Improved Stereocontrolled Synthesis of *Threo* Peptidyl Epoxides

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Introduction

α-Amino epoxides and peptidyl epoxides can be used as chiral building blocks for further chemical transformations, yielding products of predetermined (stereo and regio) structures. As part of an ongoing project aimed at development of selective protease inhibitors, we were interested in such optically active peptidyl epoxides. The first synthesis of an α-amino epoxide (derived from an α-amino acid) was nonstereoselective, yielding a racemic mixture of the product.[1] This procedure, based on direct epoxidation of an α-amino aldehyde by a sulfonium ylide, was later improved to produce preferentially the *threo* isomer of the α-amino epoxide.[2] A second approach, based on stereoselective epoxidation of allylamines, yields the *threo* isomer in high enantiomeric excess, but in a poor to moderate yield.[3] This route has been extensively used for the synthesis of hydroxyethylene dipeptide isosteres.[4] An improved synthesis of the *threo* isomer of N-protected α-amino epoxides and peptidyl epoxides would contribute to such synthetic applications. In this paper we describe such an improvement, based on replacement of a crucial N-protecting group, and demonstrate its application to the synthesis of *threo* peptidyl epoxides.

Results and Discussion

Stereoselective synthesis of the *threo* isomer of N-protected α-amino epoxides was described by Luly et al.[3] It involved epoxidation of a chiral allylamine, which was in turn synthesized via a Wittig reaction between N-protected α-amino aldehyde and methylidenetriphenylphosphorane. This latter reaction proceeded in a low yield. The yield could be improved at the expense of significant loss of optical purity. We assumed that this was due to side reactions arising from proton abstraction by the Wittig reagent (acting as a base) and subsequent reactions of the amide anion thus formed. This assumption is based on the following considerations: (a) The pK_a values of the phosphonium salt and the carbamate are about 18[5,6] and 16,[7,6] respectively, and thus enable an efficient acid–base reaction between the phosphorus ylide and the carbamate proton. (b) The Wittig reactions of α-amino aldehydes with stabilized ylides (either the phosphorus ylides of acetone, ethyl acetate, acetonitrile, etc., or phosphonates) proceed in high yield.[8] The ylide in those reactions is too weak a base to remove the amide proton. (c) The Wittig reaction of unstabilized ylides with *N*-Boc-prolinal[9] and with *N*-Boc-*N,O*-isopropylideneserinal[10,11] produces high yields of the corresponding olefins. This analysis implies that a protecting group which lacks the acidic proton can improve the yield of the Wittig reaction and, hence, provide a more efficient synthesis of α-amino epoxides bearing the *threo* configuration.

We tested a few protecting groups, the best of which was the bulky triphenylmethyl (trityl) group.[12,13] It keeps the nitrogen as an amine, rather than as the carbamate present in the *N*-Boc or *N*-Cbz α-amino aldehyde. With a $pK_a \sim 35$, the amino group is a very weak acid, which does not react with a weak base such as the phosphorus ylide. In addition, the trityl protecting group shields the nitrogen from undesired interactions.

Scheme 1 outlines our synthetic route for the preparation of *threo* peptidyl epoxides. Tritylation of α-amino esters[14] was followed by DIBALH reduction.[15] *N*-trityl-α-amino aldehydes **4** were obtained either directly at this step or, in the case of full reduction, after a subsequent Swern oxidation[16] of the corresponding alcohols **3**. Both steps proceeded in very high yield (84–98%). Wittig reaction of the *N*-trityl-α-amino aldehydes **4** with methylidene triphenylphosphorane afforded the corresponding olefins **5** in high yield (85–90%). Hence, the main obstacle of the synthesis, described by Luly and co-workers,[3] has been removed. This represents a major advantage, especially when the protecting group has to be removed, as in the synthesis of peptidyl epoxides. Deprotection under acidic conditions yielded allylamines **6**. Reprotection (e.g., to

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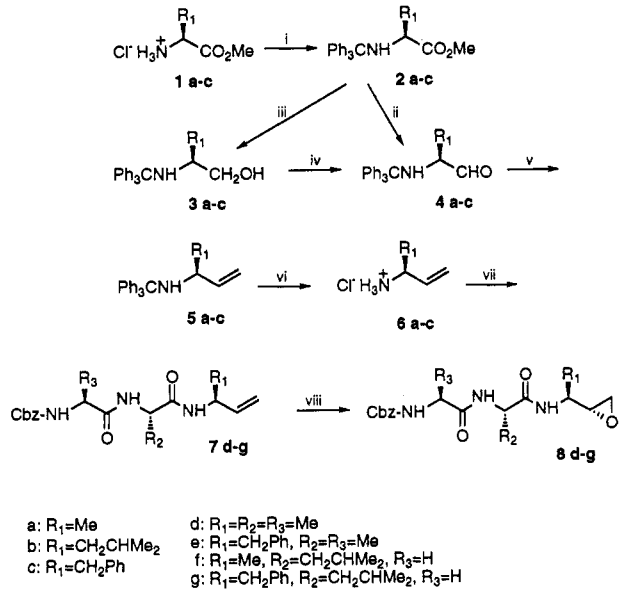
Scheme 1[a]



a: R_1=Me
b: R_1=CH_2CHMe_2
c: R_1=CH_2Ph
d: R_1=R_2=R_3=Me
e: R_1=CH_2Ph, R_2=R_3=Me
f: R_1=Me, R_2=CH_2CHMe_2, R_3=H
g: R_1=CH_2Ph, R_2=CH_2CHMe_2, R_3=H

[a] Key: (i) Ph_3CCl, Et_3N, CH_2Cl_2; (ii) DIBALH, toluene; (iii) LAH, Et_2O; (iv) DMSO, $(COCl)_2$; (v) $Ph_3P{=}CH_2$, THF; (vi) HCl, acetone; (vii) Cbz-aa$_3$aa$_2$, DCC, NHS; (viii) *m*-CPBA, CH_2Cl_2.

Table 1. Product Ratio[a] and Yield for the *m*-CPBA Epoxidation of Tripeptidyl Olefins 7

product	*erythro*	*threo*	yield (%)
Z-Gly-Leu-Phe epoxide	<5	>95[b]	78
Z-Ala-Ala-Phe epoxide	<5	>95[b]	85
Z-Ala-Ala-Ala epoxide	20	80	51
Z-Gly-Leu-Ala epoxide	33	67	30

[a] Determined by ^{1}H NMR. [b] Only one isomer was detected by ^{1}H and ^{13}C NMR.

form *N*-Boc or *N*-Cbz allylamines) and epoxidation would yield the known *threo* N-protected α-amino epoxides. Having overcome the main synthetic problem of this route (the Wittig reaction), we decided to continue directly to the peptidyl epoxides.[17] Thus, standard coupling[18] of **6** to a dipeptide afforded the tripeptidyl olefins **7**. Epoxidation of the peptidyl olefins was stereoselective, yielding excess of the *threo* isomer of the peptidyl epoxides **8** (Table 1). This stereoselectivity was observed by Luly and coworkers for the α-amino epoxides[3] and by others in some related systems.[4g,h,19]

Several points in the above synthetic route require elucidation:

The DIBALH reduction of α-amino esters was shown to stop at the aldehyde oxidation state when *N*-Boc-α-amino esters were reduced,[15,20] probably due to chelation with both the newly formed hydroxyl oxygen and the protecting amido nitrogen. (This is analogous to the chelation proposed for LAH reduction of *N*,*O*-dimethyl hydroxamates to the corresponding aldehydes.[21]) This

Table 2. Product Ratio[a] in DIBALH Reduction of *N*-Trityl α-Amino Methyl Esters 2

protecting group	R_1	aldehyde 4 (%)	alcohol 3 (%)
Cbz	CH_2Ph	>95[b]	<5
Ph_3C	CH_2Ph	<5	>95[c]
Ph_3C	CH_2CHMe_2	13[d]	59
Ph_3C	Me	>95[b]	<5

[a] Determined by ^{1}H NMR. [b] No trace of alcohol was detected. [c] No trace of aldehyde was detected. [d] The remaining 28% were unreacted ester.

chelation may be interrupted by neighboring bulky substituents, leading to full reduction to the corresponding alcohol. For the *N*-trityl-α-amino esters **2**, the extent of full reduction to an alcohol **3**, vs reduction to the aldehyde **4**, depends on the size of the side chain (see Table 2). Thus, in the alanine derivative (R = Me, **2a**), DIBALH reduction afforded the aldehyde, whereas in the phenylalanine and leucine derivatives (R = benzyl, **2c**, and R = CH_2CHMe_2, **2b**, respectively) the aldehydes were obtained by full reduction to the alcohol (either by DIBALH or LAH), followed by Swern oxidation.[16]

Enantiomeric purity of N-protected α-amino aldehydes is of major concern, since they are highly labile and easily racemize under various reaction and purification conditions.[12,22] Consequently, the enantiomeric integrity of the tripeptidyl olefins was determined. ^{1}H- and ^{13}C-NMR reveal the presence of one isomer only (data not shown). In order to ascertain this fact, we further studied the most labile amino aldehyde–that derived from phenylalanine. Thus, the tripeptidyl olefin Cbz-Gly-Leu-D-Phe olefin was synthesized from D-phenylalanine methyl ester in a similar way. Its ^{1}H and ^{13}C NMR spectra could be distinguished from those of the corresponding L isomer. ^{1}H NMR doping experiments indicate that less than 2%, at the most, of the opposite configuration at the α-carbon of the modified Phe may be present in the crude olefin product. Hence, the procedure described above does not affect any detectable epimerization on the α carbon of the modified amino acids. The same result was obtained by Luly et al.[3]

We turn now to the key step of this synthetic sequence, namely the stereoselective epoxidation of olefin **7**. This stereoselectivity is by no means trivial. The directing effect of allylic alcohols,[23] amides,[19a,24] and carbamates[3,19a,c,25] in epoxidation reactions is well documented. This effect was originally attributed, by Henbest,[23a] to hydrogen bonding between the hydroxy proton and one of the oxygens of the oxidizing reagent (**A** in Chart 1). Later, an analogous hydrogen bonding between the amido proton of an allylic amide and the same oxidant oxygen was postulated to

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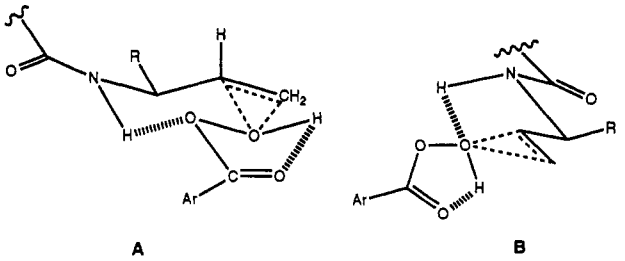
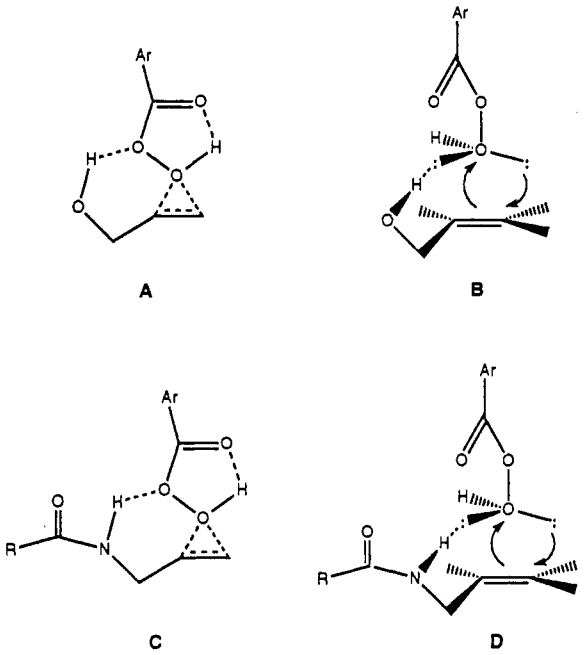


A B

Figure 1. Transition states for the *m*-CPBA epoxidation of chiral allyl amides: A, according to Henbest model, and B, according to Sharpless model.

Chart 1



A B C D

explain the steering effect of the amido group in epoxidation of allyl amides (**C** in Chart 1).[19a] On the basis of a detailed analysis of stereoelectronic effects, Sharpless suggested a modified mechanism (**B** in Chart 1) in which the hydrogen bond acceptor is the oxidizing oxygen of *m*-CPBA.[26] In light of this accepted model, Kocovsky and Stary have suggested a modified mechanism for the allylic amide directed epoxidation (**D** in Chart 1).[27] These mechanistic suggestions can directly predict the stereochemistry of epoxidation of cyclic allylic systems. However, the stereochemical outcome of epoxidation of acyclic allylic alcohols or amides is not straightforward, due to free rotation of the C–C single bonds between the two functional groups (the olefin and the directing alcohol or amide).

A possible explanation for the observed stereoselectivity in the epoxidation of chiral acyclic allylic amides (as in our system, as well as in others) can be derived from the transition state for the epoxidation reaction. The transition state, according to the "older" model,[23a] has a six-membered-ring distorted chair geometry, with the side chain R and the olefinic methylene as two vicinal substituents (**A** in Figure 1). This structure is based on a suggested hydrogen bonding between the amido proton of the olefin and one of the oxygens of the oxidant, *m*-CPBA, a second internal hydrogen bonding on *m*-CPBA, and the approach of the appropriate oxygen to the C=C double bond. This transition state is most stable when the two substituents are *trans* diequatorial, leading to the observed *threo* configuration. According to the "updated" mechanism, suggested by Kocovsky,[27] the transition state consists of a five-membered ring, with the side chain R and the olefinic methylene as two vicinal substituents (**B** in Figure 1). Molecular mechanics calculations predict that the most stable configuration of such 1,2-disubstituted cyclopentane is that where the two substituents are *trans* pseudodiequatorial. The energy difference between this geometry and the most stable *cis* isomer is 1.34 kcal/mol, compared with a 1.62 kcal/mol difference that was calculated for the cyclohexane analog. Thus, according to both models, the most stable transition state leads to a *threo* configuration of the peptidyl epoxide.

Further extension of this developed methodology, as well as its utilization for synthesis of novel protease inactivators, is currently under investigation in our laboratory and will be reported separately.

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded at 300 or 200 MHz and 75 or 50 MHz, respectively, in $CDCl_3$, unless otherwise specified. Chemical shifts are reported in ppm relative to TMS in $CDCl_3$ or relative to solvent resonance in other solvents. All ^1H NMR assignments were supported by homonuclear decoupling experiments, while ^{13}C NMR assignments were supported by off-resonance heteronuclear decoupling or 2-D hetero COSY experiments. Mass spectra were recorded in the CI mode with either isobutane or ammonia as the reagent gas, unless otherwise indicated. HPLC purification was carried out on Waters RCM 8 × 10 reversed-phase column. TLC was performed on E. Merck 0.2-mm precoated silica gel F-254 plates and viewed by Cl_2/KI–tolidine.[28] Flash column chromatography[29] was carried out on silica gel 60 (230–400 mesh ASTM, E. Merck). Molecular mechanics calculations were carried out using a PCMODEL program (Serena Software, Box 3076, Bloomington, IN 47402). Amino acids, protected amino acids, and protected peptides, all of the natural L (*S*) configuration, and D-phenylalanine methyl ester were purchased from Sigma Chemical Co. Anhydrous solvents were dried and freshly distilled (THF and ether from sodium/benzophenone, toluene from sodium, and CH_2Cl_2 from 4-Å molecular sieves).

***N*-Trityl-α-amino esters 2** were synthesized from the corresponding α-amino esters 1, in a 1 mmol scale, according to Applegate et al.[30]

***N*-Tritylalanine methyl ester (2a)** (90% yield, after crystallization from CH_2Cl_2): ^1H NMR δ 1.33 (d, J = 7.0 Hz, 3H, CH_3), 2.69 (d, J = 10.5 Hz, 1H, NH), 3.10 (s, 3H, CH_3O), 3.36 (dq, J = 10.5, 7.0 Hz, 1H, CHα), 7.15–7.50 (m, 15H, Ph); ^{13}C NMR δ 21.55 (CH_3), 51.31 (CH_3O), 51.82 (Cα), 71.02 (CPh_3), 126.18, 127.62, 128.61, 145.87 (Ph), 176.14 (CO_2); MS m/z 388 ($MC_4H_9^+$), 346 (MH^+), 285 ($M^+ - HCO_2CH_3$), 243 (CPh_3^+).

***N*-Tritylleucine methyl ester (2b)** (95% yield): ^1H NMR δ 0.86 (d, J = 6.3 Hz, 3H, CH_3), 0.88 (d, J = 7.0 Hz, 3H, CH_3), 1.59–1.63 (m, 3H, $CH_2\beta$ + CHγ), 3.17 (s, 3H, CH_3O), 3.34 (dd, J = 8.5, 5.4 Hz, 1H, CHα), 7.20–7.60 (m, 15H, Ph); ^{13}C NMR δ 17.90 (CH_3), 19.32 (CH_3), 20.53 (Cγ), 41.84 (Cβ), 47.04 (CH_3O), 50.80 (Cα), 66.94 (CPh_3), 122.15, 123.71, 124.72, 141.94 (Ph), 172.00 (CO_2); MS m/z 388 (MH^+), 243 (CPh_3^+), 146 (NH_2CH(i-Bu)-CO_2CH_3).

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N-Tritylphenylalanine methyl ester (2c) (78% yield): ^{1}H NMR δ 2.64 (d, J = 11.0 Hz, 1H, NH), 2.91 (dd, J = 8.8, 6.7 Hz, 1H, $CH_2\beta$), 2.95 (dd, J = 8.8, 6.4 Hz, 1H, $CH_2\beta$), 2.98 (s, 3H, CH_3O), 3.56 (ddd, J = 11.0, 6.7, 6.4 Hz, 1H, $CH\alpha$) 7.05–7.50 (m, 20H, Ph); ^{13}C NMR δ 42.17 ($C\beta$), 51.02 (CH_3O), 58.17 ($C\alpha$), 70.79 (CPh_3), 126.12, 126.46, 127.56, 128.03, 128.58, 129.61, 137.30, 145.67 (Ph), 174.62 (CO_2); MS m/z 422 (MH^+), 344 (MH^+ – PhH), 299 (MH^+ – $PhCH_2$ – CH_3OH), 285 (M^+ – Ph – HCO_2CH_3), 91 ($C_7H_7^+$).

N-Tritylleucinol (3b). A solution of 400 mg (1.0 mmol) of N-tritylleucine methyl ester (**2b**) in 30 mL of dry ether, under argon atmosphere at 0 °C, was treated with 38 mg (1.0 mmol) of lithium aluminum hydride. After 2 h, the reaction was quenched by 1 N HCl solution. Water (30 mL) was added, and the aqueous phase was extracted with 10 mL of methylene chloride. The combined organic phases were washed with water, dried over magnesium sulfate, filtered, and evaporated to afford clean product (302 mg, 84% yield): ^{1}H NMR δ 0.55 (d, J = 6.4 Hz, 3H, CH_3), 0.59 (m, 1H, $CH_2\beta$), 0.66 (d, J = 6.3 Hz, 3H, CH_3), 1.23–1.47 (m, 2H, $CH_2\beta$ + $CH\gamma$), 2.63 (tt, J = 7.0, 2.6 Hz, 1H, $CH\alpha$), 3.02 (dd, J = 10.8, 2.6 Hz, 1H, CH_2OH), 3.19 (dd, J = 10.8, 2.6, 1H, CH_2OH), 7.10–7.60 (m, 15H, Ph); ^{13}C NMR δ 21.48 (CH_3), 23.65 (CH_3), 24.72 ($C\gamma$), 42.52 ($C\beta$), 51.57 ($C\alpha$), 62.67 (CH_2OH), 71.24 (CPh_3), 126.29, 127.69, 128.67, 146.56 (Ph).

N-Tritylphenylalaninol (3c) was similarly prepared from **2c** in 84% yield: ^{1}H NMR δ 2.14 (dd, J = 13.0, 4.7 Hz, 1H, $CH_2\beta$), 2.39 (dd, J = 13.0, 9.2 Hz, 1H, $CH_2\beta$), 2.70 (dddd, J = 9.2, 4.7, 4.0, 2.5 Hz, 1H, $CH\alpha$), 2.79 (dd, J = 10.8, 4.0 Hz, 1H, CH_2O), 2.99 (dd, J = 10.8, 2.5 Hz, 1H, CH_2O), 6.95–7.65 (m, 20H, Ph); ^{13}C NMR δ 39.14 ($C\beta$), 55.28 ($C\alpha$), 62.33 (CH_2OH), 71.26 (CPh_3), 126.44, 127.81, 127.86, 128.20, 128.67, 129.38, 138.97, 146.54 (Ph); MS (EI) m/z 393 (M^+), 362 (M^+ – CH_2OH), 316 (M^+ – Ph), 302 (M^+ – C_7H_7), 91 ($C_7H_7^+$), 77 (Ph).

N-Tritylleucinal (4b) was prepared from 300 mg (0.84 mmol) of N-tritylleucinol (**3b**) by Swern oxidation[16] in 84% yield, crude. It was transferred to the subsequent Wittig reaction without further purification: ^{1}H NMR δ 0.81 (d, J = 6.5 Hz, 6H, CH_3), 1.35 (t, J = 7.0 Hz, 2H, $CH_2\beta$), 1.68 (m, J = 7 Hz, 1H, $CH\gamma$), 3.30 (td, J = 7.0, 2.7 Hz, 1H, $CH\alpha$), 7.18–7.52 (m, 15H, Ph), 8.95 (d, J = 2.7 Hz, 1H, CHO); ^{13}C NMR δ 22.48 (CH_3), 23.32 (CH_3), 24.20 ($C\gamma$), 41.77 ($C\beta$), 60.22 ($C\alpha$), 71.02 (CPh_3), 126.61, 127.85, 128.66, 146.05 (Ph), 203.00 (CHO); MS m/z 183 ($Ph_2CNH_3^+$), 116 (H_3N^+-CH(i-Bu)CHO), 85 ($NHCHCH_2CHMe_2$).

N-Tritylphenylalaninal (4c) was similarly prepared from 330 mg (0.84 mmol) of N-tritylphenylalaninol (**3c**) in 86% yield: ^{1}H NMR δ 2.53 (dd, J = 14.5, 7.0 Hz, 1H, $CH_2\beta$), 2.58 (dd, J = 14.5, 7.0 Hz, 1H, $CH_2\beta$), 3.40 (td, J = 7.0, 2.2 Hz, 1H, $CH\alpha$), 6.92–7.23 (m, 20H, Ph), 8.65 (d, J = 2.2 Hz, 1H, CHO); ^{13}C NMR δ 38.46 ($C\beta$), 62.85 ($C\alpha$), 70.85 (CPh_3), 126.49, 126.94, 127.77, 127.86, 128.48, 136.56, 145.68 (Ph), 202.70 (CHO); MS m/z 434 ($MC_3H_7^+$), 392 (MH^+), 362 (MH^+ – CH_2O), 314 (MH^+ – PhH), 285 ($CPh_3C_3H_7^+$).

N-Tritylalaninal (4a) was prepared, in 98% yield, from 345 mg (1 mmol) of the corresponding methyl ester **2a** by DIBALH reduction, according to a published procedure.[15] It was transferred to the subsequent Wittig reaction without further purification: ^{1}H NMR δ 0.88 (d, J = 7.2 Hz, 3H, CH_3), 2.61 (d, J = 7.9 Hz, 1H, NH), 3.17 (dqd, J = 7.9, 7.2, 1.7 Hz, 1H, $CH\alpha$), 7.00–7.40 (m, 15H, Ph), 8.82 (d, J = 1.7 Hz, 1H, CHO); ^{13}C NMR δ 16.85 (CH_3), 57.20 ($C\alpha$), 70.66 (CPh_3), 126.35, 127.47, 127.74, 145.55 (Ph), 202.32 (CHO); MS m/z 316 (MH^+), 285 (MH^+ – CH_2OH).

N-Trityl-α-amino Olefins 5. A 570-mg (1.4 mmol) portion of methyl triphenylphosphonium iodide was suspended in 30 mL of dry THF, under argon atmosphere at 0 °C. BuLi (0.9 mL of a 1.6 M solution in toluene) was added. The suspension dissolved, and the solution turned orange. After 10 min, the aldehyde (0.7 mmol in 5 mL of dry THF) was added and the ice bath removed. After 3 h, hexane (70 mL) was added, and the precipitate was filtered off. The solution was extracted with water, and the organic phase was dried over magnesium sulfate. Filtration, rotary evaporation, and purification by flash chromatography afforded the clean olefin.

N-Tritylalanyl olefin 5a (eluted with CH_2Cl_2/hexane (1:10), 90% yield): ^{1}H NMR δ 0.67 (d, J = 6.6 Hz, 3H, CH_3), 1.53 (bs, 1H, NH), 3.16 (qd, J = 6.6, 6.1 Hz, 1H, $CH\alpha$), 4.82 (ddd, J = 10.3, 1.7, 1.2 Hz, 1H, CH_2=), 5.04 (ddd, J = 17.2, 1.7, 1.4 Hz, 1H, CH_2=), 5.64 (ddd, J = 17.3, 10.3, 6.1 Hz, 1H, CH=), 7.10–7.65 (m, 15H, Ph); ^{13}C NMR δ 23.06 (CH_3), 51.07 ($C\alpha$), 71.56 (CPh_3), 111.62 (CH_2=), 126.17, 127.64, 128.91 (Ph), 144.17 (CH=), 147.09 (Ph); MS m/z 370 ($MC_4H_9^+$), 356 ($MC_3H_7^+$), 314 (MH^+), 299 (MH^+ – CH_3), 285 (MH^+ – C_2H_5).

N-Tritylleucyl olefin 5b (eluted with ether/hexane (1:9), 86% yield): ^{1}H NMR δ 0.57 (d, J = 6.5 Hz, 3H, CH_3), 0.69 (d, J = 6.6 Hz, 3H, CH_3), 0.71 (ddd, J = 13.6, 10.0, 4.3 Hz, 1H, $CH_2\beta$), 1.06 (ddd, J = 13.6, 9.6, 4.0 Hz, 1H, $CH_2\beta$), 1.33–1.49 (m, 1H, $CH\gamma$), 2.93 (ddddd, J = 10.1, 7.9, 4.3, 0.8, 0.5 Hz, 1H, $CH\alpha$), 4.80 (ddd, J = 16.2, 1.9, 0.8 Hz, 1H, CH_2=), 4.81 (ddd, J = 11.4, 1.9, 0.5 Hz, 1H, CH_2=), 5.59 (ddd, J = 16.3, 11.4, 8.1 Hz, 1H, CH=), 7.15–7.60 (m, 15H, Ph); ^{13}C NMR δ 21.24 (CH_3), 23.72 (CH_3), 24.44 ($C\gamma$), 46.50 ($C\beta$), 54.65 ($C\alpha$), 71.71 (CPh_3), 112.95 (CH_2=), 126.15, 127.57, 129.10 (Ph), 142.40 (CH=), 147.08 (Ph); MS m/z 412 ($MC_4H_9^+$), 398 ($MC_3H_7^+$), 356 (MH^+), 299 (MH^+ – C_4H_9), 113 (NH_2CH(i-Bu)$CHCH_2$).

N-Tritylphenylalanyl olefin 5c (eluted with CH_2Cl_2/hexane (1:10), 84% yield): ^{1}H NMR δ 2.09 (dd, J = 12.9, 8.1 Hz, 1H, $CH_2\beta$), 2.22 (dd, J = 12.9, 5.1 Hz, 1H, $CH_2\beta$), 3.16 (ddddd, J = 8.1, 7.0, 5.1, 1.1, 0.8 Hz, 1H, $CH\alpha$), 4.65 (ddd, J = 10.3, 1.9, 0.8 Hz, 1H, CH_2=), 4.69 (ddd, J = 17.2, 1.9, 1.1 Hz, 1H, CH_2=), 5.45 (ddd, J = 17.2, 10.3, 7.0 Hz, 1H, CH=), 6.70–7.55 (m, 20H, Ph); ^{13}C NMR δ 43.65 ($C\beta$), 57.35 ($C\alpha$), 71.57 (CPh_3), 113.34 (CH_2=), 125.92, 126.24, 127.66, 127.89, 128.97, 129.75, 138.61 (Ph), 141.56 (CH=), 146.91 (Ph); MS m/z 390 (MH^+).

α-Amino Olefin·HCl Salts 6. N-Trityl-α-amino olefin **5** (~0.6 mmol) was dissolved in 5 mL of acetone, 0.1 mL of 32% HCl solution was added, and the solution was refluxed for 3 h. CH_2Cl_2 (20 mL) was added, and the solution was extracted with 20 mL of 1 N HCl. The aqueous phase was made basic (pH ~10, Na_2CO_3) and extracted with CH_2Cl_2. This organic phase was acidified with 1 equiv of 32% HCl and dried over magnesium sulfate. Filtration and evaporation afforded the clean HCl salt of the amino olefin.

Alanyl olefin·HCl salt 6a (76% yield): ^{1}H NMR (in acetone-d_6) δ 1.46 (d, J = 6.7 Hz, 3H, CH_3), 4.02 (quintet, J = 6.7 Hz, 1H, $CH\alpha$), 5.27 (d, J = 10.5 Hz, 1H, CH_2=), 5.42 (d, J = 17.3 Hz, 1H, CH_2=), 6.03 (ddd, J = 17.3, 10.5, 6.7 Hz, 1H, CH=); ^{13}C NMR δ 19.17 (CH_3), 50.32 ($C\alpha$), 119.13 (CH_2=), 136.73 (CH=); MS m/z 72 (MH^+).

Leucyl olefin·HCl salt 6b (56% yield): ^{1}H NMR (in acetone-d_6) δ 0.94 (d, J = 5.9 Hz, 3H, CH_3), 0.96 (d, J = 5.9 Hz, 3H, CH_3), 1.55–1.85 (m, 3H, $CH_2\beta$ + $CH\gamma$), 3.96 (m, 1H, $CH\alpha$), 5.37 (d, J = 10.5 Hz, 1H, CH_2=), 5.53 (d, J = 17.2 Hz, 1H, CH_2=), 6.00 (ddd, J = 17.1, 10.3, 8.2 Hz, 1H, CH=), ^{13}C NMR δ 21.45 (CH_3), 22.71 (CH_3), 24.28 ($C\gamma$), 41.79 ($C\beta$), 52.97 ($C\alpha$), 120.55 (CH_2=), 133.63 (CH=); MS m/z 170 ($MC_4H_9^+$), 156 ($MC_3H_7^+$), 152 ($MC_3H_3^+$), 114 (MH^+).

Phenylalanyl olefin·HCl salt 6c (79% yield): ^{1}H NMR (in acetone-d_6) δ 3.09 (dd, J = 13.0, 10.3 Hz, 1H, $CH_2\beta$), 3.55 (dd, J = 13.0, 3.8 Hz, 1H, $CH_2\beta$), 4.18 (ddd, J = 10.3, 7.4, 3.8 Hz, 1H, $CH\alpha$), 5.22 (d, J = 10.0 Hz, 1H, CH_2=), 5.29 (d, J = 17.0 Hz, 1H, CH_2=), 6.01 (ddd, J = 17.3, 10.3, 7.4 Hz, 1H, CH=), 7.13–7.50 (m, 5H, Ph); ^{13}C NMR δ 39.75 ($C\beta$), 56.29 ($C\alpha$), 121.37 (CH_2=), 127.68, 129.39, 130.66 (Ph), 134.39 (CH=), 137.44 (Ph); MS m/z 148 (MH^+).

Tripeptidyl olefins 7 were prepared by coupling of an N-protected dipeptide with an α-amino olefin·HCl salt **6** in a solution-phase synthesis, according to a standard procedure.[18] Final purification was achieved by flash chromatography (elution with a step gradient of 1:3 to 1:1 of ether/hexane).

Cbz-alanyl-alanyl-alanyl olefin 7d (83% yield): ^{1}H NMR δ 1.21 (d, J = 6.7 Hz, 3H, CH_3), 1.36 (d, J = 7.4 Hz, 3H, CH_3), 1.37 (d, J = 6.1 Hz, 3H, CH_3), 4.25 (quintet, J = 6.5 Hz, 1H, $CH\alpha$), 4.46 (quintet, J = 7.1 Hz, 1H, $CH\alpha$), 4.49 (quintet, J = 6.9 Hz, 1H, $CH\alpha$), 5.01 (dt, J = 10.4, 1.5 Hz, 1H, CH_2=), 5.10 (bs, 2H, Cbz-CH_2), 5.16 (dt, J = 17.3, 1.5 Hz, 1H, CH_2=), 5.55 (d, J = 6.5 Hz, 1H, NH), 5.81 (ddd, J = 17.3, 10.4, 5.0 Hz, 1H, CH=), 6.52 (d, J = 7.1, Hz, 1H, NH), 6.92 (d, J = 6.9 Hz, 1H, NH), 7.33 (bs, 5H, Ph); ^{13}C NMR δ 18.18 (CH_3), 18.57 (CH_3), 20.12 (CH_3), 46.85 ($C\alpha$), 48.97 ($C\alpha$), 50.87 ($C\alpha$), 67.10 (Cbz-CH_2), 114.11 (CH_2=), 128.03, 128.23, 128.54, 136.05 (Ph), 139.11 (CH=), 156.04 (OCON), 171.10 (CON), 172.29 (CON); MS m/z 348 (MH^+), 277 (Cbz-alanyl-alanyl), 240 (MH^+ – $PhCH_2OH$), 91 ($C_7H_7^+$).

Cbz-alanyl-alanyl-phenylalanyl olefin 7e (88% yield): ^{1}H NMR δ 1.35 (d, J = 7.1 Hz, 3H, CH_3), 1.44 (d, J = 7.1 Hz, 3H, CH_3), 2.89 (dd, J = 13.8, 7.0 Hz, 1H, $CH_2\beta$), 2.95 (dd, J = 13.8, 7.3 Hz, 1H, $CH_2\beta$), 4.28 (qd, J = 7.0, 4.9 Hz, 1H, Ala-CHα), 4.49 (quintet, J = 7.2 Hz, 1H, Ala-CHα), 4.76 (quintet.t, J = 7.1, 1.5 Hz, 1H, Phe-CHα), 5.10 (dt, J = 10.5, 1.3 Hz, 1H, CH_2=), 5.12 (d, J = 12.4 Hz, 1H, Cbz-CH_2), 5.18 (dt, J = 17.1, 1.4 Hz, 1H, CH_2=), 5.19 (d, J = 12.4 Hz, 1H, Cbz-CH_2), 5.90 (ddd, J = 17.0, 10.5, 5.4 Hz, 1H, CH=), 6.60 (d, J = 5.8 Hz, 1H, Ala-NH), 7.20–7.50 (m, 11H, Phe-NH + Ph), 7.53 (d, J = 7.0 Hz, 1H, Ala-NH); ^{13}C NMR δ 18.12 (Ala-CH_3), 18.51 (Ala-CH_3), 41.04 (Phe-Cβ), 49.15 (Cα), 50.83 (Cα), 52.24 (Cα), 67.13 (Cbz-CH_2), 115.19 (CH_2=), 125.36, 126.92, 127.04, 127.24, 127.29, 128.49, 136.11 (Ph), 137.25 (CH=), 156.90 (OCON), 171.14 (CON), 172.20 (CON); MS m/z 424 (MH^+), 316 (MH^+ – $PhCH_2OH$), 277 (Cbz-alanyl-alanyl), 148 (H_3N^+CH(benzyl)$CHCH_2$), 91 ($C_7H_7^+$).

Cbz-glycyl-leucyl-alanyl olefin 7f (73% yield): ^{1}H NMR δ 0.88 (d, J = 6.3 Hz, 3H, Leu-CH_3), 0.90 (d, J = 6.4 Hz, 3H, Leu-CH_3), 1.16 (d, J = 6.9 Hz, 3H, Ala-CH_3), 1.50–1.70 (m, 3H, Leu-$CH_2\beta$ + CHγ), 3.89 (d, J = 5.4 Hz, 2H, Gly-CH_2), 4.48 (dqdt, J = 8.3, 6.9, 5.1, 1.3 Hz, 1H, Ala-CHα), 4.55 (m, 1H, Leu-CHα), 5.08 (s, 2H, Cbz-CH_2), 5.11 (dt, J = 17.2, 1.3 Hz, 1H, CH_2=), 5.32 (dt, J = 10.4, 1.3 Hz, 1H, CH_2=), 5.77 (ddd, J = 17.2, 10.4, 5.1 Hz, 1H, CH=), 6.06 (t, J = 8.3 Hz, 1H, Gly-NH), 6.94 (d, J = 8.3 Hz, 1H, Ala-NH), 7.31 (s, 5H, Ph), 7.39 (d, J = 8.3 Hz, 1H, Leu-NH); ^{13}C NMR δ 20.05 (Ala-CH_3), 22.18 (Leu-CH_3), 22.77 (Leu-CH_3), 24.80 (Leu-Cγ), 41.45 (Leu-Cβ), 44.53 (Gly-CH_2), 46.90 (Leu-Cα), 52.04 (Ala-Cα), 67.05 (Cbz-CH_2), 114.03 (CH_2=), 127.92, 128.07, 128.44 (Ph), 136.25 (CH=), 139.27 (Ph), 156.8 (OCON), 169.29 (CON), 171.11 (CON); MS m/z 393 (MNH_4^+), 376 (MH^+), 268 (MH^+ – $PhCH_2OH$).

Cbz-glycyl-leucyl-phenylalanyl olefin 7g (80% yield): ^{1}H NMR δ 0.86 (d, J = 5.9 Hz, 3H, Leu-CH_3), 0.89 (d, J = 5.9 Hz, 3H, Leu-CH_3), 1.35–1.67 (m, 3H, Leu-$CH_2\beta$ + CHγ), 2.80 (dd, J = 13.8, 7.4 Hz, 1H, Phe-$CH_2\beta$), 2.87 (dd, J = 13.8, 6.6 Hz, 1H, Phe-$CH_2\beta$), 3.74 (dd, J = 8.8, 5.0 Hz, 1H, Gly-CH_2), 3.80 (dd, J = 8.8, 5.6 Hz, 1H, Gly-CH_2), 4.40 (td, J = 8.5, 5.9 Hz, 1H, Leu-CHα), 4.73 (m, 1H, Phe-CHα), 5.10 (dt, J = 10.4, 1.5 Hz, 1H, CH_2=), 5.11 (dt, J = 17.2, 1.5 Hz, 1H, CH_2=), 5.12 (s, 2H, Cbz-CH_2), 5.47 (t, J = 5.3 Hz, 1H, Gly-NH), 5.81 (ddd, J = 17.2, 10.4, 5.4 Hz, 1H, CH=), 6.39 (d, J = 9.1 Hz, 1H, Phe-NH), 6.49 (d, J = 8.5 Hz, 1H, Leu-NH), 7.08–7.36 (m, 10H, Ph); ^{13}C NMR δ 22.10 (Leu-CH_3), 22.74 (Leu-CH_3), 24.76 (Leu-Cγ), 40.63 (Leu-Cβ), 40.90 (Phe-Cβ), 44.61 (Gly-CH_2), 51.86 (Cα), 52.11 (Cα), 67.33 (Cbz-CH_2), 115.25 (CH_2=), 126.50, 127.93, 128.10, 128.30, 128.57, 129.41 (Ph), 137.29 (CH=), 157.0 (OCON), 169.00 (CON), 170.88 (CON); MS (EI) m/z 452 (MH^+), 360 (M^+ – $C_7H_7^+$), 305 (Cbz-glycyl-leucyl), 277 (MH^+ – $CONHCH(CH_2Ph)CHCH_2$), 176 ($HCONHCH(CH_2Ph)CHCH_2^+$), 91 ($C_7H_7^+$).

Cbz-glycyl-leucyl-D-phenylalanyl olefin 7h (98% yield, crude): ^{1}H NMR (in $CDCl_3$/$(CD_3)_2CO$) δ 0.78 (d, J = 2.9 Hz, 6H, Leu-CH_3), 1.31 (m, 3H, Leu-$CH_2\beta$ + CHγ), 2.76 (dd, J = 13.8, 8.5 Hz, 1H, Phe-$CH_2\beta$), 2.88 (dd, J = 13.8, 6.4 Hz, 1H, Phe-$CH_2\beta$), 3.75 (dd, J = 16.5, 5.5 Hz, 1H, Gly-CH_2), 3.84 (dd, J = 17.2, 5.5 Hz, 1H, Gly-CH_2), 4.39 (q, J = 7.9 Hz, 1H, Leu-CHα), 4.69 (quintet, J = 7 Hz, 1H, Phe-CHα), 5.00 (dt, J = 10.4, 1.4 Hz, 1H, CH_2=), 5.06 (s, 2H, Cbz-CH_2), 5.10 (dt, J = 17, 1.5 Hz, 1H, CH_2=), 5.78 (ddd, J = 17.2, 10.4, 5.4 Hz, 1H, CH=), 6.17 (bt, 1H, Gly-NH), 7.05 (d, J = 8.5 Hz, 1H, Phe-NH), 7.15–7.36 (m, 10H, Ph); ^{13}C NMR δ 21.72 (Leu-CH_3), 22.39 (Leu-CH_3), 24.26 (Leu-Cγ), 40.55 (Leu-Cβ), 40.81 (Phe-Cβ), 44.11 (Gly-CH_2), 51.84 (Cα), 52.36 (Cα), 66.71 (Cbz-CH_2), 114.76 (CH_2=), 126.16, 127.65, 127.82, 128.02, 128.20, 129.08, 136.02 (Ph), 137.20 (CH=), 137.44 (Ph), 156.9 (OCON), 169.31 (CON), 171.54 (CON).

Tripeptidyl Epoxides (*Threo* Isomer) 8. A 210-mg (0.6 mmol) portion of *m*-CPBA (50%) was added to a CH_2Cl_2 solution (10 mL) containing 0.5 mmol of the tripeptidyl olefin 7 and 105 mg (0.6 mmol) of K_2HPO_4 in 0.1 mL of water. After 20 h of stirring at rt, ethyl acetate (30 mL) was added, and the solution was washed consecutively with 30 mL of saturated $NaHCO_3$, 10% $NaHSO_3$, saturated $NaHCO_3$, water, and brine. It was then dried over magnesium sulfate, filtered, and evaporated to dryness. Flash chromatography (ether/hexane (2:1)) afforded the clean product (as a mixture of isomers). The two isomers were separated from small samples by reversed-phase HPLC (Waters RCM 8 × 10 RP column, 2 mL/min, a gradient of 50% CH_3CN/H_2O to 100% CH_3CN for 5 min, followed by 3 min at 100% CH_3CN).

Cbz-alanyl-alanyl-alanyl epoxide (8d) (51% yield, *threo*/*erythro* (4:1)): ^{1}H NMR δ (*threo*) 1.22 (d, J = 7.0 Hz, 3H, CH_3), 1.25 (d, J = 7.4 Hz, 3H, CH_3), 1.34 (d, J = 7.5 Hz, 3H, CH_3), 2.55 (dd, J = 4.6, 2.7 Hz, 1H, CH_2O), 2.73 (dd, J = 4.6, 4.0 Hz, 1H, CH_2O), 3.01 (dt, J = 4.0, 2.7 Hz, 1H, CHO), 4.17–4.50 (m, 3H, CHα), 5.12 (bs, 2H, Cbz-CH_2), 5.49 (d, J = 7.0 Hz, 1H, NH), 6.33 (d, J = 6.8 Hz, 1H, NH), 6.78 (bs, 1H, NH), 7.35 (bs, 5H, Ph); (*erythro*) 2.75 (m, 2H, CH_2O), 2.94 (m, 1H, CHO); MS m/z 381 (MNH_4^+), 364 (MH^+), 256 (MH^+ – $PhCH_2OH$); HPLC t_R (*threo*) 2.17 min, (*erythro*) 4.40 min.

Cbz-alanyl-alanyl-phenylalanyl epoxide (8e) (85% yield, only the *threo* isomer was detected by NMR): ^{1}H NMR δ 1.28 (d, J = 7.0 Hz, 3H, Ala-CH_3), 1.37 (d, J = 6.8 Hz, 3H, Ala-CH_3), 2.52 (dd, J = 4.5, 2.7 Hz, 1H, CH_2O), 2.68 (dd, J = 4.5, 4.1 Hz, 1H, CH_2O), 2.93 (d, J = 7.3 Hz, 2H, Phe-$CH_2\beta$), 3.05 (m, 1H, CHO), 4.19 (m, 1H, Ala-CHα), 4.35 (m, 1H, Ala-CHα), 4.47 (m, 1H, Phe-CHα), 5.12 (bs, 2H, Cbz-CH_2), 5.33 (d, J = 6.9 Hz, 1H, Ala-NH), 6.24 (d, J = 8.4 Hz, 1H, Ala-NH), 6.55 (d, J = 6.2 Hz, 1H, Phe-NH), 7.20–7.35 (m, 10H, Ph); ^{13}C NMR δ 18.35 (Ala-CH_3), 18.59 (Ala-CH_3), 39.12 (Phe-Cβ), 44.59 (CH_2O), 49.17 (CHO), 49.28 (Cα), 50.69 (Cα), 52.42 (Cα), 67.09 (Cbz-CH_2), 126.67, 127.95, 128.19, 128.50, 129.26, 136.21, 137.06 (Ph), 156.02 (OCON), 171.85 (CON), 172.29 (CON); MS m/z 468 ($MC_2H_5^+$), 440 (MH^+), 91 ($C_7H_7^+$); HPLC t_R (*threo*) 2.52 min.

Cbz-glycyl-leucyl-alanyl epoxide (8f) (30% yield, *threo*/*erythro* (2:1)): ^{1}H NMR δ 0.92 (d, J = 6 Hz, 3H, Leu-CH_3), 0.94 (d, J = 6 Hz, 3H, Leu-CH_3), 1.23 (d, J = 7 Hz, 3H, Ala-CH_3), 1.40–1.65 (m, 3H, Leu-$CH_2\beta$ + CHγ), 2.54 (dd, J = 4.5, 3.0 Hz, 1H, CH_2O), 2.72 (dd, J = 4.5, 4.1 Hz, 1H, CH_2O), 3.00 (dt, J = 4.1, 3.0 Hz, 1H, CHO), 3.83 (bs, 2H, Gly-CH_2), 4.42–4.53 (m, 2H, Ala-CHα + Leu-CHα), 5.18 (s, 2H, Cbz-CH_2), 5.67 (bt, 1H, Gly-NH), 6.51 (d, J = 6.8 Hz, 1H, NH), 6.93 (d, J = 6.7 Hz, 1H, NH), 7.37 (s, 5H, Ph); MS m/z 409 (MNH_4^+), 392 (MH^+); HPLC t_R (*threo*) 3.50 min, (*erythro*) 3.72 min.

Cbz-glycyl-leucyl-phenylalanyl epoxide (8g) (78% yield, only the *threo* isomer was detected by NMR): ^{1}H NMR δ 0.86 (d, J = 7.1 Hz, 3H, Leu-CH_3), 0.87 (d, J = 7.1 Hz, 3H, Leu-CH_3), 1.45–1.62 (m, 3H, Leu-$CH_2\beta$ + CHγ), 2.48 (dd, J = 4.1, 3.6 Hz, 1H, CH_2O), 2.62 (t, J = 4.1 Hz, 1H, CH_2O), 2.87 (dd, J = 13.1, 7.2 Hz, 1H, Phe-$CH_2\beta$), 2.90 (dd, J = 13.1, 7.2 Hz, 1H, Phe-$CH_2\beta$), 3.01 (m, 1H, CHO), 3.71 (dd, J = 17.1, 5.0 Hz, 1H, Gly-CH_2), 3.80 (dd, J = 17.1, 5.8 Hz, 1H, Gly-CH_2), 4.52 (m, 2H, Leu-CHα + Phe-CHα), 5.01 (s, 2H, Cbz-CH_2), 6.20 (bt, J = 5 Hz, 1H, Gly-NH), 6.56 (d, J = 7.9 Hz, 1H, NH), 6.73 (d, J = 8.2 Hz, 1H, NH), 7.10–7.55 (m, 10H, Ph); ^{13}C NMR δ 22.04 (Leu-CH_3), 22.71 (Leu-CH_3), 24.79 (Leu-Cγ), 39.02 (Phe-Cβ), 40.91 (Leu-Cβ), 44.56 (CH_2O), 44.68 (Gly-CH_2), 49.32 (CHO), 52.00 (Cα), 52.51 (Cα), 67.27 (Cbz-CH_2), 126.64, 128.05, 128.24, 128.45, 128.54, 129.30, 136.11, 137.07 (Ph), 156.67 (OCON), 169.13 (CON), 171.71 (CON); MS m/z 485 (MNH_4^+), 468 (MH^+), 452 (MH^+ – O), 377 (MNH_4^+ – $PhCH_2OH$), 360 (MH^+ – $PhCH_2OH$); HPLC t_R (*threo*) 5.13 min.

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of all compounds (44 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.