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A New Approach to the Synthesis of Alpha-Methylene-beta-hydroxy-gamma-butyrolactones

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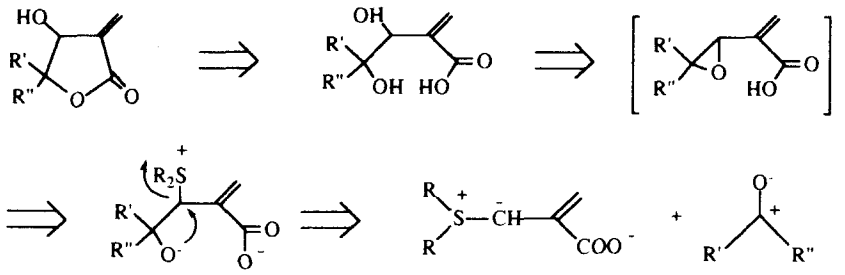
Abstract:

Ylides generated from the sulfonium salts of methacrylic acid derivatives reacted with aldehydes and ketones in a "one-pot" synthesis of α-methylene-β-hydroxy-γ-butyrolactones.

Unsaturated sesquiterpene lactones are common constituents of most genera of compositae and have been reported to have a wide range of biological activity. [1] The α-methylene-β-hydroxy-γ-butyrolactone system is one of several observed structural modifications. [2] The presence of the β-hydroxyl appears to inhibit the allergic contact dermatitis (ACD) often observed with other unsaturated lactones. [3] It also results in an enhancement of its cytotoxic properties. [4]

Although several methods have been developed for the synthesis of α-methylene-β-hydroxy-γ-lactones, [1,5] the protocols often involve multiple steps and give overall low yields. A retrosynthetic analysis of the hydroxy lactone system (I, Scheme 1)) suggests that the availability of a suitable epoxide would provide a new opportunity for synthesis not previously examined. It appeared that the epoxide could be generated conveniently from an aldehyde or ketone and a sulfonium ylide. Moreover, this approach would provide an opportunity for the synthesis of a wide array of structures.

Scheme 1: The Retrosynthetic Analysis of α-Methylene-β-hydroxy-γ-butyrolactones



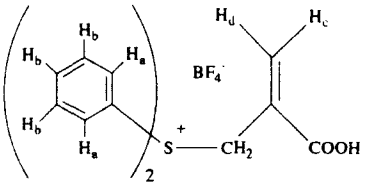
The diphenyl sulfonium salt was prepared from commercially available α-bromomethylacrylic acid, diphenyl sulfide and silver tetrafluoroborate. The less reactive diaryl sulfide was chosen to avoid rearrangement of the allylic sulfonium ylide generated from alkyl sulfides. Several bases were evaluated for ylide generation (CH_3Li, LDA, n-butyl lithium, t-butyl lithium) with the best overall results obtained from a fresh bottle of t-butyl lithium. The formation of the ylides and the addition of the aldehyde and ketone were performed at low temperatures (-78°C) under nitrogen. After acidification in the same flask, the desired β-hydroxy-α-methylene-γ-butyrolactone was isolated in generally high yields. It has not been possible to determine whether the epoxide is opened by the carboxylate anion or if the ring opens during the acidification process as no intermediates have been observed under the experimental conditions used.

General Procedures for the Preparation of α-Methylene-β-Hydroxy-γ-Butyrolactones (2)-(7) [7]

The carbonyl compound (1.2mmol) was introduced via syringe to the stirred solution of sulfonium ylide at -78°C. The mixture was stirred for an additional 45 min at -78°C and then warmed to 0°C and stirred for 45 min. Sulfuric acid (6M) was then used to acidify (at 0°C) the solution to pH 5-6. The system was warmed to room temperature (20°C) and kept for 50 min. Finally, the THF was evaporated in vacuo, and the resulting mixture extracted with ether (3 x 15ml). The combined ether extract were dried overnight with $MgSO_4$. Removal of the solvent in vacuo gave a yellow-green viscous oil.

A solution of silver tetrafluoroborate (5.85g, 30 mmol) and diphenyl sulfide (11.16g, 60 mmol) in anhydrous acetone (20ml) was protected from light with aluminum foil and stirred at 0°C for 15 min. 2-(Bromomethyl)acrylic acid (5.94g, 36mmol) in anhydrous acetone (15ml) was dropwise added during 10 min. After 30 min, the mixture was raised to room temperature (20°C) and stirred for an additional 24 hrs, the mixture was then gravity filtered, and the precipitate washed with anhydrous acetone. The

Figure 1.

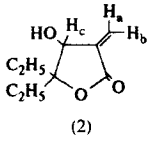
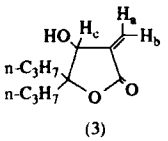
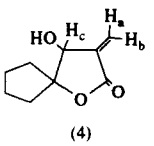
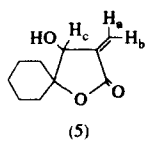
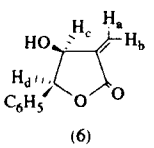
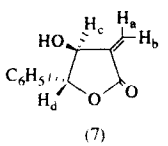


(1)

1700cm-1 (carbonyl), 1630cm-1 (vinyl), 1130cm-1, 117cm-1 (fluoroborate).

δ 8.2[m, 4H, H_a], 7.8[m, 6H, H_b], δ 6.6[s, 1H, H_c cis to carbonyl group], δ 6.3[s, 1H, H_d cis to -CH_2-];], δ 5.4[d, 2H, -CH_2-, J_{gem}=0.72Hz].

Table 1. The MS, IR, and NMR (200 MHz) data for products 2 - 7.

	Yield (%)	MS (m/e)	IR (cm^{-1})	^{1}H-NMR (ppm)
 (2)	70	141 (M^+ -C_2H_5), 123, 113, 95, 87, 84, 67, 57, 56, 55.	3200-3600cm^{-1}(OH), 1745cm^{-1}(C=O), 1672cm^{-1}(C=C), 1200cm^{-1}, 1270cm^{-1}(C-O).	0.90-0.99[m(d-t), 6H, 2-CH_3], 1.63-1.77[m(d-q), 4H, 2-CH_2-], 4.60[t, 1H, H_c, J=2.26Hz], 5.90[d, 1H, H_b, J_{bc}=2.13Hz], 6.35[d, 1H, H_a, J_{ac}=2.47Hz].
 (3)	32	155 (M^+ -C_3H_7), 137, 127, 115, 109, 97, 84, 81, 73, 56, 55.	3200-3600cm^{-1}(OH), 1743cm^{-1}(C=O), 1675cm^{-1}(C=C), 1195cm^{-1}, 1280cm^{-1}(C-O).	0.90-1.00[m, 10H, 2CH_2CH_3], 1.30-1.50[m, 4H, 2-CH_2-], 4.60[t, 1H, H_c], 5.87[d, 1H, H_b, J_{bc}=1.80Hz], 6.43[d, 1H, H_a, J_{ac}=2.16Hz].
 (4)	82	168 (M^+), 140 (M^+ -H_2O), 122, 111, 85, 84, 67, 57, 56, 55.	3200-3600cm^{-1}(OH), 1743cm^{-1}(C=O), 1673cm^{-1}(C=C), 1280cm^{-1}(C-O).	1.60-1.80[m, 8H, -$(CH_2)_4$-], 4.67[t, 1H, H_c, J=1.93Hz], 5.68[d, 1H, H_b, J_{bc}=1.87Hz], 6.29[d, 1H, H_a, J_{ac}=2.09Hz].
 (5)	82	182 (M^+) 164 (M^+ -H_2O), 139, 111, 99, 84, 81, 56, 55.	3200-3600cm^{-1}(OH), 1746cm^{-1}(C=O), 1675cm^{-1}(C=C), 1265cm^{-1}, 1190cm^{-1}(C-O)	1.40-1.90[m, 10H, -$(CH_2)_5$-], 4.44[t(d-d), 1H, H_c, J=1.95Hz], 5.91[d, 1H, H_b, J_{bc}=1.84Hz], 6.38[d, 1H, H_a, J_{ac}=2.16Hz].
 (6)	87	190 (M^+), 172 (M^+ -H_2O), 144, 107, 106, 105, 84, 79, 77, 56, 55.	3200-3699cm^{-1}(OH), 1764cm^{-1}(C=O), 1678cm^{-1}(C=C), 1600cm^{-1}, 1580cm^{-1}, 1500cm^{-1}, 1480cm^{-1}(C C), 1265cm^{-1}(C-O).	4.69-4.73[(d-t), 1H, H_c], 5.19-5.21[d, 1H, H_d, J=5.17Hz], 5.96-5.97[d, 1H, H_b, J_{bc}=2.18Hz], 6.45-6.46[d, 1H, H_a, J_{ac}=2.50Hz], 7.30-7.41[m, 5H,C_6H_5].
 (7)				5.00-5.05[(d-t), 1H, H_c], 5.56-5.59[d, 1H, H_d, J=6.01Hz], 6.00-6.01[d, 1H, H_b, J_{bc}=1.70Hz], 6.49-6.50[d, 1H, H_a, J_{ac}=2.50Hz], 7.30-7.40[m, 5H,C_6H_5].

combined filtrate was evaporated in vacuo and the resulting oil crystallized after dissolving in ethanol and the subsequent addition of ether. Recrystallization in a similar fashion produced a white powder (5.75g, 53%), mp 113-115°C. The structure of the sulfonium fluoroborate (**1**) was confirmed by **IR** and **NMR** (Figure 1). Diphenyl acrylic acid sulfonium fluoroborate (**1**) (0.2g, 0.56mmol) was dissolved in anhydrous THF (4ml) at -78°C under nitrogen. After 20 min. to allow temperature equilibrium to be established, t-BuLi (1.7M in pentane), (0.71ml, 1.2mmol) was added to the solution via syringe during 5 min. The mixture rapidly turned dark red with the formation of ylide.

The crude lactone was chromatographed on silica gel 60 (9.4g in a 1 x 24 cm column and eluted successively with hexane-ether (120 ml 4:1 and 80 ml 1:1) and ether [9]. The lactones were traced by GC/MS, and were found in the hexane-ether (1:1) extract. The five α-methylene-β-hydroxy-γ-butyrolactones (**2**)-(**7**) synthesized using this method were examined by **GC/MS, IR,** and **NMR** (Table 1). [6,8,9] A 3:2 ratio of diastereomers is observed for compound mixture (**6**/**7**) based on ^{1}H-NMR. High resolution mass spectrometry (CI, NH_3, Finnigan MAT 95) confirmed the molecular formulas for each new hydroxy lactone ($M + NH_4^+$; **2**, 188.1271 **3**, 216.1586 **4**, 186.1125 **5**, 200.1297 **6**/**7**, 208.0961)

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