the residue was neutralized with saturated $NaHCO_3$(aq). The mixture was shaken with CH_2Cl_2, and after the mixture was dried over Na_2SO_4, the solvent was evaporated. The remaining oil was distilled in a Kugelrohr apparatus to afford **29a** (277 mg, 61%) in an almost pure state: bp 150–155 °C (17 mmHg); IR (neat) ν_{max} 3270, 2955, 2870, 2110, 1710, 1366, 1165 cm^{-1}; NMR δ 1.0 (6 H, d, J = 8.7 Hz), 1.1–2.8 (7 H, m), 2.09 (3 H, s).

Solanol (30). A mixture of the ethynyl ketone **29a** (277 mg, 1.57 mmol) and catecholborane (456 mg, 3.61 mmol) was stirred at 70 °C for 2 h under N_2, and benzene (2 mL) and 2 M EtONa in EtOH (1.4 mL, 2.83 mmol) were added. This solution was added to a mixture obtained by stirring $Pd(PPh_3)_4$ (36 mg, 0.0314 mmol) and 2-bromopropene (172 mg, 1.42 mmol) in benzene (3.1 mL). The mixture was refluxed for 2 h, and a solution of 3 M NaOH (0.08 mL) and 30% H_2O_2 (0.08 mL) was added and the mixture stirred at room temperature for 1 h. An equal volume of water was added, and the mixture was extracted with pentane. The solution was passed through a Florisil column, and the solvent was removed by evaporation. The residual material was purified by distillation with a Kugelrohr apparatus to afford solanol: 201 mg; bp 180–190 ° (3 mmHg). The IR spectrum completely coincided with that of the natural product:[11] IR (neat) ν_{max} 3330, 3070, 2950, 2860, 1607, 1455, 1370, 1120, 967, 880 cm^{-1}; NMR, δ 0.8–1.1 (6 H, m), 1.1–2.2 (6 H, m), 1.09 (3 H, d, J = 7 Hz), 1.79 (3 H, s), 3.14 (1 H, br s), 3.43–3.77 (1 H, m), 4.77 (2 H, s), 5.27 and 5.96 (2 H, AB q, J = 16 Hz, upper field signals further split into doublet with J = 9 Hz).

D-**Solanone (25).** To a solution of **30** (147 mg, 0.75 mmol) in acetone (10 mL) was added Jones reagent (0.125 mL, 1 mmol) at 0 °C. The mixture was stirred for 3 h at 0–5 °C, and the solution was concentrated to half its volume by evaporation in vacuo. The solution was neutralized with a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried over Na_2SO_4, and the solvent was removed to afford solanone (82 mg) in an almost pure state. Further purification was performed by preparative HPLC; $[\alpha]^{18.5}_D$ +10.4° (c 0.011 g/mL, CCl_4). The IR, NMR, and mass spectra coincided with those of the natural product.[11]

Registry No. **7a**, 693-89-0; **7b**, 591-49-1; **7c**, 1195-31-9; **7d**, 1453-25-4; **7e**, 23070-53-3; **8a**, 74067-03-1; **8b**, 66241-43-8; **8b** ethylene ketal, 74066-95-8; **8c**, 84098-59-9; **8d**, 74067-00-8; **8d** ethylene ketal, 81504-99-6; **8e**, 81505-00-2; **9a**, 84098-60-2; **9b**, 66241-44-9; **9c**, 81522-17-0; **9e**, 81505-01-3; **10**, 84129-72-6; **11a**, 1674-10-8; **11b**, 81505-02-4; **11c**, 20053-89-8; **11d**, 36616-90-7; **12a**, 66241-45-0; **12b** (R^1 = CH_3; R^2 = C_2H_5), 81505-04-6; **12b** (R^1 = C_2H_5; R^2 = CH_3), 84098-61-3; **12c**, 81505-03-5; **12d**, 81505-05-7; **13a**, 1759-64-4; **13b**, 72018-30-5; **13c**, 81505-09-1; **13d**, 81505-07-9; **13e**, 84098-62-4; *cis*-**13f**, 84098-63-5; *trans*-**13f**, 84098-64-6; **14a**, 81505-10-4; **14b**, 84098-65-7; **14c**, 81505-13-7; **14d**, 81505-11-5; **14e**, 84098-66-8; **14f**, 81505-12-6; **17b**, 24403-63-2; **18**, 74066-96-9; **20a**, 18650-13-0; **20b**, 7029-11-0; **21a**, 19985-86-5; **24a**, 66432-75-5; **24b**, 74066-99-2; **25**, 1937-54-8; **28**, 84098-67-9; **29a**, 21889-84-9; **29b**, 84098-68-0; **30**, 40525-38-0; **36**, 84098-69-1; $FeCl_3$, 7705-08-0; *cis*-3,5-dimethylcyclohexanone, 27922-05-0; 2-ethyl-3,5-dimethylcyclohexanone, 84098-70-4; 2-methylcyclododecanone, 16837-94-8; 2-methylcyclohexanone tosylhydrazone, 52826-41-2; 2-methylcyclooctanone tosylhydrazone, 84098-71-5; 6,8-tetradecadiyne-2,13-dione ethylene ketal, 74066-98-1; 2-bromopropene, 557-93-7.

Synthesis of Protected 2-Amino-8-oxo-9,10-epoxydecanoic Acid from 2-Aminosuberic Acid Derivatives[1]

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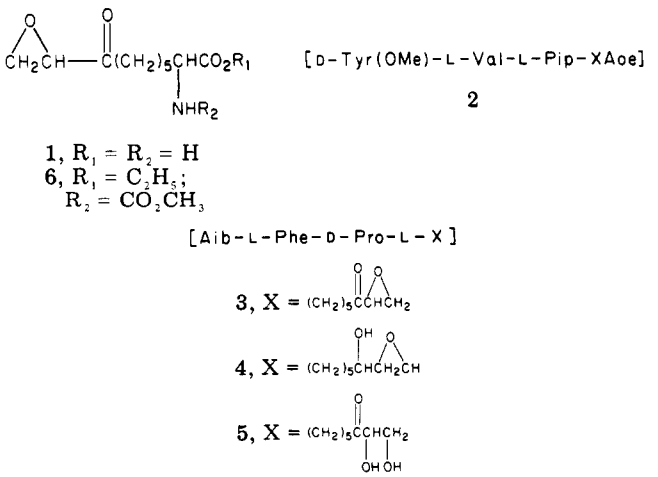
A method is reported for synthesizing derivatives of 2-amino-8-oxo-9,10-epoxydecanoic acid (Aoe) from 2-aminosuberic acid (Asu) derivatives under conditions that do not disrupt peptide bonds. The epoxy ketone amino acid Aoe is found in three biologically active cyclic peptides. Ethyl 2-(acetylamino)suberate was converted to ethyl 2-DL-(acetylamino)-8-oxo-(*RS*)-9,10-epoxydecanoate in 45–50% yield by sequential reactions with phosphorus pentachloride followed by reaction with tetravinyltin and benzylchlorobis(triphenylphosphine)palladium(II) to give the vinyl ketone in 70% yield. Epoxidation of enone with *tert*-butyl hydroperoxide using triton B as catalyst gave the *N*-acetyl ethyl ester of Aoe in 70% yield. Methods for preparing protected 2-aminosuberic acid derivatives from glycine ester benzal imine are also described.

Introduction

The amino acid 2-amino-8-oxo-9,10-epoxydecanoic acid (Aoe, **1**, Chart I),[2] has been found in three natural products, the phytotoxins Cy1-2 (**2**)[3a] and HC-toxin[3b] and chlamydocin (**3**), a cytostatic cyclic tetrapeptide.[4] In the latter case Aoe seems to be essential for biological activity because both the reduced ketone analogue dihydrochlamydocin (**4**) and the diol derivative of chlamydocin **5** are essentially inactive,[5] suggesting an important role, possibly as an alkylating agent, for the epoxy ketone functional group. Closse and Huguenin synthesized the Aoe derivative **6** via a seven-step route in order to confirm

Chart I



(1) Abstracted in part from the Ph.D. Dissertation of Jasbir Singh, University of Wisconsin–Madison, 1982.

(2) Abbreviations: Aoe, 2-amino-8-oxo-9,10-epoxydecanoic acid; Asu, 2-aminosuberic acid (2-amino-1,6-octanedioic acid); LDA, lithium diisopropylamine; Bzl, benzyl; Aib, α-aminoisobutyric acid; Pip, pipicolic acid.

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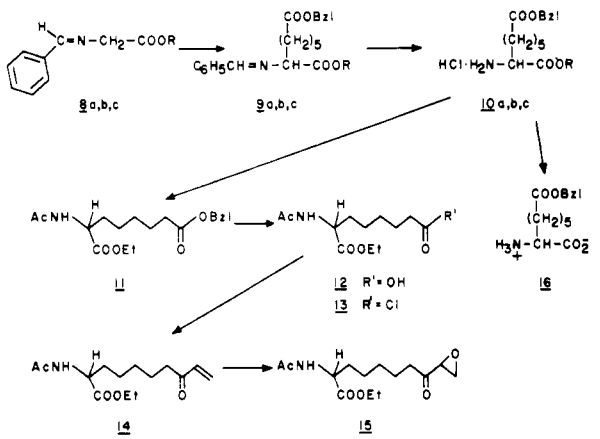
Scheme I[a]



[a] a, R = Et; b, R = Bzl; c, R = *t*-Bu.

the structure of the amino acid.[4]

In conjunction with our attempts to synthesize chlamydocin analogues with improved biological specificities[6] and for conformational studies,[7-9] we needed an efficient method for synthesizing Aoe that would be compatible with methods used to synthesize the cyclic tetrapeptide ring system. We report here the synthesis of Aoe from 2-aminosuberic acid derivatives by methods in which the labile epoxy ketone group is added to preformed peptides.

Results

Synthesis of Racemic Ethyl 2-(Acetylamino)-8-oxo-9,10-epoxydecanoate (Ac-Aoe-OEt) (Scheme I). The synthesis began with a protected derivative of 2-aminosuberic acid (Asu). The starting *N*-acetyl benzyl ester **11** was obtained by alkylation of the benzylidene glycine ester **8a** with benzyl 6-bromohexanoate following a modification of the procedure reported by Stork et al.[10] (Scheme I). The product imine **9a** (>90% pure by ^{1}H NMR) could be purified by Kugelrohr distillation but in general was immediately hydrolyzed to amine **10a** with aqueous $KHSO_4$. Subsequent acetylation gave the pure diester **11** in >80% overall yield from **8a**. This alkylation sequence was also carried out on the benzyl and *tert*-butyl esters (**7b,c** → **10b,c**). Acid cleavage of the *tert*-butyl ester **10c** gave ω-benzyl-α-aminosuberic acid [Asu(OBzl), (**16**)]. Compound **16** was also prepared by the Cu^{2+}-catalyzed selective hydrolysis[11] of the α-benzyl ester group from the dibenzyl ester derivative **10b**. Thus this synthetic route provided compounds **10a**, **10c**, and **16**, which are useful for selective incorporation of racemic α-aminosuberic acid into peptides.

The protected aminosuberic acid derivative **11** was transformed to the corresponding Aoe derivative **15** by means of the following reactions. Hydrogenolysis of benzyl ester **11** gave the free acid **12**, which was converted to the corresponding acid chloride **13** by reaction with phosphorus pentachloride in anhydrous ether. Reaction of the acid chloride **13** with tetravinyltin in hexamethylphosphoramide using benzylchlorobis(triphenylphosphine)palladium(II) as catalyst[12,13] at 56 °C gave the enone **14** in a 70% yield. Epoxidation of enone **14** with *tert*-butyl hydroperoxide in tetrahydrofuran using a catalytic amount of triton B afforded the *N*-acetyl Aoe-OEt **15** in 77% yield. Alternate methods for epoxidation (aqueous H_2O_2, *tert*-butyl hydroperoxide, potassium *tert*-butoxide[14]) gave lower yields of epoxide.

Discussion

To confirm the structure of the amino acid Aoe found in chlamydocin, Closse and Huguenin synthesized the Aoe derivative **6** in 3% overall yield via a seven-step route.[4] Compound **6** was not suitable for the synthesis of chlamydocin because **6** contained the reactive epoxy ketone group, which would be degraded by the repetitive exposure to the acid and base conditions needed to synthesize the linear peptide precursors. We therefore investigated the approach of assembling the Aoe residue by addition of the epoxide moiety (or its equivalent) onto the ξ-carboxyl group of 2-aminosuberic acid (Asu) containing peptides including the preformed cyclic tetrapeptide ring system. The use of Asu as a precursor would allow cyclic tetrapeptide synthesis to be achieved from either an L-Phe[15] or a dehydrophenylalanine linear tetrapeptide precursor.[16]

The protected 2-aminosuberic acid derivative **11** was selected as a model compound to devise conditions for converting the ξ-carboxyl group of Asu peptides to Aoe in the presence of amide and ester bonds (Scheme I). Reaction of the acid chloride **13** with tetravinyltin in the presence of the Pd(II) catalyst gave vinyl ketone **14** in 70% yield. Epoxidation with *tert*-butyl hydroperoxide, catalyzed by triton B, gave the epoxy ketone **15** in 77% yield. By means of these reactions *N*-acetyl-Aoe ethyl ester **15** was obtained in about 50% yield overall from the protected aminosuberic acid derivative **11**. This represents about a 15-fold improvement in yield of comparable Aoe derivatives over the previously reported procedure. In addition the availability of selectively protected Asu precursors (e.g., **10c**) permits the straightforward synthesis of the requisite peptide precursors.

The successful transformation of the Asu derivative **11** to the Aoe derivative **15** was carried out in the presence of amide and ester bonds. This suggests that these methods, especially the addition of the vinyl unit to the acid chloride, can be applied to the transformation of Asu residues to Aoe residues in preformed cyclic tetrapeptides. Application of these methods to the total synthesis of chlamydocin is in progress.

Experimental Section

Low-resolution mass spectra were recorded on a Finnigan quadrupole 1015 GC–mass spectrometer interfaced to a Finnigan M6000 data system, at an ionizing voltage of 70 eV. High-resolution mass spectra were obtained on an AEI-MS-9 mass spectrometer interfaced to a Kratos-DS-50 data system. Melting points are uncorrected and were determined on a Thomas-Hoover Uni-Melt apparatus.

NMR spectra were recorded in indicated solvents on a JEOL FX-90Q (90 MHz) or a Bruker WH-270 (270 MHz) instrument operated in FT mode. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane and coupling constants are given in hertz.

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Commercially available analytical reagent (AR) grade solvents were used as received except for the following. Hexamethylphosphoric acid triamide (HMPA) was dried over CaH_2, distilled under reduced pressure, and stored over 4-Å molecular sieves; tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use; benzaldehyde was distilled under reduced pressure. Tetravinyltin was purchased from ICN-Pharmaceuticals Inc., Plainview, NY. Anhydrous *tert*-butyl hydroperoxide in dichloromethane (ca. 4.1 M solution) was prepared according to the reported literature procedure.[20]

General Procedure A. Deprotection of Benzyl Ester Group. The cleavage of the benzyl ester from the amino acid derivative or the peptide was carried out by suitably modifying the reported procedure.[17]

General Procedure B. Alkylation of *N*-Benzylideneglycine Esters. The esters were prepared essentially as described, and the alkylation reactions were carried out according to a modification of the literature procedure.[10] To a flame-dried flask cooled under argon atmosphere were added potassium *tert*-butoxide (10 mmol) and 50 mL of anhydrous THF. The contents were cooled to −78 °C. A solution of a *N*-benzylideneglycine ester (10 mmol) in 20 mL of THF was added slowly over 5–7 min via a syringe. After 10–20 min of vigorous stirring at −78 °C, a solution of alkyl bromide (11–12 mmol in 10 mL of THF) was added slowly over 15–20 min. The reaction mixture was stirred at −78 °C for 3–4 h and then stirred at 25 °C for 1–2 h, to give a light reddish or yellowish solution. The reaction was quenched with saturated ammonium chloride solution and diluted with 2 volumes of ether. The organic layer was washed with brine (3×), dried over anhydrous $MgSO_4$, and concentrated in vacuo to obtain crude alkylated product.

General Procedure C. Cleavage of the Benzylidine Group. The oil obtained in part A (5.5 g) was stirred vigorously in a 5:1 mixture of H_2O:saturated $KHSO_4$ for $^1/_2$ h. The resulting aqueous solution (~180 mL) was extracted with skelly B (3 × 100 mL) and then basified with solid $NaHCO_3$ until a pH of 9–10 was obtained. This aqueous phase was extracted with ethyl acetate (2 × 150 mL). The ethyl acetate extracts were combined, washed with H_2O (200 mL) and saturated NaCl (200 mL), dried over Na_2SO_4, and evaporated to dryness, yield 2.9 g (65% calculated from *N*-benzylideneglycine *tert*-butyl ester **9c**). The product is pure enough to be used directly, or it can be chromatographed in 2% triethylamine in ethyl acetate.

Benzyl 6-Bromohexanoate. A solution of 6-bromohexanoic acid[18] (32 g, 165 mmol), benzyl alcohol (22 g), and *p*-toluenesulfonic acid monohydrate (1.3 g) in 500 mL of anhydrous benzene was refluxed for 6 h with azeotropic removal of water. The reaction mixture was cooled, and solid $CaCO_3$ (5 g) was added. The solution was filtered and concentrated in vacuo. The crude product was distilled (bp 143–46 °C (2.5 mmHg)) to yield 39.65 g (84.4%) of the benzyl ester as a colorless liquid: R_f 0.50 (100% $CHCl_3$), 0.70 (50% EtOAc–skelly B); ^{1}H NMR ($CHCl_3$) δ 1.3–2.0 (6 H, cp), 2.38 (2 H, t, *J* = 7.0 Hz), 3.40 (2 H, t, *J* = 7.0 Hz), 5.17 (2 H, s), 7.4 (5 H, s); MS, *m/e* (relative intensity) 270 (M^+, 0.22).

Anal. Calcd for $C_{13}H_{17}BrO_2$: C, 54.75; H, 6.01. Found: C, 54.96; H, 6.23.

α-Ethyl ω-Benzyl DL-α-Aminosuberate Hydrochloride (10a). *N*-Benzylideneglycine ethyl ester (**8a**) prepared by the reported procedure[10] (2.56 g, 13.4 mmol) was alkylated with benzyl 6-bromohexanoate (4.04 g, 14.17 mmol) and potassium *tert*-butoxide (1.50 g, 13.4 mmol) by general procedure B to give 4.3 g of a crude product: bp 140 °C (0.07 mmHg); MS, *m/e* (relative intensity) 396 (MH, 2.13), 350 (1.14), 322 (12.38), 304 (6.59), 260 (24.69), 232 (21.80), 204 (20.73), 105 (33.33), 91 (100), 77 (30.8).

The benzylidene group was cleaved from the crude product by general procedure C to yield 3.32 g (72%) of amino acid hydrochloride **10a** as a white solid: mp 75–76 °C (EtOAc–skelly B); R_f 0.38 (5% triethylamine–EtOAc), 0.23 (5% MeOH–$CHCl_3$ containing 0.4% triethylamine).

Anal. Calcd for $C_{17}N_{26}NO_4$·HCl: C, 59.38; H, 7.62; N, 4.07. Found: C, 59.54; H, 7.54; N, 4.08.

α-Ethyl ω-Benzyl DL-α-(Acetylamino)suberate (11). A solution of amine **10a** (150 mg, 0.437 mmol), acetic anhydride (100 μL), triethylamine (128 μL), and 4-(dimethylamino)pyridine (12 mg) in 5 mL of methylene chloride was stirred at room temperature for 3 h. The solvent was removed under reduced pressure and the residue purified by chromatography from silica gel eluting with 40% acetone–skelly B to yield **11** (150 mg, 98.4%) as a clear viscous liquid: R_f 0.46 (50% acetone–skelly B), 0.3 (75% EtOAc–skelly B); ^{1}H NMR ($CDCl_3$) δ 1.18–1.9 (11 H, cp; includes 3 H, t, *J* = 7.3 Hz at δ 1.27), 2.01 (3 H, s), 2.35 (2 H, t, *J* = 7.5 Hz), 4.27 (2 H, q, *J* = 7.3 Mz), 4.58 (1 H, m), 5.10 (2 H, s), 6.10 (1 H, d, *J* = 7.9 Hz, CON*H*COCH), 7.35 (5 H, s); MS, *m/e* (relative intensity) 350 (M + 1, 0.72).

Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.10; H, 7.84; N, 3.96.

Ethyl (*R*,*S*)-2-Acetamido-8-oxo-9-decenoate (14). The benzyl ester **11** (1.00 g, 2.86 mmol) was hydrogenated according to the reported procedure[17] to give 739 mg (99%) of the free acid **12** as a white solid. A solution of the free acid **12** (263 mg, 1.01 mmol) in 5 mL of anhydrous DME was stirred with solid PC_5 (220 mg, 1.05 mmol) at 0 °C for 0.5 h and then at room temperature for 0.5 h to give a clear solution. The solvent was evaporated and dried in vacuo over P_2O_5/KOH for 2 h to give the acid chloride **13** as a viscous syrup.

The acid chloride **13** was dissolved in 1 mL of HMPA. Tetravinyltin (272 μL, 1.50 mM) and a solution of the Pd(II) complex[12,13,19] (1 mg, 0.001 32 mM) in 1 mL of HMPA were added, and the solution was heated to 56 °C in an oil bath for 20 min. After 3–4 min, the reaction mixture turned black. The reaction mixture was cooled, and 20 mL of water was added. The aqueous layer was extracted with ether (3 × 5 mL), and the ether layer was washed with saturated brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was dissolved in 60 mL of ether, and 70 mL of a saturated ethanolic KF solution was added. A white precipitate formed immediately. The solution was filtered, and the filtrate was concentrated in vacuo. Chromatography over silica gel using 60% EtOAc–40% skelly B as eluent gave 188 mg (69%) of the enone **14** as a clear liquid: R_f 0.28 (75% EtOAc–skelly B), 0.33 (100% (EtOAc), 0.15 (100% ether), 0.38 (2.5% EtOH–EtOAc), 0.35 (2.5% MeOH–$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.09–1.92 (11 H, cp; includes t, *J* = 7.3 Hz at δ 1.28), 2.02 (3 H, s), 2.58 (2 H, t, *J* = 7.1 Hz), 4.20 (2 H, q, *J* = 7.3 Hz), 4.56 (1 H, m), 5.81 (1 H, dd, *J* = 3.17 Hz, 8.54 Hz); 5.96–6.47 (3 H, m); MS, *m/e* (relative intensity) 270 (M + 1, 4.98), 242 (0.44), 224 (2.35), 214 (5.95), 205 (24.5), 196 (33.3), 182 (28.25), 154 (33.33), 151 (33.3), 137 (30.85), 118 (24.80), 108 (22.55), 99 (27.91), 88 (19.78), 56 (100), 43 (100).

Ethyl (*R*,*S*)-2-Acetamido-8-oxo-(*R*,*S*)-9,10-epoxydecanoate (15). Epoxidation of the enone **14** (100 mg, 0.37 mmol) was carried out with a 70% aqueous solution of *tert*-butyl hydroperoxide (60 μL) in the presence of a catalytic amount of triton B (30 μL) in 10 mL of THF at room temperature for 1 h. The reaction mixture was diluted with 50 mL of ethyl acetate, and the organic layer was washed with 1 N HCl, saturated $NaHCO_3$ solution, and saturated brine, dried ($MgSO_4$), concentrated in vacuo, and dried in vacuo to give the epoxy ketone **15** as a clear viscous liquid (92 mg, 87.0%): R_f 0.31 (2.5% EtOH–EtOAc), 0.32 (2.5% MeOH–$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.2–1.90 (11 H, cp; includes a t, *J* = 7.3 Hz at δ 1.28), 2.02 (3 H, s), 2.20–2.50, 2.6–3.65 (3 H, cp with peaks at δ 2.65, 2.85, 3.0, 3.3, 3.4, 3.5, 3.65), 4.19 (2 H, q, *J* = 7.3 Hz), 4.58 (1 H, m), 6.07 (1 H, d, *J* = 8.0 Hz); MS, *m/e* calcd for $C_{14}H_{23}NO_5$ 285.1576, found M^+ 285.1585; also exact mass peaks were measured at 242 (M − acetyl), 212 (M − CO_2Et), 200 (M − $CH_2COCH - CH_2$).

Acknowledgment. This work was supported by a grant from the National Cancer Institute (CA 27985).

Registry No. **8a**, 40682-54-0; **9a**, 84175-16-6; **10a**, 84175-17-7; **11**, 84175-18-8; **12**, 84175-19-9; **13**, 84175-20-2; **14**, 84192-59-6; **15**, 84175-21-3; 6-bromohexanoic acid, 4224-70-8; benzyl 6-bromohexanoate, 78277-26-6; tetravinyltin, 1112-56-7.

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