GLC analysis (oven temperature 170 °C) of the crude reaction mixture indicated the presence of **18a** and **18b** (t_R = 12.2 and 13.4 min, respectively) in a ratio of 1.14:1. Base-catalyzed equilibration (NaOMe, MeOH, reflux, 24-30 h) provided a 2.6:1 **18a**:**18b** ratio by GLC analysis.

Acknowledgment. We are grateful for the financial support of the National Institutes of Health (Grant No. CA 42056) and the Alfred P. Sloan Foundation.

Supplementary Material Available: Full experimental details of the preparation and characterization of phenyl selenoesters **1-4**, **9**, **14**, and **17** and details of the experimental assignment of the stereochemistry of **8a-d** (18 pages). Ordering information is given on any current masthead page.

Intramolecular Acyl Radical-Alkene Addition Reactions: Macrocyclization Reactions

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Abstract: The generation of acyl radicals from phenyl selenoesters and the scope of their participation in macrocyclization free-radical alkene addition reactions are detailed. The studies illustrate that large ring ω-acryloyl radical cyclizations proceed at rates competitive with those of 5-*exo*-*trig* cyclization of 5-hexenoyl radicals and that exceed those of 6-*exo*- or 7-*endo*-*trig* cyclization of 6-heptenoyl radicals, thus providing an effective macrocyclization technique that proceeds through carbon-carbon bond formation and with introduction of useful functionality at the ring-closure site.

In recent years, the development and application of numerous techniques suitable for conducting effective macrocyclization reactions have been introduced. Most prominent among the approaches are macrolactonization[1] and macrolactamization[2] techniques, and few useful macrocyclization procedures that rely on carbon-carbon bond formation have been introduced.[3] In recent studies, we have shown that acyl radicals generated from phenyl selenoesters participate in effective intramolecular,[4] intermolecular,[5] and tandem[6] alkene addition reactions at rates greater than that of the potentially competitive tri-*n*-butyltin hydride hydrogen abstraction (reduction)[7] and decarbonylation[8] reactions. Herein, we report that acyl radicals[9] generated in this manner effectively participate in macrocyclization alkene addition reactions with the introduction of useful functionality at the radical initiator site.

Macrocyclization Reactions. Recent studies of Porter and co-workers have defined the structural requirements for successful application of alkyl radical macrocyclization reactions.[10] Acyl radicals exhibit nucleophilic character and reactivity comparable to that of alkyl radicals,[4,5] thus substrates containing an electron-deficient and terminally unsubstituted alkene acceptor group were chosen to test the viability of acyl radical participation in macrocyclization alkene addition reactions. Phenyl selenoesters **1a-e** were prepared from the corresponding ω-hydroxy acids by phenyl selenoesters formation (diethyl phosphorochloridate, Et_3N, THF; NaSePh, THF) and acylation (acryloyl chloride, pyridine, ether, 0 °C).[11] Free-radical cyclization of **1a-e** under high-dilution conditions (5-6 mM in benzene, cat. AIBN, 80 °C, slow addition of 1.2 equiv of tri-*n*-butyltin hydride over 1 h) provided good yields of macrolides **2a-e** (eq 1, Table I) with no evidence of formation of products derived from direct reduction or decarbonylation of the intermediate acyl radicals.[12,13] Thus, macrocyclization reactions involving the addition of acyl radicals to activated alkenes serve as an efficient method for the preparation of large-ring compounds of various sizes with the introduction of additional, useful functionality at the initial radical-bearing center.

Competitive Cyclizations: Macrocyclization versus Seven- to Five-Membered-Ring Cyclizations. With the viability of the acyl radical cyclization for the preparation of saturated macrolides demonstrated, the free-radical cyclization reactions of substrates possessing additional internal sites of unsaturation were examined

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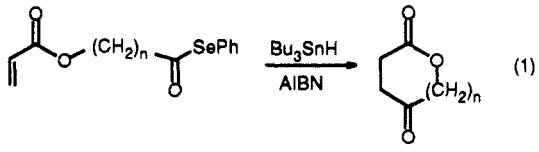
Table I



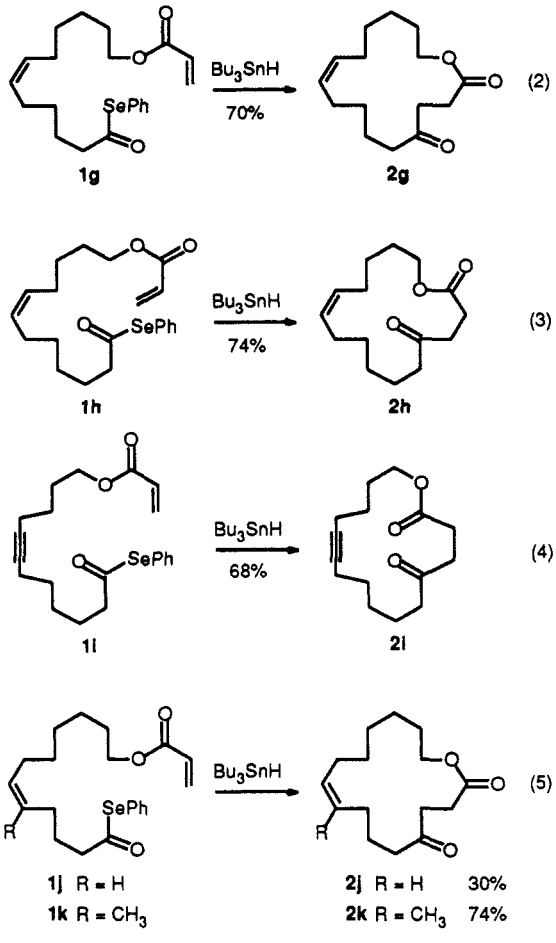
(1)

1 2

phenylseleno ester	*n*	ring size	product	% yield
1a	15	20	**2a**	57
1b	11	16	**2b**	68
1c	9	14	**2c**	55
1d	7	12	**2d**	46
1e	6	11	**2e**	47

with the intent of defining the full scope or limitations of this approach to the formation of macrocyclic compounds. Since the application of the free-radical macrocyclization reaction to such substrates might be anticipated to suffer from alternative competitive cyclization reactions, we elected to directly assess the relative rates of the potentially competitive ring-closure pathways with substrates **1g–k**, Scheme I. The studies of Porter and co-workers[10] have demonstrated that macrocyclization reactions derived from addition of primary alkyl radicals to acrylate esters proceed at rates of $1–8 \times 10^4\ s^{-1}$ (80 °C) and have proven substantially faster than 7-*exo-trig* cyclization of 7-octenyl radicals (3×10^2, 80 °C),[14] competitive with 6-*exo-trig* cyclization of 6-heptenyl radicals ($4.3 \times 10^4\ s^{-1}$, 80 °C),[14] and presumably much slower than 5-*exo-trig* cyclization of 5-hexenyl radicals ($1.4 \times 10^6\ s^{-1}$, 80 °C).[14d] Additional, unrelated studies including our demonstration of competitive intermolecular acyl radical–acrylate ester[5,6] and intramolecular 5-hexenoyl radical 5-*exo-trig* alkene[6] addition reactions (6-heptenoyl radical 6-*exo-trig* cyclization is noncompetitive) and the apparent demonstration of the rate deceleration of the 5-*exo-trig* cyclization of 1,6-heptadien-2-yl radicals[15] (5-*exo-trig* ≅ 6-*endo-trig*) have suggested that the intramolecular 5-hexenoyl 5-*exo-trig* radical cyclization may be significantly slower than the comparable 5-*exo-trig* cyclization of 5-hexenyl radicals *and* that the macrocyclization reaction of acyl radicals may be accelerated[16] relative to that of alkyl radicals. Thus, under high-dilution reaction conditions (<0.01 M), the rate of macrolide formation by intramolecular acyl radical addition to an acrylate acceptor could be expected to exceed that of a potentially competitive 6- or 7-*exo* cyclization with an unactivated acceptor and to be competitive with 5-*exo* cyclization. Treatment of phenyl selenoesters **1g–i** with tri-*n*-butyltin hydride under the reaction conditions detailed above cleanly afforded the unsaturated macrolides **2g–i**[11] in excellent yields, eqs 2–4, without formation of products derived from 6- or 7-*exo* and 7-*endo* free-radical cyclization *and* in conversions that exceed those observed with the parent, saturated macrocyclization reactions. Moreover, phenyl selenoesters **1j** provided an inseparable mixture (1:1) of

Scheme I



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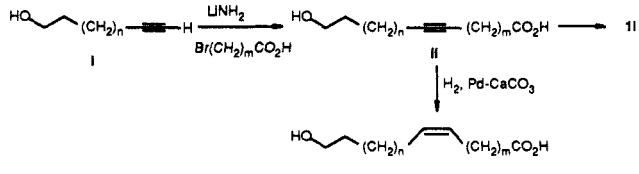
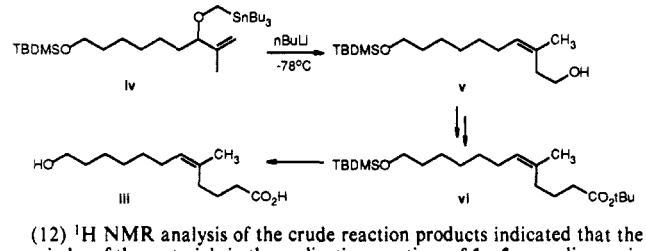
(11) (a) Unsaturated ω-hydroxy acids used for the preparation of **1g–j** were obtained by alkylation of the corresponding alkynols i (excess $LiNH_2$, liquid NH_3) with the requisite ω-bromo acids (cf.: Ames, D. E.; Goodburn, T. G.; Covell, A. N. *J. Chem. Soc.* **1963**, 5889) followed by Lindlar reduction of the resulting ω-hydroxyalkynoic acids ii.

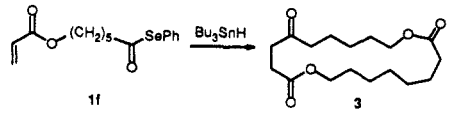


(b) The ω-hydroxy acid iii used for the preparation of **1k** was prepared by 2,3-sigmatropic Wittig rearrangement (cf.: Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927) of allyl stannylmethyl ether iv to alcohol v, two-carbon homologation (MsCl, Et_3N, CH_2Cl_2; NaI, acetone; $LiCH_2CO_2tBu$, HMPA–THF), and subsequent deprotection of vi. Full experimental details are provided in supplementary material.



(12) ^1H NMR analysis of the crude reaction products indicated that the remainder of the materials in the cyclization reactions of **1a–f** were oligomeric materials derived from competitive intermolecular alkene addition reactions.

(13) Treatment of phenyl selenoesters **1f** with tri-*n*-butyltin hydride did not afford the corresponding 10-membered macrolide **2f**, and the only characterizable product isolated was **3** (10%).



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(16) The decreased energy difference [$\Delta\Delta E$ (SOMO/LUMO) = 0.12 eV (AM1), 0.45 eV (MNDO)] between the acyl radical SOMO [acetyl radical: E_{SOMO} = −3.84 eV (AM1), −3.68 eV (MNDO)] versus alkyl radical SOMO [ethyl radical: E_{SOMO} = −3.96 eV (AM1), −4.13 eV (MNDO)] and the acrylate ester LUMO [methyl acrylate: E_{LUMO} = 0.00 eV (AM1), −0.02 eV (MNDO)] also suggests a potential rate acceleration for the acyl radical–acrylate versus alkyl radical–acrylate addition reaction.

macrolide **2j** and an isomeric compound derived from competitive 5-*exo* cyclization, eq 5, illustrating that the *rates of intramolecular acyl radical macrocyclization and 5-hexenoyl cyclization are roughly comparable.* In contrast, phenyl selenoesters **1k** provided *exclusively* the macrolide **2k** (74%), illustrating that simple substitution of the alkene at the site of 5-hexenoyl cyclization provides sufficient deceleration of the five-membered-ring closure reaction to permit clean observation of the macrocyclization reaction.

Thus, the ω-acryloyl radical cyclization reaction conducted under standard high-dilution reaction conditions (5 mM, 80 °C) provides an effective macrocyclization technique proceeding through carbon–carbon bond formation and with introduction of functionality at the site of ring closure.[17] Further studies on the scope of reactions of acyl radicals and their applications are in progress and will be reported in due course.

Experimental Section

General Procedure for the Preparation of ω-Hydroxy Phenyl Selenoesters: 12-Hydroxydodecanoyl Phenyl Selenide. A solution of 12-hydroxydodecanoic acid (Aldrich; 626 mg, 2.90 mmol) and triethylamine (312 mg, 0.43 mL, 3.08 mmol, 1.05 equiv) in 20 mL of dry tetrahydrofuran (THF) under nitrogen was treated with diethyl phosphorochloridate (0.45 mL, 3.08 mmol, 1.05 equiv). After being stirred at room temperature for 3 h, the mixture was filtered through a sintered-glass funnel under a positive pressure of dry nitrogen. The precipitate was washed with an additional 10 mL of dry THF and the combined filtrates were transferred via syringe to a second flask containing sodium phenyl selenide[18] (3.48 mmol, 1.2 equiv) in dry THF (5 mL). The cloudy yellow mixture was stirred at room temperature for 16 h and was filtered through a short pad of Celite. The filter cake was washed with ethyl acetate (2 × 20 mL), and the combined filtrates were concentrated under reduced pressure. The yellow oil was purified by flash chromatography (3 × 12 cm SiO_2, 20% EtOAc–hexane eluant) to give 568 mg (1.03 g theoretical, 55%) of 12-hydroxydodecanoyl phenyl selenide as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 1.28 (14 H, m), 1.56 (2 H, m), 1.69 (2 H, m), 2.70 (2 H, t, J = 7.5 Hz, C2-H_2), 3.64 (2H, t, J = 6.6 Hz, C12-H_2), 7.39 (3 H, m, 3 ArH), 7.50 (2 H, m, 2 ArH); IR (neat) ν_{max} 3348 (br, OH), 2926, 2854, 1726 (C=O), 1440, 1058, 738 cm^{-1}; EIMS, m/e (relative intensity) 199 (26, M^+ – SePh), 181 (15), 157 (11), 97 (43), 83 (53), 69 (63), 55 (base, $C_4H_7^+$); CIMS (isobutane), m/e 357 (M^+ + H), 199 (base, M^+ + H – HSePh); EIHRMS, m/e 356.1250 ($C_{18}H_{28}O_2Se$ requires 356.1254).

General Procedure for the Preparation of Acrylate Esters: 11-[(Phenylseleno)carbonyl]undecyl Acrylate (1b). A solution of 12-hydroxydodecanoyl phenyl selenide (325 mg, 0.913 mmol) in 6 mL of dry ether under nitrogen was cooled to 0 °C and was treated sequentially with pyridine (0.15 mL, 1.83 mmol, 2.0 equiv) and acryloyl chloride (0.15 mL, 1.83 mmol, 2.0 equiv). The light yellow suspension was stirred at 0 °C for 1.0 h and filtered under nitrogen, and the precipitate was washed with an additional 20 mL of dry ether. The combined filtrates were concentrated under reduced pressure, and the residual oil was purified by flash chromatography (2 × 12 cm SiO_2, 8% EtOAc–hexane eluant) to provide 250 mg (374 mg theoretical, 68%) of **1b** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 1.27 (14 H, br s), 1.66 (4 H, m), 2.70 (2 H, t, J = 7.4 Hz, C2-H_2), 4.15 (2 H, t, J = 6.7 Hz, C12-H_2), 5.81 (1 H, dd, J = 10.3 and 0.8 Hz, =C*H*H), 6.12 (1 H, dd, J = 17.3 and 10.4 Hz, =CHCO), 6.40 (1 H, dd, J = 17.3 and 0.8 Hz, =CH*H*), 7.38 (3 H, m, 3 ArH), 7.50 (2 H, m, 2 ArH); IR (neat) ν_{max} 2926, 2854, 1726, 1408, 1194, 984, 738, 690 cm^{-1}; EIMS, m/e (relative intensity) 253 (14, M^+ – ScPh), 181 (8), 97 (10), 83 (14), 69 (16), 55 (base, $C_3H_3O^+$); CIMS (isobutane), m/e 411 (M^+ + H), 253 (base, M^+ + H – HSePh); EIHRMS, m/e 410.1355 ($C_{21}H_{30}O_3Se$ requires 410.1360).

General Procedure for the Free-Radical Cyclization of Phenyl Selenoesters 1: 15-Hydroxy-4-oxopentadecanoic Acid Lactone (2b). A solution of **1b** (109 mg, 0.267 mmol) in 60 mL of dry benzene was degassed, treated with 5 mg of 2,2′-azobis(2-methylpropionitrile) (AIBN), and warmed to reflux. A solution of tri-*n*-butyltin hydride (76 μL, 0.282 mmol, 1.2 equiv) in 4 mL of benzene was added dropwise (syringe pump) over a period of 1 h, and the reaction mixture was warmed at reflux for an additional 1.5 h. After cooling to room temperature and removal of solvent under reduced pressure, the residual oil was purified by flash chromatography (1 × 10 cm SiO_2, 0% then 15% EtOAc–hexane eluant), to give 46.0 mg (67.8 mg theoretical, 68%) of **2b** as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 1.32 (14 H, br s, C7-H_2 through C13-H_2), 1.63 (4 H, m, C6-H_2 and C14-H_2), 2.45 (2 H, t, J = 6.4 Hz, C5-H_2), 2.57 (2 H, t, J = 6.1 Hz, C2-H_2 or C3-H_2), 2.76 (2 H, t, J = 6.1 Hz, C3-H_2 or C2-H_2), 4.14 (2 H, t, J = 5.7 Hz, C15-H_2); IR (neat) ν_{max} 2928, 2858, 1736, 1460, 1410, 1356, 1258 cm^{-1}; EIMS, m/e (relative intensity) 255 (9, M^+ + H), 254 (8, M^+), 111 (20), 99 (58, $C_6H_{11}O^+$), 98 (57), 83 (22), 69 (29), 55 (base, $C_4H_7^+$); CIMS (isobutane), m/e 255 (base, M^+ + H); EIHRMS, m/e 254.1880 ($C_{15}H_{26}O_3$ requires 254.1881).

19-Hydroxy-4-oxononadecanoic acid lactone (2a): oil; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 1.29 (22 H, br s), 1.60 (4 H, m), 2.43 (2 H, t, J = 7.0 Hz, C5-H_2), 2.56 (2 H, t, J = 6.3 Hz, C2-H_2 or C3-H_2), 2.71 (2 H, t, J = 6.3 Hz, C3-H_2 or C2-H_2), 4.09 (2 H, t, J = 6.4 Hz, C19-H_2); IR (neat) ν_{max} 2926, 2856, 1738, 1462, 1410, 1168 cm^{-1}; EIMS, m/e (relative intensity) 111 (22), 99 (96), 83 (24), 69 (35), 55 (base, $C_4H_7^+$); CIMS (isobutane), m/e 311 (base, M^+ + H); CIHRMS, m/e 311.2587 ($C_{19}H_{34}O_3$ requires 311.2586).

13-Hydroxy-4-oxotridecanoic acid lactone (2c): white solid, mp 48.5–49.5 °C (pentane); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 1.29 (10 H, m, C7-H_2 through C11-H_2), 1.57–1.80 (4 H, m, C6-H_2 and C12-H_2), 2.50 (2 H, t, J = 6.2 Hz, C5-H_2), 2.61 (2 H, t, J = 6.4 Hz, C2-H_2 or C3-H_2), 2.76 (2 H, t, J = 6.4 Hz, C3-H_2 or C2-H_2), 4.13 (2 H, t, J = 5.4 Hz, C13-H_2); IR (KBr) ν_{max} 2940, 2860, 1728, 1712, 1414, 1264 cm^{-1}; EIMS, m/e (relative intensity) 226 (2, M^+), 208 (2), 111 (16), 98 (55), 83 (12), 69 (30), 55 (base, $C_3H_3O^+$); CIMS (isobutane), m/e 227 (M^+ + H); EIHRMS, m/e 226.1568 ($C_{13}H_{22}O_3$ requires 226.1569).

Anal. Calcd: C, 68.98; H, 9.80. Found: C, 68.94; H, 10.15.

11-Hydroxy-4-oxoundecanoic acid lactone (2d): oil; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 1.37 (6 H, m, C7-H_2 through C9-H_2), 1.63 (2 H, m, C10-H_2), 1.78 (2 H, m, C6-H_2), 2.48 (2 H, t, J = 6.3 Hz, C5-H_2), 2.72 (4 H, m, C2-H_2 and C3-H_2), 4.09 (2 H, t, J = 5.2 Hz, C11-H_2); IR (neat) ν_{max} 2930, 1730, 1256, 1150, 1012 cm^{-1}; EIMS, m/e (relative intensity) 198 (1, M^+), 180 (1), 111 (18), 101 (35), 98 (42), 55 (base, $C_4H_7^+$); CIMS (isobutane), m/e 199 (M^+ + H); EIHRMS, m/e 198.1755 ($C_{11}H_{18}O_3$ requires 198.1756).

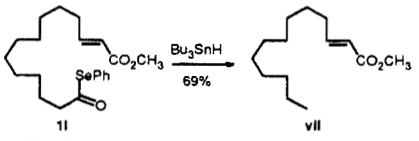
10-Hydroxy-4-oxodecanoic acid lactone (2e): oil; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 1.33 (2 H, m), 1.53 (2 H, m), 1.79 (4 H, m), 2.45 (2 H, t, J = 6.3 Hz, C5-H_2), 2.63–2.76 (4 H, m, C2-H_2 and C3-H_2), 4.06 (2 H, t, J = 4.9 Hz, C10-H_2); IR (neat) ν_{max} 2936, 1731, 1250, 1141, 992 cm^{-1}; EIMS, m/e (relative intensity) 184 (2, M^+), 156 (9), 111 (26), 101 (50), 98 (46), 83 (21), 68 (21), 55 (base, $C_4H_7^+$); CIMS (isobutane), m/e 185 (M^+ + H); EIHRMS, m/e 184.1101 ($C_{10}H_{16}O_3$ requires 184.1100).

(*Z*)-15-Hydroxy-4-oxo-9-pentadecenoic acid lactone (2g): white needles, mp 47–49 °C (petroleum ether); ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 1.15–1.62 (10 H, m), 2.01 (4 H, m), 2.37 (2 H, t, J = 7.3 Hz, C5-H_2), 2.49 (2 H, t, J = 5.7 Hz, C2-H_2 or C3-H_2), 2.68 (2 H, t, J = 5.7 Hz, C3-H_2 or C2-H_2), 3.98 (2 H, t, J = 5.7 Hz, C15-H_2), 5.28 (2 H, m, C*H*=C*H*); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm) 23.3 (CH_2), 25.7 (CH_2), 26.2 (CH_2), 26.8 (CH_2), 28.3 (CH_2), 28.4 (CH_2), 28.5 (CH_2), 28.6 (CH_2), 36.7 (CH_2), 41.9 (CH_2), 64.4 (CH_2), 129.6 (CH), 130.2 (CH), 171.8 (ester C=O), 208.9 (ketone C=O); IR (KBr) ν_{max} 2998, 2932, 2856, 1732, 1708, 1464, 1410, 1262, 990 cm^{-1}; EIMS, m/e (relative intensity) 252 (3, M^+), 234 (4, M^+ – H_2O), 111 (47), 80 (70), 67 (92), 55 (base, $C_4H_7^+$); CIMS (isobutane), m/e 253 (base, M^+ + H).

Anal. Calcd: C, 71.38; H, 9.59. Found: C, 71.17; H, 9.86.

(*Z*)-15-Hydroxy-4-oxo-10-pentadecenoic acid lactone (2h): oil; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 1.15–1.62 (10 H, m), 2.04 (4 H, m), 2.47 (2 H, t, J = 6.6 Hz, C5-H_2), 2.62 (4 H, m, C2-H_2 and C3-H_2), 4.07 (2 H, t, J = 6.5 Hz, C15-H_2), 5.32 (2 H, m, C*H*=C*H*); IR (neat) ν_{max} 2940, 2858, 1736, 1460, 1412, 1252, 1180, 994, 718 cm^{-1}; EIMS, m/e (relative intensity) 252 (3, M^+), 234 (3, M^+ – H_2O), 111 (18), 95 (17), 79 (35), 67 (67), 55 (base, $C_4H_7^+$); CIMS (isobutane), m/e 253 (M^+ + H); EIHRMS, m/e 252.1725 ($C_{15}H_{24}O_3$ requires 252.1726).

(17) In the one case examined, the substantial deceleration of macrocyclization that accompanies β-substitution of the acrylate acceptor apparently is sufficient to permit acyl radical decarbonylation (69%) to effectively compete with cyclization. For vii: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (3 H, s, CH_3), 1.22–1.26 (16 H, m, C5–C12 CH_2), 2.19 (2 H, td, J = 7.1, 6.9 Hz, C4-H_2), 3.72 (3 H, s, OCH_3), 5.81 (1 H, d, J = 15.6 Hz, C2-H), 6.97 (1 H, dt, J = 15.6, 6.9 Hz, C3-H); IR (neat) ν_{max} 2952, 1654 cm^{-1}; EIMS, m/e (relative intensity) 226 (6, M^+), 195 (10), 113 (42), 100 (24), 87 (base, $C_5H_8O_2^+$), 74 (28), 59 (10); CIMS (isobutane), m/e 227 (M^+ + H).



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(18) Liotta, D.; Sunay, U.; Santiesteban, H.; Markiewicz, W. *J. Org. Chem.* **1981**, *46*, 2605.

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15-Hydroxy-4-oxo-10-pentadecynoic acid lactone (2i): oil; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 1.38 (6 H, m), 1.50–1.77 (4 H, m, C6-H_2 and C14-H_2), 2.12 (4 H, m, C9-H_2 and C12-H_2), 2.43 (2 H, t, J = 6.0 Hz, C5-H_2), 2.50 (2 H, t, J = 5.8 Hz, C2-H_2 or C3-H_2), 2.68 (2 H, t, J = 5.8 Hz, C3-H_2 or C2-H_2), 4.03 (2 H, t, J = 6.8 Hz, C15-H_2); ^{13}C NMR (75 MHz, ppm) 18.3 (CH_2), 18.5 (CH_2), 23.3 (CH_2), 24.8 (CH_2), 27.5 (CH_2), 28.0 (CH_2), 28.1 (CH_2), 28.7 (CH_2), 37.6 (CH_2), 42.0 (CH_2), 64.2 (CH_2), 80.0 (C), 80.9 (C), 172.2 (*C*=O), 208.9 (*C*=O); IR (neat) ν_{max} 2932, 2212 (C≡C), 1736, 1412, 1256, 1164 cm^{-1}; EIMS, m/e (relative intensity) 93 (44), 79 (94), 67 (39), 55 (base, $C_4H_7^+$); CIMS (isobutane), m/e 251 (M^+ + H); EIHRMS, m/e 250.1567 ($C_{15}H_{22}O_3$ requires 250.1569).

(*Z*)-15-Hydroxy-4-oxo-8-pentadecenoic acid lactone (2j): oil; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 1.36 (6 H, m), 1.56–1.77 (4 H, m), 2.02 (4 H, m, C7-H_2 and C10-H_2), 2.46 (2 H, t, J = 6.0 Hz, C5-H_2), 2.59 (2 H, t, J = 5.9 Hz, C2-H_2 or C3-H_2), 2.75 (2 H, t, J = 5.9 Hz, C3-H_2 or C2-H_2), 4.15 (2 H, t, J = 5.3 Hz, C15-H_2), 5.40 (2 H, m, C*H*=C*H*); IR (neat) ν_{max} 2928, 1736, 1460, 1410, 1260, 1178, 1084, 1054 cm^{-1}; EIMS, m/e (relative intensity) 252 (2, M^+), 234 (2), 136 (17), 121 (15), 111 (24), 98 (40), 80 (50), 67 (91), 55 (base, $C_4H_7^+$); CIMS (isobutane), m/e 253 (base, M^+ + H); EIHRMS, m/e 252.1724 ($C_{15}H_{24}O_3$ requires 252.1725).

(*Z*)-15-Hydroxy-8-methyl-4-oxo-8-pentadecenoic acid lactone (2k): oil; ^{1}H NMR ($CDCl_3$, 300 MHz, ppm) 1.33 (6 H, br s), 1.54 (4 H, m), 1.71 (3 H, s, C8-CH_3), 1.95 (4 H, m, C7-H_2 and C10-H_2), 2.45 (2 H, t, J = 5.9 Hz, C5-H_2), 2.58 (2 H, t, J = 5.8 Hz, C2-H_2 or C3-H_2), 2.77 (2 H, t, J = 5.8 Hz, C3-H_2 or C2-H_2), 4.17 (2 H, t, J = 5.3 Hz, C15-H_2), 5.15 (1 H, t, J = 7.0 Hz, C9-H); IR (neat) ν_{max} 2928, 2858, 1736, 1460, 1258, 1182, 1142, 1048, 998, 846 cm^{-1}; EIMS, m/e (relative intensity) 266 (7, M^+), 248 (5, $M^+ - H_2O$), 123 (8), 111 (base, $C_7H_{11}O^+$), 95 (16), 81 (31), 67 (36), 55 (69); CIMS (isobutane), m/e 266.1888 ($C_{16}H_{26}O_3$ requires 266.1882).

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Supplementary Material Available: Full details of the preparation and characterization of the precursor ω-hydroxy carboxylic acids that serve as precursors to the phenyl selenoesters **1g–k** and full characterization of the ω-hydroxy phenyl selenides and **1a,c–k** are provided (13 pages). Ordering information is given on any current masthead page.

The Asymmetric Synthesis of α-Amino Acids. Electrophilic Azidation of Chiral Imide Enolates, a Practical Approach to the Synthesis of (*R*)- and (*S*)-α-Azido Carboxylic Acids

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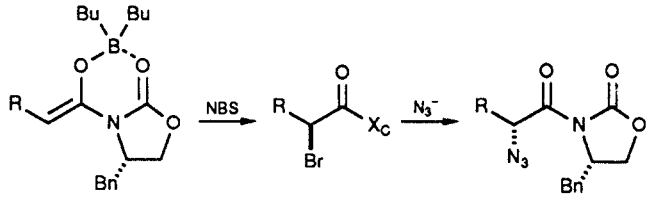
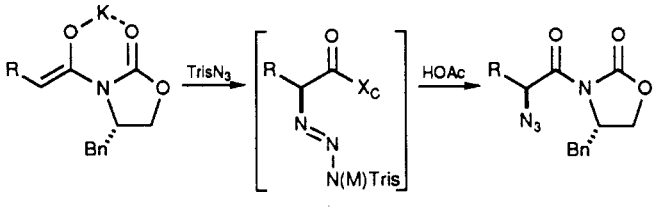
Abstract: Two complementary approaches to the asymmetric synthesis of α-amino acids have been achieved. In the initially investigated reaction sequence, the diastereoselective bromination of the illustrated boron enolate with *N*-bromosuccinimide was followed by stereospecific azide displacement by tetramethylguanidinium azide. The resulting α-azido carboximides may be readily purified to high diastereomeric purity by chromatography on silica.



In the second reaction sequence, the illustrated potassium enolate was treated with 2,4,6-triisopropylbenzenesulfonyl azide, and the intermediate sulfonyl triazene was decomposed through an acetic acid quench to give the α-azido carboximide. The diastereoselection of the reaction as a function of R is as follows: R = Me, CH_2Ph, 97:3; R = $CHMe_2$, 98:2; R = CMe_3, >99:1; R = Ph, 91:9. The important parameters of this azidation process were evaluated, and experiments were conducted to help elucidate the mechanism of the reaction.



The α-azido carboximide products have been shown to be versatile α-amino acid synthons that may be readily converted to α-amino acids as well as to N-protected α-amino acid derivatives. The racemization-free removal of the chiral auxiliary was achieved in high yield both by saponification and transesterification, either before or after reduction and acylation of the azide functionality.

As a consequence of the importance of enantiomerically pure α-amino acids, the development of new reaction methodology which provides an expedient, general approach to the synthesis of this family of compounds continues to be an active area of

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