Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

Registry No. Acetophenone trimethylsilyl enol ether, 13735-81-4; cyclooctanone trimethylsilyl enol ether, 50338-42-6; cyclododecanone trimethylsilyl enol ether, 51584-36-2; cyclohexanone trimethylsilyl enol ether, 6651-36-1; 2-methylcyclohexanone trimethylsilyl enol ether, 19980-33-7; cyclopentanone trimethylsilyl enol ether, 19980-43-9; α-chloroacetophenone, 532-27-4; 2-chlorocyclooctanone, 4828-34-6; 2-chlorocyclododecanone, 35951-28-1; 2-chlorocyclohexanone, 822-87-7; 2-chloro-6-methylcyclohexanone, 73193-05-2; 2-chlorocyclopentanone, 694-28-0; SO_2ClF, 13637-84-8; SO_2Cl_2, 7791-25-5.

A New Approach for the Regiospecific Annelation of Butenolides

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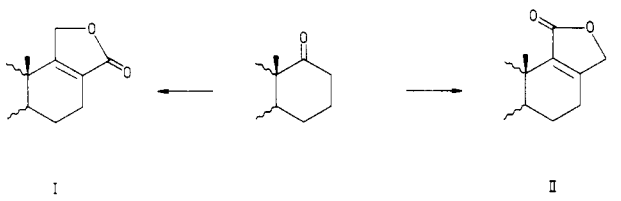
The regiospecific annelation of butenolides forms part of the problems in the total synthesis of, for instance, triptolide and congeners[1] of a number of drimane sesquiterpenes[2] and eventually of spongianes[3] and scalaranes.[4] Recently an efficient procedure was described for the construction of butenolides of type I (Figure 1), starting from a ketone.[1b] We have developed a method for the annelation of butenolides with the opposite regiochemistry (type II), starting from the same type of ketone.[2e]

This procedure, outlined in Scheme I, starts with formylation of the ketone followed by protection of the aldehyde group as the (*n*-butylthio)methylene derivative **2**.[5] Reaction of **2** with [(phenylthio)methyl]lithium followed by hydrolysis of the adduct affords the γ-(phenylthio)-α,β-unsaturated aldehyde **3**. This hydrolysis can be performed at reflux temperature in a few hours. When acid-sensitive groups are present in the molecule, as in **3c**, longer reaction times at room temperature can be applied.[2e,6] Oxidation of the sulfide **3** with $NaIO_4$ in methanol–water[7] gives the sulfoxide **4**, which can be transformed in a Pummerer-type reaction into the (phenylthio)furan **5** by heating in acetic anhydride at 110 °C. The hydrolysis of the (phenylthio)furan is complete in 4 h at reflux temperature,[8] but up to 10% of the other regioisomer is isolated under these circumstances. Hydrolysis at room temperature takes about 1 day to 1 week to complete the reaction, but only one regioisomer is formed under these conditions.

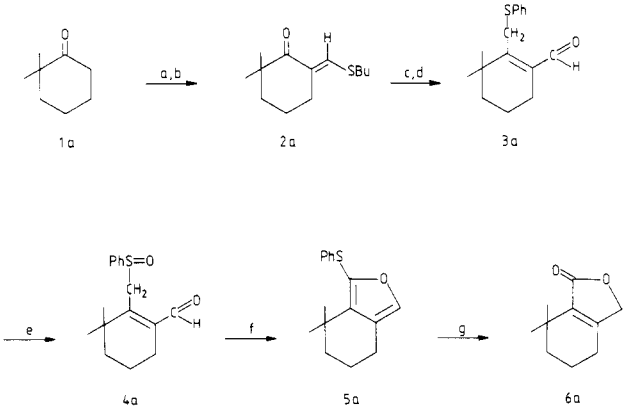
The butenolide **6** can be obtained from the ketone **1** in an overall yield of 30–40%. The utility of this procedure



I II

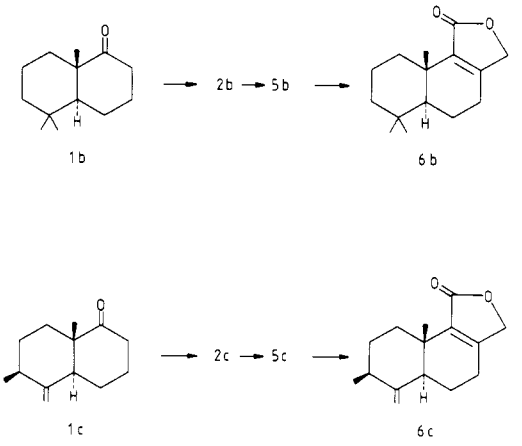
Figure 1.

Scheme I[a]



[a] (a) NaH, HCOOEt; (b) H^+, *n*-BuSH; (c) $PhSCH_2Li$; (d) H^+, H_2O, $HgCl_2$; (e) $NaIO_4$; (f) Ac_2O, 110 °C, (g) H^+, H_2O, $HgCl_2$.

Scheme II



is illustrated by the total syntheses of isodrimenin (**6b**) and colorata-4(13),8-dienolide (**6c**), starting from the ketones **1b** and **1c** (Scheme II).

Experimental Section

^1H NMR spectra were recorded on a Varian AM-390 or a Perkin-Elmer R 24B spectrometer with tetramethylsilane as an internal standard. Mass spectra and accurate mass measurements were obtained with an AEI MS-902 spectrometer. GC/MS spectra were obtained from a VG Micromass 7070-F spectrometer. Melting points are uncorrected.

(*n*-Butylthio)methylene Ketones 2a–c. The starting compounds **1a**,[5] **1b**,[9] and **1c**[2e] were prepared as described. The (*n*-butylthio)methylene ketones **2a**,[5] **2b**,[10] and **2c** were prepared following the procedure of Ireland and Marshall.[5]

Compound 2c:[2e] yield 84%; mp 54–55 °C; ^1H NMR ($CDCl_3$) δ 0.87 (s, 3 H), 0.93 (t, J = 6 Hz, 3 H), 1.06 (d, J = 6 Hz, 3 H), 1.2–2.7 (m, 14 H), 2.85 (t, J = 6 Hz, 2 H), 4.70 (d, J = 0.9 Hz, 1 H), 4.84 (d, J = 0.9 Hz, 1 H), 7.57 (br s, 1 H); mass spectrum, m/z (relative intensity) 292 (30), 253 (100), 203 (10), 175 (12), 161 (24), 159 (11), 129 (12); accurate mass calcd for $C_{18}H_{28}OS$

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292.1861, found 292.1857. Anal. Calcd: C, 73.92; H, 9.65. Found: C, 74.38; H, 9.57.

γ-(Phenylthio)-α,β-unsaturated Aldehydes 3a–c. These compounds were prepared following the procedure of Sowerby and Coates.[6]

Compound 3a: yield 90%; mp 51–51.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 6 H), 1.4–1.8 (m, 4 H), 2.1–2.3 (m, 2 H), 3.96 (s, 2 H), 7.3 (br s, 5 H), 10.28 (s, 1 H); mass spectrum, *m/z* (relative intensity) 260 (15), 150 (100), 135 (27), 107 (21), 81 (20); accurate mass calcd for $C_{16}H_{20}OS$ 260.1235, found 260.1239. Anal. Calcd C, 73.80; H, 7.74. Found: C, 73.56; H, 7.79. DNPH, mp 179–180 °C. Anal. Calcd for $C_{22}H_{24}N_4O_4S$: C, 59.98 H, 5.49. Found: C, 59.79; H, 5.66.

Compound 3b: yield 79%, obtained as a yellow oil which crystallized upon standing in the refrigerator, mp 55–57 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 3 H), 0.93 (s, 3 H), 1.13 (s, 3 H), 1.1–2.5 (m, 11 H), 3.90 (q_{AB}; δ_A 3.67, δ_B 4.12, J_{AB} = 12 Hz, 2 H), 7.24 (br s, 5 H), 9.97 (s, 1 H); mass spectrum, *m/z* (relative intensity) 328 (38), 299 (7), 218 (100), 203 (29), 175 (11), 105 (14), 91 (11), 81 (13); accurate mass calcd for $C_{12}H_{28}OS$ 328.1861, found 328.1863. Anal. Calcd: C, 76.78; H, 8.59. Found: C, 76.72; H, 8.61. DNPH, mp 173–175 °C. Anal. Calcd for $C_{27}H_{32}N_4O_4S$: C, 63.75; H, 6.34. Found: C, 63.54; H, 6.25.

Compound 3c: yield 91%; mp 89–90 °C; ^{1}H NMR ($CDCl_3$) δ 0.93 (s, 3 H), 1.07 (d, *J* = 6 Hz, 3 H), 1.5–2.6 (m, 10 H), 3.95 (q_{AB}; δ_A 3.75, δ_B 4.15, J_{AB} = 11 Hz, 2 H), 4.63 (d, *J* = 0.9 Hz, 1 H), 4.81 (d, *J* = 0.9 Hz, 1 H), 7.31 (br s, 5 H), 10.21 (s, 1 H); mass spectrum, *m/z* (relative intensity) 326 (27), 216 (100), 173 (93), 105 (17), 91 (19), 81 (16), 79 (16); accurate mass calcd for $C_{21}H_{26}OS$ 326.1704, found 326.1707. Anal. Calcd: C, 77.25; H, 8.03. Found: C, 76.93; H, 7.80. DNPH, mp 103–105 °C. Anal. Calcd for $C_{27}H_{30}N_4O_4S$: C, 64.01; H, 5.97. Found: C, 63.86; H, 5.82.

γ-(Phenylsulfinyl)-α,β-unsaturated Aldehydes 4a–c. The procedure of Leonard and Johnson[7] was followed for the preparation of these sulfoxides.

Compound 4a: yield 90%; mp 145–146 °C; ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 3 H), 1.22 (s, 3 H), 1.6–1.8 (m, 4 H), 2.2–2.6 (m, 2 H), 3.98 (q_{AB}, δ_A 3.70, δ_B 4.23, J_{AB} = 13 Hz, 2 H), 7.6 (m, 5 H), 9.80 (s, 1 H). Anal. Calcd for $C_{16}H_{20}O_2S$: C, 69.53; H, 7.29. Found: C, 69.53; H, 7.36.

Compound 4b: yield 92%; mp 139–140 °C. The diastereoisomers gave practically the same NMR spectrum: ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3 H), 0.95 (s, 3 H), 1.13 (s, 3 H), 1.3–2.6 (m, 11 H), 3.93 (q_{AB}, δ_A 3.58, δ_B 4.25, J_{AB} = 13 Hz, 2 H), 7.55 (m, 5 H), 9.95 (s, 1 H). Anal. Calcd for $C_{21}H_{28}O_2S$: C, 73.21; H, 8.19. Found: C, 73.19; H, 8.01.

Compound 4c: yield 92%, obtained as an unstable oil which proved to be a mixture of diastereoisomers. The ^{1}H NMR spectrum showed complex multiplets at δ 0.9–1.5 (CH_3), 1.5–2.7 (CH_2) and 3.2–4.5 (-$SOCH_2$), 4.70 and 4.85 (br, s, =CH_2), 7.6 (m, Ar H), 9.67 (s, -CHO) and 9.88 (s, -CHO). This material was most conveniently directly converted into **5c**.

General Procedure for the Preparation of the (Phenylthio)furans 5a–c. A solution of 7.0 mmol of the sulfoxide **4a** (1932 mg), **4b** (2408 mg), or **4c** (2394 mg) in 15 mL of acetic anhydride was stirred for 1.5 h at 110 °C under nitrogen. After cooling, the reaction mixture was poured into 80 mL of 4 N sodium hydroxide solution. The mixture was stirred for 0.5 h and extracted with ether. The ethereal solution was washed with water and brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography using 100 g of silica gel and an ether–petroleum ether, bp 40–60 °C mixture (0.3:99.7), as eluent.

Compound 5a: yield 70%; oil; ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 6 H), 1.5–1.8 (m, 4 H), 2.3–2.6 (m, 2 H), 7.1 (m, 5 H), 7.22 (s, 1 H); mass spectrum, *m/z* (relative intensity) 258 (68), 243 (100), 105 (8), 91 (9), 81 (7), 77 (8); accurate mass calcd for $C_{16}H_{18}OS$ 258.1076, found 258.1071.

Compound 5b: yield 77%; oil; ^{1}H NMR ($CDCl_3$) δ 0.89 (s, 3 H), 0.95 (s, 3 H), 1.21 (s, 3 H), 1.3–1.9 (m, 9 H), 2.6–3.0 (m, 2 H), 7.1 (m, 5 H), 7.21 (s, 1 H); mass spectrum, *m/z* (relative intensity) 326 (100), 311 (62), 201 (41), 105 (7), 91 (13), 81 (4), 77 (7), 69 (35); accurate mass calcd for $C_{21}H_{26}OS$ 326.1703, found 326.1708.

Compound 5c: yield 61%; oil; ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 3 H), 1.06 (d, *J* = 6 Hz, 3 H), 1.2–2.9 (m, 10 H), 4.52 (d, *J* = 0.9 Hz, 1 H), 4.80 (d, *J* = 0.9 Hz, 1 H), 6.8–7.1 (m, 5 H), 7.22 (s, 1 H); mass spectrum, *m/z* (relative intensity) 324 (100), 309 (54), 200 (19), 199 (15), 105 (6), 91 (14), 81 (4), 77 (9); accurate mass calcd for $C_{21}H_{24}OS$ 324.1546, found 324.1551.

General Procedure for the Preparation of the Butenolides 6a–c. To a solution of 3 mmol of the (phenylthio)furan **5a** (774 mg), **5b** (978 mg), or **5c** (972 mg) in 3 mL of water and 50 mL of methanol was added a solution of 2 mmol of $HgCl_2$ in 3 mL of 4 N hydrochloric acid and 50 mL of methanol. This reaction mixture was stirred at room temperature for 1 to 5 days, until the hydrolysis was complete. The methanol was evaporated in vacuum at room temperature and 20 mL of water was added. The water solution was extracted with ether. The ethereal solution was washed with $NaHCO_3$ solution and with brine and dried ($MgSO_4$), and the ether was evaporated. The residue was purified by column chromatography on silica gel by using an ether–petroleum ether, bp 40–60 °C mixture (30:70), as eluent.

Compound 6a: yield 90%; colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 6 H), 1.5–2.4 (m, 6 H), 4.59 (s, 2 H); mass spectrum, *m/z* (relative intensity) 166 (95), 151 (100), 138 (17), 137 (18), 123 (68), 121 (30), 95 (44), 93 (48), 91 (19), 79 (18), 77 (18); accurate mass calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0994.

Compound 6b: yield 90%; mp 88–90 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3 H), 0.95 (s, 3 H), 1.18 (s, 3 H), 1.2–2.5 (m, 11 H), 4.58 (s, 2 H); mass spectrum, *m/z* (relative intensity) 234 (28), 219 (100), 189 (11), 163 (19), 151 (54), 123 (26), 95 (11), 91 (18), 81 (13), 79 (12), 77 (11); accurate mass calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1615. Anal. Calcd: C, 76.88; H, 9.46. Found: C, 76.88; H, 9.37.

Compound 6c:[11] yield 61%; mp 101–103 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3 H), 0.96 (d, *J* = 6 Hz, 3 H), 1.1–1.9 (m, 8 H), 2.7–2.9 (m, 2 H), 3.87 (s, 2 H), 4.54 (d, *J* = 0.9 Hz, 1 H), 4.80 (d, *J* = 0.9 Hz, 1 H); mass spectrum, *m/z* (relative intensity) 232 (96), 217 (100), 204 (18), 203 (21), 189 (22), 162 (28), 151 (29), 150 (23), 107 (33), 105 (30), 91 (42), 79 (38), 77 (28); accurate mass calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1453. Anal. Calcd: C, 77.55; H, 8.68. Found: C, 77.50; H, 8.75.

Registry No. **1a**, 1193-47-1; **1b**, 16776-05-9; **1c**, 89656-00-8; **2a**, 67218-06-8; **2b**, 89708-57-6; **2c**, 89656-01-9; **3a**, 81053-99-8; **3b**, 89656-02-0; **3c**, 89656-03-1; **4a**, 81054-00-4; **4b**, 89656-04-2; **4c**, 89656-05-3; **5a**, 89656-06-4; **5b**, 89656-07-5; **5c**, 89708-58-7; **6a**, 89656-08-6; **6b**, 1684-54-4; **6c**, 60114-23-0; $PhSCH_2Li$, 13307-75-0.

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Synthesis of the Novel Marine Diterpenes (±)-Isocopal-12-ene-15,16-dial, (±)-14-Epiisocopal-12-ene-15,16-dial, and (±)-15-Acetoxyisocopal-12-en-16-al from Methyl Isocopalate

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Sesquiterpenes possessing two aldehyde groups, isolated from terrestrial and marine organisms,[1] showed a wide spectrum of biological activity.[2,3] A new series of tricyclic diterpenes **1**, **2**, and **3**, with an arrangement of functional groups similar and very related to those mentioned above,

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