Oxidative Cleavage of Mono-, Di-, and Trisubstituted Olefins to Methyl Esters through Ozonolysis in Methanolic NaOH

James A. Marshall* and Albert W. Garofalo

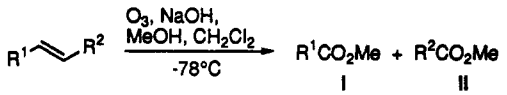
Department of Chemistry and Biochemistry, University of South Carolina, Columbia, South Carolina 29208

Received March 1, 1993

The ozonolysis of alkenes in methanolic NaOH or NaOMe with CH_2Cl_2 as cosolvent leads directly to methyl esters. The procedure has been used to prepare various α-, β-, and ω-alkoxy esters, acyloxy esters, and α- and β-*N*-acyl and *N*-sulfonyl esters from the appropriate unsaturated ethers, esters, and amides. Other examples include the formation of dimethyl octanedioate from cyclooctene (75% yield), dimethyl nonanedioate and methyl nonanoate from methyl oleate (77 and 78%, respectively), and tetradecanoic acid γ-lactone from 2-methyl-2-hexadecen-6-ol (80% yield).

We recently described preliminary findings on the direct conversion of certain olefins to methyl esters by treatment with ozone in methanolic NaOH–CH_2Cl_2 at −78 °C (Scheme I).[1] The reaction was applied to a number of allylic and homoallylic ethers having terminal double bonds and several olefins with internal double bonds. We have now carried out additional studies which further define the scope and limitations of the synthetic methodology.

Scheme I



Our initial application entailed the conversion of allylic ethers such as **1** to α-alkoxy esters **2** (Table I). Various methyl, benzyl, and silyl ethers could be employed with good results.[1] In more recent findings, the allylic acetate **1d** was smoothly converted to the α-acetoxy ester **2d** without saponification despite the presence of excess NaOH in the reaction mixture (entry 4).

The reaction could also be carried out by using NaOMe in place of NaOH with comparable results (entry 5). The use of NaO-*i*-Pr, however, was less successful leading to a nearly 1:1 mixture of isopropyl ester **3** and the benzyl ester **4** of one less carbon (Scheme II). When NaOBn was employed as the base in BnOH–CH_2Cl_2, the allylic ether **1f** was recovered unchanged along with benzaldehyde as the only oxidation product.

Acid was ineffective in promoting the reaction. Ozonolysis of benzyl ether **1e** in methanol–CH_2Cl_2 containing camphorsulfonic acid afforded the α-benzyloxy aldehyde **5** (Scheme III). This aldehyde was also the sole product in methanol–CH_2Cl_2 alone.

In order to ascertain the lability of chiral α-oxygenated esters to the basic reaction conditions, we examined the ozonolysis of several enantioenriched allylic derivatives as summarized in Scheme IV. Both the (*S*)- and (*R*)-*O*-methylmandelates of (*S*)-1-tridecen-3-ol (**6a** and **6b**)[2] were converted to the corresponding esters **7a** and **7b** with no measurable epimerization according to analysis of the ^1H NMR spectrum. Likewise, the allylic ether **8** was converted to the protected aldonic ester **9** in high yield (Scheme IV).[3]

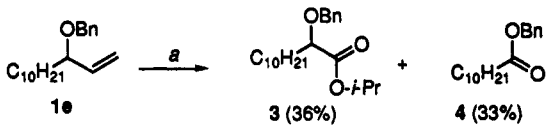
Table I. Synthesis of α-Oxygenated Methyl Esters from Olefins

1 2

entry	R^1	R^2	series	yield, %
1	*n*-C_6H_{13}	Me	a	63
2	*n*-C_6H_{13}	Bn	b	78
3	*n*-C_6H_{13}	TBS	c	69
4	*n*-$C_{10}H_{21}$	Ac	d	74
5	*n*-$C_{10}H_{21}$	Bn	e	79[b]
6	c-C_6H_{11}	Me	f	77[c]
7	c-C_6H_{11}	Bn	g	75[c]

[a] Five equivalents of NaOH in MeOH (2.5 M)/CH_2Cl_2 (1:4 vol/vol), O_3, −78 °C. [b] This ester was formed in 71% yield when NaOMe was substituted for NaOH. [c] Ten equivalents of NaOH in MeOH (2.5 M)/CH_2Cl_2 (1:2 vol/vol), O_3, −78 °C.

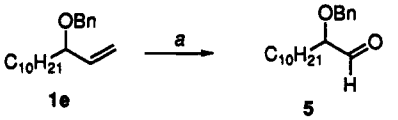
Scheme II[a]



1e 3 (36%) 4 (33%)

[a] (*a*) Five equivalents of NaO-*i*-Pr in *i*-PrOH (1.3 M)/CH_2Cl_2 (1:4 vol/vol), O_3, −78 °C.

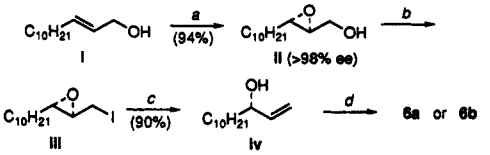
Scheme III[a]



1e 5

[a] (*a*) Five equivalents of camphorsulfonic acid in MeOH–CH_2Cl_2 (1:4 vol/vol), O_3, −78 °C.

(2) These esters were prepared using the following conditions:



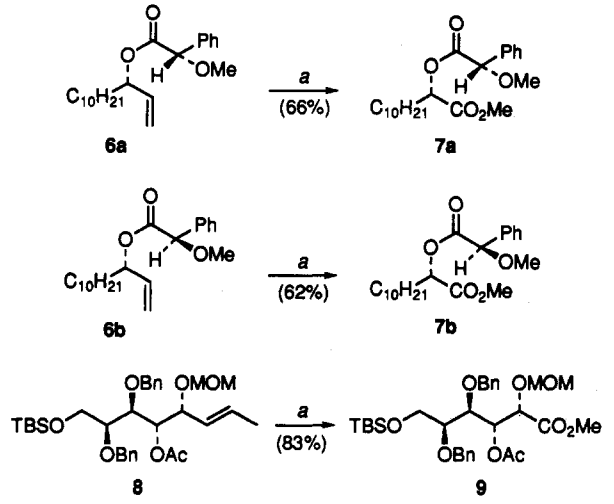
(*a*) L-(+)-DIPT, TIP, CH_2Cl_2, −23 °C; (*b*) Ph_3P, Im, I_2, CH_2Cl_2; (*c*) BuLi, THF, −78 °C; (*d*) (*S*) or (*R*)-PhCH(OMe)CO_2H, DCC, DMAP, CH_2Cl_2. *Cf.* Marshall, J. A.; Sedrani, R. C. *J. Org. Chem.* **1991**, *56*, 5496.

(3) Marshall, J. A.; Luke, G. P. *J. Org. Chem.* **1991**, *56*, 483.

(1) Marshall, J. A.; Garofalo, A. W.; Sedrani, R. C. *Synlett* **1992**, 643.

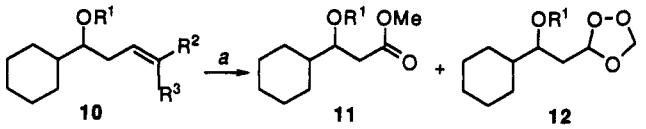
0022-3263/93/1958-3675$04.00/0

Scheme IV[a]



[a] (*a*) Five equivalents of NaOH in MeOH (2.5 M)/CH_2Cl_2 (1:4 vol/vol), O_3, −78 °C.

Table II. Synthesis of β-Oxygenated Methyl Esters from Olefins

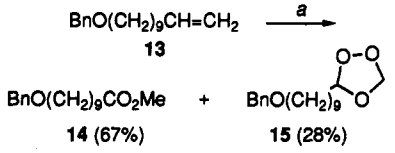


entry	R^1	R^2	R^3	series	11, %	12, %	series
1	Me	H	H	a	56	19	a
2	Bn	H	H	b	57	29	b
3	Bn	Me	Me	c	95	0	b

[a] Five equivalents of NaOH in MeOH (2.5 M)/CH_2Cl_2 (1:4 vol/vol), O_3, −78 °C.

A number of homoallylic ethers were also examined (Table II).[4] The vinyl systems **10a** and **10b** afforded mixtures of the β-alkoxy esters 11 and the secondary ozonides **12** upon ozonoloysis in methanolic NaOH–CH_2Cl_2. The isopropylidene homologue **10c**, on the other hand, afforded only the ester **11b** in near quantitative yield. The benzyl ether of 10-undecen-1-ol (**13**) afforded a mixture of ester **14** and secondary ozonide **15** (Scheme V).

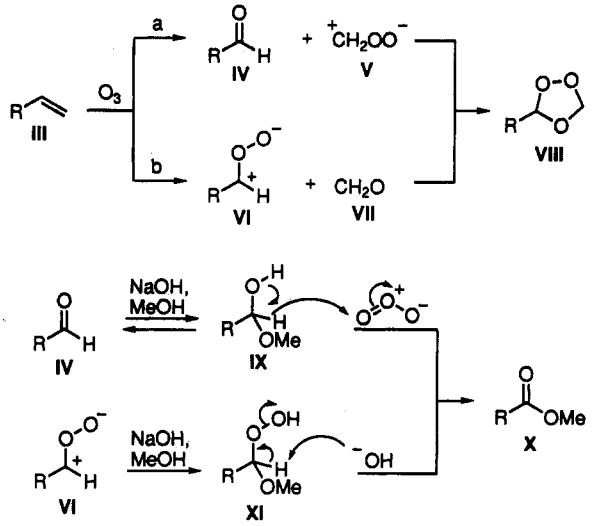
Scheme V[a]



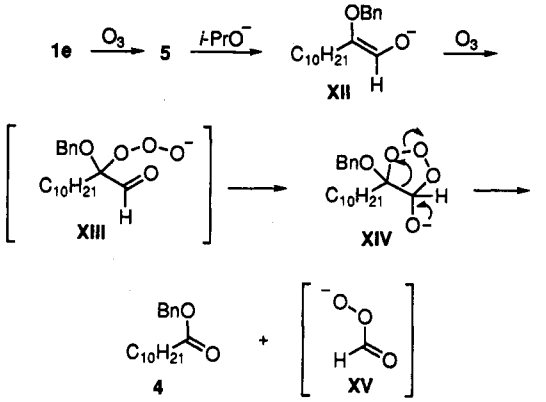
[a] Five equivalents of NaOH in MeOH (2.5 M)/CH_2Cl_2 (1:4 vol/vol), O_3, −78 °C.

The foregoing results are compatible with a reaction pathway in which the aldehyde and carbonyl oxide fragments **IV** and **VI**, derived from the primary ozonide, react with methoxide and methanol to afford the hemiacetal **IX** and the hydroperoxide **XI**, respectively.[5] The former undergoes base-assisted hydride abstraction by O_3[6]

Scheme VI



Scheme VII



and the latter dehydrates as shown to afford the methyl ester **X** (Scheme VI).

The extent to which the primary fragments recombine to form the secondary ozonide **VIII** should depend, to a first approximation, on steric effects. Thus, no secondary ozonide is observed with the α-substituted olefins **1**, whereas the β- and ω-substituted systems **10a**, **10b**, and **13** give rise to significant quantities. Recombination of fragments arising from the isopropylidene system **10c** is disfavored by steric factors. Previous findings indicate that formaldehyde may be the predominant carbonyl fragment (path b) from the primary ozonide of terminal alkenes.[7] With internal alkenes, both pathways are followed.[8]

Ozonolysis of the benzyl ether **1e** in the presence of NaO-*i*-Pr in *i*-PrOH–CH_2Cl_2 affords the nor benzyl ester **4** in addition to the expected isopropyl ester **3** (Scheme II). Apparently, the aldehyde intermediate **5** (Scheme III) is formed in a significant amount. It must undergo enolate formation and subsequent reaction with ozone ([3 + 2] or stepwise as shown) to produce the benzyl ester **4** via the ozonide **XIV** (Scheme VII). The isopropyl ester **3** is presumably formed from the carbonyl oxide fragment as in **VI** → **XI** → **X** (Scheme VI).

It was of interest to apply the ozonolysis methodology to allylic and homoallylic amine derivatives as a possible

(4) Prepared by methylation (MeI, NaH, THF) or benzylation (BnBr, NaH, THF) of the homoallylic alcohols.

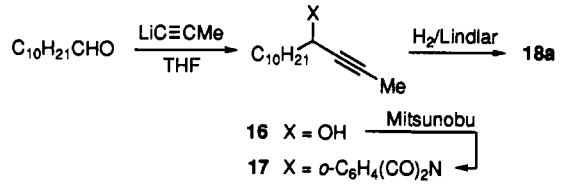
(5) *Cf.* Kuczkowski, R. L. *Acc. Chem. Res.* **1983**, *16*, 42; Murray, R. W. *Acc. Chem. Res.* **1968**, *1*, 313.

(6) *Cf.* Deslongchamps, P.; Atlani, P.; Fréhel, D.; Molaval, A.; Moreau, C. *Can. J. Chem.* **1974**, *52*, 3651.

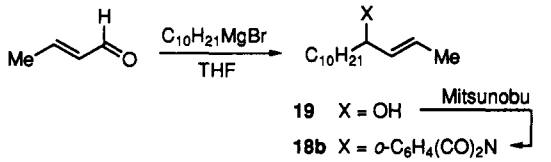
(7) Murray, R. W.; Williams, G. J. *J. Org. Chem.* **1969**, *34*, 1981.

(8) Loan, L. D.; Murray, R. W.; Story, P. R. *J. Am. Chem. Soc.* **1965**, *87*, 737. Lorenz, O.; Parks, C. R. *J. Org. Chem.* **1965**, *30*, 1976.

Scheme VIII



Scheme IX



Scheme X

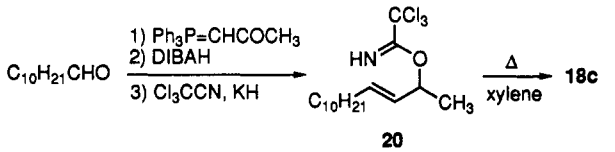
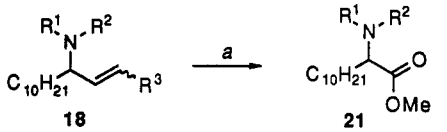


Table III. Synthesis of α-Amino Ester Derivatives from Olefins



entry	R^1	R^2	R^3	series	yield, %	series
1	o-$C_6H_4(CO)_2$		(*Z*)-Me	a	82	a
2	o-$C_6H_4(CO)_2$		(*E*)-Me	b	76	a
3	Cl_3CCO	H	(*E*)-Me	c	48	b

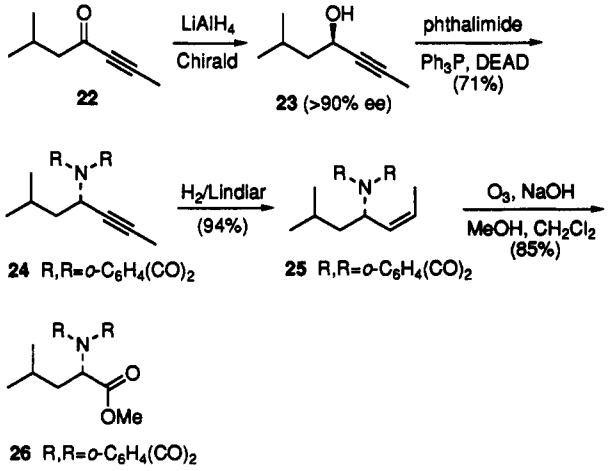
[a] Five equivalents of NaOH in MeOH (2.5 M)/CH_2Cl_2 (1:4 vol/vol), O_3, −78 °C.

route to protected α- and β-amino esters. The allylic amine derivatives were prepared through Mitsunobu displacement of propargylic alcohol **16** or the (*E*)-allylic alcohol **19** with phthalimide (Schemes VIII and IX).[9] Hydrogenation of the derived propargylic imide **17** afforded the (*Z*)-allylic derivative **18a**.[10] The corresponding *N*-trichloroacetyl compound **18c** was prepared by rearrangement of imine **20**, available in three steps from undecanal (Scheme X).[11]

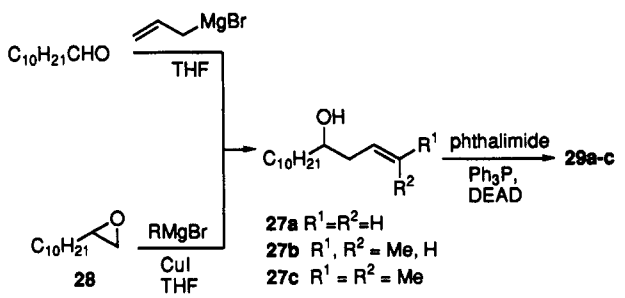
Upon ozonolysis in methanolic NaOH–CH_2Cl_2, the phthalimides **18a** and **18b** gave the expected ester **21a** in high yield. The *N*-trichloroacetyl derivative **18c** was somewhat less efficiently converted to ester **21b** (Table III).

As a check on the optical stability of α-amido esters to the reaction conditions, we carried out the synthesis of the (*S*)-leucine derivative **26** (Scheme XI). The (*R*)-propargylic alcohol **23** of >90% ee was prepared by reduction of the ynone **22** with the $LiAlH_4$–Chirald complex.[12] Mitsunobu displacement with phthalimide[9] led to the imide **24** which was hydrogenated to the (*Z*)-alkene **25** over Lindlar's catalyst.[10] Ozonolysis of **25**

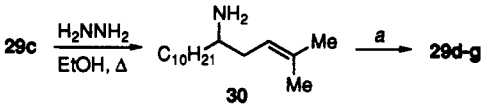
Scheme XI



Scheme XII



Scheme XIII[a]



[a] (*t*-BOC)$_2$O, DMF or CbzCl, DMF or Ac_2O, DMF or *p*-TsCl, Et_3N, CH_2Cl_2.

afforded the protected leucine ester **26** in 85% yield. An authentic sample of this ester was prepared by esterification of the known (*S*)-leucine phthalimide derivative with CH_2N_2.[13] The ^1H NMR spectra and optical rotations of the two samples were in excellent agreement.

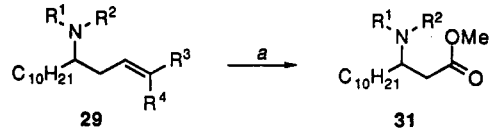
The homoallylic amine derivatives **29a-c** were likewise obtained through Mitsunobu displacement of the appropriate homoallylic alcohols **27a-c** with phthalimide (Scheme XII).[9] Hydrazinolysis of phthalimide **29c** led to amine **30** which was used to prepare the remaining amides **29d-g** (Scheme XIII).

Ozonolysis of these amides, as summarized in Table IV, proceeded readily to afford the methyl esters **31a-e** in satisfactory yield. In several cases, small amounts of secondary ozonides were formed. Slight differences in yields and byproduct formation may not be mechanistically or synthetically significant as the experimental conditions were not optimized for each reaction.

Finally, we examined several internal olefins and one hydroxy olefin as ozonolysis substrates. Thus, methyl oleate (**32**) was converted to a separable mixture of methyl nonanoate (**33**) and dimethyl nonanedioate (**34**) in 78 and 77% yields, respectively (Scheme XIV). Cyclooctene (**35**) smoothly afforded dimethyl octanedioate (**36**) in 75% yield (Scheme XV). The unsaturated alcohol **37** was directly

(9) Mitsunobu, O. *Synthesis* **1981**, 1.
(10) Lindlar, H.; Dubuis, R. *Organic Syntheses;* Wiley: New York, 1973; Collect. Vol V, p 880.
(11) Roush, W. R.; Straub, J. A.; Brown, R. J. *J. Org. Chem.*. **1987**, *52*, 5127.
(12) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870. Brinkmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339.
(13) Nefkens, H. G. L.; Tesser, G. I.; Nivard, R. J. F. *Recl. Trav. Chim Pays-Bas* **1960**, *79*, 688.

Table IV. Synthesis of β-Amino Ester Derivatives from Olefins

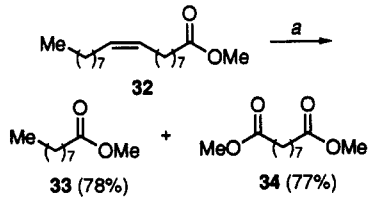


29 31

entry	R^1	R^2	R^3	R^4	series	yield, %	series
1	o-$C_6H_4(CO)_2$	H	H		a	53[b]	a
2	o-$C_6H_4(CO)_2$	H	Me[c]		b	77	a
3	o-$C_6H_4(CO)_2$	Me	Me		c	84	a
4	t-BOC	H	Me	Me	d	76	b
5	Cbz	H	Me	Me	e	65[d]	c
6	Ac	H	Me	Me	f	82	d
7	Ts	H	Me	Me	g	63	e

[a] Five equivalents of NaOH in MeOH (2.5 M)/CH_2Cl_2 (1:4 vol/vol), O_3, −78 °C. [b] 26% of secondary ozonide was produced. [c] A 1:4 mixture of (*E*) and (*Z*) isomers. [d] 13% of aldehyde and 5% of secondary ozonide were produced.

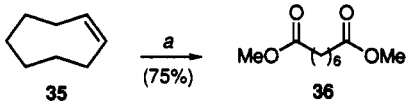
Scheme XIV[a]



32 33 (78%) 34 (77%)

[a] Five equivalents of NaOH in MeOH (2.5 M)/CH_2Cl_2 (1:4 vol/vol), O_3, −78 °C.

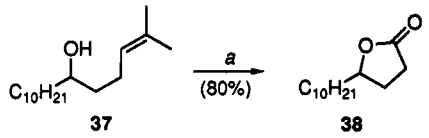
Scheme XV[a]



35 36

[a] Five equivalents of NaOH in MeOH (2.5 M)/CH_2Cl_2 (1:4 vol/vol), O_3, −78 °C.

Scheme XVI[a]



37 38

[a] Five equivalents of NaOH in MeOH (2.5 M)/CH_2Cl_2 (1:8 vol/vol), O_3, −15 °C.

transformed to the known γ-lactone **38** in 80% yield (Scheme XVI).[14] In this case, cooling the reaction mixture to −78 °C caused formation of a gel that was difficult to stir so the ozonolysis was conducted at −15 °C.

Thus the one-step conversion of mono-, vicinal di-, and trisubstituted olefins to methyl esters through ozonolysis in basic methanol appears to be general. Presumably the ethyl esters could likewise be prepared. The formation of benzyl esters is precluded by the facile conversion of benzyl alcohol to benzaldehyde by ozone under the reaction conditions. Enolate formation and subsequent ozonolysis of the enolate preclude the use of this methodology for direct access to isopropyl and, presumably, other branched α-alkoxy esters in systems where ester formation proceeds via an α-alkoxy aldehyde intermediate. Undoubtedly inefficient hemiacetal formation (Scheme VI) contributes to the problem in these applications. We have not examined the use of isopropyl alcohol with other olefins that might afford less readily enolizable aldehyde intermediates.

(14) Takano, S.; Tsuji, K. *J. Am. Oil Chem. Soc.* **1983**, *60*, 1798.

Experimental Section[15]

Methyl 2-Methoxyoctanoate (2a). A solution of 0.30 g (1.9 mmol) of 3-methoxy-1-nonene (**1a**) in 15 mL of CH_2Cl_2 and 3.8 mL of 2.5 M methanolic NaOH was stirred at −78 °C as ozone was passed through the solution. After 75 min, the initially yellow reaction mixture acquired the blue characteristic color of ozone and a yellow precipitate had formed. The reaction mixture was diluted with ether and water, allowed to warm to room temperature, and extracted with ether. The organic layer was dried over $MgSO_4$ and the solvent was removed by distillation under reduced pressure. Purification of the material on a silica gel column using 1:9 Et_2O–hexanes as eluant afforded 0.22 g (63%) of ester **2a**:[16] ^1H NMR ($CDCl_3$, 300 MHz) δ 3.73 (s, CO_2CH_3), 3.73 (t, *J* = 6.2 Hz, H2), 3.36 (s, OCH_3), 1.73–1.21 (m, CH_2s), 0.85 (bt, *J* = 6.8 Hz, CH_3).

Methyl 2-(Benzyloxy)octanoate (2b). The procedure described for **2a** was employed with 0.32 g (1.4 mmol) of 3-(benzyloxy)-1-nonene (**1b**) in 11 mL of CH_2Cl_2 and 2.8 mL of 2.5 M methanolic NaOH. After 1 h and isolation as described, chromatography on a silica gel column using 1:9 Et_2O–hexanes as eluant afforded 0.29 g (78%) of ester **2b**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.32 (m, C_6H_5), 4.68, 4.38 (ABq, *J* = 11.7, CH_2Ar), 3.92 (t, *J* = 6.4 Hz, H2), 3.73 (s, CO_2CH_3), 1.77–1.24 (m, CH_2s), 0.85 (t, *J* = 6.7 Hz, CH_3). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.56; H, 9.12.

Methyl 2-Cyclohexyl-2-(benzyloxy)acetate (2g). The procedure described for **2a** was employed with 0.36 g (1.6 mmol) of 1-cyclohexyl-1-(benzyloxy)-2-propene (**1g**) in 13 mL of CH_2Cl_2 and 3.2 mL of 2.5 M methanolic NaOH. After 30 min, the initially yellow reaction mixture acquired the blue characteristic color of ozone and a yellow precipitate had formed. ^1H NMR analysis of a sample showed consumption of the olefin and formation of ester **2g**. However, the aldehyde was also detected indicating incomplete reaction. An additional 3.2 mL of 2.5 M methanolic NaOH was added whereupon the reaction mixture again turned yellow. Admission of ozone was continued until the solution turned blue. Water was added and the mixture was allowed to warm to room temperature and extracted with ether. The organic layer was dried over $MgSO_4$ and the solvent was removed by distillation under reduced pressure. Purification of the material on a silica gel column using 1:19 EtOAc–hexanes as eluant afforded 0.31 g (75%) of ester **2g**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31 (m, C_6H_5), 4.66, 4.34 (ABq, *J* = 11.8 Hz, CH_2Ar), 3.73 (s, CO_2CH_3), 3.71 (d, *J* = 5.7 Hz, H2), 1.85 (m, c-C_6H_{11}), 1.18 (m, c-C_6H_{11}). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.40; H, 8.49.

Isopropyl 2-(Benzyloxy)dodecanoate (3) and Benzyl Undecanoate (4). A suspension of 0.14 g (5.9 mmol) of NaH in 14 mL of dry CH_2Cl_2 was stirred and cooled to 0 °C as 4.4 mL of *i*-PrOH was added dropwise. A solution of 0.31 g (1.1 mmol) of 3-(benzyloxy)-1-tridecene (**1e**) was added and the resulting solution was cooled to −78 °C. Ozone was passed through the solution. After 50 min, the initially yellow reaction mixture was orange and a yellow precipitate had formed. The reaction mixture was diluted with ether and water, allowed to warm to room temperature, and extracted with ether. The organic layer was dried over $MgSO_4$ and the solvent was removed by distillation under reduced pressure. Purification of the material on a silica gel column using 1:9 Et_2O–hexanes as eluant afforded 0.10 g (33%) of ester **4**: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.34 (m, C_6H_5), 5.10 (s, CH_2Ar), 2.33 (t, *J* = 7.6 Hz, H2), 1.62 (m, H3), 1.23 (m,

(15) For typical experimental protocols and parameters see Marshall, J. A.; Wang, X-j. *J. Org. Chem.* **1991**, *56*, 960. Although we experienced no difficulties with the formation of potentially explosive peroxides and ozonides on the small-scale experiments in this study, it is recommended that reaction mixtures be tested for peroxides and if present that appropriate reductive procedures be employed before product isolation.

(16) Reinheckel, H; Gross, H; Haage, K; Sonnek, G. *Chem. Ber.* **1967**, *101*, 1736.

CH_2s), 0.86 (bt, J = 7.0 Hz, CH_3); HRMS calcd for $C_{18}H_{28}O_2$ (M^+) 276.2089, found 276.2080.

Continued elution afforded 0.14 g (36%) of ester **3**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34 (m, C_6H_5), 5.09 (sept, J = 6.3 Hz, CH(CH_3)$_2$), 4.67, 4.38 (ABq, J = 11.7 Hz, CH_2Ar), 3.86 (dd, J = 7.2, 5.6 Hz, H2), 1.71 (m, H3), 1.45–1.21 (m, CH_2s), 1.26 (d, J = 6.3 Hz, CH(CH_3)$_2$), 1.25 (d, J = 6.3 Hz, CH(CH_3)$_2$), 0.86 (bt, J = 7.0 Hz, CH_3). Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.96; H, 10.37.

2-(Benzyloxy)dodecanal (5). A solution of 0.33 g (1.1 mmol) of 3-(benzyloxy)-1-tridecene (**1e**) and 1.3 g (5.6 mmol) of (±)-10-camphorsulfonic acid in 8.8 mL of CH_2Cl_2 and 2.2 mL of MeOH was stirred at −78 °C as ozone was passed through the solution. After 5 min, the reaction mixture acquired the blue characteristic color of ozone. The reaction mixture was diluted with ether and water, allowed to warm to room temperature, and extracted with ether. The organic layer was dried over $MgSO_4$ and the solvent was removed by distillation under reduced pressure to afford aldehyde **5**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.63 (d, J = 2.2 Hz, CHO), 7.34 (m, C_6H_5), 4.59 (ABq, J = 11.6 Hz, CH_2Ar), 3.73 (m, H2), 1.67–1.23 (m, CH_2s), 0.86 (bt, J = 6.7 Hz, CH_3).

(*S*)-*O*-Methylmandelate of Methyl (*S*)-2-Hydroxydodecanoate (7a). The procedure described for **2a** was employed with 0.31 g (0.89 mmol) of the (*S*)-*O*-methylmandelate of (*S*)-1-tridecen-3-ol (**6a**) in 7.2 mL of CH_2Cl_2 and 1.8 mL of 2.5 M methanolic NaOH. After 35 min, the initially yellow reaction mixture acquired the blue characteristic color of ozone and a yellow precipitate had formed. ^{1}H NMR analysis of a sample of the reaction mixture showed consumption of the olefin and formation of ester **7a**. However, the aldehyde was also detected indicating incomplete reaction. An additional 0.8 mL of 2.5 M methanolic NaOH was added whereupon the reaction mixture again turned yellow. Admission of ozone was continued until the solution again turned blue. Water was added and the mixture was allowed to warm to room temperature and extracted with ether. The organic layer was dried over $MgSO_4$ and the solvent was removed by distillation under reduced pressure. Purification of the material on a silica gel column using 1:9 EtOAc–hexanes as eluant afforded 0.21 g (62%) of ester **7a**: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 7.46–7.30 (m, C_6H_5), 5.05 (dd, J = 6.9, 6.0 Hz, H2), 4.83 (s, CHOCH_3), 3.57 (s, CO_2CH_3), 3.47 (s, OCH_3), 1.83–1.79 (m, H3), 1.28–1.22 (m, CH_2s), 0.86 (bt, J = 7.0 Hz, CH_3). Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.89; H, 9.00.

(*R*)-*O*-Methylmandelate of Methyl (*S*)-2-Hydroxydodecanoate (7b). The procedure described for **2a** was employed with 0.24 g (0.70 mmol) of the (*R*)-*O*-methylmandelate of (*S*)-1-tridecen-3-ol (**6b**) in 5.6 mL of CH_2Cl_2 and 2.0 mL of 2.5 M methanolic NaOH. After 40 min and isolation as described, chromatography on a silica gel column using 1:9 EtOAc–hexanes as eluant afforded 0.18 g (66%) of ester **7b**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.46–7.32 (m, C_6H_5), 4.99 (t, J = 6.5 Hz, H2), 4.87 (s, CHOCH_3), 3.70 (s, CO_2CH_3), 3.43 (s, OCH_3), 1.74 (m, H3), 1.23–1.11 (m, CH_2s), 0.87 (bt, J = 6.8 Hz, CH_3). Anal. Calcd for $C_{22}H_{34}O_5$: C, 69.81; H, 9.05. Found: C, 69.88; H, 9.07.

Methyl 3-Cyclohexyl-3-methoxypropanoate (11a). The procedure described for **2a** was employed with 0.46 g (2.7 mmol) of olefin **10a** in 21.6 mL of CH_2Cl_2 and 5.4 mL of 2.5 M methanolic NaOH. After 80 min and isolation as described, chromatography on a silica gel column using 1:9 EtOAc–hexanes as eluent afforded 0.11 g (19%) of 3-(2-methoxy-2-cyclohexylethyl)-1,2,4-trioxalane (**12a**) as a ~60:40 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.33 (m, H3 minor), 3.28 (m, H3 minor), 5.17 (s, H5 major), 5.13 (s, H5 minor), 5.07 (s, H5 minor), 5.04 (d, J = 0.3 Hz, H5 major), 3.35 (s, OCH_3 major), 3.34 (s, OCH_3 minor), 3.15 (m, CHOCH_3 major), 3.08 (m, CHOCH_3 minor), 1.93–1.54 (m, C_6H_{11}), 1.24–0.95 (m, C_6H_{11}).

Continued elution afforded 0.30 g (56%) of ester **11a**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.67 (s, CO_2CH_3), 3.43 (ddd(apparent q), J = 5.9 Hz, H3), 3.34 (s, OCH_3), 2.44 (d, J = 5.8 Hz, H2), 1.75–0.81 (m, C_6H_{11}).

Methyl 3-Cyclohexyl-3-(benzyloxy)propanoate (11b). A. From 1-Cyclohexyl-1-(benzyloxy)-3-butene (10b). The procedure described for **2a** was employed with 0.34 g (1.4 mmol) of olefin **10b** in 11 mL of CH_2Cl_2 and 2.8 mL of 2.5 M methanolic NaOH. After 50 min and isolation as described, chromatography on a silica gel column using 1:9 EtOAc–hexanes as eluent afforded 0.12 g (29%) of 3-[2-(benzyloxy)-2-cyclohexylethyl]-1,2,4-trioxalane (**12b**) as a ~70:30 mixture of diastereomers: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (m, C_6H_5), 5.34 (m, H3), 5.15 (s, H5 major), 5.12 (s, H5 minor), 5.08 (s, H5 minor), 5.05 (s, H5 major), 4.53 (m, CH_2Ar), 3.36 (m, H1 major), 3.45 (m, H1 minor), 2.01–0.81 (m, H2, c-C_6H_{11}). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.88; H, 8.25.

Continued elution afforded 0.22 g (57%) of ester **11b**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (m, C_6H_5), 4.53 (s, CH_2Ar), 3.71 (dt, J = 7.6, 5.2, H3), 3.65 (s, CO_2CH_3), 2.51 (dd, J = 7.6, 5.0, H2), 1.77–1.54 (m, c-C_6H_{11}), 1.23–0.98 (m, c-C_6H_{11}). Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.99; H, 8.76.

B. From 1-Cyclohexyl-1-(benzyloxy)-4-methyl-3-pentene (10c). The procedure described for **2a** was employed with 0.48 g (1.8 mmol) of olefin **10c** in 14 mL of CH_2Cl_2 and 3.6 mL of 2.5 M methanolic NaOH. After 50 min and isolation as described, chromatography on a silica gel column using 1:5 Et_2O–hexanes as eluant afforded 0.46 g (95%) of ester **11b** identified by comparison of the ^{1}H NMR spectrum with that of the material prepared above in part A.

Methyl 2-(2,2,2-Trichloroacetamido)dodecanoate (21b). The procedure described for **2a** was employed with 0.31 g (0.90 mmol) of olefin **18c** in 7.2 mL of CH_2Cl_2 and 1.8 mL of 2.5 M methanolic NaOH. After 60 min and isolation as described, chromatography on a silica gel column using 1:9 EtOAc–hexanes as eluant afforded 0.16 g (48%) of ester **21b**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.18 (bd, J = 7.7 Hz, NH), 4.55 (dt, J = 7.1, 5.3 Hz, H2), 3.79 (s, CO_2CH_3), 1.93 (m, H3), 1.77 (m, H4), 1.23 (m, CH_2s), 0.86 (bt, J = 6.7 Hz, CH_3). Anal. Calcd for $C_{15}H_{26}Cl_3NO_4$: C, 48.07; H, 6.99. Found: C, 48.15; H, 6.98.

(*R*)-6-Methyl-2-heptyn-4-ol (23). A solution 5.8 mL (5.8 mmol) of 1.0 M $LiAlH_4$ in THF in 140 mL of dry Et_2O was stirred at 0 °C as a solution of 4.9 g (17 mmol) of Chirald in 50 mL of Et_2O was added over 1.5 min.[12] The mixture was immediately cooled to −78 °C and a solution of 0.61 g (4.9 mmol) of heptynone **22** in 25 mL of Et_2O was added dropwise over 75 min. The reaction mixture was then stirred at −78 °C for 5 h, then it was quenched with 1 N HCl and extracted with ether. The organic layer was dried over $MgSO_4$ and the solvent was removed by distillation under reduced pressure. Bulb-to-bulb distillation (44 °C, 1.0 mm) afforded 0.47 g (75%) of heptynol **23**: $[\alpha]^{23}_D$ +13.28° (*c* 4.9, $CHCl_3$); 90% ee based on lit. $[\alpha]^{23}_D$ +13.48° (*c* 4.9, $CHCl_3$).[17]

(*S*)-6-Methyl-4-phthalimido-2-heptyne (24). The procedure described for **17** was employed with 0.35 g (2.8 mmol) of heptynol **23**, 0.56 g (3.9 mmol) of phthalimide, 1.0 g (3.9 mmol) of triphenylphosphine, and 0.67 g (3.8 mmol) of diethyl azodicarboxylate in 20 mL of dry THF. After 2 h and isolation as described, chromatography on a silica gel column using 1:9 EtOAc–hexanes as eluant afforded 0.50 g (71%) of imide **24**: $[\alpha]^{23}_D$ -14.80° (*c* 2.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.82 (dd, J = 5.4, 3.1 Hz, ArH), 7.69 (dd, J = 5.5, 3.0 Hz, ArH), 5.06 (tq, J = 8.1, 2.4 Hz, H4), 1.92 (m, H5), 1.79 (d, J = 2.4 Hz, H1), 1.63 (sept, J = 6.7 Hz, H6), 0.92 (dd(apparent t), J = 6.6 Hz, H7). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.17; H, 6.73; N, 5.44.

(*E*)-(*S*)-6-Methyl-4-phthalimido-2-heptene (25). The procedure described for **16** was employed with 0.50 g (2.0 mmol) of imide **24** and 0.13 g of Lindlar's catalyst in 20 mL of benzene. After 2 h and isolation as described, chromatography on a silica gel column using 1:9 EtOAc–hexanes as eluant afforded 0.47 g (94%) of olefin **25**: $[\alpha]^{23}_D$ +63.31° (*c* 5.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (dd, J = 5.6, 3.1 Hz, ArH), 7.67 (dd, J = 5.4, 2.9 Hz, ArH), 5.89 (m, H3), 5.57 (ddq, J = 10.7, 6.9, 1.1 Hz, H2), 5.16 (m, H4), 1.98 (ddd, J = 13.6, 8.9, 6.0 Hz, H5), 1.70 (dd, J = 6.9, 1.8 Hz, H1), 1.65 (m, H5), 1.47 (m, H6), 0.94 (d, J = 6.5 Hz, H7), 0.89 (d, J = 6.6 Hz, H7). Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.57; H, 7.40; N, 5.47.

***N*-Phthalimidoleucine Methyl Ester (26). A. From (*E*)-(*S*)-6-Methyl-4-phthalimido-2-heptene (25).** The procedure described for **2a** was employed with 0.43 g (1.7 mmol) of olefin **25** in 13.6 mL of CH_2Cl_2 and 3.4 mL of 2.5 M methanolic NaOH. After 45 min and isolation as described, chromatography on a silica gel column using 1:9 EtOAc–hexanes as eluant afforded

(17) Chan, K-K.; Cohen, N.; De Noble, J. P.; Specian, A. C. Jr.; Saucy, G. *J. Org. Chem.* **1976**, *41*, 3497.

0.39 g (85%) of ester **26**: $[\alpha]^{23}_D$ −20.28° (*c* 1.8, $CDCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.84 (dd, *J* = 5.4, 3.1 Hz, ArH), 7.72 (dd, *J* = 5.5, 3.0 Hz, ArH), 4.93 (dd, *J* = 11.6, 4.3 Hz, H2), 3.70 (s, CO_2CH_3), 2.31 (ddd, *J* = 14.2, 11.6, 4.0 Hz, H3), 1.93 (ddd, *J* = 14.4, 10.3, 4.4 Hz, H3), 1.46 (m, H4), 0.92 (d, *J* = 6.6 Hz, H5), 0.90 (d, *J* = 6.6 Hz, H5). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.23; N, 5.09. Found: C, 65.54; H, 6.25; N, 5.07.

B. From Phthaloyl-L-leucine. A solution of 0.21 g (1.6 mmol) of (L)-leucine, 0.23 g (1.8 mmol) of $Na_2CO_3 \cdot H_2O$, and 0.42 g (1.9 mmol) of *N*-carbethoxyphthalimide in 16 mL of distilled water was stirred at room temperature for 20 min.[13] The reaction mixture was filtered and the filtrate was brought to pH 2 with 1 N HCl and extracted with ether. The organic layer was dried over $MgSO_4$ and the solvent was removed by distillation under reduced pressure to afford phthaloyl-L-leucine.

A solution of *N*-(nitrosomethyl)urea in 20 mL of Et_2O was stirred at 0 °C as 1.4 mL of 40% KOH was added dropwise. The yellow ether layer was then added to a solution of the above phthaloyl-L-leucine in 10 mL of Et_2O at 0 °C until a yellow color persisted. The solvent was removed by distillation under reduced pressure and the material was purified by chromatography on a silica gel column using 1:9 EtOAc–hexanes to afford 0.31 g (70%) of ester **26** identified by comparison of the ^{1}H NMR spectrum with that of the material prepared above in part A, $[\alpha]^{23}_D$ −20.80° (*c* 5.6, $CDCl_3$).

5-[(*tert*-Butoxycarbonyl)amino]-2-methyl-2-pentadecene (29d). A solution of 0.49 g (1.3 mmol) of phthalimide **29c** and 0.44 g (7.3 mmol) of hydrazine hydrate in 10 mL of absolute EtOH was refluxed for 5 h, resulting in the formation of a white precipitate. The reaction mixture was cooled to room temperature and 2.0 mL of concentrated HCl was added. The solids were removed by fitration through Celite, and the filtrate was concentrated under reduced pressure to a semisolid residue. The residue was taken up in 30 mL of 2:1 EtOH–H_2O and the insoluble portion was removed by filtration. The filtrate was brought to pH > 10 with 1 N NaOH and extracted with ether. The organic layer was dried over $MgSO_4$ and the solvent was removed by distillation under reduced pressure to afford 0.35 g of the crude amine **30**.

A solution of amine **30**, 0.17 g (1.7 mmol) of Et_3N, and 0.36 g (1.6 mmol) of di-*tert*-butyl carbonate in 15 mL of dry DMF was stirred at room temperature. After 45 min, water was added and the mixture was extracted with hexanes. The organic layer was dried over $MgSO_4$ and the solvent was removed by distillation under reduced pressure. Purification of the material on a silica gel column using 1:9 EtOAc–hexanes as eluent afforded 0.37 g (82%) of olefin **29d**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.09 (m, H3), 4.25 (m, NH), 3.55 (m, H5), 2.11 (m, H4), 1.69 (s, H1), 1.59 (s, H1), 1.42 (s, $C(CH_3)_3$), 1.23 (m, CH_2s), 0.86 (bt, *J* = 6.7 Hz, H15). Anal. Calcd for $C_{21}H_{41}NO_2$: C, 74.28; H, 12.17; N, 4.13. Found: C, 74.48; H, 12.00; N, 4.05.

Methyl 3-Phthalimidotridecanoate (31a). A. From 4-Phthalimido-1-tetradecene (29a). The procedure described for **2a** was employed with 0.29 g (0.80 mmol) of 4-phthalimido-1-tetradecene (**29a**) in 6.4 mL of CH_2Cl_2 and 1.6 mL of 2.5 M methanolic NaOH. After 30 min and isolation as described, chromatography on a silica gel column using 1:9 EtOAc–hexanes as eluant afforded 0.08 g (26%) of rel-(*R*,*R*) and (*R*,*S*)-3-(2-phthalimidododecyl)trioxalane: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (m, ArH), 7.68 (m, ArH), 5.13 (m, CHO_2), 5.06 (m, CH_2O_2), 5.05 (m, CH_2O_2), 4.97 (m, CH_2O_2), 4.94 (m, CH_2O_2), 4.41 (m, NCH), 2.65 (m, CH_2), 2.09 (m, CH_2), 1.64 (m, CH_2), 1.19 (m, CH_2s), 0.84 (bt, *J* = 6.7 Hz, CH_3). Anal. Calcd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60. Found: C, 67.75; H, 8.04; N, 3.54.

Continued elution afforded 0.17 g (53%) of ester **31a**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.81 (dd, *J* = 5.4, 3.1 Hz, ArH), 7.69 (dd, *J* = 5.5, 3.0 Hz, ArH), 4.62 (tt, *J* = 9.8, 5.3 Hz, H3), 3.58 (s, CO_2CH_3), 3.15 (dd, *J* = 16.0, 9.6 Hz, H2), 2.76 (dd, *J* = 16.0, 5.3 Hz, H2), 2.05 (m, H4), 1.70 (m, H4), 1.19 (m, CH_2s), 0.84 (bt, *J* = 6.8 Hz, H13). Anal. Calcd for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37; N, 3.75. Found: C, 70.66; H, 8.43; N, 3.70.

B. From (Z) and (E)-5-Phthalimido-2-pentadecene (29b). The procedure described for **2a** was employed with 0.52 g (1.5 mmol) of a 1:4 (*E*)/(*Z*) mixture of 5-phthalimido-2-pentadecene (**29b**) in 12 mL of CH_2Cl_2 and 3.0 mL of 2.5 M methanolic NaOH. After 45 min and isolation as described, chromatography on a silica gel column using 1:4 EtOAc–hexanes as eluant afforded 0.42 g (84%) of ester **31a** identified by comparison of the ^{1}H NMR spectrum with that of the material prepared above in part A.

C. From 2-Methyl-5-phthalimido-2-pentadecene (29c). The procedure described for **2a** was employed with 0.46 g (1.2 mmol) of 2-methyl-5-phthalimido-2-pentadecene (**29c**) in 9.6 mL of CH_2Cl_2 and 2.4 mL of 2.5 M methanolic NaOH. After 35 min and isolation as described, chromatography on a silica gel column using 1:4 EtOAc–hexanes as eluant afforded 0.39 g (84%) of ester **31a** identified by comparison of the ^{1}H NMR spectrum with that of the material prepared above in part A.

Methyl Nonanoate (33) and Dimethyl Azelate (34). The procedure described for **2a** was employed with 0.51 g (1.7 mmol) of methyl oleate (**32**) in 14 mL of CH_2Cl_2 and 3 mL of 2.5 M methanolic NaOH. After 45 min and isolation as described, chromatography on a silica gel column using 1:19 EtOAc–hexanes as eluant afforded 0.23 g (78%) of methyl nonanoate (**33**):[18] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.65 (s, CO_2CH_3), 2.28 (t, *J* = 7.5 Hz, H2), 1.62–1.54 (m, H3), 1.26–1.23 (m, CH_2s), 0.86 (bt, *J* = 6.7 Hz, H9).

Continued elution afforded 0.29 g (77%) of dimethyl azelate (**34**):[19] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.64 (s, CO_2CH_3), 2.27 (bt, *J* = 7.5 Hz, H2, H8), 1.61–1.57 (m, H3,H7), 1.33–1.22 (m, CH_2s).

Tetradecanoic Acid γ-Lactone (38). A solution of 0.27 g (1.1 mmol) of 2-methyl-2-hexadecen-6-ol in 8.0 mL of CH_2Cl_2 and 2.2 mL of 2.5 M methanolic NaOH was stirred at −15 °C as ozone was passed through the solution. After 15 min, the solution became thick and a white precipitate formed. The reaction mixture was diluted with 10 mL of CH_2Cl_2 and after an additional 15 min, ether and water were added and the mixture was allowed to warm to room temperature and extracted with ether. The organic layer was dried over $MgSO_4$ and the solvent was removed by distillation under reduced pressure. Purification of the material on a silica gel column using 1:4 EtOAc–hexanes as eluant afforded 0.19 g (80%) of lactone **38**:[14] ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 4.46 (m, H4), 2.51 (m, H2), 2.30 (m, H3), 1.90–1.24 (m, CH_2s, H3), 0.86 (bt, *J* = 6.7 Hz, H14).

Acknowledgment. Support for this work through a research grant (CHE 8912745) from the National Science Foundation is gratefully acknowledged. We thank Molecular Design, Ltd. for the use of their reaction data base.

Supplementary Material Available: Experimental procedures for compounds **1a-g**, **2c-f**, **6a-b**, **8**, **9**, **10a-c**, **13**, **14**, **16**, **17**, **18a-c**, **19**, **21a**, **22**, **27a-c**, **28**, **29a-c**, **29e-g**, **31b-e**, **32**, **36**, and **37** and selected ^{1}H NMR spectra are reported (40 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.

(18) Swern, D.; Parker, W. E. U.S. Patent No. 2 813 885, 1957.
(19) Holman, R. T.; Edmonson, P. R. *Anal. Chem.* **1956**, *28*, 1533.