in 2 mL of distilled water. After being stirred at room temperature for 48 h, the solution was poured into 100 mL of water, neutralized with solid $NaHCO_3$, and extracted with chloroform. The combined chloroform solution was washed with saturated $NaHCO_3$ and brine, dried (calcium sulfate), and concentrated. Flash chromatography of the residue with chloroform-ethyl acetate (2:1) provided 255 mg (27%) of a red solid: mp 251-253 °C; IR (KBr) 3360, 3150, 1580, 1550, 1260 cm^{-1}; mass spectrum, m/e 189 (M^+).

3-Amino-5-hydroxy-1,4-naphthoquinone (2b). To 506 mg (2.0 mmol) of bromonaphthoquinone **14** in 25 mL of ethanol was added 200 mg (2.47 mmol) of potassium azide. After being stirred at room temperature for 20 h, the solution was diluted with water and filtered, and the orange solid was washed with water to provide 408 mg (95%) of the azidonaphthoquinone: IR ($CHCl_3$) 2120, 1635, 1580, 1255 cm^{-1}.

To 317.2 mg (1.48 mmol) of the azidonaphthoquinone in 25 mL of ethanol was added 30 mg of platinum oxide. The suspension was stirred for 8 h under 1 atm of hydrogen. The catalyst was removed by filtration, and O_2 gas was bubbled through for 2 h. Concentration afforded a solid which was purified by flash chromatography using chloroform-ethyl acetate (2:1) to give 200 mg (72%) of a red-orange solid: mp 253-255 °C; the spectra were identical with those reported above for **2b**.

5-Acetoxy-2-amino-1,4-naphthoquinone (16). To 295 mg (1.0 mmol) of bromonaphthoquinone **15** in 15 mL of ethanol was added 100 mg (1.23 mmol) of potassium azide. After stirring at room temperature for 20 h, the solution was diluted with water and filtered. The yellow precipitate was washed with water to provide 214 mg (83%) of the azidonaphthoquinone: IR ($CHCl_3$) 2130, 1760, 1670, 1640, 1595, 1365, 1265, 1180 cm^{-1}.

To 186.7 mg (0.726 mmol) of the azidonaphthoquinone in 20 mL of ethanol was added 20 mg of platinum oxide. The suspension was stirred for 8 h under 1 atm of hydrogen. The catalyst was removed by filtration and O_2 gas bubbled through for 2 h. Filtration gave 50 mg of orange plates. Concentration of the filtrate afforded a solid which was purified by flash chromatography using chloroform-ethyl acetate (2:1) to give 66 mg for a total of 116 mg (69%) of an orange solid: mp 192-193 °C; IR ($CHCl_3$) 3480, 3400, 3360, 1745, 1620, 1260 cm^{-1}; mass spectrum, m/e 231 (M^+).

2-Amino-5-hydroxy-1,4-naphthoquinone (13). To 20 mg (0.087 mmol) of acetoxynaphthoquinone **16** in 2 mL of ethanol was added 5 mL of 5% sodium hydroxide solution. After being stirred for 1 h at room temperature, the solution was diluted with water and extracted with chloroform. The combined chloroform solution was washed with brine, dried (calcium sulfate), and concentrated. Flash chromatography of the residue with chloroform-ethyl acetate (2:1) provided 10.6 mg (65%) of a red solid: mp 269-270 °C; IR (KBr) 3490, 3120, 1610, 1450, 1260 cm^{-1}; mass spectrum, m/e 189 (M^+).

5-Acetoxy-3-amino-1,4-naphthoquinone (2c) and 5-Acetoxy-2-amino-1,4-naphthoquinone (16). To 108 g (5.0 mmol) of 5-acetoxy-1,4-naphthoquinone (**17**) in 25 mL of glacial acetic acid was added 650 mg (10.0 mmol) of sodium azide in 2 mL of distilled water. After being stirred at room temperature for 72 h, the solution was poured into 100 mL of water, stirred for 15 min, and filtered. The filtrate was neutralized with solid $NaHCO_3$ and extracted with chloroform. The combined chloroform solution was washed with saturated $NaHCO_3$ and brine, dried (calcium sulfate), and concentrated. Trituration of the residue with chloroform afforded 281 mg of a mixture of acetoxyaminonaphthoquinone **2c** and aminohydroxynaphthoquinone **2b**. The ratio of **2c** and **2b** was 88:12, as determined by ^1H NMR integration. On the basis of this ratio, the yield of compound **2c** is 21% and the yield of compound **2b** is 4%. Preparative liquid chromatography of an aliquot of this mixture with chloroform provided aminonaphthoquinone **2c** as an orange solid: mp 148-150 °C; IR ($CHCl_3$) 3480, 3360, 1755, 1615, 1345, 1180 cm^{-1}; mass spectrum m/e 231 (M^+).

Preparative liquid chromatography of the trituration washes with chloroform as eluent provided 328 mg of a mixture of aminonaphthoquinone **2c** and aminonaphthoquinone **16**. The ratio **2c** to **16** was 64:36, as determined by ^1H NMR integration. On the basis of this ratio, the yield of compound **2c** is 18%, and the yield of compound **16** is 10%.

3-Amino-5-hydroxy-1,4-naphthoquinone (2b). To 25 mg (0.108 mmol) of acetoxynaphthoquinone **2c** in 2 mL of ethanol was added 5% sodium hydroxide solution. After being stirred for 1 h at room temperature, the solution was diluted with water and extracted with chloroform. The combined chloroform solution was washed with brine, dried (calcium sulfate), and concentrated. Flash chromatography of the residue with chloroform-ethyl acetate (2:1) provided 12.2 mg (60%) of a red solid: mp 253-255 °C; the spectra were identical with those reported above for **2b**.

Acknowledgment. The authors are grateful to Professor Ronald G. Lawler, Mr. Jack Syage, and Mr. Walter Smith of Brown University and Mr. Peter Demou of the Southern New England High Field NMR Facility for assistance in obtaining and simulating NMR spectra. We acknowledge with thanks financial support from the National Cancer Institute (Grant CA16524), the Sloan Foundation, and the Dreyfus Foundation.

Registry No. 2a, 56568-58-2; **2b**, 77507-72-3; **2c**, 77507-73-4; **3**, 4923-61-9; **4**, 71186-96-4; **5**, 13261-50-2; **6**, 77507-74-5; **7**, 83-56-7; **8**, 69833-10-9; **9**, 77507-75-6; **10**, 69833-09-6; **11**, 77507-76-7; **12**, 481-39-0; **13**, 77507-77-8; **14**, 52431-65-9; **15**, 77189-69-6; **16**, 77507-78-9; **17**, 5196-28-1; **18**, 77197-58-1; 3-azido-5-hydroxy-1,4-naphthoquinone, 77507-79-0; 5-acetoxy-2-azido-1,4-naphthoquinone, 77507-80-3.

Stereospecific Syntheses of Both Diastereomers of (±)-2-Amino-4-methyl-5-hexenoic Acid

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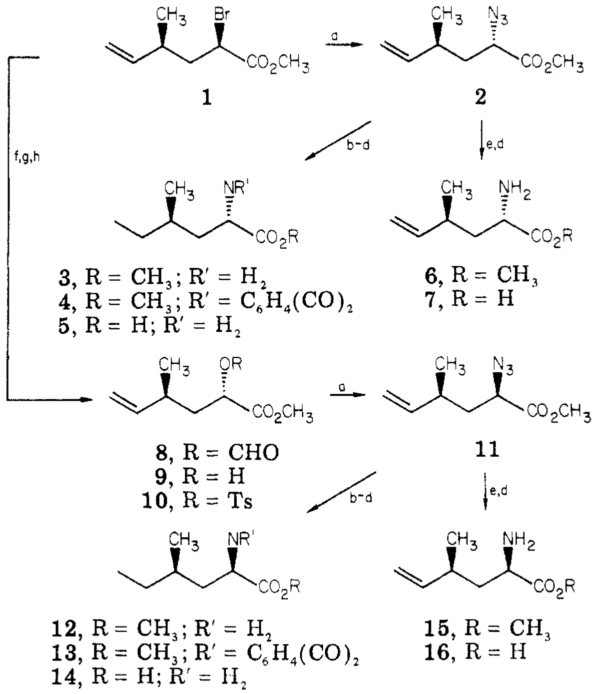
Received March 16, 1981

Both diastereomers of 2-amino-4-methyl-5-hexenoic acid (**7** and **16**) have been synthesized stereospecifically from methyl (2*R**,4*S**)-2-bromo-4-methyl-5-hexenoate (**1**), the product of the $EtAlCl_2$-catalyzed ene reaction of methyl α-bromoacrylate and *trans*-2-butene. This synthesis establishes the stereochemistry of the ene reaction and establishes that the amino acid isolated from a *Streptomyces* fermentation is **7**.

A variety of nonprotein amino acids with the 2-amino-4-methylhexanoic skeleton are known. Fowden and Smith isolated (2*S*)-2-amino-4-methyl-4-hexenoic acid and (2*S*,4*S*)-2-amino-4-methylhexanoic acid (**14**) from the seeds of *Aesculus californica*.[2] Kelly et al. isolated (2*S*)-2-amino-4-methyl-5-hexenoic acid, an antimetabolite antibiotic,[3] of unknown configuration at C4 from a *Strepto-*

(1) Fellow of the Alfred P. Sloan Foundation, 1979-1981.
(2) Fowden, L.; Smith, A. *Phytochemistry* 1968, 7, 809.

Scheme I[a]



[a] (a) NaN_3, R_4PBr; (b) H_2, Ni; (c) phthalic anhydride, H^+; (d) NaOH, $MeOH-H_2O$; (e) $CrCl_2$; (f) tetraethylammonium formate; (g) K_2CO_3, MeOH; (h) toluenesulfonyl chloride, pyridine.

myces fermentation.[4] Rudzats et al. isolated 2-amino-4-methyl-5-hexenoic acid (**16**),[5] which they later showed to be 2*S*,4*R*,[6] from a New Guinea fungus, *Boletus*. Bernasconi et al. and Gellert et al. synthesized (2*R*,4*S*)- and (2*S*,4*S*)-2-amino-4-methylhexanoic acid by unambiguous routes starting with (*S*)-2-methyl-1-butanol and using an enzymatic hydrolysis to separate diastereomers and assign the stereochemistry at C2. This allowed assignment of stereochemistry to the amino acid isolated from *Aesculus californica* and the unsaturated amino acid from *Boletus*.

We have recently obtained methyl 2-bromo-4-methyl-5-hexenoate in 51% yield as a 19:1 mixture of diastereomers (now known to be predominantly 2*R**,4*S**, i.e., **1**) from the $EtAlCl_2$-catalyzed ene reaction of methyl α-bromoacrylate[8] with *trans*-2-butene.[9,10] Determination of the relative stereochemistry of **1** could not be accomplished by spectral means. Conversion of **1** (see Scheme I) to 2-amino-4-methylhexanoic acid derivatives appeared to be the easiest means of chemical correlation of **1** with compounds of known stereochemistry. Bromo ester **1** was also an attractive intermediate for the synthesis of both diastereomers of 2-amino-4-methyl-5-hexenoic acid (**7** and **16**). In addition to providing the first synthesis of these compounds, this would allow us to determine the relative stereochemistry of the amino acid from *Streptomyces*.[4]

Results and Discussion

The stereospecific synthesis of amino acids from **1** depended on the use of displacement reactions on the bromide which proceed with complete inversion. In this case stereochemical integrity can be lost by abstraction of the basic α-proton as well as in the displacement reaction. Thus, reaction of **1** with potassium phthalimide under phase-transfer conditions gave a 1:1 mixture of diastereomeric phthalimides even though these conditions led to complete inversion with 2-octyl tosylate.[11] Fortunately, treatment of **1** with nonbasic sodium azide, with hexadecyltributylphosphonium bromide as a phase-transfer catalyst,[12] gave (2*S**,4*S**)-azido ester **2** in 70% yield as a ca. 19:1 mixture of diastereomers. The azide ester was unstable, undergoing an intramolecular 1,3-dipolar cycloaddition at 25 °C to give a triazoline.[13] It was therefore used immediately.

Hydrogenation of the double bond and reduction of the azide[14] of **2** over W-2 Raney nickel[15] gave the unstable (2*S**,4*R**)-amino ester **3**. Treatment of **3** with phthalic anhydride in ether and then at reflux in acidic methanol[16] gave the (2*S**,4*R**)-phthalimide **4** in 40% yield from **2**. Bernasconi et al. have synthesized **4** and **13** and shown that these compounds can be easily distinguished by NMR, most notably the C2-proton which absorbs as a dd (J = 4.45, 11.2 Hz) for **4** and as a dd (*J* = 6.6, 8.3 Hz) for **13**.[7] The NMR spectrum of **4** is superimposable with that of authentic (2*R*,4*S*)-**4**. This establishes the relative configuration of the ene adduct **1** as 2*R**,4*S**. Hydrolysis of amino ester **3** with NaOH in aqueous methanol gave (2*S**,4*R**)-2-amino-4-hexanoic acid (**5**) in 53% yield from **2**.

Reduction of the azide without affecting the double bond was accomplished by treatment of **2** with chromous chloride in aqueous acetone[17] which gave (2*S**,4*S**)-amino ester **6**, which was hydrolyzed to (2*S**,4*S**)-2-amino-4-methyl-5-hexenoic acid (**7**). As expected, the NMR spectrum of this material was quite different from that of the 2*S*,4*R* isomer **16** isolated from the New Guinea *Boletus*. The spectrum was, however, superimposable with that of the sample isolated from the *Streptomyces*,[4] which therefore has the 2*S*,4*S* configuration.

The diastereomeric series of amino acids was prepared by a route involving two inversions. Treatment of **1** with tetraethylammonium formate[18] in acetone gave the (2*S**,4*S**)-formate **8**, which was hydrolyzed with potassium carbonate to the (2*S**,4*S**)-hydroxy ester **9** (62% from **1**). Treatment of **9** with *p*-toluenesulfonyl chloride in pyridine gave the unstable tosylate **10** which was treated with sodium azide with hexadecyltributylphosphonium bromide as a phase-transfer catalyst to give the unstable (2*R**,4*S**)-azide **11**. Reduction and hydrogenation over Raney nickel gave the (2*R**,4*R**)-amino ester **12** which was

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converted to the ($2R^*,4R^*$)-phthalimide **13** (24% from **1**) whose NMR spectrum was superimposable with that of an authentic 2*S*,4*S* sample.[7] Hydrolysis of **12** gave ($2R^*,4R^*$)-2-amino-4-methylhexanoic acid (**14**, 30% from **1**). Reduction of **11** with chromous chloride gave the ($2R^*,4S^*$)-amino ester **15** which was hydrolyzed to give ($2R^*,4S^*$)-2-amino-4-methyl-5-hexenoic acid (**16**, 26% from **1**) whose NMR spectrum was identical with that of a sample of (2*S*,4*R*)-amino acid isolated from the New Guinea *Boletus*.[5]

Conclusion

We have described the stereospecific syntheses of ($2R^*,4S^*$)- and ($2S^*,4S^*$)-2-amino-4-methyl-5-hexenoic acids. This has allowed us to establish that both diastereomers, in the 2*S* form, are naturally occurring and provides one of the increasingly rare occurrences where total synthesis is used for structure determination of a natural product. The ready availability of bromo ester **1** provides a simple means of testing the stereospecificity of displacement reactions on α-halo esters without the use of optically active materials. We are presently developing methods for asymmetric induction in the ene reaction which will allow the facile production of novel amino acids in optically active form.

Experimental Section

Proton magnetic resonance spectra were recorded at 90 MHz on a JEOLCO FX-90Q or Perkin-Elmer R32 spectrometer or at 60 MHz on a Varian A-60. Spectra in $CDCl_3$ or CCl_4 used Me_4Si as an internal standard. Spectra in D_2O used sodium 3-(trimethylsilyl)propionate-*2,2,3,3-d₄* as an internal standard (δ 0.0, ^{1}H; δ -1.94, ^{13}C). Elemental analyses were performed by Galbraith Laboratories.

Methyl ($2R^*,4S^*$)-2-Bromo-4-methyl-5-hexenoate (1). Methyl α-bromoacrylate (3.56 g, 21.6 mmol) containing 1% hydroquinone, *trans*-2-butene (6.04 g, 108 mmol, 5 equiv), and $EtAlCl_2$ (6.19 mL of a 1.57 M solution in heptane, 0.45 equiv) in 10 mL of anhydrous benzene was heated for 80 h at 70 °C in a pressure bottle. Addition of saturated sodium bicarbonate solution and vacuum filtration of the precipitated alumina through Celite, followed by extraction of the filtrate with three portions of ether which was washed with brine, dried (Na_2SO_4), and evaporated, gave 2.95 g of crude product. Evaporative distillation gave 2.46 g (51.5%) of pure **1** as a colorless oil which ^{13}C NMR showed to be a 19:1 mixture of diastereomers: bp 45 °C (0.05 torr); NMR (CCl_4) δ 5.56 (ddd, 1, J = 7.7, 9.5, 17.3 Hz), 5.07 (dd, 1, J = 2.3, 17.3 Hz), 5.00 (dd, 1, J = 2.3, 9.5 Hz), 4.13 (dd, 1, J = 7.3, 7.3 Hz), 3.75 (s, 3), 2.44 (m, 1), 1.95 (dd, 2, J = 7.3, 7.3 Hz), 1.09 (d, 3, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 170.4, 141.8, 115.1, 52.8, 44.8, 41.0, 36.4, 20.6 (the minor isomer shows peaks at 142.0, 114.4, 41.5, 36.0, and 20.0); IR (neat) 3090, 1748, 996, 920 cm^{-1}.

Anal. Calcd for $C_8H_{13}BrO_2$: C, 43.46; H, 5.93; Br, 36.14. Found: C, 43.26; H, 5.98; Br, 36.14.

Methyl ($2S^*,4S^*$)-2-Azido-4-methyl-5-hexenoate (2). A suspension of **1** (1.00 g, 4.53 mmol) in a solution of sodium azide (0.588 g, 9.05 mmol, 2 equiv) and hexadecyltributylphosphonium bromide (0.230 g, 0.45 mmol, 0.1 equiv) in 2.3 mL of water was vigorously stirred for 4 h at 25 °C. Ether (10 mL) was added, and the organic phase was extracted three times with brine, dried (Na_2SO_4), and evaporated to give 1.03 g of crude azide contaminated with phase-transfer catalyst. Chromatography on silica gel (1:1 petroleum ether–ether) gave 0.582 g (70.4%) of **2** as an unstable colorless oil: NMR (CCl_4) δ 3.78 (m, 1); IR (neat) 3085, 2105, 1748, 1016, 916 cm^{-1}.

Methyl ($2S^*,4R^*$)-2-Amino-4-methylhexanoate (3). The purified azide **2** (164 mg, 0.9 mmol) was hydrogenated over W-2 Raney nickel (25 mg, 0.4 mmol) in 2 mL of ethanol under hydrogen for 20 h at 25 °C. The solution was filtered through Celite which was washed with several portions of methylene chloride. The filtrate was evaporated, giving 116 mg (81%) of unstable amino ester **3** as a colorless oil which was used immediately: NMR ($CDCl_3$) δ 3.78 (m, 1); IR (CCl_4) 3390, 3330, 1740 cm^{-1}.

Methyl ($2S^*,4R^*$)-2-Phthalimido-4-methylhexanoate (4). The crude amino ester **3** (66 mg, 0.42 mmol) was added to a stirred solution of phthalic anhydride (61.5 mg, 0.4 mmol) in 1 mL of anhydrous ether. The solution was stirred for 24 h at 25 °C. The solvent was removed, and 1 mL of 4% HCl in MeOH was added. The mixture was refluxed for 15 h under nitrogen and evaporated to dryness, yielding 125 mg of crude phthalimide. Chromatography on silica gel (3:1 hexane–EtOAc) gave 68 mg (57% from **3**, 33% from **1**) of pure **4** whose NMR spectrum was superimposable on that of an authentic sample of the 2*R*,4*S* isomer:[7] NMR (CCl_4) 4.85 (dd, 1, J = 4.2, 11.8 Hz); IR (CCl_4) 1780, 1753, 1722 cm^{-1}.

($2S^*,4R^*$)-2-Amino-4-methylhexanoic Acid (5). The amino ester **3** (obtained from 66.4 mg of purified azide **2**) was dissolved in 4 mL of methanol, and 4.2 mL of 0.1 N NaOH solution was added. The solution was stirred for 44 h at 25 °C and carefully acidified to pH 6 by addition of concentrated hydrochloric acid. The solution was extracted with three portions of CH_2Cl_2 to remove organic impurities and evaporated to give 39.3 mg (35% from **1**) of a 1:1 molar mixture of **5** and sodium chloride: NMR (D_2O) δ 3.76 (dd, 1, J = 5.5, 8.6 Hz), 1.9–1.0 (m, 5), 0.97–0.88 (m, 6); ^{13}C NMR (D_2O) δ 54.2, 38.6, 31.3, 30.1, 18.5, 11.3 (the C=O carbon was not observed); IR (KBr) 3035, 2970, 2930, 1625, 1595, 1517, 1457, 1412, 1360, 760, 700 cm^{-1}.

Methyl ($2S^*,4S^*$)-2-Amino-4-methyl-5-hexenoate (6). Crude azide **2** (obtained from 0.5 g of **1**) was added immediately to a stirred suspension of $CrCl_2$ (0.582 g, 4.7 mmol) in 9 mL of acetone and 2.3 mL of water under N_2. Rapid evolution of nitrogen resulted. After 15 min, 10 mL of saturated aqueous sodium bicarbonate solution was added, and the resulting solution was extracted with five 10-mL portions of ether which were dried (Na_2SO_4) and evaporated to give 0.53 g of the unstable amino ester **6** which was used immediately: NMR (CCl_4) δ 3.78 (m, 1); IR (neat) 3390, 3330 cm^{-1}.

($2S^*,4S^*$)-2-Amino-4-methyl-5-hexenoic Acid (7). Crude **6** (0.53 g, from 0.5 g of **1**) was added to a stirred solution of 22.6 mL of 0.1 NaOH and 22.6 mL of MeOH under nitrogen. After 44 h, the solution was acidified to pH 6 by dropwise addition of hydrochloric acid. Extraction with three 10-mL portions of CH_2Cl_2 removed organic impurities. The aqueous layer was evaporated in vacuo to give 0.248 g (54% from **1**) of a 1:1 mixture of **7** and NaCl as a white solid: NMR (D_2O) δ 5.82 (ddd, 1, J = 7.5, 9.2, 17.4 Hz), 5.12 (dd, 1, J = 2.2, 17.4 Hz), 5.06 (dd, 1, J = 2.2, 9.2 Hz), 3.71 (dd, 1, J = 6.6, 6.6 Hz), 2.36 (apparent heptuplet, 1, J = 7 Hz), 2.0–1.4 (m, 2), 1.06 (d, 3, J = 6.6 Hz); ^{13}C NMR (D_2O) δ 144.1, 115.0, 54.3, 38.3, 35.1, 20.2 (the C=O carbon was not observed); IR (KBr) 3430, 3080, 3060, 3030, 2960, 2930, 1630, 1590, 1510, 1452, 1410, 1350, 1135, 1110, 995, 910, 750, 692 cm^{-1}. The NMR spectra were superimposable with that of a sample of natural amino acid isolated by Kelly et al. from *Streptomyces*.[4]

Methyl ($2S^*,4S^*$)-2-Hydroxy-4-methyl-5-hexenoate (9). Bromo ester **1** (1.00 g, 4.53 mmol) was added to a solution of tetraethylammonium formate (4.76 g, 27.2 mmol) in 23 mL of anhydrous acetone under nitrogen. The solution was vigorously stirred for 24 h at 25 °C and quenched by the addition of 50 mL of water. Product was isolated by extraction with three 30-mL portions of ether which were dried (Na_2SO_4) and evaporated to give 1.17 g (138%) of crude formate **8** (tetraethylammonium salts were present): NMR (CCl_4) δ 8.05 (s, 1), 5.12 (dd, 1, J = 7, 7 Hz); IR (CCl_4) 1765, 1735 cm^{-1}.

Crude **8** (0.5 g) was added to a suspension of 0.372 g of K_2CO_3 in 2.75 mL of anhydrous MeOH. The resulting mixture was stirred 40 min at 25 °C. Saturated NaH_2PO_4 solution (10 mL) was added, and the resulting solution was extracted three times with ether. The combined organic layers were dried (Na_2SO_4) and evaporated to give 0.37 g of product. Chromatography on silica gel (1:1 petroleum ether–ether) gave 0.19 g (62% from **1**) of pure **9**: NMR (CCl_4) δ 4.14 (dd, 1, J = 6.5, 6.5 Hz); IR (CCl_4) 3555, 1740, 980, 915 cm^{-1}.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.53; H, 8.90.

Methyl ($2R^*,4S^*$)-2-Azido-4-methyl-5-hexenoate (11). A solution of crude hydroxy ester **9** (282 mg, 1.8 mmol) and *p*-toluenesulfonyl chloride (0.341 g, 1.8 mmol) in 0.2 mL of dry pyridine was stirred for 6 h at 25 °C and added to 3 mL of saturated cupric sulfate solution. Extraction with three 3-mL portions of ether, which were combined, dried (Na_2SO_4), and evaporated, gave 0.51 g (92%) of the unstable tosylate **10**: NMR ($CDCl_3$) δ 4.85 (dd, 1, J = 6.4, 7.0 Hz); IR (neat) 1741 cm^{-1}. Addition of 0.415 g of crude **10** to a solution of hexadecyltributylphosphonium bromide (0.067 g, 0.1 equiv) and sodium azide (0.173 g, 2 equiv) in 0.7 mL of water followed by stirring for 18 h at 25 °C and a normal workup gave 230 mg of crude **11** which was used immediately for the next step.

Methyl (2*R,4*R**)-2-Amino-4-methylhexanoate (12).** Crude azido ester **11** (150 mg) was hydrogenated over W-2 Raney nickel (50 mg) as previously described to give 159 mg of crude amino ester **12** which was used immediately: NMR (CCl_4) δ 3.76 (m, 1); IR (CCl_4) 3390, 3330, 1741 cm^{-1}.

Methyl (2*R,4*R**)-2-Phthalimido-4-methylhexanoate (13).** Crude amino ester **12** (0.053 g) was converted to 0.113 g of crude phthalimide as previously described. Chromatography on silica gel (1:1 petroleum ether–ether) gave 17.3 mg (24% from **1**) of pure phthalimide **13** whose NMR was identical with that of an authentic sample of the 2*S*,4*S* isomer:[7] NMR ($CDCl_3$) δ 4.95 (dd, 1, J = 7, 8 Hz); IR ($CDCl_3$) 1780, 1745, 1719 cm^{-1}.

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62. Found: C, 66.53; H, 6.71.

(2*R,4*R**)-2-Amino-4-methylhexanoic Acid (14).** Crude amino ester **12** (92 mg) was hydrolyzed as previously described to give 30 mg of a 1:1 mixture of amino acid **14** and NaCl (30% from **1**): NMR (D_2O) δ 3.78 (dd, 1, J = 6.9, 6.9 Hz), 2.10–1.20 (m, 5), 1.0–0.70 (m, 3), 0.93 (d, 3, J = 5.9 Hz); ^{13}C NMR (D_2O) δ 38.6, 31.3, 29.0, 19.4, 11.1 (the C=O and α-carbons were not observed); IR (KBr) 3460, 2970, 2930, 1610, 1495, 1455, 1425, 1385, 1340, 1315, 1225, 1115, 700 cm^{-1}.

Methyl (2*R,4*S**)-2-Amino-4-methyl-5-hexenoate (15).** Crude **11** (71.0 mg) was reduced with $CrCl_2$ as previously described to give 57.3 mg of crude amino ester **15** which was used immediately: NMR (CCl_4) δ 3.73 (m, 1); IR (CCl_4) 3390, 3330, 1740 cm^{-1}.

(2*R,4*S**)-2-Amino-4-methyl-5-hexenoic Acid (16).** Hydrolysis of crude **15** (57.3 mg) as previously described gave 20.2 mg of a 1:1 mixture of amino acid **16** and NaCl (26% from **1**): NMR (D_2O) δ 5.80 (ddd, 1, J = 7.7, 9.8, 17.7 Hz), 5.15 (dd, 1, J = 17.7, 2 Hz), 5.12 (dd, 1, J = 9.8, 2 Hz), 3.70 (dd, 1, J = 5.2, 8.0 Hz), 2.34 (apparent heptuplet, 1, J = 7 Hz), 1.7–1.97 (m, 2), 1.07 (d, 3, J = 6.6 Hz); ^{13}C NMR (D_2O) δ 175.9, 143.7, 115.8, 54.4, 38.1, 35.3, 21.0; IR (KBr) 3425, 2950, 1590, 1522, 1402, 1361, 1337, 1308, 1188, 1136, 1061, 990, 912, 855, 830, 770, 692 cm^{-1}. The NMR spectrum was superimposable with that of a sample of natural amino acid isolated by Rudzats et al. from *Boletus*.[5]

Acknowledgment. The authors are grateful to the National Institutes of Health (Grant No. GM-23159) for financial support.

Registry No. (±)-(R*,S*)-1, 78019-18-8; (±)-(R*,R*)-1, 78019-19-9; (±)-**2**, 78019-20-2; (±)-**3**, 78019-21-3; (±)-**4**, 78086-84-7; (±)-**5**, 78086-85-8; (±)-**6**, 78019-22-4; (±)-**7**, 78086-86-9; (±)-**8**, 78019-23-5; (±)-**9**, 78019-24-6; (±)-**10**, 78019-25-7; (±)-**11**, 78019-26-8; (±)-**12**, 78019-27-9; (±)-**13**, 78086-87-0; (±)-**14**, 78019-28-0; (±)-**15**, 78019-29-1; (±)-**16**, 78086-88-1; methyl α-bromoacrylate, 4519-46-4; *trans*-2-butene, 624-64-6.

Synthesis of Electrophilic Allyl Dichlorides

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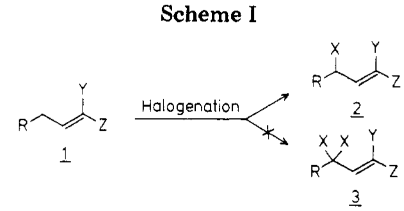
Received September 16, 1980

Electrophilic allyl dichlorides have been prepared by starting from 2,2-dichloro aldehydes by various condensation reactions forming carbon–carbon double bonds. The Emmons–Wadsworth reaction gave rise to γ,γ-dichloro-α,β-unsaturated esters and nitriles, while γ,γ-dichloro-α,β-unsaturated ketones were produced on condensation with 1,3-diketones. Allyl dichlorides geminally substituted with two electron-withdrawing groups in the γ-position were obtained by a Knoevenagel condensation with titanium tetrachloride–pyridine.

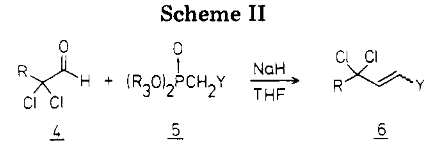
In the course of our studies toward the reactivity of geminally activated allyl halides[3] **2**, we wanted to investigate the chemistry of mono- and diactivated alkenes **3** bearing two halogen atoms in the γ-position. The synthesis of the monohalogen alkenes did not give major problems as allylic halogenation of electrophilic alkenes gave rise to monohalogenation.[3] Chlorination of α,β-unsaturated esters and cyanides with *tert*-butyl hypochlorite led to monochloro compounds,[4] while bromination of α,β-unsaturated esters,[5] cyanides,[6] ketones,[7] and alkylidene malonates[8] never afforded geminal dibromo electrophilic alkenes **3** (Scheme I). Consequently, we sought an efficient and

Scheme I



R = Me, Et, n-Pr, i-Pr, t-Bu, Ph, $PhCH_2$
X = Cl, Br
Y, Z = H, $COOR_1$, COR_2, CN

Scheme II



Y = $COOR_2$, CN

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