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# A PRACTICAL ROUTE TOWARDS α,β-UNSATURATED δ-LACTONES BASED ON A [3+3] STRATEGY. SYNTHESIS OF (-)-ARGENTILACTONE

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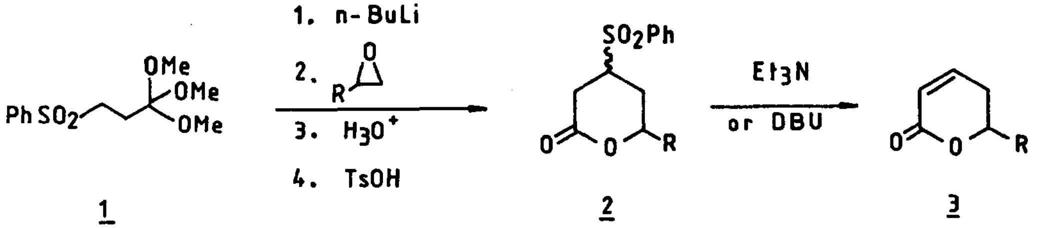
Abstract : The lithio derivative of methyl 3-phenylsulphonylorthopropionate 1 reacts with epoxides to give, after acidic work-up and treatment with p-toluenesulphonic acid, β-phenylsulphonyl δ-lactones 2. These are directly converted into the corresponding α,β-unsaturated δ-lactones 3 upon treatment with triethylamine or DBU. An application of this new method to the synthesis of (-)-argentilactone 4 is described.

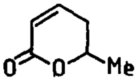
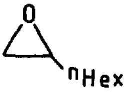
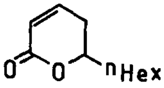
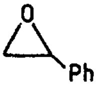
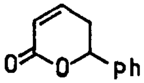
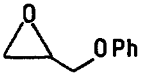
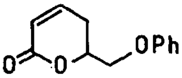
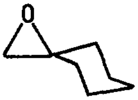
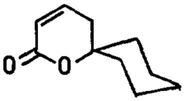
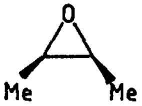
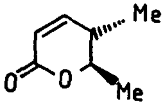
Methyl 3-phenylsulphonylorthopropionate 1 is a cheap and practical homoenolate reagent which has been used in efficient synthetic routes to cyclopentanones[1] or butenolides[2]. We report here the reaction of 1 with epoxides as a practical method of synthesis of α,β-unsaturated δ-lactones[3]. These are key structural units of many natural products as well as valuable synthetic intermediates[4].

The lithio derivative of 1 was reacted with a variety of epoxides[5] at room temperature to yield, after acidic work-up, the corresponding δ-hydroxy esters together with a variable amount of lactones 2 (Scheme 1). The crude mixtures were converted into 2 with a catalytic amount of p-toluenesulphonic acid. δ-Lactones 2 could be isolated as mixtures of diastereoisomers after flash chromatogaphy. More conveniently the crude lactones 2 were directly converted into the corresponding unsaturated lactones 3 by treatment with triethylamine or DBU. Overall yields[6] from 1 without purification of intermediates are shown in Table 1. They are good with monosubstituted epoxides (entries a-d) but significantly lower with the more sterically hindered disubstituted epoxides (entries e-f).



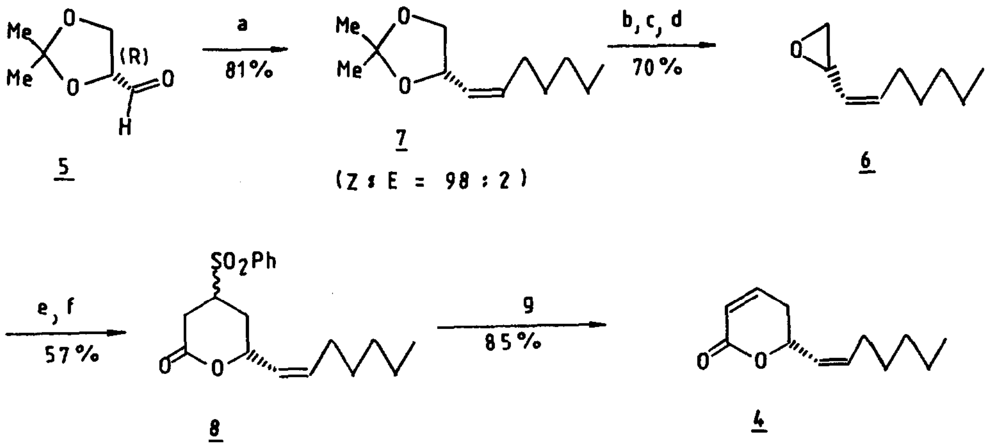
Scheme 1

Table I : Synthesis of α,β-unsaturated δ-lactones 3.

| Entry | Epoxide | Lactone 3 | Yield (%)[a] |
|---|---|---|---|
| a |  |  | 82 |
| b |  |  | 67 |
| c |  |  | 55 |
| d |  |  | 74 |
| e |  |  | 31 |
| f |  |  | 35 |

[a] Overall yield of pure products after silica gel chromatography (0.5 - 1.0 mmole scale)

The method was applied to an enantioselective synthesis of (-)-argentilactone 4[7] from the acetonide of (R)-glyceraldehyde 5 (Scheme 2). The chiral vinyl epoxide 6 was obtained in a straightforward manner. The Wittig reaction on 5 is highly cis-stereoselective in THF at -50°C to 20°C. The conversion of 7 into the epoxide 6 was effected by a standard method. Reaction of the lithio derivative of 1 with 6 and cyclisation gave the lactones 8. In this case, better overall yields were obtained by isolation and purification of 8 by chromatography. Reaction of 8 with triethylamine gave (-)-argentilactone[8]. The overall yield from 5 was 27.5 %.



*a : $Ph_3\overset{+}{P}$-$\overset{-}{C}H$-$(CH_2)_4CH_3$, THF, -50°C → 20°C, 2hrs; b : 1M HCl, $CH_3OH$, 20°C, 24hrs; c : TsCl (1.15 equiv), pyridine, 0°C → 20°C, 3hrs; d : 4M NaOMe (1.0 equiv) in MeOH, THF, 0°C, 1hr; e : $PhSO_2$- CHLi-$CH_2CH(OMe)_3$ (1 equiv), THF-HMPA, -20°C → 20°C, 6 hrs then 3M $H_2SO_4$, 20°C, 30 min.; f: TsOH (0,25 equiv), $CH_2Cl_2$, 20°C, 18hrs, chromatography ; g : $Et_3N$ (5 equiv.), $CH_2Cl_2$, 20°C, 1hr, chromatography.*

Scheme 2

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## References and Notes

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