

LITHIUM TRIENOLATE OF SORBIC ACID AS A d^6 SYNTHON. SYNTHESIS
OF 7-HYDROXY 2,4-DIENOIC ACIDS.

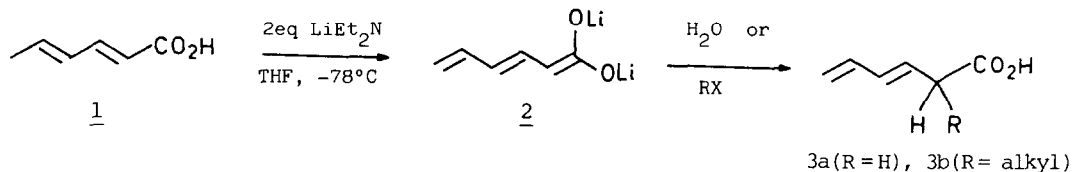
P. Ballester, A. Costa, A. García-Raso, A. Gómez-Solivellas,
and R. Mestres*

Departamento de Química Orgánica, Universidad de Palma de Mallorca,
Palma de Mallorca 07071, SPAIN.

Abstract: The trienolate 2 of sorbic acid is an easily available d^6 synthon. Preparation of 7-hydroxy dienoic acids 5 from ketones is here described.

Acyclic 1,n bifunctional compounds can be disconnected into readily accessible acceptors and monofunctional donor synthons when n equals 5 or less. A plethora of synthetic procedures are consequently at hand for these systems. For values of n larger than 5, synthetic targets are disconnected either into a cyclic system, or subject to a stepwise disconnection, as monofunctional d^4 synthons and donors of higher order are rare¹. It has been already shown that unsaturated carboxylic acid dienolates behave as d^4 synthons²⁻⁵, and we wish to introduce now the lithium trienolate 2 of the cheap commercially available sorbic acid 1 as a d^6 synthon.

We hoped that the trienolate 2 would parallel the behaviour of dienolates of unsaturated carboxylic acids. These are protonated and alkylated at their



α -carbon atom^{4,6}. Interaction with carbonyl compounds occurs fast and reversibly through α -addition and slowly through γ -addition, and allows both kinds of adducts being obtained^{2,3,5}. Indeed, protonation or alkylation of the lithium trienolate derived from sorbic acid or from its methyl ester have been reported

by several authors to occur at the α -carbon atom⁷⁻⁹. Similarly, we have found that the trienolate 2 interacts first with carbonylic compounds through the α -carbon atom, and that this addition is reversible for ketones. 7-Hydroxy-2,4-dienoic acids are obtained by interaction through the ω -carbon atom on long reaction time at room temperature in THF.

The trienolate 2 was generated by slow addition of a solution of sorbic acid in THF to 2 equivalents of lithium diethylamide (from lithium naphthalenide) in THF at -78°C ¹⁰. The carbonylic compound (one equivalent) was added at -78°C and the solution allowed to warm up. Reactions were monitored by ¹H-NMR spectra of esterified aliquots. When compared to equivalent runs for dienolates^{3,5,10}, addition and rearrangement processes were now found to occur slower. This was evidenced by the presence of 3,5-hexadienoic acid 3a resulting from unreacted trienolate for short reaction times or low temperatures. For unhindered carbonyl substrates only α -adducts 4 were observed first. ω -Adducts 5 developed more slowly along with simultaneous decrease of the α -adducts 4. Rates for α - or ω -additions became closer for hindered substrates, paralleling again earlier findings for dienolates¹¹. For an aldehyde, namely benzaldehyde, as substrate only α -adduct was observed after 24h at room temperature.

Experimental conditions for preparative runs, along with yields of pure adducts and methods of purification have been included in the Table I.

Table I: Reaction of trienolate 2 with carbonylic compounds R_1COR_2

Entry	R ₁	R ₂	temp. (°C)	time (h)	Crude yield (%)	<u>4</u> (%)	<u>5</u> (%)
1	-(CH ₂) ₅ -		-78	0,5	83	80 ^a	
2	"		30	24	70		28 ^b
3	-(CH ₂) ₁₁ -		0	3	85	76 ^c	
4	"		30	72	64		15 ^b
5	H	Ph	-78	0,5	87	75 ^b	
6	Me	<u>t</u> -Bu	30	24	65		42 ^b
7	Me	Ph	30	24	90		58 ^c
8	Me	(CH ₂) ₂ CH=C(CH ₃) ₂	30	24	86		55 ^b
9	Ph	Ph	30	3	85		68 ^c

a) Characterized spectroscopically.

b) Isolated as methyl ester by column chromatography on silica gel and elution with hexane/ethyl ether (8:2 v/v).

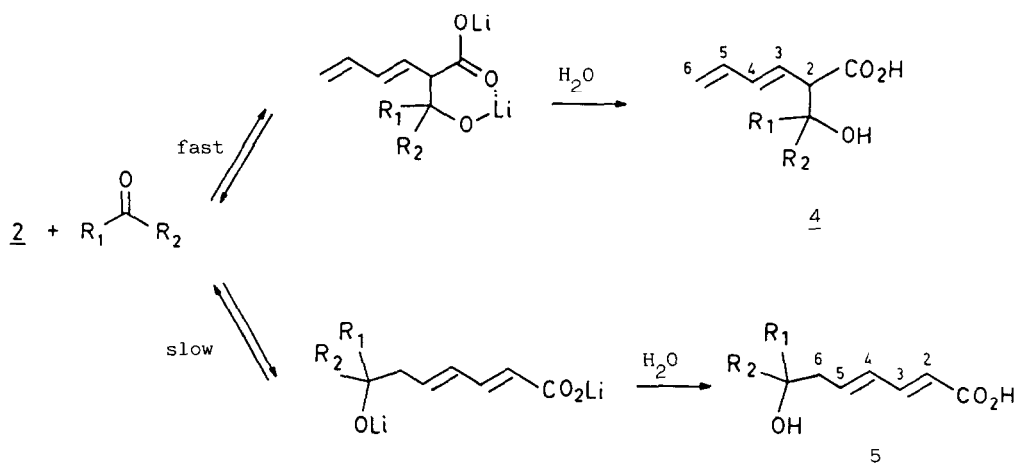
c) Isolated as acid by crystallization.

Due to their easy polymerization⁹, 2-(1-hydroxyalkyl)-3,5-dienoic acids 4 were purified only when the crude mixtures obtained from runs carried out at low temperature resulted free from 3,5-hexadienoic acid 3a or ω -adducts 5 (entries 1,3 and 5). For the same reason these isolated adducts were

characterized just spectroscopically¹², except for the hydroxy dienoic acid 4 derived from cyclododecanone (entry 3), which was obtained as a crystalline stable material¹³.

Crudes for ω -adducts contained 3,5-hexadienoic acid 3a and polymeric materials which troubled the purification of the 7-hydroxy acids 5. This drawback was especially important for runs carried out under heating, in the presence of excess of ketone or of HMPA, as well as for higher concentrations of reagents¹⁴. Poor crude yields for acid fractions were then obtained, and the spectra showed low or no incorporation of carbonyl compound. The presence of those undesirable materials is due to the basic character of the trienolate, which is capable of removing a proton from the ketone, and the resulting sorbic and 3,5-hexadienoic lithium salts are prone to Michael and Diels-Alder additions.

2(E),4(E)-configurations for all 7-hydroxy-2,4-dienoic acids 5 obtained



have been established by 1H -NMR (200 MHz)¹². A trans configuration is similarly observed for the internal double bond of the α -adducts 4. These features are clearly indicative of the all trans shape, as depicted above, of the trienolate dianion 2¹⁵, and strongly suggest that the α to ω rearrangement occurs through a α -retroaddition and ω -addition mechanism, and not through a [1,5] sigmatropic concerted process, for which a cis configuration of the α -adduct would be required in order to attain the cyclic transition state, and which would be expected to lead to 2(E),4(Z) dienic system.

Work is in progress in order to evaluate the scope and synthetic possibilities of the present and other trienolates.

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- 12.- Selected spectral data are given: compound 4 ($R_1, R_2 = -(CH_2)_{11}-$) (200 MHz, $CDCl_3$) δ 1,1-1,5(m, 22H); 3,00(d, H_2 , $J = 9,7$ Hz); 3,35(OH); 3,67(s, 3H); 5,05(dd, H_6 , $J = 10,0$ and 2,0Hz); 5,12(dd, H_6 , $J = 16,5$ and 2,2 Hz); 5,83(dd, H_3 , $J = 9,7$ and 14,6 Hz); 6,14(dd, H_4 , $J = 10,1$ and 14,7 Hz); 6,29(ddd, H_5 , $J = 16,6$, 10,1 and 10,1 Hz).
Compound 5 ($R_1 = CH_3$, $R_2 = t-Bu$) (200 MHz, Acetone- D_6) δ 0,95(s, 9H); 1,08(s, 3H); 2,28(dd, H_6 , $J = 13,9$ and 8,0 Hz); 2,50(ddb, $J = 13,7$ and 5,2 Hz) 5,82(d, H_2 , $J = 15,4$ Hz); 6,27(ddb, H_4 , $J = 10,5$ and 15,4 Hz); 6.39(ddd, H_5 , $J = 8,2$, 5,6 and 15,4 Hz); 7,25(dd, H_3 , $J = 10,0$ and 15,4 Hz).
- 13.- Unless otherwise stated in the text, all new compounds gave satisfactory elemental analyses and consistent NMR and IR spectra.
- 14.- In a typical run, 18 mmols of sorbic acid in 60 ml of THF were added to a solution of lithium diethylamide in 80 ml of THF at $-78^\circ C$ (from 40 mmols of lithium wire). To that mixture 18 mmols of the ketone in 60 ml of THF were added. At the end of these operations a total volume of 210-240 ml was reached.
- 15.- For a review on the shape of related dianions, see R. Bates in E. Buncl and T. Durst, Editors, "Comprehensive Carbanion Chemistry" Part A, Elsevier 1980, p. 1.

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