHCl_3$) 3009, 2968, 1637, 1513, 1247 cm^{-1}; MS (FD$^+$) m/z 291 (M)$^+$. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.27; H, 8.85; N, 4.61.

Deprotection of 23 and 24 Using CAN. 23 and **24** (as a 3:1 mixture) were subjected to the conditions for the preparation of **15**. This gave **25** and **26** as a 3:1 mixture, which was separated by flash chromatography, as described.

(2*R*,5*S*)-5-*sec*-Butyl-2-methylmorpholin-3-one (25) (55%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89 (m, 6H), 1.22 (m, 1H), 1.40−1.60 (m, 2H), 1.42 (d, 3H, J = 6.9 Hz), 3.40−3.56 (m, 2H), 3.92 (dd, 1H, J = 11.1 and 3.6 Hz), 4.07 (q, 1H, J = 6.9 Hz), 6.65 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.1, 14.2, 17.3, 25.0, 36.9, 56.4, 65.7, 73.7, 172.5; IR ($CHCl_3$) 3398, 3010, 2971, 1664, 1451, 1118 cm^{-1}; MS (FD$^+$) m/z 171 (M)$^+$.

(2*S*,5*S*)-5-*sec*-Butyl-2-methylmorpholin-3-one (26) (20%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (m, 6H), 1.22 (m, 1H), 1.45 (d, 3H, J = 6.9 Hz), 1.55 (m, 1H), 1.67 (m, 1H), 3.19 (m, 1H), 3.75 (dd, 1H, J = 12.2 and 3.7 Hz), 3.91 (dd, 1H, J = 12.2 and 3.1 Hz), 4.20 (q, 1H, J = 6.9 Hz), 6.21 (bs, 1H); IR ($CHCl_3$) 3395, 3015, 2967, 1669, 1450, 1120 cm^{-1}; MS (FD$^+$) m/z 171 (M)$^+$.

(*R*)-*N*-(2-Chloropropionyl)-(*S*)-isoleucinol, *tert*-Butyldimethylsilyl Ether (27). To a solution of 500 mg (4.61 mmol) of (*R*)-(+)-2-chloropropionic acid in 40 mL of methylene chloride at 0 °C was added 622 mg (4.61 mmol) of 1-hydroxybenzotriazole (HOBt), followed by 883 mg (4.61 mmol) of 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDC). The reaction mixture was stirred at 0 °C for 1.5 h, after which 1.07 g (4.61 mmol) of (*S*)-isoleucinol, *tert*-butyldimethylsilyl ether in 10 mL of methylene chlorice was added. The reaction mixture was stirred for 2 h at 0 °C. The reaction mixture was worked up by washing with saturated sodium bicarbonate solution (2×), brine (2×) and 1 M citric acid (2×). The organic solution was dried over sodium sulfate and concentrated *in vacuo* to give 855 mg (58%) of **27** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.05 (s, 6H), 0.88−1.02 (m, 6H), 0.95 (s, 9H), 1.18 (m, 1H), 1.55 (m, 1H), 1.73 (m 1H), 1.79 (d, 3H, J = 7.1 Hz), 3.63 (dd, 1H, J = 12.3 and 3.0 Hz), 3.80 (m, 2H), 4.46 (q, 1H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.3, 15.5, 18.2, 22.9, 25.5, 25.7, 25.8, 35.4, 54.8, 56.3, 62.3, 169.0; IR ($CHCl_3$) 3279, 2963, 1656, 1258, 1124 cm^{-1}; MS (FD$^+$) m/z 322 (M+1)$^+$. Anal. Calcd for $C_{15}H_{32}NO_2Cl$: C, 55.96; H, 10.02; N, 4.35. Found: C, 55.91; H, 9.88; N, 4.63.

Preparation of (2*S*,5*S*)-5-*sec*-Butyl-2-methylmorpholin-3-one (26) from (*R*)-*N*-(2-Chloropropionyl)-(*S*)-isoleucinol, *t*-butyldimethylsilyl ether (27). A solution containing 842 mg (2.61 mmol) of **27** in 20 mL of chloroform was cooled to 0 °C under a nitrogen atmosphere. To this solution was added 0.35 mL (2.87 mmol) of boron trifluoride etherate, and the reaction mixture was allowed to slowly warm to 25 °C, where it was stirred for an additional 1.5 h. An additional 0.35 mL of boron trifluoride etherate was added, and the reaction mixture was stirred for an additional 1 h at 25 °C. The reaction was quenched with water, and the organic solution was washed with water (2×) and a saturated sodium bicarbonate solution (2×), dried over sodium sulfate, and concentrated *in vacuo* to give the (*R*)-*N*-(2-Chloroproprionyl)-(*S*)-isoleucinol as a white amorphous solid (mp 89−90 °C), which was characterized on the basis of its NMR spectrum: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.85−0.95 (m, 6H), 1.21 (m, 1H), 1.57 (m, 1H), 1.77 (m, 1H), 1.80 (d, 3H, J = 7.1 Hz), 3.70−3.88 (m, 3H), 4.50 (q, 1H, J = 7.1 Hz), 6.79 (bs, 1H). A solution of 50 mg (0.24 mmol) of this material, which was used without further purification, in 5 mL of THF was added to a suspension of 154 mg (0.96 mmol) of potassium hydride (25% in oil) in 5 mL of THF and 1 mL of DMF at 0 °C. The reaction mixture was stirred at 0 °C for 4 h, and the reaction was quenched by pouring the reaction mixture into methanol. The mixture was diluted with ethyl acetate and the organic phase washed with 1 N HCl, dried over sodium sulfate, and concentrated *in vacuo* to give 29 mg (72%) of **26**. This material was identical to the minor isomer (**26**) from the alkylation sequence described above.

(*S*)-5-*sec*-Butyl-4-(methoxymethyl)morpholin-3-one (28). 28 was prepared according to the procedure for the preparation of **13a**, with the reaction being quenched with 1.2 molar equiv of chloromethyl methyl ether (instead of *p*-methoxybenzyl chloride). **28** (85%)**:** $[\alpha]^{25}_D$ = +16.4 (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (m, 6H), 1.31 (m, 2H), 1.90 (m, 1H), 3.31 (s, 3H), 3.42 (m, 1H), 3.73 (dd, 1H, J = 12.3 and 3.9 Hz), 3.94 (dd, 1H, J = 12.3 and 3.5 Hz), 4.16 (s, 2H), 4.52 (d, 1H, J = 10.3 Hz), 5.23 (d, 1H, J = 10.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.3, 14.2, 26.6, 35.6, 56.4, 56.5, 64.5, 67.5, 73.9, 169.2; IR ($CHCl_3$) 3020, 2968, 1658, 1461, 1112 cm^{-1}; MS (FD$^+$) m/z 201 (M)$^+$. Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.42; H, 9.31; N, 7.10.

(2*R*,5*S*)-2-Benzyl-5-*sec*-butyl-4-(methoxymethyl)morpholin-3-one (29). A solution containing 350 mg (1.74 mmol) of **28** in 5 mL of THF was cooled to −78 °C under a nitrogen atmosphere. To this solution was added 1.30 mL of *n*-butyllithium (2.09 mmol, 1.6 M in hexane) *via* syringe. The bright yellow reaction mixture was stirred at −78 °C for 20 min, after which 0.228 mL (1.91 mmol) of benzyl bromide was added *via* syringe. The reaction mixture was stirred at −78

°C for 30 min, the cooling bath was removed, and the reaction mixture was allowed to warm to 25 °C and stirred for an additional 30 min. The reaction mixture was poured into water and diluted with ethyl acetate. The organic phase was separated, dried over sodium sulfate, and concentrated *in vacuo*. This crude material was purified by flash chromatography on a silica gel column using 50% ethyl acetate−hexane as the eluent. The major fractions were combined and concentrated to give 380 mg (75%, 10:1 selectivity) of **29** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (d, 3H, J = 6.8 Hz), 0.93 (t, 3H, J = 7.3 Hz), 1.21 (m, 1H), 1.28 (m, 1H), 1.88 (m, 1H), 3.09 (dd, 1H, J = 14.3 and 8.2 Hz), 3.12 (s, 3H), 3.30 (dd, 1H, J = 14.3 and 3.3 Hz), 3.52 (m, 1H), 3.65 (dd, 1H, J = 12.1 and 7.1 Hz), 3.88 (dd, 1H, J = 12.1 and 4.4 Hz), 4.34 (dd, 1H, J = 8.2 and 3.3 Hz), 4.50 (d, 1H, J = 10.4 Hz), 5.28 (d, 1H, J = 10.4 Hz), 7.15−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.3, 13.3, 26.4, 34.4, 37.8, 56.0, 56.7, 62.2, 73.6, 78.0, 126.5, 128.2, 129.8, 137.9, 171.1; IR ($CHCl_3$) 3012, 2967, 1656, 1454, 1114 cm^{-1}; MS (FD$^+$) m/z 291 (M)$^+$. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.99; H, 8.84; N, 5.04.

29 could be converted directly to (*S*,*R*)-isoleucine-Ψ[CH_2O]-phenylalanine·HCl (**16**), by acid hydrolysis (5 N HCl, 2 h, reflux) as described above. This single operation accomplishes MOM removal and lactam hydrolysis.

(2*S*,5*S*)-2-Benzyl-5-*sec*-butyl-4-(methoxymethyl)morpholin-3-one (30). A solution containing 350 mg (1.74 mmol) of **28** in 5 mL of THF was cooled to −78 °C under a nitrogen atmosphere. To this solution was added 1.30 mL of *n*-butyllithium (2.09 mmol, 1.6 M in hexane) *via* syringe. The bright yellow reaction mixture was stirred at −78 °C for 20 min, after which 0.228 mL (1.91 mmol) of benzyl bromide was added *via* syringe. The reaction mixture was stirred at −78 °C for 30 min, the cooling bath was removed, and the reaction mixture was allowed to warm to 25 °C and stirred for an additional 30 min. The reaction mixture was recooled to −78 °C, and another 1.30 mL of *n*-butyllithium was added. The reaction mixture was stirred at −78 °C for 30 min, after which the enolate was quenched by the dropwise addiition of 200 μL of glacial acetic acid in 1 mL of THF. The reaction mixture was warmed to 25 °C, poured into water, and diluted with ethyl acetate. The organic phase was washed with saturated sodium bicarbonate solution, dried over sodium sulfate, and concentrated *in vacuo*. This crude material was purified by flash chromatography on a silica gel column using 50% ethyl acetate−hexane as the eluent. The major fractions were combined and concentrated to give 365 mg (72%, 5:1 selectivity) of **30** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.83 (d, 3H, J = 7.0 Hz), 0.88 (t, 3H, J = 7.3 Hz), 1.25 (m, 2H), 1.68 (m, 1H), 3.03 (dd, 1H, J = 14.1 and 8.4 Hz), 3.27−3.36 (m, 2H), 3.33 (s, 3H), 3.64 (dd, 1H, J = 12.4 and 3.5 Hz), 4.04 (d, 1H, J = 12.4 Hz), 4.32 (dd, 1H, J = 8.4 and 3.5 Hz), 4.48 (d, 1H, J = 10.2 Hz), 5.26 (d, 1H, J = 10.2 Hz), 7.18−7.35 (m, 5H); IR ($CHCl_3$) 3011, 2967, 1655, 1455, 1092 cm^{-1}; MS (FD$^+$) m/z 291 (M)$^+$. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.99; H, 8.69; N, 4.86.

30 could be converted directly to (*S*,*S*)-isoleucine-Ψ[CH_2O]-phenylalanine·HCl (**21**), by acid hydrolysis (5 N HCl, 2 h, reflux) as described above. This single operation accomplishes MOM removal and lactam hydrolysis.

(5*R*,6*S*)-5-Methyl-6-phenylmorpholin-3-one (31). 31 was prepared according to the procedure for **12a**. **31** (78%) (mp 128−129 °C): $[\alpha]^{25}_D$ = +205.2 (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (d, 3H, J = 6.5 Hz), 3.72 (m, 1H), 4.33 (d, 1H, J = 16.9 Hz), 4.46 (d, 1H, J = 16.9 Hz), 4.93 (d, 1H, J = 2.6 Hz), 6.86 (bs, 1H), 7.25−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.3, 50.4, 67.0, 76.0, 124.5, 126.7, 127.4, 136.6, 168.4; IR (KBr) 3264, 2980, 1691, 1446, 1116 cm^{-1}; MS (FD$^+$) m/z 191 (M)$^+$. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.79; H, 6.75; N, 7.61.

(5*R*,6*S*)-4-(Methoxymethyl)-5-methyl-6-phenylmorpholin-3-one (32). 32 was prepared according to the procedure for **28**. **32** (82%): $[\alpha]^{25}_D$ = +81.2 (*c* 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (d, 3H, J = 6.5 Hz), 3.37 (s, 3H), 3.78 (dq, 1H, J = 6.5 and 2.6 Hz), 4.37 (d, 1H, J = 17.0 Hz), 4.47 (d, 1H, J = 17.0 Hz), 4.53 (d, 1H, J = 10.2 Hz), 4.92 (d, 1H, J = 2.4 Hz), 5.21 (d, 1H, J = 10.2 Hz), 7.28−7.40 (m 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.1, 54.2, 56.4, 67.8, 74.9, 78.0, 125.5, 127.8, 128.4, 137.6, 168.0; IR ($CHCl_3$) 3012, 1658, 1452, 1108 cm^{-1}; MS (FD$^+$) m/z 235 (M)$^+$. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.34; H, 7.32; N, 5.82.

(2*S*,5*R*,6*S*)-2-Benzyl-4-(methoxymethyl)-5-methyl-6-phenylmorpholin-3-one (33). 33 was prepared using the *n*-butyllithium alkylation condition as described in the preparation of **29**. **33** (76%, 3:1 selectivity): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.95 (d, 3H, J = 6.5 Hz), 3.22−3.31 (m, 2H), 3.33 (s, 3H), 3.72 (dq, 1H, J = 6.5 and 2.0 Hz), 4.51 (d, 1H, J = 10.2 Hz), 4.68 (dd, 1H, J = 7.2 and 4.8 Hz), 4.88 (d, 1H, J = 2.0 Hz), 5.28 (d, 1H, J = 10.2 Hz), 7.18−7.45 (m, 10H); IR ($CHCl_3$) 3010, 1657, 1453, 1103 cm^{-1}; MS (FD$^+$) m/z 325 (M)$^+$.

Acknowledgment. We thank the Physical Chemistry Department at Eli Lilly and Co. for their help in the characterization of products. We specifically thank Jonathan Paschal for his NOE studies which allowed us to make the necessary stereochemical assignments.

Supporting Information Available: 300 MHz ^{1}H and/or 75 MHz ^{13}C spectra for compounds lacking combustion data (25 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.

JO960496W