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A Regioselective Annulation of Butenolides. The Total Synthesis of (±) Confertifolin.

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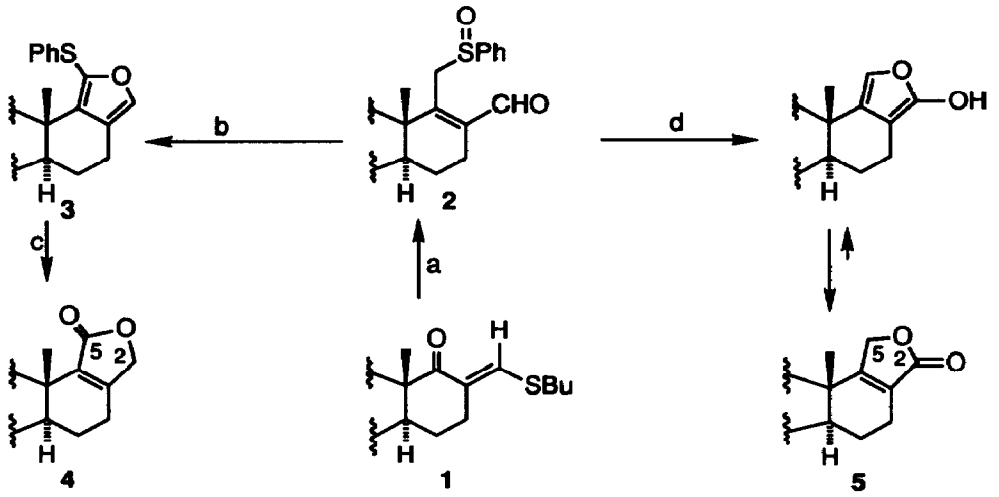
Abstract: γ-(Phenylsulfinyl)-α,β-unsaturated aldehydes **2**, prepared from α-(*n*-butylthio)methylene ketones **1** *via* addition of [(phenylthio)methyl]lithium followed by hydrolysis and oxidation, are converted into butenolides **4** or **5** depending upon the reaction conditions.

The regioselective annulation of butenolides is a recurrent problem in the synthesis of natural products. Several solutions for this problem have been developed, especially in connection with the total synthesis of drimane sesquiterpenes[1]. The working method often emanates from ketones in which the two required additional carbon atoms that end up as C-2 and C-5 of the annulated ring are introduced *via* formylation and *via* addition of a suitable functionalized organolithium reagent.

Scheme 1

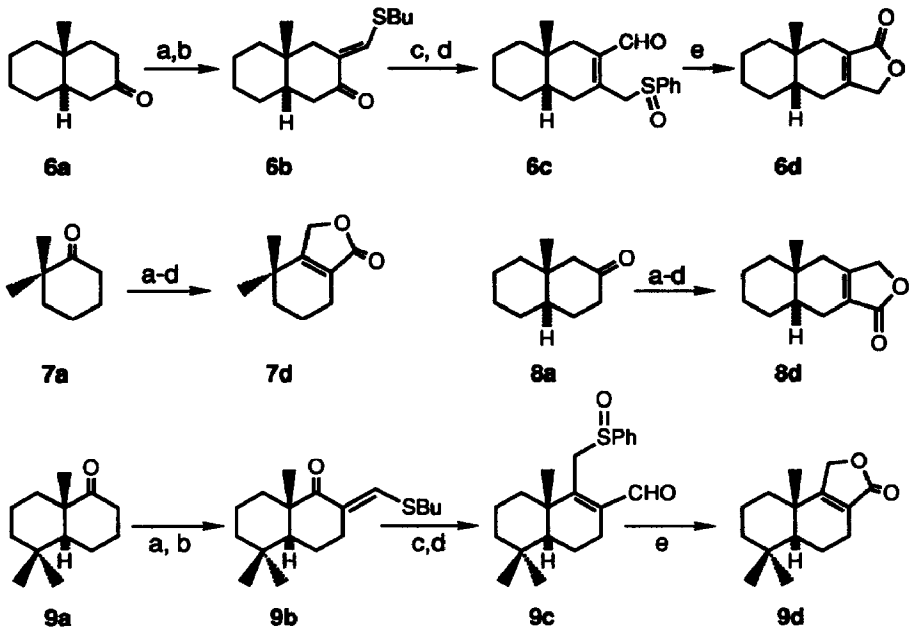


a: $PhSCH_2Li$; H_2O, H^+, $HgCl_2$; $NaIO_4$, MeOH; *b*: Ac_2O, 110 °C; *c*: H_2O, H^+, $HgCl_2$; *d*: Dioxane or toluene, H_2O, K_2CO_3, Δ.

When [(phenylthio)methyl]lithium[2] is added to α-(*n*-butylthio)methylene ketones **1**, derived from the corresponding α-hydroxymethylene ketones[3], rather unstable adducts are formed which are usually hydrolized immediately to afford γ-(phenylthio)-α,β-unsaturated aldehydes in good yields[4]. Oxidation of these sulfides then afforded the corresponding sulfoxides **2** as mixtures of stereoisomers. These sulfoxides are flexible and versatile intermediates in the regioselective annulation of butenolides. The conversion of sulfoxides into (phenylthio)furans *via* a Pummerer-type reaction and the subsequent hydrolysis into butenolides of type **4** was shown[1c]. Now we report on the transformation of these sulfoxides into butenolides of type **5** with the opposite regiochemistry (Scheme 1).

The γ-phenylsulfinyl-α,β-unsaturated aldehydes studied were prepared from the corresponding ketones analogous to **6c** as is shown in scheme 2.

Scheme 2



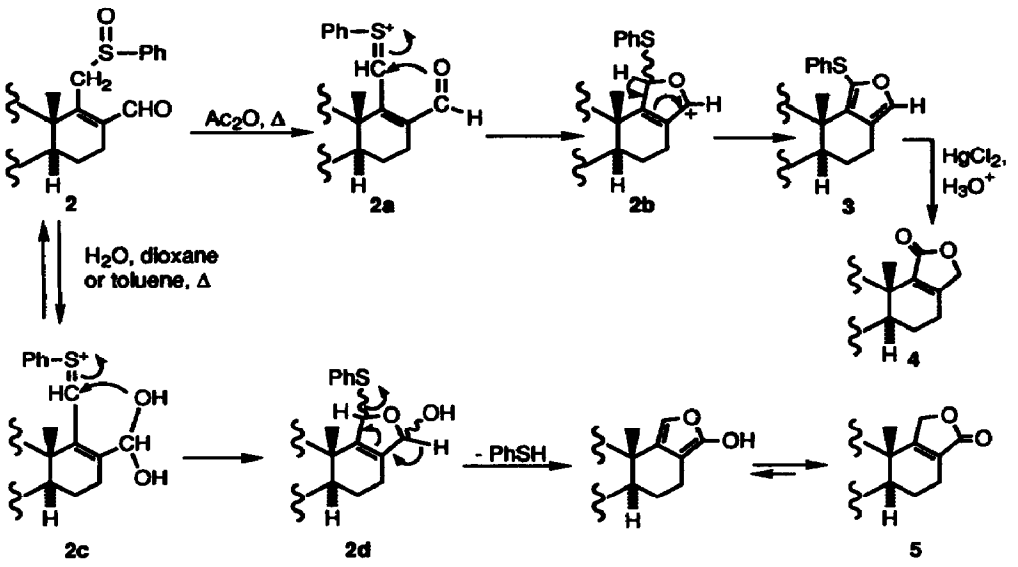
a: NaH, HCOOEt, Et_2O; *b*: *n*BuSH, *p*TsOH, benzene; *c*: $PhSCH_2Li$, THF; $HgCl_2$, H_2O, H^+; *d*: $NaIO_4$, MeOH; *e*: Dioxane or toluene, H_2O, K_2CO_3, Δ.

The conversion of **6c** into butenolide **6d** proved to be a simple and straightforward reaction which was performed in refluxing toluene with a small amount of water, in the presence of one equivalent of potassium carbonate to give **6d** in 50% yield, without a trace of the regioisomer[5]. So, there is now the possibility to synthesize both types of regioisomeric butenolides from the same intermediate sulfoxide.

The reaction was also tested with the sulfoxides derived from ketones **7a** and **8a**, and the butenolides **7d** and **8d** were obtained in 56% and 35% overall yield, respectively. When this sequence of reactions was applied to decalone **9a**[6], a total synthesis of (±)- confertifolin **9d** could be achieved in 65% overall yield, as depicted in scheme 2. It is interesting to note, that in this case the temperature should be kept below 75°C otherwise an elimination of phenylsulfenic acid is the main reaction[1a].

A possible mechanism of the transformation of sulfoxides of type **2** into the two regioisomeric butenolides of type **4** and **5** is given in scheme 3.

scheme 3



When the reaction is carried out in acetic acid anhydride at 110°C it is assumed that intermediate **2a** will be formed and because there are no nucleophiles present in the reaction mixture, the carbonyl group will attack the sulfonium ion to give the more oxy-stabilized ion **2b**[7]. Loss of a proton then leads to (phenylthio)furan **3**, which is hydrolized into butenolide **4** in a separate reaction.

Thermal elimination[8] of water from sulfoxide **2** may lead to the sulfonium ion **2c**, which is attacked by a hydroxyl group of the hydrated aldehyde to yield **2d**. Elimination of thiophenol from this unstable intermediate will then lead to a hydroxyfuran , which will tautomerize into butenolide **5**.

Regioisomerically annulated butenolides are often found in nature side by side within the same class of terpenes such as drimanes, lactaranes, or spongianes. The approach, described here, enables the synthesis of such a set of related natural products from one common intermediate allylic sulfoxide.

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References and Notes

1. (a) Jansen, B. J. M. *Total Synthesis of Insect Antifeedant Drimane Sesquiterpenes*, Agricultural University, Wageningen, **1993**. (b) Jansen, B. J. M.; de Groot, Ae. *Nat. Prod. Reports* **1991**, *8*, 319. (c) de Groot, Ae.; Jansen, B. J. M. *J. Org. Chem.* **1984**, *49*, 2034. (d) Nakano, T. *Studies in Natural Products Chemistry. Stereoselective Synthesis*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, vol. 4, **1989**; pp. 403-429. (e) Jommi, G.; Pagliarin, R.; Sisti, M.; Travecchia, P. *Synthetic Commun.* **1989**, *19*, 2467. (f) Ley, S. V.; Mahon, M. *J. Chem. Soc. Perkin Trans. I 1983, 1379.*
2. (a) Corey, E. J.; Jautelat, M. *Tetrahedron Lett.* **1968**, 5787. (b) Ager, D. J. *J. Chem. Soc. Perkin Trans. I* **1983**, 1131. (c) Mathew, J. *J. Org. Chem.* **1990**, *55*, 5294.
3. Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1962**, *27*, 1615.
4. Sowerby, R. L.; Coates, R. M. *J. Am. Chem. Soc.* **1972**, *94*, 4758.
5. Reuvers, J. T. A.; de Groot, Ae. *J. Org. Chem.* **1984**, *49*, 1110.
6. Satisfactory spectroscopic data, together with HRMS data, were obtained for all compounds.

   6d mp 97-99°C; ^{1}H NMR δ= 0.72 (s, 3H), 1.1-2.3 (m, 13H), 4.63 (t, *J* = 2 Hz, 2H); IR (cm^{-1}) 1750, 1670; HRMS, calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1304; MS *m/e* (%) 206 (49, M$^+$), 191 (4), 177 (12), 111 (76), 96 (100), 81 (93).

   7d mp 39-40°C; ^{1}H NMR δ = 1.17 (s, 6H), 1.5-2.4 (m, 6H), 4.70 (t, *J* = 2 Hz, 2H); IR (cm^{-1}) 1765, 1675; HRMS, calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0994; MS *m/e* (%) 166 (52, M$^+$), 151 (43), 137 (19), 123 (37), 121 (100), 97 (63), 95 (36), 93 (45), 70 (67).

   8d mp 113-115°C; ^{1}H NMR δ = 1.06 (s, 3H), 1.2-1.9 (m, 11H), 2.1-2.4 (m, 2H), 4.69 (t, *J* = 2.3 Hz, 2H); IR (cm^{-1}) 1745, 1670; HRMS, calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1306; MS *m/e* (%) 206 (35, M$^+$), 191 (18), 161 (81), 112 (100), 95 (97), 91 (56).

   9d mp 120-122°C (lit[1f] 120-123°C); ^{1}H NMR δ = 0.92 (s, 3H), 0.95 (s, 3H), 1.16 (s, 3H), 1.1-2.0 (m, 9H), 2.2-2.4 (m, 2H), 4.69 (ddd, *J* = 0.75, 2, 3 Hz, 2H); IR (cm^{-1}) 1745, 1665; HRMS, calcd for $C_{15}H_{22}O_2$ 234.1620, found 234.1615; MS *m/e* (%) 234 (17, M$^+$), 219 (100), 189 (26), 151 (56), 123 (18), 77 (20).
7. In the presence of 3 equivalents of sodium acetate the reaction takes another pathway and (±)-confertifolin **5** was obtained in 75 % yield.
8. Wladislaw, B.; Marzorati, L.; Biaggio, F. C. *J. Org. Chem.* **1993**, *58*, 6132.

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