evaporation to dryness resulted in a yellow solid which on sublimation at 70 °C (10^{-3} mm) gave white crystals of **7** (21.3 g, 95%): mp 59.5–60 °C; R_f (silica) (5% CH_3OH in $CHCl_3$) 0.56, (ether) 0.26; IR ν_{max} 1690 (w, C=O), 1630 (s, C=C—OCH_3) cm^{-1}; NMR δ 1.6 (s, 3 H), 2.2 (m, 2 H), 2.65 (m, 2 H), 4.00 (s, 3 H); MS *m/e* 126 (100), 111 (25), 96 (62), 95 (32), 83 (45).

Preparation of the Acid 11. To a 1 M THF solution of lithium diisopropylamide [84.5 mmol; prepared from 11.83 mL of diisopropylamine and 34.9 mL of *n*-butyllithium (2.42 M)] was added **7** (10.642 g, 84.5 mmol, 1 M in THF) at such a rate as to keep the internal temperature of the reaction below −67 °C. After addition was complete, the mixture was stirred for 20 min, whereupon methyl acrylate (84.5 mmol, neat) was added sufficiently slowly to keep the internal temperature of the reaction below −65 °C. The resulting mixture was stirred for 2 h at −78 °C and then quenched at −78 °C with 18 mL of 6 N HCl followed by 10 mL of water. Extraction with ether (3 × 100 mL) and drying the combined extracts first over $NaSO_4$ and then by filtration through $MgSO_4$ followed by evaporation gave 16.85 g of an oil (94% crude yield) consisting of a 82:18 mixture (NMR analysis) of the esters **9** and **10**, respectively.

A portion of this mixture (7.626 g, 36 mmol) dissolved in methanol (36 mL) was treated with 2.37 g of 85% KOH in water (36 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 30 min and then at room temperature for 2 h, followed by extraction with ether (100 mL). Acidification of the aqueous phase to pH 3 with 6 N HCl, extraction with CH_2Cl_2, and drying first over Na_2SO_4 and then by filtration through $MgSO_4$ followed by evaporation of the solvent gave 6.6 g of **11** (mp 105–110 °C; 92.5% yield). Two recrystallizations from ether/$CHCl_3$ gave **11**: mp 119–120 °C; IR ν_{max} 1735–1690 (broad, CO_2H and C=O), 1630 (s, C=C—OCH_3) cm^{-1}; NMR δ 1.6 (s, 3 H), 1.6–3.0 (m, 7 H), 3.95 (s, 3 H); MS *m/e* 198 (34), 153 (12), 139 (68), 126 (100).

Preparation of Ester 4. Methyllithium (89 mL, 1.7 M) was added dropwise to a solution of the acid **11** (12 g, 60.6 mmol; mp 105–110 °C; 0.5 M in THF) at −78 °C (internal temperature not exceeding −68 °C). The resulting dark orange solution was stirred for 12 h, quenched by pouring into 60 mL of 3 N HCl at 0 °C, and extracted with CH_2Cl_2 (2 × 100 mL), and the organic extracts were then evaporated to dryness. The resulting oil was dissolved in saturated Na_2CO_3 (40 mL) containing water (20 mL), and the aqueous solution was extracted with ether (100 mL). The aqueous phase was acidified with 6 N HCl (40 mL) and then extracted with CH_2Cl_2 (2 × 200 mL). The organic extract was dried first over Na_2SO_4 and second by filtration through $MgSO_4$ and then evaporated to an oil (10.55 g, 96% crude mass balance) consisting of the acids **12** and **11** in a ratio of 3:1 (NMR analysis), respectively.

This mixture of acids dissolved in CH_2Cl_2 was methylated with diazomethane (prepared in ether) at 0 °C, and the resulting mixture of the esters **4** and **9** was chromatographed on silica (100 g) by elution with 1:1 hexane/ether and then ether. From this chromatography there was obtained pure **4** (oil, 5.982 g) and pure **9** (oil, 2.89 g), which is a 77% overall yield of **4** from **11** based on recovered and reused ester **9**: R_f (silica) (ether) 0.63; IR ν_{max} 1735 (s, CO_2CH_3), 1695 (s, C=O), 1645 (m, C=C) cm^{-1}; NMR δ 1.65 (s, 3 H), 2.20 (s, 3 H), 1.9–2.85 (m, 7 H); MS *m/e* 196 (30), 165 (9), 123 (100).

Preparation of the Pentalenedione 5. Sodium methoxide (1.08 mL of a 1 M solution in methanol) was added to benzene (12 mL), and the resulting mixture was distilled until the head temperature reached 80 °C. Ester **4** (0.212 g, 1.08 mmol) in a small amount of benzene was then added, and the resulting mixture was distilled (80 °C head temperature, 120 °C pot temperature) for 5 min. The mixture was rapidly cooled to 0 °C, poured into a saturated solution of potassium dihydrogen phosphate, stirred for 3 min, extracted with CH_2Cl_2 (3 × 10 mL), dried over Na_2SO_4 followed by filtration through $MgSO_4$, and then evaporated to a yellow waxy solid which on sublimation at 70 °C (10^{-6} mm) gave a white solid (0.115 g, 70%): mp 83–84 °C; R_f (silica) (1:1 ether/$CHCl_3$) 0.48, (ether) 0.39; IR ν_{max} 1760 (s, C=O), 1700 (m, C=O), 1650 (w, C=C) cm^{-1}; NMR δ 1.65 (s, 3 H), 2.15 (s, 3 H), 2.28 (m, 4 H). 2.50 (d, 1 H), 3.20 (m, 1 H); MS *m/e* 164 (100), 136 (15), 135 (9), 122 (24), 121 (26), 108 (65). Anal. C, 73.16; H, 7.33.

Preparation of the Esters 14 and 15. To a solution of potassium hexamethyldisilizane (1.2 mmol, 1 M in THF) was added at −78 °C diketone **5** (200 mg, 1.2 mmol, 1 M in THF), and the resulting mixture was then stirred for 35 min before methyl iodoacetate (0.12 mL, 1.2 mmol) was added. The reaction was stirred at −78 °C for 20 min and then warmed to 0 °C and stirred for an additional 20 min. Saturated ammonium chloride (1 mL) was added to quench the reaction, which was then extracted with ether (3 × 2 mL). The organic extract was washed with 10% $NaHSO_3$ (1 mL), dried by filtration through $MgSO_4$, and evaporated to give essentially pure **14** as an oil (285 mg, ca. 99%). Preparation of the ester **15** from **5** and *tert*-butyl iodoacetate was carried out in the manner just described for **14**. Physical data for the esters **14** and **15** are as follows.

Compound **14**: R_f (silica) (ether) 0.74; IR ν_{max} 1755 (s, C=O), 1730 (m, CO_2CH_3), 1700 (m, C=O), 1650 (w, C=C) cm^{-1}; NMR δ 1.65 (s, 3 H), 2.15 (s, 3 H), 2.30 (m, 4 H), 2.90 (AB q, J_{AB} = 18 Hz, $\Delta\nu_{AB}$ = 70.2, 2 H), 3.25 (m, 1 H), 3.60 (s, 3 H); MS *m/e* 236 (98), 205 (43), 194 (78), 177 (20), 176 (26), 163 (60), 135 (100).

Compound **15**: R_f (silica) (ether) 0.86; IR ν_{max} 1755 (s, C=O), 1730 (m, CO_2-*t*-Bu), 1700 (m, C=O), 1650 (w, C=C) cm^{-1}; NMR δ 1.4 (s, 9 H), 1.65 (s, 3 H), 2.15 (s, 3 H), 2.20 (m, 4 H), 2.83 (AB q, J_{AB} = 16 Hz, $\Delta\nu_{AB}$ = 62, 2 H), 3.25 (m, 1 H); MS *m/e* 278 (0), 222 (100), 206 (76), 180 (80), 135 (32), 122 (64).

Acknowledgment This research was supported by P.H.S. Grant CA-21496-01. Support from the Hoffmann-La Roche Foundation is gratefully acknowledged.

Registry No.—**4**, 67226-55-5; **5**, 67226-56-6; **7**, 3883-56-5; **9**, 67226-57-7; **10**, 67226-58-8; **11**, 67226-59-9; **12**, 67226-60-2; **14**, 67226-61-3; **15**, 67226-62-4; 2-methylcyclopentane-1,3-dione,765-69-5; methyl acrylate, 96-33-3; methyl iodoacetate, 5199-50-8; *tert*-butyl iodoacetate, 49827-15-8.

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(9) We thank Dr. Pius A. Wehrli of the Hoffmann-La Roche Co. for a generous sample of this material as well as an excellent experimental description for the preparation of it.
(10) The regiointegrity of this enolate was determined by quenching with DCl. This enolate undergoes alkylation reactions in excellent yield, and thus it parallels the behavior already found for the six-membered ring cases (ref 7).
(11) We have found that base treatment for 30 min at 0 °C brings about the retro-Michael reaction of **10** to the ester **9** and that hydrolysis of **9** occurs only at room temperature or above.
(12) Longer reaction times lead to products derived from the carboxylic acid portion of **11**.
(13) This excellent quenching procedure is described in ref 5.
(14) Other bases attempted for the cyclization of **4** into **5** include lithium and potassium methoxide, potassium *tert*-butoxide, lithium and potassium hexamethyldisilizane, and lithium diisopropylamide. The amide bases did not give cyclization products, and all of the alkoxide bases gave lower yields of **5** relative to sodium methoxide.

Cis to Trans Interconversion of Cyclic α-Hydroxy Epoxides

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During the course of pondering synthetic strategies directed toward the synthesis of the sesquiterpene eriolangin (**1**),[1] it occurred to us that the synthon **2** possessed a number of functional and stereochemical features potentially amenable to an expeditious resolution of this interesting problem. Mo-

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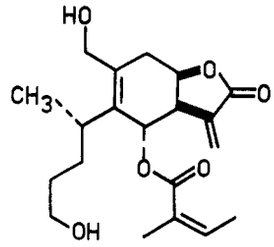
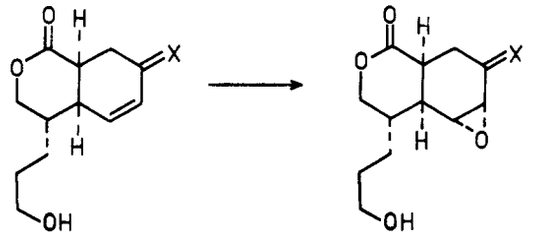


1

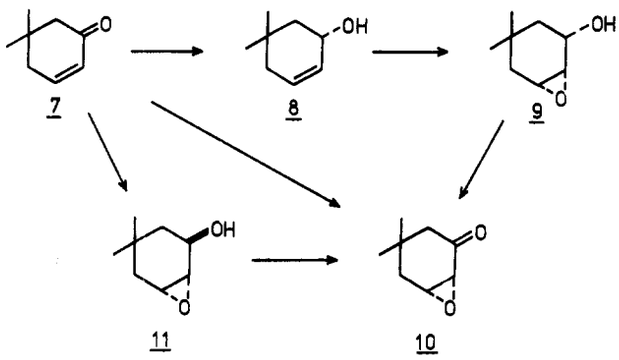
lecular models revealed that epoxidation of **2** would occur from the β face of the molecule if it occurred at all, and further that reduction of **2** would clearly result in formation of the α-allylic alcohol **3**. The latter reaction was not considered entirely without merit, however, for Henbest epoxidation of **3** should yield the *cis*-epoxy alcohol **4**,[2] from which the desired *trans*-



2, X = O
3, X = αOH, βH
4, X = αOH, βH
5, X = αH, βOH
6, X = O

epoxy alcohol **5** could, in principle, be obtained by oxidative conversion of **4** into the α-epoxy ketone **6** followed by stereospecific reduction of **6** into **5**. Elaboration of **5** into the *cis*-lactone functionality present in **1** could then be achieved using existing technology developed both by Danishesfky and ourselves.[3] We immediately commenced a search for methods applicable to the conversion of **4** → **6** → **5** but found, to our surprise, the literature to be exiguous in relevant analogies. It is the purpose of this note therefore to outline simple efficacious methodology germane to this problem.

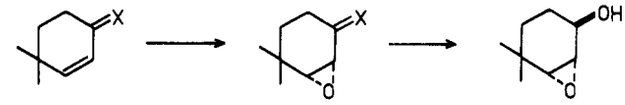
The enone **7** was reduced to the corresponding allylic alcohol **8** in the usual manner and then epoxidized with *m*-chloroperbenzoic acid to afford the α-hydroxy epoxide **9**.



7 **8** **9** **11** **10**

Several methods were considered for the oxidation of **9** into the desired epoxy ketone **10**, and while a number of methods partially succeeded, it was found that pyridinium chlorochromate buffered with sodium acetate[4] gave excellent yields of **10**. The authenticity of this material was established by hydrogen peroxide epoxidation of **7**, which gave a substance identical with **10**. A variety of reducing agents intended to give the *trans*-epoxy alcohol **11** from **10** were examined with highly variable success, the usual result being formation of mixtures of **11** and the *cis*-epoxy alcohol **9**. This lack of stereoselectivity in reduction was, however, finally overcome by employment of triisobutylaluminum as the reducing agent. With this reagent, stereospecific and high yield reduction of **10** into **11** was observed with the product being essentially uncontaminated with the epimeric alcohol **9**. The authenticity of **11**, prepared by the method described above, was confirmed by independent preparation of **11** from the enone **7** using the method described by Heathcock.[5,6]

A similar series of transformations has been carried out starting from the enone **12**, proceeding through the alcohol **13**, the epoxy alcohol **14**, and the epoxy ketone **15**, to finally yield the *trans*-epoxy alcohol **16**.



12, X = O
13, X = H, OH
14, X = H, OH
15, X = O
16

Since the reactions described herein are simple to carry out and proceed with high stereoselectivity, it seems reasonable to assume that this type of manipulative process could be applied to compound **2** as well as other synthetic intermediates intended to lead to sesquiterpene systems.

Experimental Section

General Section. Nuclear magnetic resonance (NMR) spectra were recorded at 100 MHz on a Jeolco Model JNM-MH-100 high-resolution spectrometer. Samples were examined in deuteriochloroform containing 1% by volume of tetramethylsilane. Infrared spectra were recorded on a Perkin-Elmer Model 467 grating spectrophotometer. Samples were analyzed in spectrograde chloroform solutions of 0.1 mm thickness. Mass spectra were obtained on a Dupont Model 21-940 B mass spectrometer.

Gas chromatography was performed on a Hewlett-Packard series 5700 A gas chromatograph with a series 5702 A temperature programmer and 5705 A thermal conductivity detector. The columns were either 6 ft × 0.125 in or 2 ft × 0.125 in aluminum tubing packed with 15% SE-30 on acid washed Chromosorb W, 80–100 mesh, and they were cured at 270 °C. The carrier gas was dry helium, and a flow rate of 20 ± 2 mL/min was maintained.

Chromatography was performed as follows. The silica, #7731 gel G type 60 for TLC, was placed in a sintered glass funnel packed dry. Solvent was flushed through the silica gel under water aspirator vacuum, and the silica was repressed to avoid channeling between the glass and the silica. The compound was deposited with a minimal amount of solvent and then eluted with solvent using the water aspirator as a vacuum source.

Preparation of Alcohol 8. To a mixture of lithium aluminum hydride (0.30 g, 8.0 mmol) in ether (20 mL) at 0 °C was slowly added the enone **7** (1.0 g, 8.0 mmol). After stirring the resulting mixture for 15 min, saturated Na_2SO_4 (1 mL) was added followed by water (0.5 mL). The suspension was diluted with ether, stirred for 1 h, filtered through $MgSO_4$, and then evaporated to yield the allylic alcohol **8** (0.90 g, 88%): retention time (150 °C–2 min, 32 °C/min to 250 °C–6 min), 1.3 min; IR ν_{max} 3400 cm^{-1} (broad, OH); NMR δ 0.90 (s, 3 H), 1.00 (s, 3 H), 1.00–2.00 (m, 4 H), 2.50–3.50 (broad, OH), 4.20 (m, 1 H), 5.70 (s, 2 H); MS *m/e* 126.

Preparation of the *cis*-Epoxy Alcohol 9. To a solution of *m*-chloroperbenzoic acid (0.70 g, 4.2 mmol, 1.3 equiv, 99%) in methylene chloride (10 mL) at 0 °C was added over a period of 4 min the allylic alcohol **8** (0.40 g, 3.1 mmol). The resulting solution was stirred for 15 min at 0 °C and then for 12 h at room temperature. The precipitated *m*-chlorobenzoic acid that formed during the reaction was filtered off and washed with methylene chloride (5 mL). Ether (30 mL) was added to the filtrate, which was then washed with freshly prepared saturated $NaHSO_3$ (2 × 10 mL) and saturated $NaHCO_3$ (3 × 10 mL), filtered through $MgSO_4$, and evaporated to dryness to yield crude **9** (0.39 g, 88%). This material was chromatographed using silica (10 g) eluting with 1:1 ether/hexane to give pure **9** (0.250 g, 57%): retention time (150 °C–2 min, 32 °C/min to 250 °C–6 min), 1.4 min; IR ν_{max} 3350 cm^{-1} (broad, OH); NMR δ 0.85 (s, 3 H), 0.91 (s, 3 H), 1.00–1.60 (m, 2 H), 1.60 (s, 2 H), 2.60 (OH), 3.40 (s, 2 H), 4.18 (m, 1 H); MS *m/e* 142.

Preparation of the Keto Epoxide 10. To methylene chloride (2.5 mL) was added **9** (93 mg, 0.65 mmol), sodium acetate (100 mg, 2.0 equiv, 1.3 mmol), and pyridinium chlorochromate (280 mg, 2.0 equiv, 1.3 mmol). The resulting orange suspension became brown within 2 min, and the reaction was stirred for 6 h at room temperature. Ether

(5 mL) was added, and stirring was continued for 10 min, whereupon the organic solvent was decanted from the oily brown sludge present in the reaction mixture. Ether (2 × 5 mL) was used to wash the brown residue, and the combined organic solutions were then filtered through a Florisil/$MgSO_4$ pad. Evaporation of the filtrate gave pure **10** (78 mg, 80%): retention time (130 °C–2 min, 32 °C/min to 250 °C–6 min), 1.40 min; IR ν_{max} 1710 cm^{-1} (s, C=O); NMR δ 0.95 (s, 3 H), 1.08 (s, 3 H), 1.65–2.15 (m, 3 H), 2.65 (d, 1 H), 3.19 (d, 1 H), 3.46 (t, 1 H); MS *m/e* 140.

Preparation of the *trans*-Epoxy Alcohol 11. To a solution of **10** (100 mg, 0.72 mmol) in toluene (2 mL) at 0 °C was added over a period of 5 min triisobutylaluminum (Texas Alkyls; 1.23 M in toluene, 0.60 mL, 1 equiv). The solution was stirred for 15 min and then quenched by the successive addition of methanol (0.3 mL), saturated NH_4Cl (0.3 mL), ether (6 mL), and Celite (0.5 g). This mixture was stirred for 1 h and then filtered through a $MgSO_4$ pad, and the filtrate was evaporated to give **11** (98% pure by GC and NMR; 101 mg, 99%): retention time (130 °C–2 min, 32 °C/min to 250 °C–6 min), 2.0 min; IR ν_{max} 3460 cm^{-1} (broad, OH); NMR δ 0.90 (s, 3 H), 0.98 (s, 3 H), 1.00–1.82 (m, 4 H), 2.75 (OH), 3.07 (d, 1 H), 3.20 (t, 1 H), 4.09 (m, 1 H); MS *m/e* 142.

Preparation of the Allylic Alcohol 13. To a stirred suspension of lithium aluminum hydride (320 mg, 8.0 mmol) in ether (14 mL) was slowly added at room temperature a solution of the enone **12** (2.0 g, 16.1 mmol) in ether (16 mL). After the addition was complete, the reaction mixture was stirred for 1 h and then cooled to 0 °C and quenched with saturated sodium sulfate. The resulting mixture was filtered through $MgSO_4$ and the solvent evaporated to give **13** (1.64 g, 82%): IR ν_{max} 3600 (s, OH), 3450 (broad, OH) cm^{-1}; NMR δ 1.20–1.80 (m, 4 H), 1.95 (s, 3 H), 1.95 (OH), 2.05 (s, 3 H), 5.60 (m, 2 H); MS *m/e* 126.

Preparation of the *cis*-Epoxy Alcohol 14. To a solution of **13** (785 mg, 6.23 mmol) in methylene chloride (7 mL) at 0 °C was added dropwise a solution of *m*-chloroperbenzoic acid (1.60 g, 9.35 mmol, 85%) in methylene chloride (15 mL) and ethyl acetate (3.5 mL). The resulting mixture was stirred at 0 °C for 8 h and then quenched with 5% sodium hydroxide (28 mL) and extracted with methylene chloride (4 × 15 mL). The combined extracts were filtered through $MgSO_4$ and evaporated to an oil. Chromatography of this oil on silica eluting with 2:1 ether/hexane gave pure **14** (565 mg, 64%): retention time (120 °C–2 min, 32 °C/min to 250 °C–6 min), 1.52 min; R_f (2:1 hexane/ether) 0.175; IR ν_{max} 3350 cm^{-1} (broad, OH); NMR δ 1.00 (s, 3 H), 1.05 (s, 3 H), 1.20–1.42 (m, 4 H), 2.60 (m, 1 H), 2.90 (d, 1 H), 3.30 (t, 1 H), 3.92 (OH); MS *m/e* 142.

Preparation of the Keto Epoxide 15. Pyridinium chlorochromate (378 mg, 1.75 mmol), alcohol **14** (100 mg, 0.877 mmol), sodium acetate (143 mg, 1.74 mmol), and methylene chloride (1.8 mL) were stirred at room temperature for 6 h. The organic solution was decanted, and the remaining brown residue was washed with methylene chloride (3 × 5 mL). The combined organic washes were filtered through Florisil and then evaporated to give pure **15** (88 mg, 88%): retention time (120 °C–2 min, 32 °C/min to 250 °C–6 min), 1.92 min; R_f (hexane/ether, 2:1) 0.55; IR ν_{max} 1710 cm^{-1} (s, C=O); NMR δ 1.04 (s, 3 H), 1.25 (s, 3 H), 1.80–2.60 (m, 4 H), 3.30 (s, 2 H); MS *m/e* 140.

Preparation of the *trans*-Epoxy Alcohol 16. To **15** (100 mg, 0.714 mmol) in toluene (1.5 mL) at 0 °C was slowly added triisobutylaluminum (0.638 mL, 1.23 M in toluene), and the resulting mixture was stirred at 0 °C for 40 min. The reaction mixture was diluted with ether (4 mL) and then quenched by the addition of methanol (0.5 mL), saturated NH_4Cl (1 mL), and Celite. After stirring for 1 h, the mixture was filtered through $MgSO_4$ and the filtrate was evaporated to dryness, giving **16** (93 mg; 93% pure by GC and NMR analysis): retention time (120 °C–2 min, 32 °C/min to 250 °C–2 min), 1.52 min; R_f (hexane/ether, 2:1) 0.175; IR ν_{max} 3460 cm^{-1} (broad, OH); NMR δ 1.00 (two overlapping singlets, 6 H), 1.15–1.70 (m, 4 H), 2.65, (d, 1 H), 2.95 (d, 1 H), 3.30 (OH), 3.85 (t, 1 H); MS *m/e* 142.

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Registry No.—**7**, 4694-17-1; **8**, 25866-56-2; **9**, 38309-46-5; **10**, 17421-93-1; **11**, 66036-65-5; **12**, 1073-13-8; **13**, 5020-09-7; **14**, 38309-45-4; **15**, 1074-26-6; **16**, 66036-66-6.

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Reaction of *tert*-Butyldimethylsilyl Esters with Oxalyl Chloride–Dimethylformamide: Preparation of Carboxylic Acid Chlorides under Neutral Conditions

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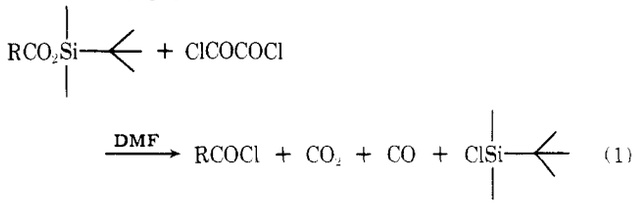
One of the more common transformations encountered in organic synthesis is the conversion of a carboxylic acid to the corresponding carboxylic acid chloride. Most current methods[1] which accomplish this conversion involve acidic conditions and consequently, if a carboxylic acid contains an acid sensitive functionality, it is likely that the desired carboxylic acid chloride may be obtained in low yield or not at all. In this communication we describe a new method for forming carboxylic acid chlorides under neutral conditions.

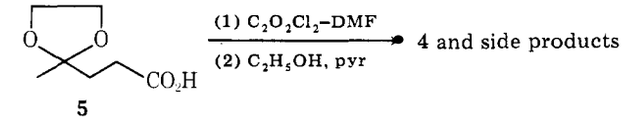
The *tert*-butyldimethylsilyl group has recently been reported to be of value as a protecting group for alcohols and carboxylic acids.[2] Furthermore, the report of the conversion of trimethylsilyl pyruvate to its corresponding acid chloride[3] encouraged us to investigate the reaction of *tert*-butyldimethylsilyl esters with oxalyl chloride in the presence of a catalytic amount of dimethylformamide (DMF) as a potential method of forming carboxylic acid chlorides under neutral conditions (eq 1).



(1)

Treatment of *tert*-butyldimethylsilyl heptanoate (**1**) with 1.2 equiv of oxalyl chloride in methylene chloride in the presence of a catalytic quantity of DMF resulted in slow gas evolution over a period of 2 h. Removal of the solvent and exposure of the resulting acid chloride to ethanol in pyridine gave ethyl heptanoate (**2**) in 92% yield. In a similar manner, treatment of the various *tert*-butyldimethylsilyl esters listed in Table I with oxalyl chloride–DMF gave, after treatment of the resulting acid chlorides with ethanol–pyridine, the respective ethyl esters in the indicated isolated yields.

The results presented in Table I indicate that this reaction will tolerate an acid sensitive functionality quite well. For example, while the conversion of the *tert*-butyldimethylsilyl ester **3** which contains an acid sensitive ketal moiety to the ethyl ester **4** proceeds in excellent yield, the reaction of the corresponding carboxylic acid **5**[4] with oxalyl chloride–DMF



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under identical conditions followed by the reaction with ethanol–pyridine gives **4** in much lower yield; moreover the product is accompanied by at least three additional less volatile side products (see Experimental Section).

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