flask immersed in cold (10 °C) water, and Dowex 50 resin, H+ form (4 g or, for aspartic acid, 6 g), added. After the mixture was stirred for 10 min, it was filtered, the filtrate was evaporated in vacuo, and the crude derivative was recrystallized from the appropriate solvent (see Table I). In some cases, examination of the crude trifluoroacetyl derivative by NMR spectroscopy showed the presence of methyl ester, undoubtedly formed during treatment with the ion exchange resin. Ester formation can be minimized, as described, by keeping the reaction mixture cold and by using a short reaction time. Alternately, after removal of methanol in vacuo, the reaction with resin may be carried out in water (40 mL) or in 50% aqueous THF (20 mL). In one run with serine as the amino acid, evaporation of methanol gave a crystalline triethylammonium salt, which was treated with an excess of dilute hydrochloric acid and extracted with ethyl acetate to recover the free trifluoroacetyl derivative as an oil.

With tyrosine, TMG (1.25 mL, 10 mmol) was substituted for triethylamine, and the reaction mixture was filtered prior to resin treatment to remove a small amount of unreacted amino acid. With cystine, sodium methoxide in methanol (2.77 mL of 3.6 M, 10 mmol) was used as base, and the reaction mixture was again filtered prior to resin treatment to remove a trace of unreacted amino acid.

When DCHA (2.0 mL, 10 mmol) was used as a base, the reaction mixture was either evaporated in vacuo and the residue recrystallized (DL-alanine) or else the DCHA salt was recrystallized directly from the reaction mixture (serine and glycylglycine). For the latter two compounds, additional methanol (30 mL) had to be added during the reaction with ethyl trifluoroacetate in order to obtain a stirrable slurry.

***N*-(Trifluoroacetyl)-L-serine Benzyl Ester.** L-Serine (1.5 g, 10 mmol) suspended in dry DMF (5 mL) was treated with ethyl trifluoroacetate and ethyldiisopropylamine (1.71 mL, 10 mmol) as described above. After 24 h, most of the amino acid had dissolved. After 34 h, the reaction mixture, which still contained a small amount of undissolved amino acid, was immersed in cold water, and benzyl bromide (1.2 mL, 10 mmol) was added. Further stirring for 17 h at room temperature, followed by workup and purification as previously described,[1] gave 2.20 g (76%) of *N*-(trifluoroacetyl)-L-serine benzyl ester, mp 73–74 °C (lit.[1] mp 74–75 °C).

Acknowledgments. We wish to thank the National Cancer Institute for partial support of this work through contract N01 CP55708.

Registry No. Ethyl trifluoroacetate, 383-63-1; DL-alanine, 302-72-7; L-alanine, 56-41-7; L-asparagine, 70-47-3; L-aspartic acid, 56-84-8; L-cystine, 56-89-3; glycylglycine, 556-50-3; L-phenylalanine, 63-91-2; L-serine, 56-45-1; L-tryptophan, 73-22-3; L-tryosine, 60-18-4; L-valine, 72-18-4; *N*-(trifluoroacetyl)-DL-alanine, 1597-49-5; *N*-(trifluoroacetyl)-DL-alanine DCHA salt, 7609-58-7; *N*-(trifluoroacetyl)-L-alanine, 407-23-8; *N*-(trifluoroacetyl)-L-asparagine, 35146-48-6; *N*-(trifluoroacetyl)-L-aspartic acid, 369-08-4; *N,N'*-bis(trifluoroacetyl)-L-cystine, 402-91-5; *N*-(trifluoroacetyl)glycylglycine, 400-58-8; *N*-(trifluoroacetyl)-L-phenylalanine, 350-09-4; *N*-(trifluoroacetyl)-L-serine DCHA salt, 70333-05-0; *N*-(trifluoroacetyl)-L-serine benzyl ester, 67815-09-2; *N*-(trifluoroacetyl)-L-tryptophan, 363-39-3; *N*-(trifluoroacetyl)-L-tryosine, 350-10-7; *N*-(trifluoroacetyl)-L-valine, 349-00-8.

Application of Dithioester Reactions with Grignard Reagents to Carbon–Carbon Bond Formation: Synthesis of Egomaketone and *ar*-Turmerone

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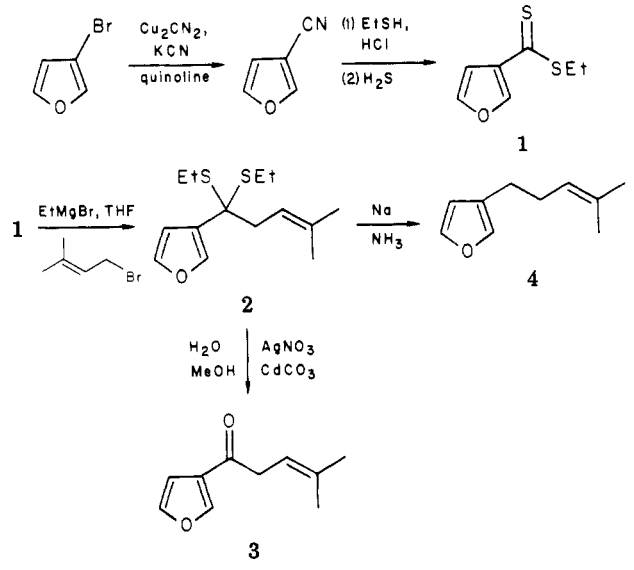
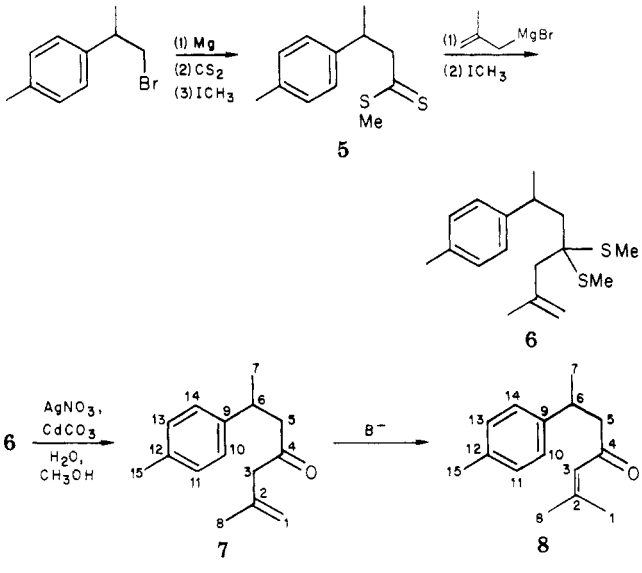
The addition of alkyl- and allylmagnesium halides to dithioesters can occur respectively in a thiophilic and carbophilic manner.[1,2] We have shown previously that these two regioselective reactions occur, under appropriate experimental conditions, in nearly quantitative yields and can be usefully applied in organic synthesis. In particular, we developed various paths for the preparation of β-unsaturated ketones[2] and achieved a convenient synthesis of isoartemisia and artemisia ketones from a β-unsaturated dithioester.[3] Herein we describe a convenient synthesis of egomaketone (**3**),[4] perillene (**4**),[6] iso-*ar*-turmerone (**7**), and *ar*-turmerone (**8**).[7,8]

Egomaketone (**3**) and perillene (**4**) were synthesized by utilizing a thiophilic addition reaction as depicted in Scheme I. Ethyl 3-furandithiocarboxylate (**1**) was pre-

Scheme I



Scheme II



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(9) The reaction of carbon disulfide with 3-furylmagnesium bromide was also investigated as a route to this dithioester, but attempted synthesis of the Grignard reagent failed.

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pared in 67% overall yield from 3-bromofuran.[11] Reaction of 1 and ethylmagnesium bromide, in the presence of prenyl bromide,[10] occurred in a thiophilic manner to afford a quantitative amount of the dithioketal **2**. Subsequent hydrolysis of the thioketal moiety gave egomaketone (**3**) in 68% yield. Perillene (**4**) was obtained in 73% yield by reductive cleavage of the dithioketal **2** with sodium in liquid ammonia.

Carbophilic addition of β-methallylmagnesium chloride (Scheme II) to methyl 3-(4-methylphenyl)butanedithioate **5** followed by in situ methylation afforded the dithioketal **6**. Hydrolysis of **6** gave iso-*ar*-turmerone (**7**) which was converted to *ar*-turmerone (**8**) by base-catalyzed isomerization. Ketone **8** was obtained in 42% overall yield from 2-(4-methylphenyl)-1-bromopropane.

Experimental Section

^1H NMR spectra and ^{13}C NMR spectra were respectively recorded on Varian EM 360 and Brucker WP 60 spectrometers with tetramethylsilane as internal standard. IR spectra were obtained with a Perkin-Elmer 225 spectrometer, and UV spectra were obtained with a Beckman Acta VI spectrometer. GLC were performed on a Girdel 300 chromatograph equipped with a 0.25 in. × 12 ft, 5% DC 550, Chromosorb GAW column.

3-Bromofuran (41% yield from furan) and 3-cyanofuran (78% yield) were prepared according to Stibor et al.[11] 2-(4-Methylphenyl)-1-bromopropane was obtained from commercially available *p*-methylacetophenone as described in the literature.[18,19]

Ethyl 3-Furandithiocarboxylate (1). The dithioester was prepared according to the known procedures.[12,13] Reaction of 3-cyanofuran (43.4 g, 0.46 mol) and ethanethiol (1.2 equiv) in a saturated HCl–$PhCH_3$ solution at 0 °C afforded 84 g of crude ethyl 3-furanthiocarboximidate hydrochloride, and subsequent reaction with H_2S (excess) in pyridine gave 68.7 g (87%) of **1** as a red liquid: bp 73 °C (0.4 mm); ^1H NMR (CCl_4) δ 1.31 (t, J = 7.1 Hz, 3 H), 3.25 (q, J = 7.1, 2 H), 6.80 (m, 1 H on C^4), 7.27 (m, 1 H on C^5), 8.01 (m, 1 H on C^2); IR (film) 3120, 1541, 1497, 1151, 866, 730 cm^{-1} (furan ring); UV (EtOH) λ_{max} 311 nm (ε 12600, π → π*), 491 nm (ε 53, n → π*); ^{13}C NMR ($CDCl_3$) δ 12.63 (CH_3 of Et), 29.63 (CH_2 of Et), 109.28 (C^4), 134.9 (C^3), 142.43 (C^5), 144.01 (C^2), 216.01 (C=S).[14]

Egomaketone Dithioketal (2). Prenyl bromide (36.9 g, 0.25 mol) in 40 mL of THF and the dithioester **1** (17.2 g, 0.1 mol) in 50 mL of THF were added successively to ethylmagnesium bromide (0.3 mol) in 500 mL of THF at −78 °C under N_2 over a 2.5-h period. The reaction mixture was stirred for an additional 1.5 h and then carefully hydrolyzed with 20 mL of a 50% water–THF solution. The reaction mixture was allowed to come to room temperature, and a saturated solution of ammonium chloride was added to dissolve the magnesium salts. The mixture was extracted with pentane, and the organic layer was dried over Na_2SO_4. Evaporation of the solvent and excess prenyl bromide in vacuo gave 27.0 g (100%) of **2**: NMR (CCl_4) δ 1.15 (t, J = 7.25 Hz, 6 H), 1.49 (s, br, 3 H), 1.64 (s, br, 3 H), 2.46 (q, J = 7.25 Hz, 4 H), 2.58 (d, br, J = 7 Hz, 2 H), 5.08 (t, br, J = 7 Hz, 1 H), 6.34 (m, 1 H on C^4 furan), 7.34 (m, 2 H on C^2 and C^5).

Egomaketone (3). To dithioketal **2** (20.2 g, 0.075 mol) in 750 mL of methanol were added cadmium carbonate (63.6 g) and silver nitrate (27.6 g, 0.16 mol) in 55 mL of water, and the reaction mixture was heated for 15 h at 40 °C.[23] Usual workup afforded 11.2 g of crude ketone. Distillation through a Vigreux column afforded 8.2 g (68%) of pure **3**: mp 17 °C; bp 116–117 °C (13 mm); ^1H and ^{13}C NMR, IR, and mass spectra were in complete agreement with those reported previously.[5,16]

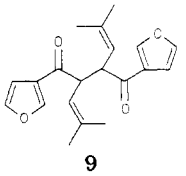
Perillene (4). The Na/NH_3 reduction procedure was used.[17] To the dithioketal **2** (9 g, 0.033 mol) in 200 mL of ether was added liquid NH_3 (1000 mL). Sodium (10 g) was then added over a 5-min period, and the reaction mixture was stirred for 15 mn. Ethanol was then added dropwise until the blue color disappeared and the ammonia was allowed to evaporate. Workup left 6.43 g of crude product which was chromatographed on silica gel. Elution with pentane followed by distillation gave 3.64 g (73%) of pure perillene **4**: bp 53 °C (13 mm); ^1H NMR of **4** was identical with the reported spectrum;[5] IR (film) 3126, 1555, 1496, 1159, 869, 720 (furan ring), 1668, 821 (C=C) cm^{-1}.

Methyl 3-(4-Methylphenyl)butanedithioate (5). Carbon disulfide (2.8 g, 32 mmol) in 10 mL of THF was added over a 10-min period to 2-(4-methylphenyl)propylmagnesium bromide (32 mmol) in 33 mL of THF at 0 °C under N_2. The reaction mixture was stirred for an additional hour at 0 °C and then allowed to warm to 22 °C over a 1-h period. Methyl iodide (5.26 g, 37 mmol) was added at 15 °C within 5 min, and the reaction mixture was stirred for 1.5 h at room temperature and 0.5 h at 45 °C. Usual workup afforded 6.8 g of crude material which was used without purification since its impurities[22] did not interfere with the following reaction.

From NMR studies, the crude product contained about 5.7 g of pure **5**, 79%: NMR (CCl_4) δ 1.22 (d, J = 7 Hz, 3 H), 2.22 (s, 3 H), 2.44 (s, 3 H), 3.00–3.68 (m, 3 H), 6.95 (m, 4 H).

Iso-*ar*-turmerone (7). A mixture of crude **5** (5.7 g, 0.025 mol) and methyl iodide (11.2 g, 0.079 mol) in 25 mL of THF was added slowly (1 h) to β-methallylmagnesium chloride[24] (0.106 mol) in 100 mL of THF at −78 °C. Stirring was continued for 1.5 h at −78 °C, and the temperature was allowed to rise to −20 °C in order to achieve methylation. Careful hydrolysis of excess Grignard reagent and usual workup gave 8.3 g of crude **6** (7.49 g of **6**, 97% from NMR): NMR (CCl_4) δ 1.23 (d, J = 7 Hz, 3 H), 1.74 (s, 6 H), 1.93 (s, 3 H), ~2.0 (d partially masked, 2 H), 2.25 (s, 3 H), 2.32 (s, br, 2 H), 2.83–3.28 (m, 1 H), 4.78 (s, br, 2 H), 6.97 (m, 4 H).

Crude dithioketal **6** (2.2 g) was hydrolyzed by the same procedure used for **2** to afford 1.6 g of crude **7**. Chromatography on silica gel and elution with pentane gave 0.96 g (58%) of pure iso-*ar*-turmerone (**7**): IR (film) 1708 (C=O), 1645, 890 (C=C), 1509, and 814 cm^{-1}; ^1H NMR (CCl_4) δ 1.18 (d, J = 7 Hz, 3 H), 1.60 (d, J = 1 Hz, 3 H), 2.25 (s, 3 H), 2.55 (m, 2 H), 2.85 (s, 2 H), 2.80–3.37 (m, 1 H), 4.67 (m, 1 H), 4.78 (m, 1 H), 6.95 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ (C numbering of formula **7**, Scheme II) 20.95 (15), 21.98 (7), 22.46 (8), 35.09 (6), 50.27 and 52.88 (3 or 5), 114.99 (1),



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9 [mp 139 °C; ^1H NMR (CCl_4) δ 1.69 (s, 6 H), 1.73 (d, J ~ 1 Hz, 6 H), 4.22 (m, 2 H), 4.89 (m, 2 H), 6.63 (m, 2 H on C^4 furan), 7.32 (m, 2 H on C^5), 7.94 (m, 2 H on C^2); IR (KBr) 3122, 1556, 1506, 1150, 858, 746 (furan ring), 1649 (C=O), 1616 and 837 (C=C) cm^{-1}; *m/e* 326 (M^+, 9), 164 (34), 135 (20), 95 (100), 28 (34)] was isolated with **3**.

(10) Addition of the alkylating reagent before starting the thiophilic addition is essential in order to trap the unstable sulfur carbanion as soon as it is formed.

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(22) 2-(4-Methylphenyl)propene and 2-(4-methylphenyl)propane (~10% each) were formed in the reaction and were only eliminated at the time of the purification of iso-*ar*-turmerone.

(23) When the hydrolysis of **2** was run at higher temperature or for a longer reaction time, an oxidative coupling was observed, and the bis adduct

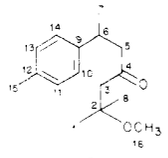
(24) Free of excess magnesium. Removed by filtration.

126.83 (10 + 14), 129.32 (11 + 13), 135.69 (12), 139.27 (2), 143.40 (9), 207.15 (4); *m/e* 216 (M^+, 47), 119 (93), 83 (100), 55 (20).

***ar*-Turmerone (8).** Iso-*ar*-turmerone (7) (0.96 g, 4.4 mmol) and a catalytic amount of piperidine[25] (130 μL) in 10 mL of Et_2O were stirred for 64 h at room temperature. Workup afforded 0.92 g (95%) of *ar*-turmerone (8). The infrared and ^1H NMR spectra were identical with those reported in the literature.[7,8] The mass spectrum was essentially the same as that for iso-*ar*-turmerone: ^{13}C NMR ($CDCl_3$) δ (C numbering of formula 8, Scheme II) 20.64 (8), 20.95 (15), 22.04 (7), 27.50 (1), 35.39 (6), 52.76 (5), 124.28 (3), 126.83 (10 + 14), 129.19 (11 + 13), 135.45 (12), 143.83 (9), 154.63 (2), 199.50 (4).

Registry No. 1, 70369-23-2; 2, 70369-24-3; 3, 59204-74-9; 4, 539-52-6; 5, 70369-25-4; 6, 70369-26-5; 7, 70369-27-6; 8, 532-65-0; 9, 70369-28-7; 10, 70369-29-8; 3-cyanofuran, 30078-65-0; ethyl 3-furanthiocarboximidate hydrochloride, 70369-30-1; prenyl bromide, 870-63-3; ethyl bromide, 74-96-4; 2-(4-methylphenyl)propyl bromide, 23430-51-5; β-methallyl chloride, 1458-98-6.

(25) Isomerization of the double bond with sodium hydroxide in methanol afforded 8 and a 1,4 addition product 10: IR (film) 1702 (C=O),



10

1510, 811 (aromatic), 2822 and 1072 (OCH_3) cm^{-1}; ^1H NMR (CCl_4) δ 1.11 (m, 9 H), 2.22 (s, 3 H), 2.31 (s, 2 H), 2.59 (m, 2 H), 2.87–3.58 (m, 1 H), 3.05 (s, 3 H), 6.93 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ (multiplicity determined by an off-resonance study) 20.95 (q, 15), 22.10 (q, 7), 24.83 (q, 1 + 8), 34.91 (d, 6), 49.12 (q, 16), 53.37 (t, 3 + 5), 74.31 (s, 2), 126.89 (10 + 14), 129.25 (11 + 13), 135.57 (12), 143.64 (9), 208.36 (4); *m/e* 216 (45), 119 (86), 83 (100), 32 (15), 31 (19).

Stoichiometry of the Oxidation of Primary Alcohols with Pyridinium Chlorochromate. Evidence for a Two-Electron Change

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Received March 12, 1979

The oxidation of secondary alcohols to ketones with aqueous chromic acid has long been a standard synthetic procedure.[2,3] Primary alcohols, under similar conditions, produce esters.[4] The oxidation of primary alcohols with Collins' reagent, however, affords the desired aldehydes in moderate yields.[5] Pyridinium chlorochromate (PCC) oxidizes a wide variety of alcohols to carbonyl compounds with high efficiency.[6] The reaction involves simply the addition of alcohols to a well-stirred suspension of PCC in methylene chloride.

Extensive kinetic and mechanistic studies on the oxidation of alcohols with chromic acid have revealed that such reactions ordinarily involve a three-electron change, whereby the oxidant, Cr(VI) species, is reduced to Cr(III).[2,7,8] Although PCC has been widely used since its discovery, no systematic study of the stoichiometry of PCC oxidation is reported in the literature.[9,10] Therefore, in connection with our studies on the oxidation of organoboranes with this reagent,[11] we undertook to examine the stoichiometry in the oxidation of a representative alcohol.

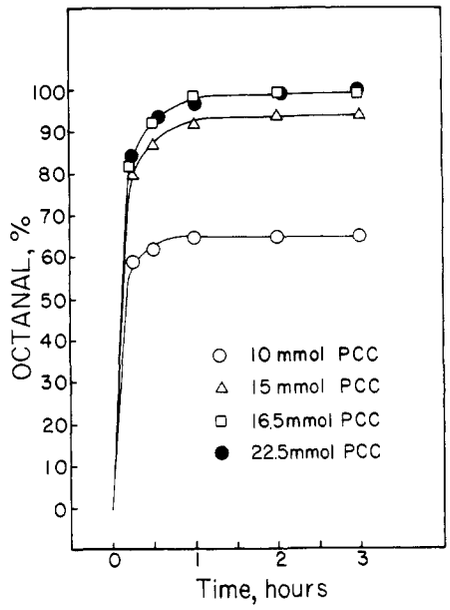

Figure 1. Oxidation of 15.0 mmol of 1-octanol with different quantities of PCC in 15 mL of refluxing methylene chloride.

In a typical experiment, 15 mmol of 1-octanol was added to a well-stirred suspension of varying amounts (10, 15, 16.5, and 22.5 mmol) of PCC in 15 mL of methylene chloride, and the mixture was heated under reflux. The progress of the reaction was followed by analyzing the reaction mixture for octanal by GC (Figure 1).

It is evident from Figure 1 that when 10 mmol of PCC is used, the stoichiometric amount of reagent assuming a three-electron change, 9.4 mmol of the aldehyde (64%) is produced. On the other hand, use of 15 mmol of PCC, the stoichiometric amount of reagent assuming a two-electron change, forms 14.1 mmol of aldehyde, a yield of 94%. Both 16.5 and 22.5 mmol of PCC afford a quantitative yield (by GC) of octanal. Considering the purity of commercial PCC (Aldrich, 98% specified), it appears that 15 mmol is the theoretical amount required to oxidize 15 mmol of 1-octanol to octanal. Use of 22.5 mmol, the amount used by the original authors,[6] appears to be unnecessary. Therefore, we conclude that the oxidation of primary alcohols to aldehydes by PCC under the conditions employed involves the transfer of only two electrons, contrary to the three-electron transfers observed in aqueous chromic acid oxidations

(1) (a) Postdoctoral research associate on a grant from Exxon Research and Engineering Co.; (b) postdoctoral research associate on Grant No. GM 10937-16 from the National Institutes of Health.

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(9) The original workers[6] employed 1.5 molar equiv of PCC. Others have followed this procedure. There is one report on the kinetic studies of PCC oxidation in a nitrobenzene–methylene chloride mixture where the three-electron transfer has been proposed.[10] But those conditions are different from usual experimental conditions employed in the oxidation of alcohols.

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