Diastereoselective Rh-Mediated Construction of 2,3,5-Trisubstituted Tetrahydrofurans

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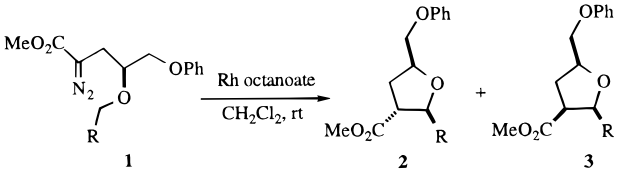
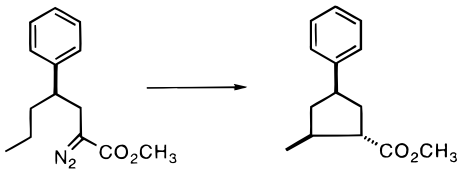
Dirhodium(II) carboxylate catalyzed cyclization of a series of γ-alkoxy-α-diazo esters **1** has been shown to proceed with substantial diastereoselectivity, producing the 2,3,5-trisubstituted tetrahydrofurans **2** and **3**. The diastereoselectivity of the cyclization improved as the electron-withdrawing ability of the substituent R increased. A mechanistic hypothesis is presented.

We recently reported[1] that Rh-mediated cyclization[2−4] of **1** (R = CH_3) proceeded with high diastereoselectivety, to give predominantly **2**. We describe here a detailed study of the scope of this cyclization. It is particularly noteworthy that the diastereoselectivity of the cyclization is a function of the electron-withdrawing ability of the substituent R.



1 **2** **3**

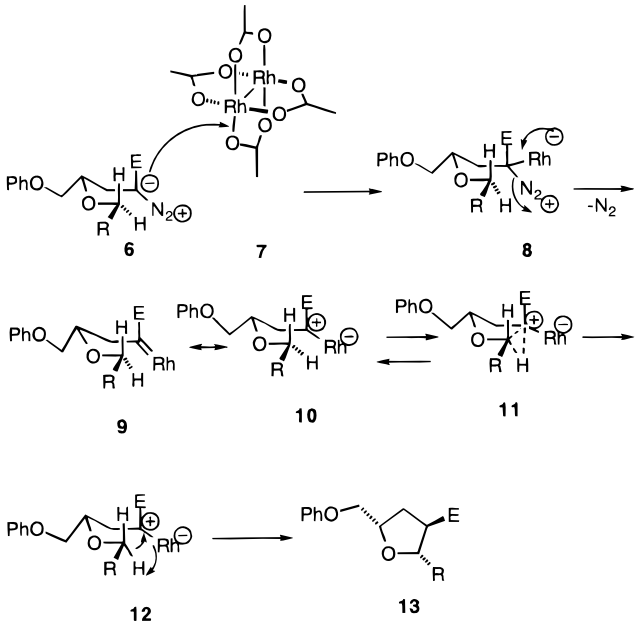
We have presented[5,6] a computational model that accurately predicts the dominant diastereomer from the Rh-mediated cyclizations of simple α-diazo esters (*e.g.*, **4** → **5**). Applying this model to the cyclization of **1**



4 **5**

(Scheme 1), the point of commitment to a particular diastereomer is represented by transition state **12**, in which there is overlap between the C═Rh bond and the target C−H bond. There are four diastereomeric chair-like transition states (**12**) for the cyclization of **1**, each leading to one of the four possible diastereomeric products. With the positions of the ligands on Rh locked and the angles and bonds defined as before,[5] we minimized each of the four transition states with molecular mechanics. The transition state **12** in which both substituents are equatorial on the "chair" was found to be 3.5 kcal/mol lower in energy then the next most stable transition state. Consequently, we predicted that **2** should be the dominant product from the cyclization of **1**.

Scheme 1



⊗ Abstract published in *Advance ACS Abstracts*, September 1, 1996.

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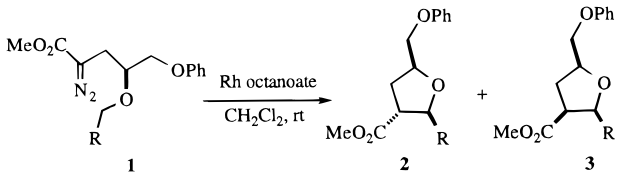
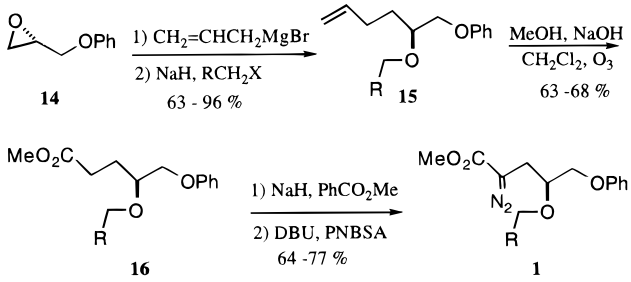
Table 1. Diastereoselectivity in the Cyclization of α-Diazo Esters 1



1 2 3

entry	R	yield, % (2 + 3)	ratio (2/3)
1	**1a:** 4-MeOPh	89	1.7:1 (**2a:3a**)
2	**1b:** Ph	92	3:1 (**2b:3b**)
3	**1c:** 4-BrPh	93	3.1:1 (**2c:3c**)
4	**1d:** 4-NO_2Ph	94	3.2:1 (**2d:3d**)
5	**1e:** CH=CH_2	94	3:1 (**2e:3e**)
6	**1f:** CH_2CH_3	93	3.3:1 (**2f:3f**)
7	**1g:** CH_2CH_2OMe	92	3.4:1 (**2g:3g**)
8	**1h:** CH_3	93	4 :1 (**2h:3h**)
9	**1i:** CH_2OMe	92	8:1 (**2i:3i**)
10	**1j:** CH_2OPh	89	11.4:1 (**2j:3j**)

Scheme 2

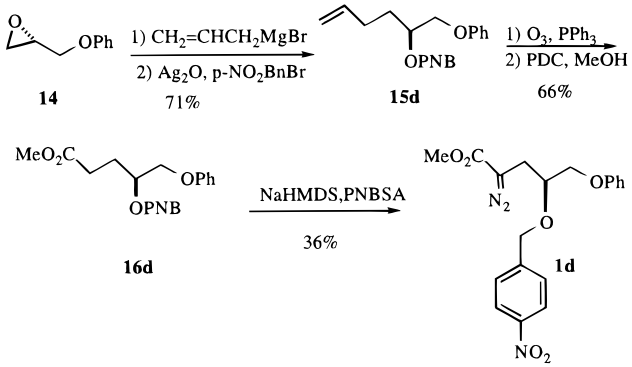


Results and Discussion

The γ-alkoxy-α-diazo esters **1a**−**1j** (Table 1) were generally prepared from 1,2-epoxy-3-phenoxypropane (**14**) (Scheme 2). The epoxide was opened with allylmagnesium bromide, and the resultant secondary alcohol was alkylated with an alkyl halide to give the phenyl ethers **15**. Ozonolysis in CH_2Cl_2 following the procedure of Marshall[7,8] gave the γ-alkoxy esters **16**. Diazo transfer[10,11] was then effected by benzoylation[12] of the esters **16** followed by exposure to DBU[13] and 4-nitrobenzenesulfonyl azide (PNBSA).[14]

The γ-alkoxy-α-diazo ester **1d** was prepared by a different route, because the 4-nitrobenzyl group is readily decomposed by NaH and by NaOH. As shown in Scheme 3, the secondary alcohol from the opening of the expoxide was alkylated with Ag_2O[15] and 4-nitrobenzyl bromide to give phenyl ether **15d**. Selective ozonolysis of **15d** in CH_2Cl_2 followed by reduction with PPh_3 gave the aldehyde. This phenoxy aldehyde was further oxidized with PDC[10] in DMF and MeOH to give the γ-alkoxy ester **16d**.

Scheme 3

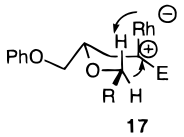


Diazo transfer was then effected directly by treating **16d** with NaHMDS and PNBSA.[14b]

Catalytic rhodium octanoate in CH_2Cl_2 at room temperature smoothly cyclized **1a**−**j** to mixtures of **2a**−**j** and **3a**−**j** (Table 1). No β-H elimination product[4] was detected in any of these cyclizations. This may be due to the inductively electron-withdrawing γ-alkoxy group,[16] which makes the β-H less electron rich.

As two new stereogenic centers are created in the cyclization of **1**, *four* diastereomeric products are possible. However, in general only two diastereomers were observed.[17] The major diastereomer was the 2,3-trans-3,5-trans trisubstituted tetrahydrofuran **2**, and the minor diastereomer was the 2,3-cis-3,5-cis trisubstituted tetrahydrofuran **3**, as demonstrated by NOE experiments. As shown in Figure 1, irradiation of H_1 in **2e** gave a 6.5% enhancement of H_{2b} and irradiation of H_3 in **2e** gave a 3.9% enhancement of H_{2a}. For the minor diastereomer, irradiation of H_1 in **3e** gave a 2.0% enhancement of H_3 and H_4. The irradiation of H_3 in **3e** gave a 5.8% enhancement of H_4.

The diastereoselectivity observed for the cyclization of **1b** and **1e** was lower than that which we had observed in cyclopentane-forming cyclizations.[5] Even more striking, the minor diastereomer observed was the *least* likely from the analysis in Scheme 1 (both substituents axial in the chairlike transition state leading to cyclization). This observation led us to an intriguing hypothesis. The computational analysis[5] that we employ does not distinguish between "chair" transition states such as **12** and



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"boat" transition states such as **17**. Empirically, the products observed in the all-carbon case were derived from chair transition states, suggesting an electronic preference for a chairlike transition state. We recognized that the C−H insertion site adjacent to oxygen was particularly electron rich and thus more reactive than the C−H of a simple alkyl group.[3e] Thus, the point of commitment to bond formation might be occurring earlier on the reaction coordinate, when the chair preference might not be as pronounced. We therefore hypothesized

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(8) Substrate **15b** was ozonized to the aldehyde (O_3/CH_2Cl_2, Ph_3P), which was then oxidized to the methyl ester (PDC/MeOH).[10]
(9) O'Connor, B.; Just, G. *Tetrahedron Lett.* **1987**, *28*, 3235.
(10) Taber, D. F.; You, K.; Song, Y. *J. Org. Chem.* **1995**, *60*, 1093.
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(17) For R = 4-MeOPh, all four diasteromers are observed, in a ratio of 56:33:4:4.

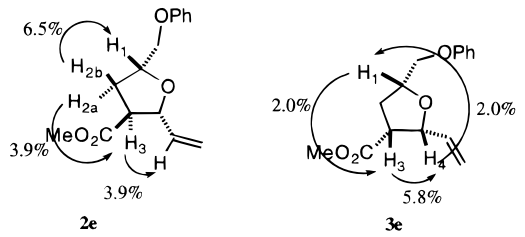
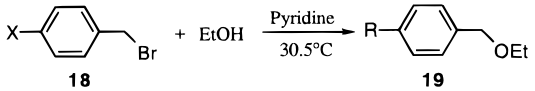


Figure 1. NOE of tetrahydrofuans **2e** and **3e**

that the diastereoselectivity of the cyclization might improve if the reactivity of the target C−H were attenuated by an electron-withdrawing substituent.[16]

Two sets of experiments are summarized in Table 1: a substituted benzyl series and a substituted ethyl series. In the substituted benzyl series, when the substituent R was the strongly electron-donating 4-methoxyphenyl group (entry **1**), the ratio of the two major diastereomers was only 1.7:1, *and* all *four* of the possible diastereomers were observed.[17] When the substituent R was phenyl, only two diastereomers were observed, with the ratio of major to minor increasing to 3:1. When the substituents were electron-withdrawing, 4-bromophenyl and 4-nitrophenyl (entries 3 and 4), the diastereoselectivity increased slightly, to 3.1:1 and 3.2:1, respectively. This experimental result agrees well with the rate of solvolysis of substituted benzylic halides.[18] As reported,[19] the solvolysis rate of 4-methoxybenzyl bromide (**18b**) is 160 times faster than that of benzyl bromide (**18a**), whereas the solvolyses of the 4-bromobenzyl and 4-nitrobenzyl bromides **18c** and **18d**, are only slightly slower than that of benzyl bromide (**18a**) (0.67 and 0.35, respectively).



18 **19**

X	Relative Rates
a, H	1
b, 4-MeO	160
c, 4-Br	0.67
d, 4-NO_2	0.35

In the substituted ethyl series (Table 1), the electron-withdrawing effect on the diastereoselectivity of C−H insertion is more pronounced. Comparing the substituents (R) vinyl and ethyl (entries 5 and 6), the diastereoselectivity ratio increased only slightly from 3:1 to 3.3:1. The influence of the β-methoxy group is stronger, with the ratio increasing to 8:1 (entry 9).[18] The β-phenoxy group, still more strongly electron-withdrawing, gave a ratio of 11.4:1.

These two series of experiments strongly support the hypothesis that the diastereoselectivity of the cyclization improves if the reactivity of the target C−H is attenuated by an electron-withdrawing substituent. To further probe this hypothesis, we cyclized **1f** with rhodium trifluoroacetate, a catalyst that is known to make a very reactive carbene,[6c] with a very early (and thus open) transition state. In fact, exposure of **1f** to rhodium trifluroacetate gave an approximately *equal* mixture of *all four* of the product diastereomers.

It is apparent that both steric and electronic effects can contribute to diastereoselectivity in Rh-mediated intramolecular C−H insertion. We expect that the family of diazo esters **1** and their derivatives will become very useful probes for the study of electronic effects in these Rh-mediated cyclizations.[3] The work described here also opens the way for the highly diastereocontrolled construction of 2,3,5-trisubstituted tetrahydrofurans.

Experimental Section[20]

Methyl 2-Diazo-4-((4-methoxyphenyl)methoxy)-5-phenoxypentanoate (**1a**). At 0 °C, NaH (185 mg, 4.62 mmol, 60% in mineral) was added to **16a** (0.53 g, 1.54 mmol) in 4 mL of dry THF. After 10 min at 0 °C, methyl benzoate (422 mg, 3.1 mmol) was added all at once; then the reaction mixture was heated to reflux for 10 h. The reaction was cooled and quenched by cautiously adding 1 N aqueous HCl, to pH = 4. The mixture was partitioned between 20% EtOAc/petroleum ether and, sequentially, 1 N aqueous HCl and saturated aqueous NaCl. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give methyl 2-benzoyl-4-((4-methoxyphenyl)methoxy)-5-phenoxypentanoate (0.533 g, yield 77%).

DBU (468 mg, 3.08 mmol) was added to a solution of methyl 2-benzoyl-4-((4-methoxyphenyl)methoxy)-4-phenoxypentanoate (0.69 g, 1.54 mmol) in 4 mL of CH_2Cl_2 at 0 °C. After 10 min, 702 mg of 4-nitrobenzenesulfonyl azide (3.08 mmol) was added. The reaction mixture was warmed up to rt for 2 h; then the mixture was partitioned between 6 mL of 0.5 M aqueous phosphate buffer (pH = 7.0) and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give **1a** (490 mg, 66% yield from **16a**) as a bright yellow oil: TLC R_f(20% EtOAc/petroleum ether) = 0.38; ^{1}H NMR δ 7.23 (m, 4H), 6.85 (m, 5H), 4.66 (d, 1H, J = 11.3 Hz), 4.55 (d, 1H, J = 11.3 Hz), 4.01 (m, 2H), 3.93 (m, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 2.66 (dd, 1H, J = 4.5, 15.4 Hz), 2.56 (dd, 1H, J = 7.1, 15.4 Hz); ^{13}C NMR δ u, 167.7, 159.3, 158.5, 130.0, 72.0, 69.2, 26.5; d, 129.5, 129.4, 121.0, 114.5, 113.8, 75.6, 55.2, 51.8; IR cm^{-1} 2952, 2089, 1693, 1600, 1514, 1497, 1438, 1344, 1248, 1134, 1036, 821, 755, 692.

Methyl 2-Diazo-4-(4-phenylmethoxy)-5-phenoxypentanoate (1b). The procedure described for **1a** was employed. The overall yield was 77%. **1b**: TLC R_f(20% EtOAc/petroleum ether) = 0.40; ^{1}H NMR δ 7.28 (m, 7 H), 6.95 (m, 3H), 4.73 (d, J = 11.7 Hz, 1H), 4.62 (d, J = 11.7 Hz, 1H), 4.03 (m, 2H), 3.97 (m, 1H,), 3.70 (s, 3H), 2.68 (dd, J = 4.6, 15.4 Hz, 1H), 2.56 (dd, J = 4.6, 16.4 Hz, 1H); ^{13}C NMR δ u,158.3, 137.9, 72.2, 68.9, 26.3; d, 129.3, 128.2, 127.7, 127.5, 120.9, 114.3, 75.9, 51.6; IR cm^{-1} 2089, 1694, 1599, 1497, 1437, 1346, 1245, 1133, 754, 693.

Methyl 2-Diazo-4-((4-bromophenyl)methoxy)-5-phenoxypentanoate (**1c**). The procedure described for **1a** was employed. The overall yield was 72%. **1c**: TLC R_f(20% EtOAc/petroleum ether) = 0.51; ^{1}H NMR δ 7.44 (m, 2H), 7.29 (m, 2H), 7.25 (m, 2H), 6.96 (m, 3H), 4.68 (d, 1H, J = 11.9 Hz), 4.57 (d, 1H, J = 11.9 Hz), 4.04 (d, 2H, J = 5.1 Hz), 3.94 (m, 1H), 3.71 (s, 3H), 2.68 (dd, 1H, J = 4.6, 15.3 Hz), 2.58 (dd, 1H, J = 7.2, 15.3 Hz); ^{13}C NMR δ u, 158.4, 136.9, 121.6, 71.6, 69.2, 26.5; d, 131.4, 129.5, 129.4, 121.1, 114.5, 76.2, 51.9; IR cm^{-1} 2925, 2088, 1694, 1600, 1496, 1437, 1344, 1244, 1137, 1011, 805, 755, 692.

Methyl 2-Diazo-4-((4-nitrophenyl)methoxy)-5-phenoxypentanoate (**1d**). NaHMDS (1.1 mL, 1 N in THF) was added to a solution of **16d** (186 mg) in 6 mL of dry THF at −78 °C. The mixture was stirred at −78 °C for 20 min and the warmed up to 0 °C for 10 min. After the mixture was cooled again to −78 °C, PNBSA (236 mg) was added all at once. The mixture was stirred at −78 °C for 1 h, and then 0.5 M aqueous phosphate buffer (pH = 7.0) was added. The mixture was warmed up to rt; then partitioned between the aqueous layer and EtOAc. The combined organic extract was dried

(18) Such remote substituent effects are well-known for nucleophilic displacement reactions: (a) Shaik S. S. *J. Am. Chem. Soc.* **1983**, *105*, 4395. (b) Streitwieser, A., Jr. *Solvolytic Displacement Reactions*; McGraw-Hill: New York, 1962; pp 15−17.

(19) **(**19) (a) Baker, J. W. *J. Chem. Soc.* **1932**, 2631. (b) Baker, J. W. *J. Chem. Soc.* **1933**, 1128. (c) Baker, J. W. *J. Chem. Soc.* **1936**, 1448.

(20) **(**20) Taber, D. F.; Houze, J. B. *J. Org. Chem.* **1994**, *59*, 4004.

(Na_2SO_4), concentrated, and chromatographed to give **1d** (62 mg, 36% yield) as a bright yellow oil: TLC R_f(30% EtOAc/petroleum ether) = 0.43; ^{1}H NMR δ 8.20 (m, 2H), 7.51 (m, 2H), 7.27 (m, 2H), 6.90 (m, 3H), 4.88 (d, 1H, J = 12.9 Hz), 4.76 (d, 1H, J = 12.9 Hz), 4.09 (m, 2H), 4.02 (m, 1H), 3.74 (s, 3H), 2.69 (m, 2H); ^{13}C NMR δ u, 172.4, 158.5, 146.0, 71.2, 69.3, 26.5; d,129.6, 127.9, 123.6, 121.3, 114.5, 77.2, 52.3; IR cm^{-1} 2088, 1734, 1693, 1600, 1521, 1496, 1437, 1244, 1188, 1086.

Methyl 2-Diazo-4-(2-propenyloxy)-5-phenoxypentanoate (1e). The procedure described for **1a** was employed. The overall yield was 64%. **1e**: TLC R_f(20% EtOAc/petroleum ether) = 0.50; ^{1}H NMR δ 7.28 (m, 2H), 6.92 (m, 3H), 5.89 (m, 1H), 5.21 (m, 2H), 4.21 (dd, J = 5.6, 12.6 Hz, 1H), 4.09 (dd, J = 5.6, 12.6 Hz, 1H), 4.00 (m, 2H), 3.92 (m, 1H), 3.75 (s, 3H), 2.69 (dd, J = 4.7, 5.3 Hz, 1H), 2.59 (dd, J = 4.7, 5.3 Hz. 1H); ^{13}C NMR δ u,158.5, 117.4, 71.4, 69.0, 26.4; d, 134.4, 129.4, 121.0, 114.5, 76.4, 51.9; IR cm^{-1} 2088, 1691, 1599, 1496, 1437, 1345, 1244, 1131, 755.

Methyl 2-Diazo-4-(propyloxy)-5-phenoxypentanoate (1f). The procedure described for **1a** was employed. The overall yield was 74%. **1f**: TLC R_f(20% EtOAc/petroleum ether) = 0.35; ^{1}H NMR δ 7.16 (m, 2H), 6.82 (m, 3H), 3.88 (m, 2H), 3.69 (m,1H), 3.62 (s, 3H), 3.50 (m, 1H), 3.38 (m, 1H), 2.57 (dd, J = 4.4, 15.3 Hz, 1H), 2.44 (dd, J = 4.4, 15.3 Hz, 1H), 1.46 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ u, 167.6, 158.4, 72.0, 68.8, 26.2, 23.0; d, 129.2, 120.8, 114.4, 76.9, 51.6, 10.2; IR cm^{-1} 2960, 2088, 1694, 1600, 1497, 1437, 1342, 1245, 1133, 997, 814, 754.

Methyl 2-Diazo-4-((3-methoxypropyl)oxy)-5-phenoxypentanoate (1g). The procedure described for **1a** was employed. The overall yield was 73%. **1a**: TLC R_f(20% EtOAc/petroleum ether) = 0.45; ^{1}H NMR δ 7.28 (m, 2H), 6.94 (m, 3H), 4.00 (d, J = 4.8 Hz, 2H), 3.77 (m, 2H), 3.75 (s, 3H), 3.62 (m, 1H), 3.44 (t, J = 6.3 Hz, 2H), 3.31 (s, 3H), 2.64 (m, 2H), 1.83 (t, J = 6.2 Hz, 2H); ^{13}C NMR δ u, 158.8, 69.3, 68.8, 67.3, 30.2, 26.3; d, 129.4, 121.0, 114.5, 77.2, 58.5, 51.8; IR cm^{-1} 2924, 2088, 1694, 1600, 1496, 1436, 1345, 1245, 1121.

Methyl 2-Diazo-4-ethoxy-5-phenoxypentanoate (1h). The procedure described for **1a** was employed. The overall yield was 72%. **1h**: TLC R_f(20% EtOAc/petroleum ether) = 0.50; ^{1}H NMR δ 7.2 (m, 2H), 6.85 (m, 3H), 3.9 (m, 2H), 3.8 (m, 2H), 3.7 (s, 3H), 3.6 (m, 1H), 2.6 (dd, J = 4.7, 15.3 Hz, 1H), 2.49 (dd, J = 4.7, 15.3 Hz, 1H), 1.12 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ u,158.5, 69.0, 69.5, 26.3; d, 129.4, 121.0, 114.5, 76.9, 51.9, 15.4.

Methyl 2-Diazo-(2-methoxyethoxy)-5-phenoxypentanoate (1i). The procedure described for **1a** was employed. The overall yield was 73%. **1i**: TLC R_f(20% EtOAc/petroleum ether) = 0.35; ^{1}H NMR δ 7.24 (m, 2H), 6.92 (m, 3H), 4.01 (m, 2H), 3.86 (m, 2H), 3.73 (s, 3H), 3.70 (m, 1H), 3.67 (m, 2H), 3.34 (s, 3H), 2.67 (dd, J = 4.6, 5.3 Hz, 1H), 2.56 (dd, J = 4.6, 5.3 Hz, 1H); ^{13}C NMR δ u, 167.6, 158.3, 72.0, 69.8, 68.9, 26.1; d, 129.2, 120.8, 114.3, 77.6, 58.7, 51.6; IR cm^{-1} 2927, 2086, 1600, 1498, 1439, 1344, 1246, 2235, 1042.

Methyl 2-Diazo-(2-phenoxyethoxy)-5-phenoxypentanoate (1j). The procedure described for **1a** was employed. The overall yield was 69%. **1j**: TLC R_f(20% EtOAc/petroleum ether) = 0.35; ^{1}H NMR δ 7.21 (m, 4H), 6.86 (m, 6H), 4.04−3.85 (m, 7H), 3.64 (s, 3H), 2.63 (dd, J = 4.3, 5.1 Hz, 1H), 2.52 (dd, J = 4.3, 5.1 Hz, 1H); ^{13}C NMR δ u, 158.7, 158.5, 69.3, 69.2, 67.3, 27.4; d, 129.4, 129.3, 121.0, 120.8, 114.5, 77.9, 51.8; IR cm^{-1} 2926, 2089, 1686, 1600, 1497, 1340, 1245, 1134, 754.

Methyl (*R,*S**,*R**)-2-Phenyl-5-((4-methoxyphenyl)-methoxy)-2,3,4,5-tetrahydro-3-furancarboxylate (2a) and Methyl (*R**,*R**,*R**)-2-Phenyl-5-((4-methoxyphenyl)methoxy)-2,3,4,5-tetrahydro-3-furancarboxylate (3a).** Diazo ester **1a** (370 mg, 1 mmol) in a 25 mL round bottom flask containing a magnetic stir bar was evaporated with toluene (3 × 7 mL). Methylene chloride was then added by filtration through a pad of anhydrous K_2CO_3. Dirhodium tetraoctanoate (1 mg) was added. The reaction was completed in 30 min. The reaction mixture was concentrated, and the residue was chromatographed to give 192 mg of **2a** (63% yield) and 72 mg of **3a** (37% yield). **2a**: TLC R_f(20% EtOAc/petroleum ether) = 0.34; ^{1}H NMR δ 7.30 (m, 4H), 6.93 (m, 3H), 6.87 (m, 2H), 5.04 (d, 1H, J = 8.2 Hz), 4.55 (m, 1H), 4.15 (dd, 1H, J = 4.1, 9.9 Hz), 4.10 (dd, 1H, J = 2.5, 9.9 Hz), 3.77 (s, 3H), 3.68 (s, 3H), 3.11 (q, 1H, J = 8.0 Hz), 2.51 (m, 1H), 2.35 (m, 1H); ^{13}C NMR δ u, 173.4, 159.4, 158.8, 132.4, 69.8, 33.0; d, 129.4, 127.4, 120.9, 114.5, 113.8, 83.9, 77.1, 55.2, 51.9; IR cm^{-1} 2952, 1732, 1600, 1514, 1455, 1366, 1302, 1248, 1173, 1035, 830, 755, 692; MS (*m*/*z*, relative intensity) 342 (8), 311 (1), 282 (5), 249 (12), 203 (73), 175 (28), 147 (48), 135 (100), 121 (85); HRMS calcd for $C_{20}H_{22}O_5$ 342.1467, obsd 342.474. **3a**: TLC R_f(20% EtOAc/petroleum ether) = 0.31; ^{1}H NMR δ 7.30 (m, 4H), 7.00 (m, 3H), 6.84 (m, 2H), 5.20 (d, 1H, J = 8.3 Hz), 4.44 (m, 1H), 4.35 (dd, 1H, J = 6.0, 9.5 Hz), 4.23 (dd, 1H, J = 4.3, 9.5 Hz), 3.76 (s, 3H), 3.42 (q, 1H, J = 8.3 Hz), 3.21 (s, 3H), 2.36 (m, 2H); ^{13}C NMR δ u, 172.3, 159.2, 158.8, 130.4, 69.8, 31.4; d, 129.4, 127.7, 120.9, 114.6, 113.3, 82.6, 77.5, 55.2, 51.3, 49.9; IR cm^{-1} 2950, 1732, 1600, 1514, 1496, 1456, 1378, 1302, 1248, 1173, 1097, 1036, 840, 757; MS (*m*/*z*, relative intensity) 342 (52), 282 (12), 249 (27), 203 (100), 175 (22), 147 (27), 135 (59), 121 (51); HRMS calcd for $C_{20}H_{22}O_5$ 342.1467, obsd 342.1450.

Methyl (*R,*S**,*R**)-2-Phenyl-5-(phenoxymethyl)-2,3,4,5-tetrahydro-3-furancarboxylate (2b) and Methyl (*R**,*R**,*R**)-2-Phenyl-5-(phenoxymethyl)-2,3,4,5-tetrahydro-3-furancarboxylate (3b).** The procedure described for **2a** and **3a** was employed. **2b:** TLC R_f(20% EtOAc/petroleum ether) = 0.35; ^{1}H NMR δ 7.31 (m, 7H), 6.96 (m, 3H), 5.12 (d, J = 7.9 Hz, 1H), 4.56 (m, 1H), 4.12 (m, 2H), 3.67 (s, 3H), 3.12 (m, 1H), 2.49 (m, 1H), 2.30 (m, 1H) ; ^{13}C NMR δ u, 173.3, 158.7, 140.5, 69.6, 32.9; d, 129.4, 128.3, 127.8, 126.0, 120.9, 114.5, 84.0, 77.3, 51.9; IR cm^{-1} 2951, 1734, 1599, 1497, 1455, 1364, 1245, 1172; MS (*m*/*z*, relative intensity) 312 (29), 263 (2), 252 (4), 219 (21), 205 (12), 190 (9), 187 (18), 173 (100), 159 (12), 145 (52), 131 (13), 117 (79), 115 (65); HRMS calcd for $C_{19}H_{20}O_4$ 312.1362, obsd 312.1361. **3b:** TLC R_f(20% EtOAc/petroleum ether) = 0.30; ^{1}H NMR δ 7.27 (m, 7H), 6.96 (m, 3H), 5.22 (d, J = 8.2 Hz, 1H), 4.44 (m, 1H), 4.39 (m, 1H), 4.26 (m, 1H), 3.45 (dd, J = 8.2, 15.4 Hz, 1H), 3.14 (s, 3H), 2.33 (m, 2H); ^{13}C NMR δ u, 172.2, 158.7, 138.1, 69.7, 31.3; d, 129.4, 128.3, 127.8, 126.3, 126.0, 120.8, 114.5, 82.8, 77.6, 51.2, 49.9; IR cm^{-1} 2948, 1735, 1600, 1497, 1456, 1245, 1171, 1036, 753; MS (*m*/*z*, relative intensity) 312 (4), 252 (1), 219 (75), 187 (16), 173 (100), 159 (10), 117 (78), 105 (54); HRMS calcd for $C_{19}H_{20}O_4$ 312.1362, obsd 312.1371.

Methyl (*R,*S**,*R**)-2-Phenyl-5-((4-bromophenyl)methoxy)-2,3,4,5-tetrahydro-3-furancarboxylate (2c) and Methyl (*R**,*R**,*R**)-2-Phenyl-5-((4-bromophenyl)methoxy)-2,3,4,5-tetrahydro-3-furancarboxylate (3c).** The procedure described for **2a** and **3a** was employed. **2c**: TLC R_f(20% EtOAc/petroleum ether) = 0.48; ^{1}H NMR δ 7.45 (m, 2H), 7.30 (m, 4H), 6.97 (m, 3H), 5.06 (d, 1H, J = 7.3 Hz), 4.57 (m, 1H), 4.16 (dd, 1H, J = 3.9, 10.2 Hz), 4.08 (dd, 1H, J = 4.3, 10.2 Hz), 3.70 (s, 3H), 3.06 (q, 1H, J = 7.9 Hz), 2.47 (m, 1H), 2.33 (m, 1H); ^{13}C NMR δ u, 173.1, 158.6, 139.7, 121.7, 69.6, 32.8; d, 131.4, 129.5, 127.7, 121.0, 114.5, 83.3, 77.5, 52.1; IR cm^{-1} 2951, 1732, 1600, 1494, 1454, 1367, 1244, 1070, 818, 752, 692; MS (*m*/*z*, relative intensity) 391 (4), 330 (6), 299 (36), 253 (100), 223 (23), 185 (29); HRMS calcd for $C_{19}H_{19}O_4Br$ 390.0467, obsd 390.0449. **3c**: TLC R_f(20% EtOAc/petroleum ether) = 0.44; ^{1}H NMR δ 7.40 (m, 2H), 7.30 (m, 2H), 7.22 (m, 2H), 6.98 (m, 3H), 5.18 (d, 1H, J = 8.2 Hz), 4.44 (m, 1H), 4.33 (dd, 1H, J = 6.0, 9.8 Hz), 4.22 (dd, J = 4.2, 9.8 Hz), 3.46 (q, 1H, J = 8.1 Hz), 3.2 (s, 3H), 2.33 (m, 2H); ^{13}C NMR δ u, 172.0, 158.7, 137.3, 121.7, 69.5, 31.2; d, 131.0, 129.4, 128.2, 121.0, 114.6, 82.2, 77.8, 51.4, 49.8; IR cm^{-1} 2949, 1735, 1600, 1496, 1453, 1244, 1204, 1171, 1072, 1014, 1010, 754; MS (*m*/*z*, relative intensity) 390 (6), 297 (100), 264 (21), 251 (74), 223 (21), 183 (29); HRMS calcd for $C_{19}H_{19}O_4Br$ 390.0467, obsd 390.0460.

Methyl (*R,*S**,*R**)-2-Phenyl-5-((4-nitrophenyl)methoxy)-2,3,4,5-tetrahydro-3-furancarboxylate (2d) and Methyl (*R**,*R**,*R**)-2-Phenyl-5-((4-nitrophenyl)methoxy)-2,3,4,5-tetrahydro-3-furancarboxylate (3d).** The procedure described for **2a** and **3a** was employed. **2d**: TLC R_f(30% EtOAc/petroleum ether) = 0.40; ^{1}H NMR δ 8.19 (m, 2H), 7.61 (m, 2H), 7.32 (m, 2H), 6.96 (m, 3H), 5.22 (d, 1H, J = 7.9 Hz), 4.63 (m, 1H), 4.24 (dd, 1H, J = 3.5, 10.2 Hz), 4.12 (dd, 1H, J = 4.2, 10.2 Hz), 3.75 (s, 3H), 3.11 (q, 1H, J = 7.9 Hz), 2.44 (m, 2H); ^{13}C NMR δ u, 172.8, 158.6, 148.3, 69.5, 32.6; d, 129.6, 126.8, 123.6, 121.2, 114.5, 82.8, 78.0, 52.3; IR cm^{-1} 1734, 1600, 1521,

1496, 1455, 1349, 1245, 1173, 1095, 1045; MS (*m/z*, relative intensity) 357 (24), 343 (62), 328 (100), 264 (48), 232 (36); HRMS calcd for $C_{19}H_{19}O_6N$ (m + H) 358.1291, obsd 358.1274. **3d**: TLC R_f(30% EtOAc/petroleum ether) = 0.37; ^{1}H NMR δ 8.16 (m, 2H), 7.52 (m, 2H), 7.29 (m, 2H), 6.99 (m, 3H), 5.32 (d, 1H, J = 8.4 Hz), 4.52 (m, 1H), 4.34 (m, 2H), 3.56 (q, 1H, J = 7.3 Hz), 3.2 (s, 3H), 2.40 (m, 2H); ^{13}C NMR δ u, 171.6, 158.6, 145.8, 69.3, 31.2; d, 129.5, 127.4, 123.1, 121.1, 114.6, 81.7, 78.2, 51.6, 49.9; IR cm^{-1} 1735, 1600, 1521, 1496, 1455, 1348, 1244, 1171, 1097, 1043; MS (*m/z*, relative intensity) 358 (100), 345 (4), 328 (30), 264 (44), 232 (7), 175 (3); HRMS calcd for $C_{19}H_{19}O_6N$ (m + H) 358.1291, obsd 358.1299.

Methyl (*R*,S*,R)-2-Ethenyl-5-(phenoxymethyl)-2,3,4,5-tetrahydro-3-furancarboxylate (2e) and Methyl (*R*,R*,R**)-2-Ethenyl-5-(phenoxymethyl)-2,3,4,5-tetrahydro-3-furancarboxylate (3e).** The procedure described for **2a** and **3a** was employed. **2e:** TLC R_f(20% EtOAc/petroleum ether) = 0.45; ^{1}H NMR δ 7.23 (m, 2H), 6.93 (m, 3H), 5.90 (m, 1H), 5.34 (d, J = 17.2 Hz, 1H), 5.17 (d, J = 10.4 Hz, 1H), 4.46 (m, 2H), 3.97 (dd, J = 1.2, 4.8 Hz, 2H), 3.69 (s, 3H), 2.92 (dd, J = 7.6, 16.6 Hz, 1H), 2.42 (m, 1H), 2.18 (m, 1H); ^{13}C NMR δ u, 172.9, 158.5, 116.8, 69.6, 32.2; d, 136.7, 129.2, 120.7, 114.3, 83.1, 77.0, 51.8, 49.2; IR cm^{-1} 2951, 1738, 1600, 1497, 1245, 1041, GCMS *m/z* (relative intensity) 262 (5), 230 (2), 175 (3), 168 (25), 155 (28), 123 (100); HRMS calcd for $C_{15}H_{18}O_4$ 262.1205, obsd 262.1206. **3e:** TLC R_f(20% EtOAc/petroleum ether) = 0.40; ^{1}H NMR δ 7.27 (m, 2H), 6.94 (m, 3H), 5.91 (m, 1H), 5.30 (m, 2H), 4.63 (m, 1H), 4.37 (m, 1H), 4.15 (m, 2H), 3.65 (s, 3H), 3.31 (dd, 1H, J = 8.1, 16.2 Hz), 2.23 (m, 2H); ^{13}C-NMR δ u, 172.0, 158.6, 117.8, 70.0, 31.1; d, 134.6, 129.3, 120.8, 114.5, 81.3, 77.5, 51.6, 48.3; IR cm^{-1} 2951, 1738, 1600, 1497, 1245, 1041; GCMS *m/z* (relative intensity) 262 (8), 231 (1), 185-(1), 169 (83), 137 (100); HRMS calcd for $C_{15}H_{18}O_4$ 262.1205, obsd 262.1202.

Mehtyl (*R*,S*,R)-2-Ethyl-5-(phenoxymethyl)-2,3,4,5-tetrahydro-3-furancarboxylate (2f) and Methyl (*R*,R*,R**)-2-Ethyl-5-(phenoxymethyl)-2,3,4,5-tetrahydro-3-furancarboxylate (3f).** The procedure described for **2a** and **3a** was employed. **2f**: TLC R_f(20% EtOAc/petroleum ether) = 0.30; ^{1}H NMR δ 7.17 (m, 2H), 6.85 (m, 3H), 4.31 (m, 1H), 3.91 (m, 3H), 3.62 (s, 3H), 2.72 (m, 1H), 2.31 (m, 1H), 2.00 (m, 1H), 1.60 (m, 2H), 0.87 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ u, 173.9, 158.7, 69.8, 32.6, 27.7; d, 129.3, 120.8, 114.5, 83.9, 76.8, 51.8, 48.1, 9.7; IR cm^{-1} 2963, 2878, 1736, 1600, 1497, 1455, 1369, 1246, 1174, 1045, 982; MS (*m/z*, relative intensity) 264 (1), 233 (1), 203 (1), 170 (27), 157 (41), 125 (100); HRMS calcd for $C_{15}H_{20}O_4$ 264.1362, obsd 264.1353. **3f**: TLC R_f(20% EtOAc/petroleum ether) = 0.28; ^{1}H NMR δ 7.20 (m, 2H), 6.86 (m, 3H), 4.28 (m, 1H), 4.11 (m, 1H), 3.92 (m, 2H), 3.63 (s, 3H), 3.12 (m, 1H), 2.18 (m, 2H), 1.47 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR δ u, 173.8, 158.7, 70.2, 31.5, 28.4; d, 129.2, 120.7, 114.4, 87.5, 76.6, 51.9, 46.8, 10.6; IR cm^{-1} 2927, 2359, 1734, 1600, 1497, 1456, 1436, 1386, 1245, 1200, 1171, 1077, 1047, 981, 754; MS (*m/z*, relative intensity) 264 (2), 233 (2), 203 (2), 171 (26), 157 (28), 125 (100); HRMS calcd for $C_{15}H_{20}O_4$ 264.1362, obsd 264.1352.

Methyl (*R*,S*,R)-2-(2-Methoxyethyl)-5-(phenoxymethyl)-2,3,4,5-tetrahydro-3-furancarboxylate (2g) and Methyl (*R*,R*,R**)-2-(2-Methoxyethyl)-5-(phenoxymethy)-2,3,4,5-tetrahydro-3-furancarboxylate (3g).** The procedure described for **2a** and **3a** was employed. **2g**: TLC R_f(20% EtOAc/petroleum ether) = 0.40; ^{1}H NMR δ 7.28 (m, 2H), 6.93 (m, 3H), 4.40 (m, 1H), 4.17 (m, 1H), 3.99 (d, J = 4.7 Hz, 2H), 3.72 (s, 3H), 3.48 (m, 2H), 3.30 (s, 3H), 2.89 (m, 1H), 2.39 (m, 1H), 2.15 (m, 1H), 1.92 (m, 2H); ^{13}C NMR δ u, 173.7, 158.8, 69.8, 69.4, 34.9, 32.6; d, 148.9, 129.4, 120.9, 114.5, 80.1, 76.9, 58.5, 51.9; IR cm^{-1} 2923, 1732, 1600, 1496, 1455, 1245, 1173, 1115; MS (*m/z*, relative intensity) 294 (2), 231 (5), 201 (5), 187 (7), 168 (26), 155 (60, 137 (12), 129 (100); HRMS calcd for $C_{16}H_{21}O_5$ 294.1467, obsd 294.1478. **3g**: TLC R_f(20% EtOAc/petroleum ether) = 0.35; ^{1}H NMR δ 7.21 (m, 2H), 6.86 (m, 3H), 4.22 (m, 1H), 4.08 (m, 1H), 3.92 (d, J = 4.5 Hz, 2H), 3.63 (s, 3H), 3.44 (t, J = 6.0 Hz, 2H), 3.26 (s, 3H), 3.14 (m, 1H), 2.16 (m, 2H), 1.70 (m, 2H); ^{13}C NMR δ u, 173.7, 158.8, 70.2, 69.6, 32.6, 32.0; d, 129.4, 120.9, 114.6, 77.7, 77.1, 58.6, 51.7, 47.1; IR cm^{-1} 2922, 1738, 1600, 1496, 1455, 1386, 1246, 1171, 1115, 1044; MS (*m/z*, relative intensity) 294 (2), 231 (5), 201 (29), 169 (15), 155 (100); HRMS calcd for $C_{16}H_{21}O_5$ 294.1467, obsd 294.1469.

Methyl (*R*,S*,R)-2-Methyl-5-(phenoxymethyl)-2,3,4,5-tetrahydro-3-furancarboxylate (2h) and Methyl (*R*,R*,R**)-2-Methyl-5-(phenoxymethyl)-2,3,4,5-tetrahydro-3-furancarboxylate (3h).** The procedure described for **2a** and **3a** was employed. **2h** (major): TLC R_f(10% EtOAc/petroleum ether) = 0.25; ^{1}H NMR δ 7.27 (m, 2H), 6.90 (m, 3H), 4.40 (m, 1H), 4.13 (m, 1H), 3.98 (d, J = 4.8 Hz, 2H), 3.73 (s, 3H) 2.73 (m, 1H), 2.43 (m, 1H), 2.12 (m, 1H), 1.38 (d, 3H, J = 6.0 Hz); ^{13}C NMR δ u, 173.6, 158.8, 70.1, 32.6; d, 129.4, 120.9, 114.6, 78.9, 76.9, 52.0, 50.5, 20.3; IR cm^{-1} 2952, 1736, 1600, 1497, 1372, 1246, 1200, 1043, 755; MS (*m/z*, relative intensity) 250 (4), 219 (1), 175 (1), 156 (38), 143 (68), 111(100); HRMS calcd for $C_{14}H_{18}O_4$ 250.1205, obsd 250.1216. **3h** (minor): TLC R_f(10% EtOAc/petroleum ether) = 0.20; ^{1}H NMR δ 7.27 (m, 2H), 6.90 (m, 3H), 4.3 (m, 2H), 4.16 (m, 1H), 4.05 (m, 1H), 3.70 (s, 3H), 3.14 (m, 1H), 2.23 (m, 2H), 1.22 (d, J = 6.4 Hz, 2H); ^{13}C NMR δ u, 173.6, 158.8, 70.4, 31.5; d, 129.4, 120.9, 114.6, 77.1, 76.9, 51.7, 47.7, 17.4; IR cm^{-1} 2977, 1736, 1600, 1497, 1246, 1202, 1170, 1043, 756, MS (*m/z*, relative intensity) 250 (3), 219 (2), 175 (1), 143 (48), 125 (18), 111 (100); HRMS calcd for $C_{14}H_{18}O_4$ 250.1205, obsd 250.1214.

Methyl (*S*,S*,R)-2-(Methoxymethyl)-5-(phenoxymethyl)-2,3,4,5-tetrahydro-3-furancarboxylate (2i) and Methyl (*S*,R*,R**)-2-(Methoxymethyl)-5-(phenoxymethyl)-2,3,4,5-tetrahydro-3-furancarboxylate (3i).** The procedure described for **2a** and **3a** was employed. **2i**: TLC R_f(20% EtOAc/petroleum ether) = 0.30; ^{1}H NMR δ 7.18 (m, 2H), 6.84 (m, 3H), 4.35 (m, 1H), 4.18 (m, 1H), 3.92 (m, 2H), 3.64 (s, 3H), 3.48 (m, 2H), 3.30 (s, 3H), 2.98 (m, 1H), 2.34 (m, 1H), 2.08 (m, 1H); ^{13}C NMR δ u, 173.4, 158.6, 73.7, 69.6, 32.0; d, 129.2, 120.7, 114.4, 81.2, 77.4, 59.2, 51.9, 45.1; IR cm^{-1} 2927, 1735, 1600, 1497, 1456, 1266, 1174, 1105, 1046, 910, 736; MS (*m/z*, relative intensity) 280 (2), 235 (2), 186 (11), 173 (12), 133 (50), 113 (100); HRMS calcd for $C_{15}H_{20}O_5$ 280.1311, obsd 280.1317. **3i**: TLC R_f(20% EtOAc/petroleum ether) = 0.28; ^{1}H NMR δ 7.18 (m, 2H), 6.84 (m, 3H), 4.33 (m, 2H), 4.00 (m, 2H), 3.89 (s, 3H), 3.50 (m, 2H), 3.27 (s, 3H), 3.18 (m, 1H), 2.06 (m, 2H); ^{13}C NMR δ u, 173.4, 158.6, 72.2, 69.7, 31.5; d, 129.3, 120.8, 114.5, 79.0, 77.4, 59.1, 51.7, 45.4.

Methyl (*S*,S*,R)-2-(Phenoxymethyl)-5-(phenoxymethyl)-2,3,4,5-tetrahydro-3-furancarboxylate (2j) and Methyl (*S*,R*,R**)-2-(Phenoxymethyl)-5-(phenoxymethyl)-2,3,4,5-tetrahydro-3-furancarboxylate (3j).** The procedure described for **2a** and **3a** was employed. **2j:** TLC R_f(20% EtOAc/petroleum ether) = 0.30; ^{1}H NMR δ 7.27 (m, 4H), 6.93 (m, 6H), 4.51 (m, 2H), 4.13 (m, 2H), 4.02 (d, J = 4.8 Hz, 2H), 3.73 (s, 3H), 3.21 (m, 1H), 2.45 (m, 1H), 2.28 (m, 1H); ^{13}C NMR δ u, 173.3, 158.5, 69.6, 68.9, 32.0; d, 129.3, 120.9, 114.5, 80.5, 77.7, 52.1, 45.5; IR cm^{-1} 2927, 2359, 1734, 1600, 1497, 1456, 1436, 1386, 1245, 1200, 1171, 1077, 1047, 981, 754; MS (*m/z*, relative intensity) 342 (3), 248 (10), 203 (10), 175 (16), 133 (100), 113 (97); HRMS calcd for $C_{20}H_{22}O_5$ 342.1467, obsd 342.1469. **3j**: TLC R_f(20% EtOAc/petroleum ether) = 0.28; ^{1}H NMR δ 7.27 (m, 4H), 6.86 (m, 6H), 4.43 (m, 2H), 4.06 (m, 2H), 3.96 (s, J = 4.8 Hz, 2H), 3.52 (s, 3H), 3.30 (m, 1H), 2.22 (m, 2H); ^{13}C NMR δ u, 173.4, 158.7, 70.1, 67.6, 32.2; d, 129.3, 120.9, 114.5, 78.4, 77.7, 51.9, 45.7.

6-Phenoxy-5-((4-methoxyphenyl)methoxy)-1-hexene (15a). At 0 °C, 100 mL of 2 M allylmagnesium chloride was added slowly to 1,2-epoxy-3-phenoxypropane (15 g, 100 mmol) in 100 mL of dry THF. The reaction mixture was warmed to rt. After 4 h, the reaction mixture was partitioned between the aqueous 2 N HCl and 50% EtOAc/petroleum ether. The combined organic extract was washed sequentially with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The combined organic extract was dried (Na_2SO_4) and concentrated to give 19.2 g of crude 1-phenoxy-5-hexen-2-ol.

NaH (1.1 g, 26 mmol, 60% in mineral oil) was added in portions to the crude 1-phenoxy-5-hexen-2-ol (1.69 g) in 10 mL of dry THF at 0 °C. 4-Methoxybenzyl chloride (1.65 g, 10.6 mmol) and Bu_4NI (100 mg) were then added. The reaction mixture was warmed up to rt. After 4 h, the reaction mixture was partitioned between 2 M aqueous HCl and 20% EtOAc/

petroleum ether. The combined organic extract was washed sequentially with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield 2.43 g of **15a** (88% yield from 1,2-epoxy-3-phenoxypropane) as a colorless oil: TLC R_f(20% EtOAc/petroleum ether) = 0.66; ^{1}H NMR δ 7.3 (m, 4H), 6.88 (m, 5H), 5.81 (m, 1H), 4.99 (m, 2H), 4.68 (d, 1H, J = 11.2 Hz), 4.55 (d, 1H, J = 11.2 Hz), 3.99 (m, 2H), 3.79 (s, 3H), 3.76 (m, 1H), 2.19 (m, 2H), 1.72 (m, 2H); ^{13}C NMR δ u,159.2, 158.8, 130.7, 114.8, 71.9, 70.4, 31.3, 29.5; d, 138.3, 129.4, 120.8, 114.5, 113.7, 76.3, 55.2; IR cm^{-1} 2933, 1600, 1513, 1496, 1455, 1302, 1247, 1173, 1037, 912; MS (*m*/*z*, relative intensity) 121 (100), 135 (31), 187 (2), 205 (9), 219 (2), 312 (1); HRMS calcd for $C_{20}H_{24}O_3$ 312.1725, obsd 312.1710.

6-Phenoxy-5-(phenylmethoxy)-1-hexene (15b). The procedure described for **15a** was employed. The overall yield was 92%. **15b**: TLC R_f(10% EtOAc/petroleum ether) = 0.85; ^{1}H NMR δ 7.29 (m, 7H), 6.95 (m, 3H), 5.82 (m, 1H), 5.10 (m, 2H), 4.74 (d, J = 11.6 Hz, 1H), 4.60 (d, J = 11.6 Hz, 1H), 4.00 (m, 2H), 3.80 (m, 1H), 2.21 (m, 2H), 1.74 (m, 2H); ^{13}C NMR δ u, 158.8, 138.6, 114.9, 72.3, 70.7, 31.3, 29.5; d, 138.2, 129.4, 128.3, 127.9, 127.6, 120.8, 114.5, 76.7, 120.8, 114.3, 76.1; IR cm^{-1} 3064, 3030, 2925, 2869, 1830, 1640, 1599, 1587, 1540, 1496, 1454, 1349, 1245, 1079, 912, 753; MS (*m*/*z*, relative intensity) 282 (5), 175 (23), 157 (14), 131 (5), 108 (5), 107 (59), 105 (100); HRMS calcd for $C_{19}H_{20}O_2$ 282.1620, obsd 282.1621.

6-Phenoxy-5-((4-bromophenyl)methoxy)-1-hexene (15c). The procedure described for **15a** was employed. The overall yield was 94%. **15a**: TLC R_f(10% EtOAc/petroleum ether) = 0.69; ^{1}H NMR δ 7.43 (m, 2H), 7.23 (m, 4H), 6.91 (m, 3H), 5.81 (m, 1H), 5.00 (m, 2H), 4.69 (d, 1H, J = 11.9 Hz), 4.00 (m, 2H), 3.80 (m, 1H), 2.20 (m, 2H), 1.73 (m, 2H); ^{13}C NMR δ u, 158.7, 137.7, 121.4, 115.0, 71.5, 70.4, 31.2, 29.6; d, 138.1, 131.4, 129.5, 129.4, 120.9, 114.5, 77.0; IR cm^{-1} 2924, 2868, 1641, 1600, 1496, 1456, 1348, 1300, 1244, 1070, 1012, 912, 802, 692; MS (*m*/*z*, relative intensity) 360 (1), 253 (12), 183 (32), 168 (100), 107 (56); HRMS calcd for $C_{19}H_{21}O_2Br$ 360.0725, obsd 360.0708.

6-Phenoxy-5-((4-nitrophenyl)methoxy)-1-hexene (15d). A solution of 1-phenoxy-5-hexen-2-ol (1.5 g) and 4-nitrobenzyl bromide (2.0 g) and Ag_2O (2.0 g) in 10 mL of CH_2Cl_2 was maintained under irradiation in an ultrasonic cleaning bath at rt for 24 h. The mixture was filtered, concentrated, and chromatographed to give 1.8 g of **15d** (71% yield): TLC R_f(20% EtOAc/petroleum ether) = 0.62; ^{1}H NMR δ 8.17 (m, 2H), 7.52 (m, 2H), 7.28 (m, 2H), 6.92 (m, 3H), 5.83 (m, 1H), 5.01 (m, 2H), 4.86 (d, 1H, J = 13.1 Hz), 4.04 (m, 2H), 3.84 (m, 1H), 2.24 (m, 2H), 1.80 (m, 2H); ^{13}C NMR δ u, 158.5, 147.2, 146.4, 115.1, 71.0, 70.5, 31.0, 29.5; d, 137.8, 129.4, 127.6, 123.4, 120.9, 114.4, 77.8; IR cm^{-1} 2924, 1600, 1519, 1495, 1454, 1345, 1244, 1108, 914, 850, 755; MS (*m*/*z*, relative intensity) 427 (20), 220 (71), 202 (27), 176 (25), 152 (11), 136 (100), 107 (90); HRMS calcd for $C_{19}H_{21}O_4N$ 327.1471, obsd 327.1466.

6-Phenoxy-5-(propyloxy)-1-hexene (15f). The procedure described for **15a** was employed for the alkylation of 1-phenoxy-5-hexen-2-ol with 1-iodopropane. The yield was 63%. **15f**: TLC R_f(10% EtOAc/petroleum ether) = 0.60; ^{1}H NMR δ 7.27 (m, 2H), 6.92 (m, 3H), 5.84 (m, 1H), 5.00 (m, 2H), 3.95 (m, 2H), 3.61 (m, 2H), 3.48 (m, 1H), 2.21 (m, 2H), 1.69 (m, 2H), 1.58 (m, 2 H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ u, 158.9, 114.8, 72.1, 70.1, 31.4, 29.6, 23.3; d, 138.4, 129.4, 120.7, 114.5, 10.6; IR cm^{-1} 2934, 2875, 1641, 1600, 1455, 1245, 1080, 1044, 911,753; MS (*m*/*z*, relative intensity) 234 (24), 192 (4), 179 (8), 133 (8), 127 (100), 119 (32), 107 (32); HRMS calcd for $C_{15}H_{22}O_2$ 234.1620, obsd 234.1629.

6-Phenoxy-5-((3-methoxypropyl)oxy)-1-hexene (15g). NaH (500 mg, 60% in mineral oil) was added in portions to the crude 1-phenoxy-5-hexen-2-ol (479 mg) in 4 mL of dry DMF at 0 °C. 1-Methoxy-3-chloropropane (1 g) and Bu_4NI (60 mg) were then added. The reaction mixture was irradiated in an ultrasonic cleaning bath at rt for 8 h. The reaction mixture was partitioned between 20% EtOAc/petroleum ether and, sequentially, 2 N aqueous HCl and saturated aqueous NaCl. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield 415 mg of **15g** (63% yield from 1,2-epoxy-3-phenoxypropane) as a colorless oil. The yield was 63%. **15g**: TLC R_f(10% EtOAc/petroleum ether) = 0.70; ^{1}H NMR δ 7.21 (m, 2H), 6.86 (m, 3H), 5.77 (m, 1H), 4.94 (m, 2H), 3.88 (m, 2H), 3.65 (m, 1H), 3.54 (m, 2H), 3.40 (t, J = 6.2 Hz, 3H), 3.24 (s, 3H), 2.14 (m, 2H), 1.77 (m, 2H), 1.65 (m, 2H); ^{13}C NMR δ u, 158.8, 114.8, 69.6, 67.1, 31.2, 30.4, 29.6; d, 138.3, 129.4, 120.7, 114.5, 77.4, 58.6; IR cm^{-1} 3074, 2923, 2872, 1600, 1588, 1497, 1456, 1245, 1118; MS (*m*/*z*, relative intensity) 264 (5), 174 (5), 157 (100), 119 (15); HRMS calcd for $C_{16}H_{24}O_3$ 264.1725, obsd 264.1712.

6-Phenoxy-5-ethoxy-1-hexene (15h). The procedure described for **15a** was employed for the alkylation of 1-phenoxy-5-hexen-2-ol with ethyl iodide. The yield was 93%. **15h**: TLC R_f(20% EtOAc/petroleum ether) = 0.85; ^{1}H NMR δ 7.20 (m, 2H), 6.85 (m, 3H), 5.77 (m, 1H), 5.00 (m, 2H), 3.66 (m, 1H), 3.54 (m, 2H), 2.14 (m, 2H), 1.63 (m, 2H), 1.14 (t, J = 7.0 Hz, 3H); ^{13}C-NMR δ u,158.8, 114.7, 70.1, 69.6, 31.3, 29.5; d, 138.3, 129.3, 120.7, 114.5, 77.0, 15.6; IR cm^{-1} 3075, 2975, 2926, 2872, 1600, 1588, 1497, 1245, 1172, 1110, 1080, 1044, 912, 752, 691; MS (*m*/*z*, relative intensity) 220 (25), 174 (5), 119 (35), 113 (100); HRMS calcd for $C_{14}H_{20}O_2$ 220.1463, obsd 220.1460.

6-Phenoxy-5-(2-methoxyethoxy)-1-hexene (15i). The procedure described for **15a** was employed for the alkylation of 1-phenoxy-5-hexen-2-ol with 1-iodo-2-methoxyethane. **15i**: TLC R_f(10% EtOAc/petroleum ether) = 0.65; ^{1}H NMR δ 7.26 (m, 2H), 6.92 (m, 3H), 5.82 (m, 1H), 5.03 (m, 2H), 4.01 (dd, J = 5.7, 9.8 Hz, 1H), 3.92 (dd, J = 5.7, 9.8 Hz, 1H), 3.85 (m, 1H), 3.70 (m, 2H), 3.54 (m, 2H), 3.36 (s, 3H), 2.22 (m, 2H), 1.71 (m, 2H); ^{13}C NMR δ u, 158.7, 114.7, 72.2, 70.2, 69.6, 31.1, 29.4; d, 138.2, 129.3, 120.6, 114.4, 77.8, 58.8; IR cm^{-1} 2927, 2359, 1734, 1600, 1497, 1456, 1436, 1386, 1245, 1200, 1171, 1077, 1047, 981, 754; MS (*m*/*z*, relative intensity) 250 (10), 174 (10), 143 (100), 119 (30); HRMS calcd for $C_{15}H_{22}O_3$ 250.1669, obsd 250.1562.

6-Phenoxy-5-(2-phenoxyethoxy)-1-hexene (15j). The procedure described for **15a** was employed for the alkylation of 1-phenoxy-5-hexen-2-ol with 1-bromo-2-phenoxyethane. The yield was 65%. **15j**: TLC R_f(10% EtOAc/petroleum ether) = 0.70; ^{1}H NMR δ 7.24 (m, 4H), 6.93 (m, 6H), 5.83 (m, 1H), 5.01 (m, 2H), 4.11 (m, 4H), 4.03 (m, 2H), 3.78 (m, 1H), 2.24 (m, 2H), 1.72 (m, 2H); ^{13}C NMR δ u, 158.7, 114.9, 70.4, 68.9, 67.4, 31.1, 29.4; d, 138.2, 129.3, 120.7, 114.5, 78.0; IR cm^{-1} 2925, 2873, 1600, 1587, 1497, 1456, 1301, 1246, 112; MS (*m*/*z*, relative intensity) 312 (5), 205 (9), 174 (2), 139 (4), 121 (100); HRMS calcd for $C_{20}H_{24}O_3$ 312.1725, obsd 312.1728.

Methyl 4-((4-Methoxyphenyl)methoxy)-5-phenoxypentanoate (16a). A solution of 1.1 g of **15a** (3.4 mmol) in 28 mL of CH_2Cl_2 and 7 mL of 2.5 M methanolic NaOH was stirred at −78 °C as ozone was passed through the solution. After 60 min, the reaction mixture was warmed up to rt and then partitioned between water and CH_2Cl_2. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield 0.774 g of **16a** (64% yield) as a colorless oil. **16a**: TLC R_f(20% EtOAc/petroleum ether) = 0.41; ^{1}H NMR δ 7.27 (m, 4H), 6.88 (m, 5H), 4.66 (d, 1H, J = 11.2 Hz), 4.52 (d, 1H, J = 11.2 Hz) 4.03 (dd, 1H, J = 5.5, 9.7 Hz), 3.83 (m, 1H), 3.78 (s, 3H), 3.62 (s, 3H), 2.45 (m, 2H), 1.93 (m, 2H); ^{13}C NMR δ u,173.8, 159.2, 158.6, 130.4, 71.9, 70.0, 29.8, 27.2; d, 129.5, 129.4, 120.9, 114.5, 113.7, 75.7, 55.2, 51.4; IR cm^{-1} 2950, 1736, 1600, 1514, 1497, 1455, 1301, 1247, 1173, 1035; MS (*m*/*z*, relative intensity) 344 (1), 230 (5), 207 (1), 137 (41), 121 (100), 107 (3); HRMS calcd for $C_{20}H_{24}O_5$ 344.1624, obsd 344.1653.

Methyl 4-(Phenylmethoxy)-5-phenoxypentanoate (16b). The procedure described for **16a** was employed. The overall yield was 63%. **16b**: TLC R_f(20% EtOAc/petroleum ether) = 0.40; ^{1}H NMR δ 7.29 (m, 7H), 6.95 (m, 3H), 4.73 (d, J = 11.6 Hz, 1H), 4.59 (d, J = 11.6 Hz, 1H), 4.04 (m, 2H), 3.82 (m, 1H), 3.62 (s, 3H), 2.47 (dt, J = 3.2, 7.4 Hz, 2H), 2.00 (m, 2H); ^{13}C NMR δ u, 173.8, 158.6, 138.3, 72.2, 69.9, 29.8, 27.1; d, 129.4, 128.3, 127.9, 127.6, 120.9, 114.5, 76.1, 51.5; IR cm^{-1} 3064, 2949, 2872, 1737, 1599, 1587, 1497, 1351, 1245, 1172, 1079, 755; MS (*m*/*z*, relative intensity) 221 (7), 207 (21), 133 (7), 105 (36), 107 (71), 105 (100); HRMS calcd for $C_{19}H_{22}O_3$ 221.1177, obsd 221.1178.

Methyl 4-((4-Bromophenyl)methoxy)-5-phenoxypentanoate (16c). The procedure described for **16a** was em-

ployed. The yield was 69%. **16c**: TLC R_f(20% EtOAc/petroleum ether) = 0.47; ^{1}H NMR δ 7.43 (m, 2H), 7.22 (m, 4H), 6.90 (m, 3H), 4.68 (d, 1H, J = 11.9 Hz), 4.53 (d, 1H, J = 11.9 Hz), 4.01 (m, 2H), 3.81 (m, 1H), 3.62 (s, 3H), 2.46 (t, 2H, J = 6.9 Hz), 1.98 (m, 2H); ^{13}C NMR δ u, 173.7, 158.5, 137.3, 121.5, 71.5, 70.0, 29.7, 27.0; d, 131.4, 129.4, 120.9, 114.4, 76.2, 51.5; IR cm^{-1} 3640, 2949, 1732, 1600, 1495, 1246, 1080, 1012, 805, 754, 694; MS (*m*/*z*, relative intensity) 939 2), 375 (34), 301 (42), 208 (100), 185 (32), 170 (83).

Methyl 4-((4-Nitrophenyl)methoxy)-5-phenoxypentanoate (16d). A solution of 3.6 g of **15d** and 1 mg of sudan red in 30 mL of CH_2Cl_2 was stirred at −78 °C while O_3 was passed through until the red color of the solution was discharged. Ph_3P (4.0 g) was added, and the reaction mixture was warmed up to rt for 6 h. Evaporation of the solvent and chromatography of the residue afforded 3.3 g of 4-((4-nitrophenyl)methoxy)-5-phenoxy-1-pentanal as a light yellow oil (92% yield). **16d**: TLC R_f(30% EtOAc/petroleum ether) = 0.37; ^{1}H NMR δ 9.79 (s, 1H), 8.18 (m, 2H), 7.47 (m, 2H), 7.30 (m, 2H), 6.91 (m, 3H), 4.85 (d, 1H, J = 12.9 Hz), 4.69 (d, 1H, J = 12.9 Hz), 4.05 (m, 2H), 3.87 (m, 1H), 2.63 (t, 2H, J = 7.0 Hz), 2.06 (m, 2H); ^{13}C NMR δ u, 158.4, 147.3, 145.8, 71.0, 70.1, 39.7, 24.5; d, 201.4, 129.5, 127.8, 123.5, 121.1, 114.4, 77.3; IR cm^{-1} 2928, 1722, 1600, 1519, 1496, 1345, 1244, 1108, 757, 692; MS (*m*/*z*, relative intensity) 329 (8), 236 (10), 222 (22), 136 (100), 107 (25); HRMS calcd for $C_{18}H_{19}O_5N_1$ 329.1263, obsd 329.1262. The procedure described for **16e** was employed to oxidize the aldehyde to **16d**. The overall yield was 66% from **15d**. **16d**: TLC R_f(30% EtOAc/petroleum ether) = 0.43; ^{1}H NMR δ 8.20 (m, 2H), 7.49 (m, 2H), 7.29 (m, 2H), 6.91 (m, 3H), 4.88 (d, 1H, J = 13.0 Hz), 4.72 (d, 1H, J = 13.0 Hz), 4.06 (m, 2H), 3.89 (m, 1H), 3.64 (s, 3H), 2.51 (t, 2H, J = 7.4 Hz), 2.04 (m, 2H); ^{13}C NMR δ u, 173.6, 158.5, 146.0, 71.1, 70.2, 29.8, 27.0; d, 129.5, 127.8, 123.5, 121.1, 114.5, 77.3, 51.6; IR cm^{-1} 2950, 1732, 1679, 1600, 1519, 1494, 1455, 1345, 1171, 1107, 860; MS (*m*/*z*, relative intensity) 359 (22), 266 (23), 252 (19), 231 (5), 136 (100), 120 (9) ; HRMS calcd for $C_{19}H_{22}O_6N$ (m + H) 360.1447, obsd 360.1430.

Methyl 4-(2-Propenyloxy)-5-phenoxypentanoate (16e). A solution of 2.32 g of **15e** (10 mmol) (prepared as **15a** from **14**) in 30 mL of CH_2Cl_2 was stirred at −78 °C while 10 mmol of O_3 was passed through. Then 4.0 g of Ph_3P (15 mmol) was added, and the reaction mixture was warmed up to rt for 6 h. Evaporation of the solvent and chromatography of the residue afforded 0.98 g of 4-(2-propenyloxy)-5-phenoxy-1-pentanal as a colorless oil (42% yield). **16e**: TLC R_f(20% EtOAc/petroleum ether) = 0.40; ^{1}H NMR δ 9.75 (bs, 1H), 7.27 (m, 2H), 6.93 (m, 3H), 5.95 (m, 1H), 5.22 (m, 2H), 4.22 (m, 1H), 4.04 (m, 3H), 3.70 (m, 1H), 2.57 (dt, J = 1.3, 7.0 Hz, 2H), 1.96 (m, 2 H); ^{13}C NMR δ u,158.4, 117.0, 71.1, 69.5, 39.7, 24.6; d, 201.8, 134.6, 129.3, 120.8, 114.3, 76.1; IR cm^{-1} 2928, 2872, 2727, 1723, 1600, 1497, 1456, 1247, 1079, 996; MS (*m*/*z*, relative intensity) 234 (3), 177 (13), 149 (3), 127 (100), 107 (45); HRMS calcd for $C_{14}H_{18}O_3$ 234.1256, obsd 234.1263.

PDC (6.3 g, 18 mmol) and 0.58 g of MeOH were added to 0.7 g of the aldehyde in 6 mL of dry DMF. The reaction mixture was sirred at rt for 20 h. Ether (200 mL) and celite (24 g) were added. The mixture was filtered, and the residue was washed with ether. The combined filtrate was washed with saturated aqueous NaCl and dried with Na_2SO_4. Evaporation of the solvent and chromatography of the residue afforded 600 mg of ester **16e** as a colorless oil (32% yield from **15e**). **16e**: TLC R_f(20% EtOAc/petroleum ether) = 0.50; ^{1}H NMR δ 7.26 (m, 2H), 6.90 (m, 3H), 5.88 (m, 1H), 5.22 (m, 2H), 4.06 (m, 2H), 3.98 (dd, J = 4.8, 9.8 Hz, 1H), 3.92 (dd, J = 4.8, 9.8 Hz, 1H), 3.72 (m, 1H), 3.64 (s, 3H), 2.46 (t, J = 7.4 Hz, 2H), 1.94 (m, 2H); ^{13}C NMR δ u, 173.5, 158.4, 116.6, 71.0, 69.6, 29.6, 27.0; d, 134.7, 129.2, 120.6, 114.3, 75.9, 51.2; IR cm^{-1} 2950, 1735, 1600, 1497, 1455, 1246, 1173; MS (*m*/*z*, relative intensity) 264 (2), 215 (1), 207 (16), 171 (15), 157 (58), 115 (100); HRMS calcd for $C_{15}H_{20}O_4$ 264.1362, obsd 264.1367.

Methyl 4-(Propyloxy)-5-phenoxypentanoate (16f). The procedure described for **16a** was employed. The yield was 68%. **16f**: TLC R_f(20% EtOAc/petroleum ether) = 0.35; ^{1}H NMR δ 7.18 (m, 2H), 6.82 (m, 3H), 3.85 (m, 2H), 3.58 (s, 3H), 3.56 (m, 2H), 3.34 (m, 1H), 2.40 (t, J = 7.3 Hz, 2H), 1.86 (m, 2H), 1.48 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H); ^{13}C NMR δ u, 173.8, 158.7, 72.1, 69.6, 29.8, 27.2, 23.2; d, 129.4, 120.7, 114.4, 76.7, 51.4, 10.5; IR cm^{-1} 2960, 2876, 1738, 1600, 1696, 1456, 1246, 1173, 1122, 1044, 755; MS (*m*/*z*, relative intensity) 266 (22), 206 (4), 193 (4), 159 (80), 117 (100); HRMS calcd for $C_{15}H_{22}O_4$ 266.1518, obsd 266.1515

Methyl 4-((3-Methoxypropyl)oxy)-5-phenoxypentanoate (16g). The procedure described for **16a** was employed. The yield was 68%. **16g**: TLC R_f(20% EtOAc/petroleum ether) = 0.45; ^{1}H NMR δ 7.28 (m, 2H), 6.93 (m, 3H), 3.97 (m, 2H), 3.71 (m, 2H), 3.66 (s, 3H), 3.59 (m, 1H), 3.45 (t, J = 6.3 Hz, 2H), 3.31 (s, 3H), 2.48 (m, 2H), 1.95 (m, 2H), 1.83 (m, 2H); ^{13}C NMR δ u, 173..9, 158.6, 69.6, 69.5, 67.2, 30.3, 29.8, 27.2; d, 129.4, 120.8, 114.5, 76.9, 58.5, 51.5; IR cm^{-1} 2927, 1738, 1600, 1498, 1246, 1173, 1115, 888, 756; MS (*m*/*z*, relative intensity) 296 (5), 233 (5), 203 (25), 189 (75), 133 (40), 101 (100); HRMS calcd for $C_{16}H_{24}O_5$ 296.1623, obsd 296.1615.

Methyl 4-Ethoxy-5-phenoxypentanoate (16h). The procedure described for **16a** was employed. The yield was 67%. **16h**: TLC R_f(20% EtOAc/petroleum ether) = 0.50; ^{1}H NMR δ 7.21 (m, 2H), 6.85 (m, 3H), 3.92 (dd, J = 5.4, 9.8 Hz, 1H), 3.84 (dd, J = 5.4, 9.8 Hz, 1H), 3.65 (m, 3H), 3.60 (s, 3H), 3.47 (m, 1H), 2.41 (t, J = 7.6 Hz, 2H), 1.96 (m, 2H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ u, 173.8, 158.6, 69.9, 65.2, 29.8, 27.2; d, 129.3, 120.7, 114.4, 75.6, 51.4, 15.4; IR cm^{-1} 2975, 1738, 1600, 1588, 1497, 1245, 1173, 755, 692; MS (*m*/*z*, relative intensity) 251 (2), 206 (4), 159 (13), 145 (100), 113 (15); HRMS calcd for $C_{14}H_{20}O_4$ 252.1362, obsd 252.1368.

Methy 4-(2-Methoxyethyoxy)-5-phenoxypentanoate (16i). The procedure described for **16a** was employed. The yield was 62%. **16i**: TLC R_f(20% EtOAc/petroleum ether) = 0.35; ^{1}H NMR δ 7.27 (m, 2H), 6.86 (m, 3H), 4.28 (m, 1H), 3.99 (m, 2H), 3.94 (m, 1H), 3.72 (m, 2H), 3.66 (s, 3H), 3.52 (m, 2H), 3.36 (s, 3H), 2.51 (m, 2H), 1.95 (m, 2H); ^{13}C NMR δ u, 173.7, 158.5, 72.1, 69.8, 69.6, 29.7, 27.1; d, 1129.3, 120.7, 114.3, 77.3, 58.8, 51.3; IR cm^{-1} 2928, 1734, 1653, 1600, 1497, 1457, 1246, 1173, 1108; MS (*m*/*z*, relative intensity) 282 (5), 189 (20), 175 (100), 133 (35), 115 (50); HRMS calcd for $C_{15}H_{22}O_5$ 282.1467, obsd 282.1468.

Methy 4-(2-Phenoxyethoxy)-5-phenoxypentanoate (16j). The procedure described for **16a** was employed. The yield was 68%. **16j**: TLC R_f(20% EtOAc/petroleum ether) = 0.35; ^{1}H NMR δ 7.27 (m, 4H), 6.92 (m, 6H), 4.08 (m, 4H), 4.03 (m, 2H), 3.97 (m, 1H), 3.64 (s, 3H), 2.53 (t, J = 7.4 Hz, 2H), 2.00 (m, 2H); ^{13}C NMR δ u, 173.6, 158.5, 158.4, 69.9, 68.8, 67.2, 29.5, 27.0; d, 129.2, 129.1, 120.7, 120.6, 114.3, 77.4, 51.2; IR cm^{-1} 2930, 2875, 1736, 1600, 1497, 1247; MS (*m*/*z*, relative intensity) 344 (5), 281 (1), 237 (16), 205 (45), 177 (26), 133 (21), 121 (100); HRMS calcd for $C_{20}H_{24}O_5$ 344.1623, obsd 344.1618.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds (91 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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