References and Notes

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(10) The authors thank Drs. H. Nozaki and K. Utimoto of Kyoto University for the spectral data of *dl*-muscone.

Total Synthesis of β-Elemenone

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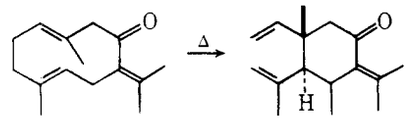
β-Elemenone (**2**) is a sesquiterpenoid isopropylidene cyclohexanone which has been isolated from Bulgarian zdravets oil[2] and *Rhododendron adamsii* Rehd.[3] The principal component of Bulgarian zdravet oil, germacrone **1**,[4] undergoes

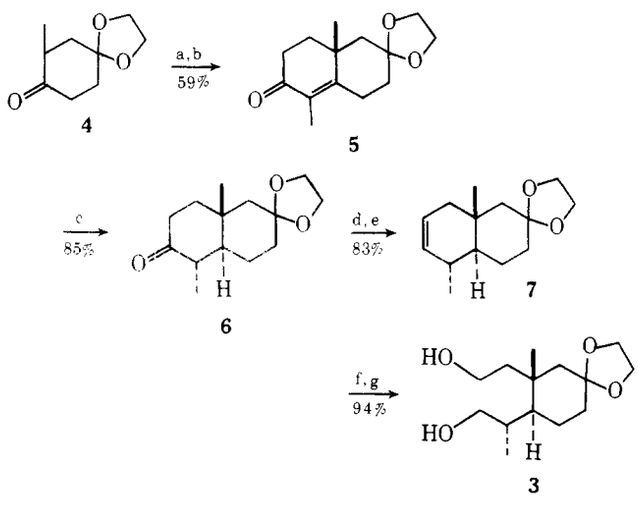


1 **2**

smooth thermal rearrangement to β-elemenone.[2,5,6] No recorded synthesis of β-elemenone has been described. This note details the total synthesis of racemic **2** which involves a facile method for the construction of the *trans*-1,2-divinylcyclohexane unit.

The key intermediate diol **3** was prepared from 2-methyl-4-ethylenedioxycyclohexanone (**4**) as outlined in Chart I. Intermediate **3** possesses appropriate functionality for the introduction of the two vinyl units as well as for construction of the isopropylidene unit. The annelated product **5** has been prepared on several previous occasions from compound **4** and various ethyl vinyl ketone equivalents including ethyl vinyl ketone.[7-10] In all cases reported the overall yield of isolated ring annelated material is less than 40%.

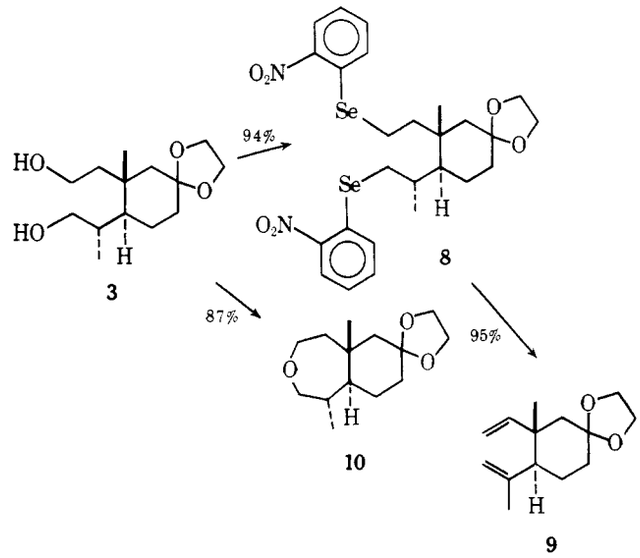
Chart I. Synthesis of Intermediate Diol 3



a, NaH, THF, $CH_3CH_2COCH_2CH_2Cl$; b, KOH, MeOH; c, Li, NH_3, *t*-BuOH, THF; d, LDA, THF, $(EtO)_2POCl$; e, Li, $EtNH_2$; f, O_3, MeOH; g, $NaBH_4$

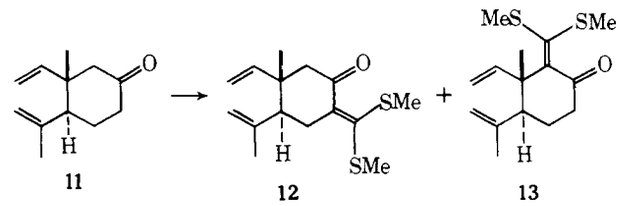
We have found that treatment of **4** with 1.3 equiv of sodium hydride in tetrahydrofuran and 1.8 equiv of 1-chloro-3-pentanone followed by treatment with methanolic potassium hydroxide gave reproducibly a 60% yield of **5** with only a trace amount of **4** remaining (see Experimental Section).

Generation of the trans ring fusion was carried out in a straightforward manner as indicated in Chart I. Introduction of the double bond in compound **6** was established by kinetic enolate formation followed by trapping of the enolate with diethyl chlorophosphate. The enol phosphate was reduced with lithium in ethylamine.[11] Ozonolysis of **7** with a sodium borohydride workup provided in very high yield intermediate diol **3**, mp 61–62°.



Construction of the *trans*-1,2-divinylcyclohexane derivative **9** was carried out in a two-step process based on the method for the direct conversion of alcohols to alkyl aryl selenides.[12] Treatment of diol **3** with 2.4 equiv of *o*-nitrophenyl selenocyanate[13] in tetrahydrofuran containing 2.4 equiv of tri-*n*-butylphosphine at room temperature for 30 min gave a 94% yield of bisselenide **8** which was directly converted to diene **9** in very high yield upon treatment with 50% hydrogen peroxide in tetrahydrofuran.[14] Utilization of only 1.0 equiv of *o*-nitrophenyl selenocyanate and 1 equiv of tri-*n*-butylphosphine during an attempted conversion of **3** → **8** resulted in spontaneous formation of the seven-membered ring ether **10**.

The conversion of compound **9** to β-elemenone is detailed below. Cleavage of ketal **9** under acidic conditions afforded ketone **11** which was converted to the α-dithiomethylene derivatives **12** and **13** in a ratio of 3:1 in disappointingly low yield.[15]



11 **12** **13**

Reaction of **12** with 2 equiv of lithium dimethylcuprate at −78 °C produced β-elemenone in 90% yield. The NMR spec-

trum of synthetic β-elemenone displayed a sharp singlet at 1.03 ppm (3 H), broad singlets at 1.80 (6 H) and 2.00 ppm (3 H), a multiplet located at 2.22–2.71 ppm (5 H), and protons characteristic of the *trans*-1,2-divinylcyclohexane unit. The NMR and infrared spectra of synthetic **2** were identical with those of a sample of β-elemenone obtained by thermolysis (165 °C, 20 mm) of natural germacrone (**1**). We are indebted to Professor V. Herout (Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Science) for a generous gift of "zdravets oil" (*Geranium sp.*) from which we readily isolated germacrone.

Experimental Section

Melting points were determined on a Fisher-Johns hot stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded at 60 MHz (Varian A-60D or T-60 spectrometer). Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (Me_4Si) (δ_{Me_4Si} 0.00 ppm) as an internal standard. Low-resolution mass spectra were recorded on an LKB-9000 instrument. High-resolution spectra were recorded on a Varian MAT CH5-DF instrument. Microanalyses were performed by Galbraith, Inc., Knoxville, Tenn.

Reactions were run under an atmosphere of nitrogen. "Dry" solvents were dried immediately before use. Tetrahydrofuran was distilled from lithium aluminum hydride. Ether was distilled from sodium metal.

6,6-Ethylenedioxy-1,10β-dimethyl-$\Delta^{1(9)}$-octal-2-one (5). 4,4-Ethylenedioxy-2-methylcyclohexanone[7] (8.31 g, 48.8 mmol) was added dropwise at room temperature to a suspension of sodium hydride (1.25 g, 63.4 mmol) in dry tetrahydrofuran (60 mL) under nitrogen. After refluxing for 2 h, the contents of the flask were cooled to room temperature and freshly distilled 1-chloropentan-3-one (8.19 g, 68.3 mmol) was added. The mixture was heated at 45 °C for 2 h followed by an additional 2.34 g of 1-chloropentan-3-one in 10 mL of tetrahydrofuran. Heating at 45 °C was continued for an additional 1 h. The reaction was quenched with 5% aqueous sodium carbonate solution and the reaction mixture was concentrated in vacuo. The product was isolated by ether extraction.[17] The residue was treated at 45 °C with ca. 7 g of solid potassium hydroxide in 150 mL of methanol. After 6 h, the methanol was evaporated under reduced pressure and the residue was taken up in ether and brine. The aqueous phase was thoroughly extracted with ether. The combined ethereal extracts were washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuo, yielding 8.9 g of residue which was chromatographed on 300 g of silica gel. Elution with ether–hexanes (2:1) yielded 6.80 g (59%) of **5**: mp 59–59.5 °C (lit.[7] 61–62 °C); bp 133–135 °C (0.2 mm) [lit.[7] 140–142 °C (0.3 mm)]; IR ($CHCl_3$) 1670, 1613 cm^{-1}; NMR (CCl_4) δ 1.32 (s, 3 H), 1.71 (s, 3 H), 3.90 (m, 4 H). Only a trace of compound **4** was recovered.

6,6-Ethylenedioxy-1α,10β-dimethyl-*trans*-2-decalone (6). To a solution of lithium (46 mg, 6.52 mmol) in 100 mL of liquid ammonia (distilled from sodium) was added dropwise a solution of octalone **5** (770 mg, 3.26 mmol) in 15 mL of dry tetrahydrofuran containing *tert*-butyl alcohol (213 mg, 2.60 mmol). The reaction mixture was stirred at reflux for 2 h followed by quenching with 1,3-butadiene. The liquid ammonia was evaporated and the product was isolated by ether extraction.[17] Evaporation of the solvent in vacuo left 762 mg of crude product which was chromatographed on 40 g of silica gel. Elution with ether–hexanes (1:3) gave 657 mg (85%) of pure decalone **6** as an oil: IR ($CHCl_3$) 1710 cm^{-1}; NMR (CCl_4) δ 0.95 (d, 3 H, J = 7 Hz), 1.20 (s, 3 H), 3.85 (m, 4 H); high-resolution mass spectrum m/e 238.1575 (calcd for $C_{14}H_{22}O_3$, 238.1569). An analytical sample was prepared by distillation [123–127 °C (bath temperature) (0.50 mmHg)].

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.59; H, 9.22.

6,6-Ethylenedioxy-1α,10β-dimethyl-Δ^2-*trans*-octalin (7). A solution of diisopropylamine (3.62 mg, 3.58 mmol) in 10 mL of dry tetrahydrofuran was treated with 1.79 mL (3.58 mmol) of a 2 M solution of *n*-butyllithium in hexane at 0 °C. After 30 min, a solution of decalone **6** (657 mg, 2.76 mmol) in 3 mL of dry tetrahydrofuran was added dropwise. After an additional 30 min 1.8 mL of tetramethylethylenediamine was added followed by 617 mg (3.58 mmol) of freshly distilled diethyl chlorophosphate in 1.0 mL of tetrahydrofuran. The resulting solution was stirred at room temperature for 2 h. The reaction was quenched by the addition of water and concentrated in vacuo. Isolation by ether extraction[17] gave 1.13 g of crude enol phosphate. Chromatography of the crude product on 46 g of silica gel (elution with ether–hexanes, 3:1) gave 973 mg (94%) of enol phosphate [IR ($CHCl_3$) 1680, 1270, 1040 cm^{-1}; NMR (CCl_4) δ 0.99 (s, 3 H), 1.10 (d, 3 H, J = 7 Hz), 1.25 (t, 6 H), 3.8–4.4 (m, 8 H), 5.40 (6 s, 1 H)] which was used directly in the next reaction.

Following the general procedure of Muchmore,[16] lithium (51 mg, 7.32 mmol) was added in small pieces to 100 mL of dry ethylamine. After ca. 1 h at reflux, a solution of enol phosphate (913 mg, 2.44 mmol) containing dry *tert*-butyl alcohol (600 mg, 7.32 mmol) in 20 mL of dry tetrahydrofuran was added dropwise. Stirring was continued for 30 min, during which time the blue color persisted. Excess lithium was consumed by careful addition of a saturated aqueous ammonium chloride solution. The ethylamine was evaporated and the product was isolated by ether extraction.[17] Chromatography of crude **7** (597 mg) on 10 g of silica gel (elution with ether–hexanes, 1:3) gave 474 mg (88%) of pure octalin **7** as an oil: IR ($CHCl_3$) 1650 cm^{-1}; NMR (CCl_4) δ 0.91 (s, 3 H), 0.98 (d, 3 H, J = 7 Hz), 3.82 (m, 4 H), 5.41 (6 s, 2 H); high-resolution mass spectrum m/e 222.1620 (calcd for $C_{14}H_{22}O_2$, 222.1618). An analytical sample was prepared by distillation [62–65 °C (bath temperature) (0.35 mmHg)].

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.86; H, 10.10.

Ozonolysis of Octalin 7. 6,6-Ethylenedioxy-1α,10β-dimethyl-Δ^2-*trans*-octalin (249 mg, 1.12 mmol) was dissolved in 40 mL of absolute methanol, cooled to −78 °C, and treated with 36 mL of a cooled (−78 °C) saturated solution of ozone (1.45 mmol) in methylene chloride. During a 1-h period, sodium borohydride (55 mg, 1.45 mmol) was added in four equal portions every 15 min at −78 °C. After warming to room temperature, the solvent was removed in vacuo and the residue was dissolved in ethyl acetate and washed with brine. The aqueous wash was extracted exhaustively with ethyl acetate. The combined organic washes were dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude diol **3** (301 mg) was chromatographed on 18 g of silica gel. Elution with ether–hexanes (3:1) gave 272 mg (94%) of pure diol **3** as an oil: IR (CCl_4) 3650, 3325 cm^{-1}; NMR (CCl_4) δ 0.77 (d, 3 H, J = 7 Hz), 0.95 (s, 3 H); high-resolution mass spectrum m/e 240.1722 (calcd for $C_{14}H_{26}O_4 - H_2O$, 240.1726). An analytical sample was prepared by distillation [150–155 °C (bath temperature) (0.5 mmHg)]. Upon standing at 0 °C overnight, diol **3** crystallized, mp 61–62 °C.

Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14. Found: C, 64.98; H, 10.16.

Bis Aryl Selenide Formation. A solution of 184 mg (0.713 mmol) of diol **3** and 388 mg (1.71 mmol) of *o*-nitrophenyl selenocyanate[13] in 6.0 mL of dry tetrahydrofuran under nitrogen was treated with tri-*n*-butylphosphine (379 mg, 1.71 mmol) at room temperature. After ca. 30 min the solvent was removed in vacuo and the residue (519 mg) was chromatographed on 30 g of silica gel. Elution with ether–hexanes (1:3) afforded 418 mg (94%) of crystalline bisselenide **8**: mp 54–56 °C; IR ($CHCl_3$) 1595, 1571, 1521, 1339, 1308 cm^{-1}; NMR (CCl_4) δ 2.81 (m, 4 H), 3.88 (bs, 4 H), 7.35 (m, 6 H), 8.18 (m, 2 H).

Anal. Calcd for $C_{26}H_{32}N_2O_6Se_2$: C, 49.85; H, 5.15; N, 4.47. Found: C, 50.03; H, 5.22; N, 4.44.

Preparation of *trans*-1,2-Divinylcyclohexane (9). A solution of 400 mg (0.64 mmol) of bisselenide **8** in 5.0 mL of tetrahydrofuran cooled to 0 °C was treated dropwise with 173 μL of 50% aqueous hydrogen peroxide (2.55 mmol). After addition was complete the reaction mixture was warmed to room temperature. After 3.5 h the solvent was removed under reduced pressure and the product was isolated by ether extraction.[17] The crude oil (271 mg) was chromatographed on 18 g of silica gel. Elution with ether–hexanes (1:3) provided 134 mg (95%) of pure **9** as an oil: IR ($CHCl_3$) 3090, 1640 cm^{-1}; NMR (CCl_4) δ 1.05 (s, 3 H), 1.69 (s, 3 H), 3.83 (m, 4 H), 4.55–5.08 (m, 4 H), 5.57–6.00 (q, 1 H); high-resolution mass spectrum m/e 222.1600 (calcd for $C_{14}H_{22}O_2$, 222.1618). An analytical sample was prepared by distillation [51–56 °C (bath temperature) (0.45 mmHg)].

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.51; H, 9.90.

***trans*-1,2-Divinylcyclohexanone (11).** A solution of 130 mg (5.85 mmol) of ketal **9** in 14.7 mL of tetrahydrofuran containing 0.30 mL of concentrated hydrochloric acid was stirred at room temperature for 8 h. The reaction was quenched by the addition of solid sodium bicarbonate and the solvent was removed under reduced pressure. Isolation of the product by ether extraction[17] gave 113 mg of crude ketone which was chromatographed on 8.0 g of silica gel. Elution with ether–hexanes (1:3) yielded 96 mg (92%) of pure ketone **11**: IR (CCl_4) 3090, 1720, 1641 cm^{-1}; NMR (CCl_4) δ 0.99 (s, 3 H), 1.78 (s, 3 H), 4.70–5.03 (m, 4 H), 5.62–6.10 (m, 1 H); high-resolution mass spectrum m/e 178.1360 (calcd for $C_{12}H_{18}O$, 178.1358).

β-Elemenone (2). To a solution of 253 mg (1.12 mmol) of 4-

methyl-2,6-di-*tert*-butylphenol in 3.0 mL of anhydrous ether (cooled to −10 °C) was added 560 μL of 2 M *n*-butyllithium in hexane. The observed precipitate dissolved upon warming to room temperature. To the homogeneous reaction mixture was added dropwise 95 mg (0.53 mmol) of ketone **11** in 1.0 mL of dry ether followed by addition of 214 mg (2.82 mmol) of carbon disulfide. After 14 h at room temperature, 196 mg (1.40 mmol) of methyl iodide was added and stirring was continued for an additional 5 h. The reaction mixture was quenched by the addition of brine and ether. The aqueous phase was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue (391 mg) was chromatographed on 30 g of silica gel. Elution with ether–hexanes (1:4) gave 45 mg (30%) of pure α-dithiomethylene derivative **12**: IR ($CHCl_3$) 3090, 1690, 1665, 1641 cm^{-1}; NMR δ (CCl_4) 1.04 (s, 3 H), 1.80 (s, 3 H), 2.30 (s, 3 H), 2.38 (s, 3 H). Continued elution gave 14 mg of pure α-dithiomethylene derivative **13**.

To a stirred suspension of copper iodide (29.6 mg, 0.16 mmol) in 1.0 mL of anhydrous ether at 0 °C was added 132 μL (0.31 mmol) of a 2.37 M solution of methyllithium in ether. After cooling to −78 °C, 22 mg (0.078 mmol) of compound **12** in 1.0 mL of dry ether was added dropwise. The reaction mixture was stirred for 20 min at −78 °C followed by quenching with methanol. Isolation of product by ether extraction[17] afforded 17 mg of crude β-elemenone which was chromatographed in 5.0 g of silica gel. Elution with ether–pentane (1:5) gave 15.4 mg (90%) of β-elemenone: IR (CCl_4) 3080, 2960, 2930, 2902, 2855, 1680, 1635, 1618, 1442, 1430, 1408, 1370, 1300, 1280, 1271, 1258, 1239, 1210, 1198, 1125, 1050, 1018, 998, 910, 891 cm^{-1}; NMR (CCl_4) δ 1.03 (s, 3 H), 1.80 (s, 6 H), 2.00 (s, 3 H), 2.22–2.71 (m, 5 H), 4.74–5.16 (m, 4 H, terminal vinyl), 5.61–6.07 (m, 1 H); high-resolution mass spectrum *m/e* 218.1667 (calcd for $C_{15}H_{22}O$, 218.1670).

Preparation of Seven-Membered Ring Ether 10. A solution of 15.0 mg (0.058 mmol) of diol **3** in 1.0 mL of tetrahydrofuran containing 13.2 mg (0.058 mmol) of *o*-nitrophenyl selenocyanate was treated with 11.7 mg (0.058 mmol) of tri-*n*-butylphosphine at room temperature. After 30 min the solvent was removed in vacuo and the residue was chromatographed on 5 g of silica gel. Elution with ether–hexane (1:2) afforded 12.1 mg (87%) of pure ether **10**: IR ($CHCl_3$) 2950, 2890, 1460, 1389, 1365, 1335, 1300, 1265, 1220, 1165, 1145, 1120, 1100, 1085, 1070, 1064, 1022, 1015, 995, 955, 900 cm^{-1}; NMR (CCl_4) δ 0.95 (d, 3 H, J = 7 Hz), 1.01 (s, 3 H), 1.1–2.3 (m, 10 H), 3.3–3.7 (m, 4 H), 3.83 (m, 4 H).

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Registry No.—**2**, 30824-86-3; **3**, 62183-43-1; **4**, 54316-77-7; **5**, 13944-80-4; **6**, 13944-79-1; **6** enol phosphate, 62183-44-2; **7**, 62183-45-3; **8**, 62183-46-4; **9**, 62183-47-5; **10**, 62183-48-6; **11**, 30824-87-4; **12**, 62183-49-7; 1-chloropentan-3-one, 32830-97-0; *o*-nitrophenyl selenocyanate, 51694-22-5; 4-methyl-2,6-di-*tert*-butylphenol, 128-37-0; carbon disulfide, 75-15-0; methyl iodide, 74-88-4; diethyl chlorophosphate, 814-49-3.

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(17) The products were isolated by extraction of the aqueous layer with several portions of the indicated solvent. The combined organic extracts were washed with water followed by saturated brine. The organic layer was usually dried with either anhydrous sodium sulfate or anhydrous magnesium sulfate. Filtration followed by removal of the solvent in vacuo (water aspirator) employing a rotary evaporator provided the products.

A General Method for the Preparation of α-Labeled Amino Acids[1]

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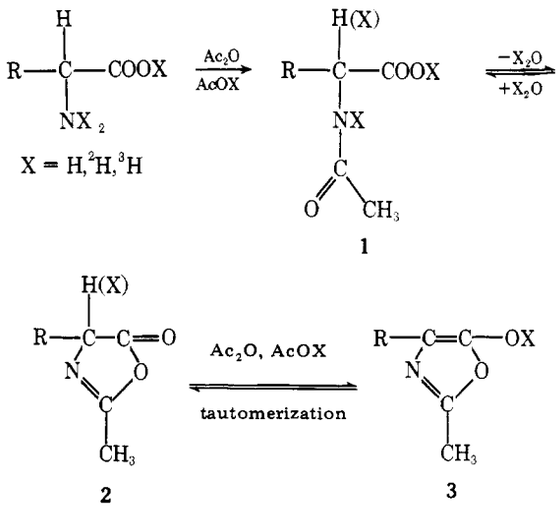
Received December 15, 1976

The usefulness of specifically deuterated amino acids for studying peptides and proteins is becoming more widely appreciated.[2-6] For example, with the deuterium labels providing unique nuclei for observation using modern biophysical techniques, information relevant to the conformation and dynamics of peptides and to the binding of peptide hormones to carrier proteins (or receptors) may be gathered.[7] One impediment for such studies has been the limited availability and/or high cost of specifically labeled amino acids.

Previous attempts to exchange the α proton of amino acids have met with limited success.[8-12] The most successful methods require high pressure and long reaction times,[13] or preparation, separation, and reduction of cobalt(III) complexes of amino acids.[14]

We report here a rapid, inexpensive, and generally applicable preparation of α amino acids starting from commercially available amino acids. The reaction is an adaptation of a method for racemization of amino acids which employs refluxing acetic acid and acetic anhydride to give racemic *N*-acetyl amino acids.[15] In our procedure, a mixture of excess acetic anhydride with D_2O is used to give a solution of Ac_2O in AcOD. Treatment of amino acids with this solution at reflux for a few minutes leads to acylation, racemization, *and* exchange at the α position. One possible mechanism for the reaction is given by the following equations [other mechanism(s) may also be used to account for the exchange].



From examination of the suggested mechanism, several points emerge. First, it is not necessary to use the more expensive stereopure L amino acids in this reaction since tautomerization proceeds through a planar intermediate. Second, this process is unlikely to affect the stereointegrity of asymmetric sites other than the α position thus simplifying the