from the cellulose with 40 ml of methanol–water (9:1). Removal of the methanol in vacuo followed by partitioning of the aqueous residue between 1 N hydrochloric acid (10 ml) and ethyl acetate (2 × 25 ml) gave 2.6 mg of crystalline, ethyl acetate soluble residue. Crystallization (benzene–cyclohexane) gave 1.9 mg of (*S*)-(−)-methylsuccinic acid, mp 109–110 °C, $[\alpha]^{25}D$ −12° (*c* 0.09, ethanol). IR ($CHCl_3$) and mass spectra were identical with spectra of authentic, racemic methylsuccinic acid.

Secalonic Acid F (2). The fast-moving band (R_f 0.29) yielded 53 mg of a yellow glass which upon crystallization (benzene–cyclohexane) gave 26 mg (3.2% of PEI) of yellow needles, mp 218–221 °C (hot stage), 253–256 °C (evacuated capillary). A high-resolution mass spectrum indicated M^+ 638.15987 (calcd for $C_{32}H_{30}O_{14}$, 638.16356). Secalonic acid F showed $[\alpha]^{20}D$ +202°, $[\alpha]^{20}_{578}$ +214° (*c* 0.13, pyridine); UV max (ethanol) 236, 263, and 388 nm (ε 19 250, 17 300, 37 000); IR (KBr) 3520, 1748, 1610, 1590, 1442, 1238, 1068, and 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (d, 6 H, *J* = 7 Hz), 2.0–3.0 (m, 6 H), 2.67 (b, 1 H, exchanges), 2.86 (b, 1 H, exchanges), 3.67 (s, 6 H), 3.87 (d, 1 H, *J* = 10 Hz), 4.09 (b, 1 H), 6.52 (d, 1 H, *J* = 9 Hz), 6.58 (d, 1 H, *J* = 9 Hz), 7.35 (d, 1 H, *J* = 9 Hz), 7.39 (d, 1 H, *J* = 9 Hz), 11.65 (s, 1 H, exchanges), 11.80 (s, 1 H, exchanges), 13.70 (s, 1 H, exchanges), 13.88 (s, 1 H, exchanges); mass spectrum (70 eV) *m/e* (rel intensity) M^+ 638 (20), 579 (100), 561 (20), and 501 (20); CD (*c* 4.8 × 10^{-2} mg/ml dioxane) λ 400 nm (Δε 0), 332 (+17), 275–260 (0), 223 (−43), and 215 (−25).

Oxidation of Secalonic Acid F (2). Secalonic acid F (57 mg) was oxidized with potassium permangate as described for secalonic acid D to give 2.6 mg of (*S*)-(−)-methylsuccinic acid, mp 109–111 °C, $[\alpha]^{25}D$ −13° (*c* 0.12, ethanol). IR ($CDCl_3$) and mass spectra were identical with spectra of authentic racemic methylsuccinic acid.

Acknowledgments. This work was supported by the National Cancer Institute (Contract 1 CP33217). We wish to thank Professor G. N. Wogan and Mr. P. Donahue, Department of Nutrition and Food Science, M.I.T., for toxicity data and Mr. J. M. Townsend for microbiological assistance.

Registry No.—1, 35287-69-5; 2, 60687-07-2; (*S*)-(−)-methylsuccinic acid, 2174-58-5.

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A Synthesis of (±)-Methyl *n*-Tetradeca-*trans*-2,4,5-trienoate, an Allenic Ester Produced by the Male Dried Bean Beetle *Acanthoscelides obtectus* (Say)[1]

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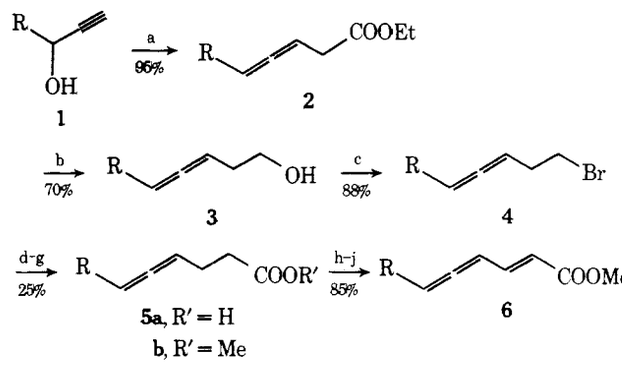
Received July 13, 1976

In 1970, Horler[2] isolated a novel optically active allenic ester from the hexane extracts of male dried bean beetles [*Acanthoscelides obtectus* (Say)] for which structure **6** was suggested based on spectrometric and chemical evidence. Subsequent total synthesis has corroborated the assigned structure.[3–6] As a putative sex pheromone, there are two aspects of **6** which are unusual: first, the compound is present in rather large amounts (ca. 0.5% of the body weight) compared with other insect sex pheromones, and second, the ester **6** is unstable ($t_{1/2}$ = 10 h at room temperature) and polymerizes readily. We report below a synthesis of racemic **6** starting with undec-1-yn-3-ol (**1**).

The synthetic plan outlined in Scheme I (R = *n*-octyl) was conceived with two strategic strictures in mind: (1) an intermediate (e.g., carboxylic acid **5a**) was desired which could be resolved and later used to ascertain the absolute configuration

Scheme I



a, $CH_3C(OEt)_3$, EtCOOH, 135 °C: b, $(i\text{-Bu})_2AlH/C_6H_6$–hexane, 0 °C; c, CBr_4–Ph_3P/CH_2Cl_2, 0 °C; d, Mg/THF; e, CO_2; f, H_3O^+; g, MeOH, *p*-TsOH; h, $(i\text{-Pr})_2NLi$/THF, −78 °C; i, PhSeSePh; j, $NaIO_4$/THF–H_2O, 25 °C, 10 h

(as yet unknown) of the allenic moiety, and (2) the instability inherent in the conjugated allenenic ester suggested that the introduction of the completely conjugated chromophore be relegated to the last step of the synthesis. A key intermediate **5** which fulfills these requirements was prepared in essentially four steps from the acetylenic alcohol **1**[7] (Scheme I).

A modified Claisen rearrangement[8,9] converted **1** to the β-allenic ester **2** in 95% yield. Reduction of **2** to the corresponding alcohol **3** with lithium aluminum hydride gave poor yields of **3**; rather, the predominant reaction was proton abstraction from the highly activated position α to the ester function (as evideced by copious gas evolution) whereupon subsequent aqueous workup returned an isomeric mixture of methyl trideca-2,4-dienoates as the major product.[10] The desired reduction was successfully achieved in 70% yield with diisobutylaluminum hydride.

The reaction of the homoallenic alcohol **3** with PBr_3 under a variety of conditions gave poor yields of the desired substitution product **4**.[11] However, the bromide **4** was conveniently prepared in 76% yield from the alcohol **3** using CBr_4–Ph_3P in CH_2Cl_2 at ice bath temperatures. Although the analogous chlorination with CCl_4–PPh_3 has been amply documented,[12] the corresponding bromination has received only sporadic attention[13] despite the often preferable reaction properties of the bromides. Since we could find no systematic evaluation of the scope and limitation of this mild bromination, we have examined a number of additional cases. Invariably, primary alcohols gave good yields of the bromide (see Table I). With the exception of 2-octanol, which gave a 90% yield of 2-bromooctane, secondary alcohols such as 3-pentanol and cyclohexanol gave consistently poor yields of the bromide. Thus the synthetic utility of the reaction appears to be restricted to primary bromides, in which case we found that best yields were obtained when the reactions were run in CH_2Cl_2 at 0–25 °C in the presence of 1.25 equiv of CBr_4 and 1.5 equiv of Ph_3P.

Table I

Alcohol	Registry no.	% yield of bromide	Registry no.
Geraniol	106-24-1	82	6138-90-5
(*Z*)-Non-3-en-1-ol	10340-23-5	89	60705-54-6
Undeca-3,4-dien-1-ol	13994-61-1	88	60705-55-7
Oleyl alcohol	143-28-2	92	6110-53-8
1-Octanol	111-87-5	91	111-83-1
2-Octanol	123-96-6	90	557-37-5

Introduction of the final carbon of the chain was effected by carboxylation of the Grignard reagent derived from **4**[14] to give the crude acid **5a** in ~30% yield, which was not purified but converted directly to the methyl ester **5b**. The major product of the reaction, hexacosa-9,10,16,17-tetraene, was derived from coupling of the homoallenic bromide. This marked propensity for coupling was not alleviated by using a large excess of magnesium and slow addition. Nonetheless, the ease of separation of the acid permitted the preparation of ester **5b** in 25% overall yield from **4**.

The thermal instability of the final allenenic ester required that the last step of the sequence, the introduction of unsaturation between C-2 and C-3 of the ester **5b**, be conducted under the mildest possible conditions. The efficiency and trans stereoselectivity of the selenoxide elimination of Sharpless and co-workers[15] seemed ideally suited to the case at hand. Thus, the lithium enolate of **5b** reacted with diphenyl diselenide to give the α-phenylseleno ester which was oxidized to the corresponding selenoxide with $NaIO_4$ in aqueous THF to give, after 10 h at room temperature, the desired allenenic ester **6** in 85% yield. The spectral properties of synthetic **6** were identical with those reported for the natural product.[2]

Experimental Section

Infrared spectra were recorded with a Perkin-Elmer 457 spectrometer, NMR spectra with a Varian HA-100 instrument using Me_4Si as an internal standard, and mass spectra with a Du Pont 29-491B spectrometer. Extracts were dried over $MgSO_4$. Unless otherwise stated, Bakerflex chromatographic sheets were used for analytical TLC separations using phosphomolybdic acid as developer.

Ethyl Trideca-3,4-dienoate (2). The experimental procedure of Henrick and co-workers[9] was used. From 19.0 g (113 mmol) of undec-1-yn-3-ol (**1**),[7] 128 g (792 mmol, 7 equiv) of $CH_3C(OEt)_3$, and 400 mg of propionic acid was obtained 25.7 g (95%) of **2** as a colorless oil: bp 98–100 °C (0.15 mm); IR (CCl_4) 1961, 1740 cm^{-1}; NMR (CCl_4) δ 5.0–5.2 (m, 2 H) 4.1 (q, 2 H), 2.9 (dd, 2 H), 2.2–2.6 (m, 2 H), 1.2–1.8 (m, 12 H), 1.25 (partially hidden t, 3 H), 0.9 (distorted t, 3 H); MS (70 eV) *m/e* 238 (M^+, 20%), 57 (100%).

Trideca-3,4-dien-1-ol (3). To a magnetically stirred solution of 11.9 g (15.1 ml, 84 mmol) of diisobutylaluminum hydride in 70 ml of 3:1 benzene–hexane was added a solution of 10.0 g (42 mmol) of ester **2** in 15 ml of benzene at a rate sufficient to maintain the temperature at ≤5 °C. After addition was complete, the mixture was allowed to stir under nitrogen for an additional 45 min at 0 °C. After excess diisobutylaluminum hydride was destroyed by dropwise addition of *i*-PrOH, the clear, colorless solution was transferred to a separatory funnel and added dropwise to 55 ml of 3 M H_2SO_4 with ice bath cooling and rapid magnetic stirring. The organic layer was washed with 2 × 50 ml of saturated $NaHCO_3$, 2 × 25 ml of H_2O, and 25 ml of brine. After drying, the solvent was removed in vacuo and the residue short path distilled to give 5.75 g (70%) of the alcohol **3** as a colorless oil: bp 82–83 °C (0.1 mm); IR (CCl_4) 3610, 1960 cm^{-1}; NMR (CCl_4) δ 5.0 (m, 2 H), 4.2 (br s, 1 H), 3.5 (t, 2 H), 2.0 (m, 4 H), 1.6–1.1 (br, 12 H), 0.9 (distorted t, 3 H); MS (70 eV) *m/e* 196 (M^+, 3%), 98 (100%).

1-Bromotrideca-3,4-diene (4). To a magnetically stirred solution of 1.96 g (10.0 mmol) of the alcohol **3** and 4.15 g (12.5 mmol) of CBr_4 in 15 ml of CH_2Cl_2 was added portionwise with ice-bath cooling 3.92 g (15.0 mmol) of Ph_3P. After addition was complete, the mixture was stirred for an additional 5 min, whereupon the solvent was removed in vacuo. Ether (15 ml) was added and the mixture filtered. The filter cake was washed with 3 × 10 ml of ether. The combined filtrate and washings were concentrated in vacuo and the residue distilled via Kugelrohr to give 2.28 g (88%) of the bromide as a nearly colorless oil: bp 70 °C (bath) (0.3 mm); IR (CCl_4) 1960 cm^{-1}; NMR (CCl_4) δ 5.15 (m, 2 H), 3.4 (t, 2 H), 2.5 (m, 2 H), 1.95 (m, 2 H), 1.3 (br, 12 H), 0.9 (distorted t, 3 H).

The alcohols listed in Table I were brominated on a 10-mmol scale as described above.

Methyl Tetradeca-4,5-dienoate (5b). A flame-dried 100-ml three-neck flask fitted with a magnetic stirrer, condenser, addition funnel, and nitrogen inlet was charged with 5.15 g (212 mg-atoms, 10 equiv) of Mg and 20 ml of THF freshly distilled from Na. A crystal of iodine was added and after several minutes 3 drops of the bromide **3** was introduced. When the iodine color discharged, the remainder of 4.89 g (21.2 mmol) of the bromide in 5 ml of THF was added dropwise over the course of 1 h with rapid magnetic stirring. After addition was complete, the mixture was allowed to stir at ambient temperature for 4 h, whereupon CO_2 gas (dried by passage through concentrated H_2SO_4 followed by anhydrous $CaSO_4$) was introduced for 30 min. The reaction mixture was poured into dilute, iced H_2SO_4 and the products extracted into ether. A TLC of the ether layer using ether–hexane (1:1) as eluent showed two major spots corresponding to the acid **5a** (R_f 0.2) and the coupling product (R_f 0.6). The carboxylic acid was extracted into 2 × 10 ml of 1.5 M NaOH and recovered by acidification with 3 M H_2SO_4 followed by extraction into ether. The ether layer was washed with water, dried, and concentrated in vacuo to a pale yellow oil which proved to be one major component (R_f 0.2) by TLC.

The crude acid was dissolved in 10 ml of MeOH to which was added 1 ml of $CH_3C(OMe)_3$ and 10 mg of *p*-TsOH. After standing at room temperature for 24 h, the mixture was concentrated in vacuo to ~⅓ volume, diluted with ether, and washed with saturated $NaHCO_3$. After drying and concentrating in vacuo, the residue was distilled via Kugelrohr to give 1.10 g (25%) of the ester **5b** as a colorless oil: bp 90 °C (bath) (0.3 mm); IR (CCl_4) 1960, 1740 cm^{-1}; NMR (CCl_4) δ 5.0 (m, 2 H), 3.6 (s, 3 H), 2.3 (m, 4 H), 1.9 (m, 2 H), 1.3 (br, 12 H), 0.9 (distorted t, 3 H); MS (70 eV) *m/e* 238 ($M^{\cdot+}$, 10%), 140 (100%).

The major, nonacidic coupling product was isolated in 50–60% yield and purified by Kugelrohr distillation: bp 120 °C (bath) (0.3 mm); IR (CCl_4) 1960 cm^{-1}; NMR (CCl_4) δ 5.0 (m, 4 H), 2.0 (m, 8 H), 1.4 (m, 34 H), 0.9 (distorted t, 6 H); MS (70 eV) *m/e* 368 (M^+).

Methyl Tetradeca-*trans*-2,4,5-trienoate (6). A flame-dried 25-ml three-neck flask fitted with a condenser, addition funnel, magnetic stirrer, and rubber septum was charged with 2.5 ml (4.0 mmol) of 1.6 M *n*-BuLi/hexane and 5 ml of THF freshly distilled from Na. Diisopropylamine (0.41 g, 4.0 mmol) was added via syringe and the mixture cooled to −78 °C. With rapid magnetic stirring, 0.47 g (2.0 mmol) of the ester **5b** in 5 ml of THF was added dropwise. The mixture was stirred under nitrogen at −78 °C for an additional 0.5 h whereupon 0.625 g (2.0 mmol) of diphenyl diselenide in 3 ml of THF was added dropwise. After a further 1 h of stirring at −78 °C, the cooling bath was removed and 10 ml of saturated NH_4Cl added. The product was extracted into 25 ml of ether and the organic layer washed with 2 × 15 ml of 10% Na_2CO_3 and dried. Evaporation of the solvent in vacuo gave a dark yellow residue which was chromatographed on silica gel packed in hexane. Unreacted diphenyl diselenide (75 mg) was eluted with hexane. The α-phenylseleno ester was then eluted with 10% Et_2O in hexane.

The α-phenylseleno ester was dissolved in 8 ml of THF. A solution of 1.08 g (5.0 mmol) of $NaIO_4$ in 4 ml of warm water was added in one portion and the mixture allowed to stir at ambient temperature for 10 h. Analytical TLC (10% ether in hexane) showed a single major component. The reaction mixture was diluted with ether, washed with 2 × 15 ml of 10% Na_2CO_3, dried, and concentrated in vacuo to give 0.39 g (85%) of the allenenic ester **6** as a pale yellow oil:[16] IR (CCl_4) 1940, 1720, 1630, and 980 cm^{-1}; NMR (CCl_4) δ 7.1 (dd, 1 H, J = 15, 10 Hz), 5.75 (d, 1 H, J = 15 Hz), 5.7, 5.3 (m, 2 H), 3.6 (s, 3 H), 2.1 (m, 2 H), 1.3 (br, 12 H), 8.9 (distorted t, 3 H); MS (70 eV) *m/e* 236 ($M^{\cdot+}$, 25%), 138 (95%), 79 (100%).

Acknowledgments. We would like to thank the SUNY Research Foundation and the Research Corporation for financial support. We are further indebted to Mr. Jon Stickles and Dr. Bruce Norcross for technical assistance.

Registry No.—**1**, 60705-48-8; **2**, 60705-49-9; **3**, 60705-50-2; **4**, 60705-51-3; **5a**, 60705-52-4; **5b**, 60705-53-5; **6**, 34656-68-3; $CH_3C(OEt)_3$, 78-39-7; CBr_4, 558-13-4; $CH_3C(OMe)_3$, 1445-45-0; hexacosa-9,10,16,7-tetraene, 60705-56-8; diphenyl diselenide, 1666-13-3; methyl α-phenylselenotetradeca-*trans*-2,4,5-trienoate, 60705-57-9.

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Stereospecific Synthesis of (2*S*,3*R*)-2-Amino-3-mercaptobutyric Acid—an Intermediate for Incorporation into β-Methyllanthionine-Containing Peptides

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Received July 6, 1976

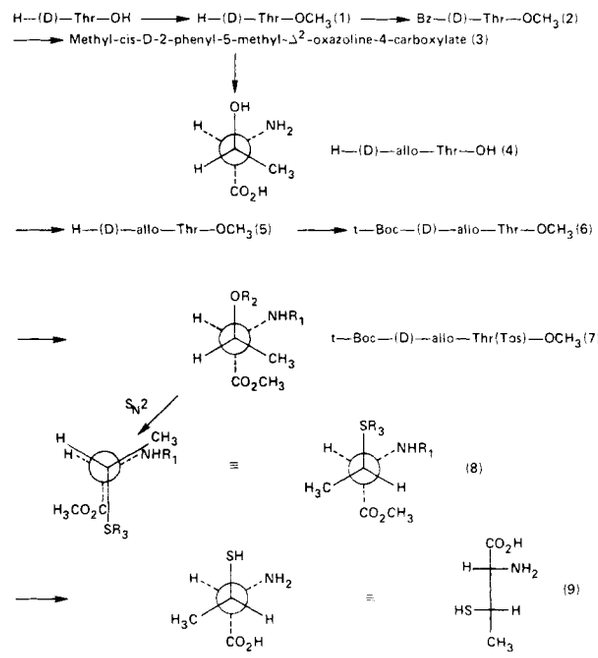
Access to the correct isomer[1] of β-methyllanthionine is a prerequisite for the synthesis of fragments of heterodetic polycyclic peptides, such as nisin.[2] A reasonable approach requires the preparation of *threo*-β-methyl-D-cysteine. Formation of the thioether bridge is anticipated to be accomplished by a substitution or addition reaction on a suitable alanine derivative before or after incorporation into the peptide chain.

Carter et al.[3] prepared the diastereoisomeric pairs of *S*-benzyl-β-methylcysteine which they called amino acids A and B and which have been assigned the threo and allo configurations, respectively.[1]

Hoogmartens et al.[4] began with the same method of preparation and by derivatization and crystallization with the aid of optically active bases resolved each of the pairs into the respective D and L amino acid.

This procedure is elaborate if only one of the four possible isomers is desired. Yields of the final product are low as the result of lack of stereospecificity in the synthesis.

We have devised a stereospecific synthesis outlined in the scheme (R_1 = *tert*-butyloxycarbonyl; R_2 = tosyl; R_3 = acetyl) below. Good yields of the desired isomer are obtained by a series of simple steps in a relatively short time. The crucial step involves an SN2 displacement of tosylate by thiolacetate anion. Although the products of such reactions are often mixtures resulting from elimination, O-alkylation of thiolacetate, or SN1 mechanisms, no evidence for these processes was observed here. Examination of the crude reaction mixture after hydrolysis and S-benzylation showed the only sulfur



containing product to be *threo*-*S*-benzyl-β-methyl-D-cysteine. A small amount of unreacted *allo*-*O*-tosyl-D-threonine was also present but had no effect on the subsequent steps.

The reactions were also applied to *allo*-DL-threonine and gave pure *allo*-β-methyl-DL-cysteine as determined by S-benzylation and amino acid analysis.

Experimental Section

Melting points are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the National Institutes of Health. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter.

Amino acid analyses were performed on a modified Phoenix analyzer using the Moore, Stein, and Spackman system. *S*-Benzyl-β-methylcysteines were analyzed on a 60 × 0.9 cm column using pH 4.25, 0.2 N Na citrate buffer at a flow rate of 60 ml/h. Elution volumes of the threo and allo isomers of *S*-benzyl-β-methylcysteine are 163 and 187 ml, respectively.

Countercurrent distribution was run in a 200 tube Craig machine with lower and upper phase volumes of 10 ml each.

D-Threonine Methyl Ester Hydrochloride (1). D-Threonine, 180 g, $[\alpha]^{23}D$ +30.5° (*c* 1, water) [lit.[7] $[\alpha]^{26}D$ +28° (*c* 1–2, water)], obtained from Pierce, Rockford, Ill., was refluxed twice for 1 h in 1.5 l. of 2 N HCl in methanol to give 205 g (98%) of **1** as an oil which crystallized on standing under vacuum.

***N*-Benzoyl-D-threonine Methyl Ester (2).** **1** (205 g) was benzoylated without further purification by the dropwise addition of 175 ml of benzoyl chloride (1.5 mol) to a solution in 1.5 l. of water–dioxane (2:1) over 1 h using 5 N NaOH to maintain a pH of 8.5–9.0 and an ice bath to keep the temperature at 30 °C. The dioxane was removed under reduced pressure and the aqueous phase extracted with ethyl acetate. Evaporation of the solvent yielded 285 g (80%) of crude **2**. Recrystallization from benzene gave 220 g (63%) of pure **2**, mp 92–94 °C, $[\alpha]^{22}D$ −22.0° (*c* 8, ethanol) [lit.[5] mp 96.0 °C, $[\alpha]^{26}D$ −23.2° (*c* 6, ethanol)].

Methyl *cis*-D-2-Phenyl-5-methyl-Δ²-oxazoline-4-carboxylate (3). **3** (205 g, 0.875 mol) was prepared by treating **2** with thionyl chloride (twice distilled from triphenyl phosphite[6]) according to the literature.[5]

***allo*-D-Threonine (4).** Crude crystalline **3** (205 g) was hydrolyzed in 1 l. of 6 N HCl at 90 °C for 5 h. Workup according to the literature[5] yielded 76 g (65% based on **2**) of pure **4**, $[\alpha]^{27}D$ −32.5° (*c* 8, 1 N HCl in water) [lit.[5] *allo*-L-threonine $[\alpha]^{27}D$ +32.5° (*c* 8.2, 1 N HCl in water)].

***allo*-D-Threonine Methyl Ester Hydrochloride (5).** **4** (75 g, 0.625 mol) was esterified in the same manner as D-threonine. The yield