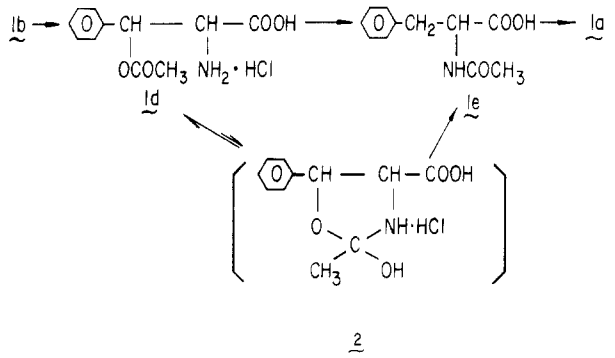
Scheme I



an *O*-acetyl derivative of β-phenylserine, was prepared in three steps according to the procedure described by Carrara.[6] The hydrogenolysis went smoothly in the presence of palladium catalyst to give *N*-acetylphenylalanine ethyl ester (**1g**) in 86% yield. The investigation was extended to *threo*-*O*-acetyl-β-phenylserine hydrochloride (**1d**), which was prepared directly from *threo*-β-phenylserine[7] in 96% yield. Hydrogenolysis of **1d** was carried out in acetic acid–water in the presence of $Pd/BaSO_4$. Surprisingly, this reaction gave mainly *N*-acetylphenylalanine (**1e**), an O → N acyl shift hydrogenolysis product, accompanied by a small amount (<10%) of phenylalanine and β-phenylserine. The major product **1e** was isolated by crystallization from water in about 82% yield.

As expected, when optically pure *threo*-*O*-acetyl-β-phenyl-L-serine hydrochloride (**1d**)[3b] was subjected to the above-mentioned hydrogenolysis condition, we obtained *N*-acetyl-L-phenylalanine (**1e**). Since the conversion of **1e** to **1a** by acidic hydrolysis is well-known, the hydrogenolysis route reported here completed a three-step sequence from *threo*-β-phenyl-L-serine to L-phenylalanine.

Mechanism

A probable mechanism for the unexpected formation of *N*-acetylphenylalanine in the hydrogenolysis reaction is shown in Scheme I. The key to this mechanism is the formation of the oxazolidine **2**—a generally accepted common intermediate for the O ⇄ N acyl migration in the acylated amino alcohol system.[8] The reduction of this cyclic intermediate **2** leads to the observed acyl shift hydrogenolysis product **1e**.[9] The two minor components, phenylalanine and β-phenylserine, found in this reaction are believed to be the hydrolysis products[10] of **1e** and **1d**, respectively.

We believe that the facile cleavage of the benzylic C–O bond of **2** drives the equilibrium from **1d** to **2** even in the acidic medium, which should favor **1d**. Furthermore, the fact that only a small amount of phenylalanine was detected indicates that direct acetoxy bond cleavage of **1d**, if it occurs at all, is much slower than the benzylic C–O bond cleavage of **2**, which gives the acyl shift product **1e**.

Experimental Section

^1H NMR spectra were taken on a Varian T-60 NMR spectrometer with Me_4Si as an internal standard. Hydrogenolysis reactions were performed in a 100-mL glass bottle on a Parr shaker apparatus. Optical rotations were recorded on a Perkin-Elmer Model 141 polarimeter, using a 10-cm microcell. Reaction progress was monitored with a liquid chromatograph (Waters Associates) equipped with a UV detector (210 nm). The column (C18) was eluted with 20% acetonitrile in 0.01 M phosphoric acid. Gas chromatographic data was obtained on a Varian 3700 instrument (FID, 3% OV-101 on Chromosorb). *threo*-β-Phenyl-DL-serine was purchased from Sigma Chemical Co., St. Louis, MO.

Hydrogenolysis Procedure. *N*-Acetyl-DL-phenylalanine Ethyl Ester (1g). Compound **1f** (0.8 g, 2.73 mM) in 10 mL of ethanol, 1 mL of triethylamine,[11] and 0.4 g of 5% $Pd/BaSO_4$ was hydrogenated at 50 psi for 6 h at 70 °C. Catalyst was removed by filtration. GC analysis indicated that the starting material **1f** was completely converted to **1g**. Solvent was removed in vacuo. The resulting solid was triturated with ether to give product **1g** (0.55 g, 86% yield): ^1H NMR ($CDCl_3$) δ 7.2 (s, 5 H), 6.6 (m, 1 H), 4.8 (q, 1 H), 4.2 (q, 2 H), 3.1 (d, 2 H), 2.0 (s, 3 H), 1.3 (t, 3 H). A similar result was obtained when this reaction was carried out with 5% $Pd/BaSO_4$ in acetic acid solution.

***N*-Acetyl-DL-phenylalanine (1e).** Compound **1d** (2 g, 7.7 mM) was dissolved in 22 mL of water–acetic acid (1:4 ratio) solution. Catalyst (98 mg of 5% $Pd/BaSO_4$) was added and then hydrogenated at 50 psi for 8 h at 60 °C. Catalyst was removed by filtration and the filtrate concentrated in vacuo. The resulting oily residue solidified on standing. *N*-Acetyl-DL-phenylalanine (**1e**) was isolated (1.3 g, 81.8% yield) after triturating the above crude solid with water. This material displayed the same physical and spectroscopic properties as an authentic sample: ^1H NMR (Me_2SO-d_6) δ 8.2 (d, 1 H), 7.3 (s, 5 H), 4.4 (m, 1 H), 3.1 (m, 2 H), 1.9 (s, 3 H).

The hydrogenolysis of optically pure **1d**, $[\alpha]^{20}_D$ −50.4° (*c* 0.4, 4:1 HOAc–H_2O), was conducted in the same manner. Solvent was removed to give a crude reaction residue whose rotation was $[\alpha]^{20}_D$ +48.5° (*c* 1.0, 4:1 HOAc–H_2O) after correction for the two minor side products (**1a** and **1b**). Pure authentic sample: $[\alpha]^{20}_D$ +52.1° (*c* 1.3, 4:1 HOAc–H_2O).

Registry No. DL-*threo*-**1d**, 88854-16-4; L-*threo*-**1d**, 88854-17-5; DL-**1e**, 2901-75-9; L-**1e**, 2018-61-3; DL-*threo*-**1f**, 88854-18-6; DL-**1g**, 4134-09-2; L-phenylalanine, 63-91-2.

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(10) When the stirring time was extended on completion of hydrogen uptake, the relative amount of phenylalanine was clearly increased while that of β-phenylserine was essentially unchanged as evidenced by HPLC analysis. The other possible path that would also account for the formation of phenylalanine is direct reduction of the starting material **1d**.
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Synthesis of 3-Methoxycycloheptatrienones

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Received August 30, 1983

Methods have been developed to convert cycloheptatrienone into hydroazulenes,[3a] (*E*)- or (*Z*)-cyclodecenes,[3b] and bicyclo[5.4.0]undecanes.[3c] Extension of these model studies to naturally occuring substances will require efficient preparations of substituted cyclo-

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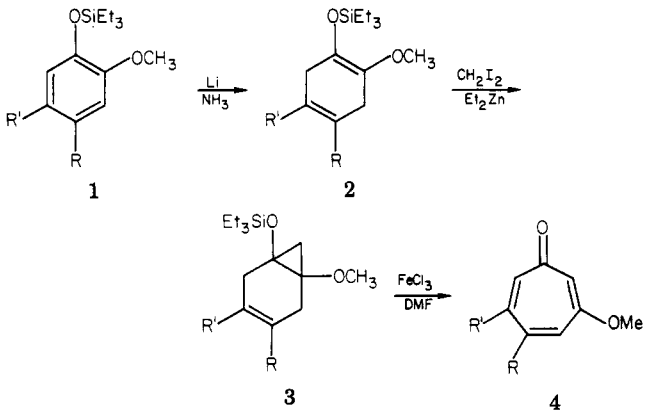
0022-3263/84/1949-1136$01.50/0

Scheme I[a]



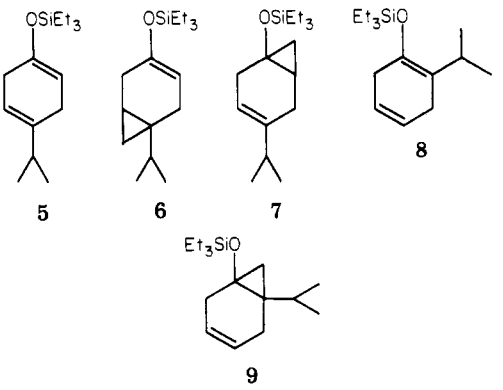
[a] a, R = R' = H; b, R = H, R' = CH_3; c, R = CH_3, R' = H.

heptatrienones. Previously, 3-methoxycycloheptatrienones have been prepared by a five-step sequence developed by Chapman and Fitton.[4] Difficulties in processing the required lithium-in-ammonia reduction[5] prompted us to develop this four-stage sequence for 3-methoxycycloheptatrienones.

An obvious route to 3-methoxycycloheptatrienones would be via a dialkoxynorcaradiene. Unfortunately, direct carbenoid ring expansion of catechol or resorcinol derivatives provides 2-hydroxycycloheptatrienones or complex mixtures.[7,8] Instead, using the strategy of other cycloheptatrienone syntheses,[6,9,10] we converted the aromatic substrate into the cycloheptatrienone by Birch reduction and cyclopropanation of this diene followed by oxidation to the cycloheptatrienone.

Guaiacol silyl ethers (**1**) were reduced to cyclohexadienes **2** by using standard conditions in 60–86%. These enol ethers **2** were regioselectively cyclopropanated with diiodomethane and diethyl zinc.[11] Treatment of the cyclopropanes with ferric chloride–dimethylformamide (DMF) complex[12] in DMF solvent (Scheme I) provided the 3-methoxycycloheptatrienones **4** in about 50% yield after chromatography.[13] Other oxidants or processing procedures failed to increase the yield of **4**.

To illustrate the selectivity of this sequence 6-methyl-3-methoxycycloheptatrienone (**4b**) and 5-methyl-3-methoxycycloheptatrienone (**4c**) have been prepared from the silyl ether of 2-methoxy-5-methylphenol (**1b**) and 2-methoxy-4-methylphenol (**1c**), respectively.[14] We briefly examined this sequence with enol ethers **5** and **8**. Surprisingly, diene **5** gave a mixture of carbene adducts **6** and **7**. Diene **8** cleanly yielded **9**, but oxidation of **9** failed to provide any 3-isopropylcycloheptatrienone. This diethylzinc mediated cyclopropanation exhibits regioselectivity with electron-rich olefins which is different than that of dichlorocarbene.[10] This short sequence should find application for the synthesis of cycloheptatrienones.



Experimental Section

General Methods. Infrared spectra were recorded on a Beckman IR 18 AX spectrophotometer; bands yielding structural information are reported in reciprocal centimeters (cm^{-1}) with polystyrene calibration. UV spectra were recorded on a Uvikon 810 spectrometer. NMR spectra were recorded on a Varian EM 390 at 35 °C in $CDCl_3$ and peak positions are reported in parts per million from Me_4Si internal standard, with multiplet (m), quartet (q), triplet (t), doublet (d), or singlet (s).

Tetrahydrofuran (THF) was distilled from sodium benzophenone immediately prior to use. DMF was distilled from calcium hydride at reduced pressure.

Silyl Ethers 2. Silylation of the phenols was completed by standard conditions,[10] and the aromatic was reduced by the procedures of Macdonald[10] and of Fuchs.[15]

2a: 70% yield; NMR 0.35–1.15 (m, 15 H), 2.80 (br, s, 4 H), 3.54 (s, 3 H), 5.55 ppm (br, s, 2 H).

2b: 85% yield; NMR 0.35–1.15 (m, 15 H), 1.70 (br, s, 3 H), 2.80 (br, s, 4 H), 3.50 (s, 3 H), 5.20 ppm (br, s, 1 H).

2c: 68% yield; NMR 0.35–1.15 (m, 15 H), 1.65 (br, s, 3 H), 2.60 (br, s, 4 H), 3.50 (s, 3 H), 5.25 ppm (br, s, 1 H).

Bicyclo[4.1.0]heptene (3). The procedure of Ito et al.[11] was used. The use of diethyl zinc as either a 25% solution in hexanes or as a neat liquid gave similar results.

3a: 86% yield; IR 3040, 2960, 2880, 2840, 1660 (w), 1460, 1240, 1140, 1020, 735 cm^{-1}; NMR 0.30–1.00 (m, 17 H), 2.55 (br, s, 4 H), 3.36 (s, 3 H), 5.37 ppm (br, s, 2 H).

3b: 90% yield; IR 1460, 1240, 1120, 1080, 1010, 740 cm^{-1}; NMR 0.30–1.10 (m, 17 H), 1.60 (br, s, 3 H), 2.50 (br, s, 4 H), 3.35 (s, 3 H), 5.15 ppm (br, s, 1 H).

3c: 65% yield; IR 1460, 1240, 1120, 1075, 1010, 740 cm^{-1}; NMR 0.30–1.00 (m, 17 H), 1.65 (br, s, 3 H), 2.60 (br, s, 4 H), 3.33 (s, 3 H), 5.15 ppm (br, s, 1 H).

3-Methoxy-2,4,6-cycloheptatrien-1-one (4). The yellow-green ferric chloride-DMF complex was prepared by the method of Tobinaga and Kotani.[12] This complex (16.2 g, 0.030 mol) was placed in a 100-mL flask under nitrogen and cooled to 0 °C. Anhydrous DMF (10 mL) was added slowly by syringe while the mixture was being stirred vigorously. The resulting solution was stirred for 0.5 h at 0 °C until the complex had dissolved. A solution of **3a** (1.70 g, 0.006 mol) in 10 mL of anhydrous DMF was added to the cooled mixture of the complex over a period of 3 h. The resulting solution was stirred at room temperature for 24 h. The solution was again cooled to 0 °C, and 30 mL of ice-cold 10% HCl was cautiously added. The mixture was extracted with 5 × 40 mL of chloroform, and the combined chloroform layers were washed with 10-mL portions of ice-cold saturated EDTA aqueous solution until the aqueous layer was no longer colored. After being dried over magnesium sulfate, the solvent was removed at reduced pressure at a temperature no greater than 30 °C. Chromatography on silica gel (ethyl acetate) yielded 0.32 g (48%) of 3-methoxy-2,4,6-cycloheptatrien-1-one (**4a**):[4] IR 3450, 1642, 1590, 1552 (br),

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1460, 1253, 1205, 1167, 1015, 782 cm^{-1}; NMR 3.73 (s, 3 H), 6.43 (br, s, 1 H), 6.75 (m, 2 H), 6.90 (m, 2 H); ^{13}C NMR 185.7 (s), 165.5 (s), 141.8 (d), 133.5 (d), 133.1 (d), 131.9 (d), 116.9 (d), 55.5 (q). This workup was necessary to remove the iron.

4b: 45% yield; UV (MeOH) 245, 253, 290, 307 nm (sh); IR 3400, 2900, 1680 (w), 1630, 1540 (br), 1200, 1160 cm^{-1}; NMR 2.15 (s, 3 H), 3.70 (s, 3 H), 6.35 (m, 1 H), 6.65 (m, 2 H), 6.80 (m, 1 H); MS, m/z 150 (M^+), 122, 121.

4c:[4] 48% yield; UV (MeOH) 238 (br), 281, 288, 305 (sh) nm; IR 3450, 2950, 1700 (w), 1660, 1590, 1540, 1210 cm^{-1}; NMR 2.25 (s, 3 H), 3.75 (s, 3 H), 6.30–7.00 (m, 4 H); MS, m/z 150 (M^+), 122, 121.

Registry No. **1a**, 18406-12-7; **1b**, 88841-50-3; **1c**, 88841-49-0; **2a**, 88780-25-0; **2b**, 88780-26-1; **2c**, 88780-27-2; **3a**, 88780-28-3; **3b**, 88780-29-4; **3c**, 88780-30-7; **4a**, 54445-60-2; **4b**, 88780-31-8; **4c**, 88780-32-9; **5**, 66967-07-5; **6**, 88780-33-0; **7**, 88780-34-1; **8**, 88780-35-2; **9**, 88780-36-3.

Solid–Liquid Phase-Transfer Catalysis Reactions without Solvent; Very Mild Conditions for β-Eliminations

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Received July 11, 1983

We have recently shown that alkylations of acetate[1,2a] and indole anions[1,2b] can be run without solvent in the presence of catalytic amounts of quaternary tetraalkylammonium salts (solid–liquid PTC conditions). These reaction conditions present many advantages: no need for organic solvent, low temperatures, and short reaction times as well as very easy workup.

We describe here the extension of this method to base-induced β-eliminations. Secondary halide dehydrohalogenations are well-known either in solution[3] or under classical PTC conditions.[4] 2-Bromooctane behavior was studied as a typical weak halide which exhibits the possibility of competitive Saytzeff vs. Hofmann orientations.

Experimental Section

All reagents were purchased and used without further purification. 2-Bromooctane (1.93 g, 10 mmol) is added to 25 mmol of base finely ground in a blender and 2 % mol (relative to the base) of tetraalkylammonium salt. After being vigorously stirred for 10 min with a mechanical stirrer, the mixtures are allowed to sit for the indicated periods at the appropriate temperature (see tables). Organic products were removed by a simple filtration on Florisil (on which ammonium salts remain adsorbed) after addition of 50 mL of diethyl ether. They were identified by comparison with authentic samples and analyzed by GPC (internal standard): (OV 1 column) 25 m, 0.1–0.15 μm, carrier N_2, p = 0.5 kg, 40 °C, t_R 1-octene 4.2 min, t_R *trans*-2-octene 4.6 min, *cis*-2-octene 4.8 min, t_R nonane (standard) 8.6 min; (SE 30 column) 1 m, 15% Chromosorb WAW 020–025, carrier N_2, p = 1.2 kg, 80 °C, t_R nonane (standard) 1.1 min, t_R 2-bromooctane 3.7 min.

Table I. Influence of the Type of Ammonium Salt in the Reaction of 2-Bromooctane and *t*-BuOK under PTC Conditions[a]

	starting material, %	octenes, %
	68	25
NBu_4I	69	31
NBu_4Br	53	40
NBu_4Cl	66	28
NBu_4HSO_4	80	17
$C_6H_5CH_2NEt_3Br$	87	13
$C_{16}H_{33}NMe_3Br$	54	40
Aliquat 336	4	92

[a] Reaction conditions: 2% ammonium salt, 2.5 equiv/mol of *t*-BuOK for 2 h at room temperature.

Results

The influence of the nature of the tetraalkylammonium salts is examined for the 2-bromooctane reaction with *t*-BuOK (2 h at room temperature) (Table I). Aliquat 336 (essentially $Oct_3MeN^+Cl^-$)[5] appears to be the most efficient reagent: quasi-quantitative β-elimination is observed.

The orientation of the reaction (Table II) is only slightly affected by the nature of ammonium salts (1-octene/2-octenes > 80:20), whereas Aliquat 336 is 66:34.

On the other hand, the orientation is strongly dependent on the nature of the base: the 1-octene/2-octenes ratios increase according to $tBuO^- > HO^- > EtO^- \gtrsim MeO^-$ (Table III).

Discussion

t-BuOK-induced reactions are quantitative in 20 h at room temperature in the absence of any tetraalkylammonium salts. They can be catalyzed by 2% Aliquat (reaction completion within 2 h). The 1-octene/2-octene ratios remain constant independent of reaction times and temperatures, implying that there is no further olefin equilibration under these conditions.

With the other bases, no reaction takes place for 20 h at room temperature unless Aliquat 336 is added; yields are thus >92%. As previously proposed for acetate alkylation,[1,2a] we are certainly dealing with solid–liquid PTC reactions without solvent: the reactive basic species are the loose $RO^-//N^+R_4$ ion pairs, the organic phase being constituted by 2-bromooctane and octenes. The cation

$$RO^-, M^+ + R_4N^+, X^- \rightleftarrows RO^-//^+NR_4 \text{ (soluble in 2-bromooctane or 1-octene + 2-octenes)}$$

effect (MeOK more efficient than MeONa) is consistent with such an explanation: in connection with a lower lattice energy in the K salt,[6] the equilibrium must be more shifted to the ammonium pairs.

Hofmann vs. Saytzeff Orientation. The 1-octene/2-octene ratios are markedly dependent on the nature of the base. These results are compared (Table IV) to the results obtained in solvents with 2-bromohexane.

Regioselectivites of elimination at room temperature in our conditions (no added solvent) are very close to those obtained when the reactions are performed at reflux in

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