

Enediolates and Dienediolates of Carboxylic Acids in Synthesis. Synthesis of β,γ -Epoxyacids from α -Chloroketones.

Eva M. Brun, Salvador Gil, Ramon Mestres, Margarita Parra* and Félix Villar

Departament de Química Orgànica, Universitat de València, Burjassot, València, Spain.

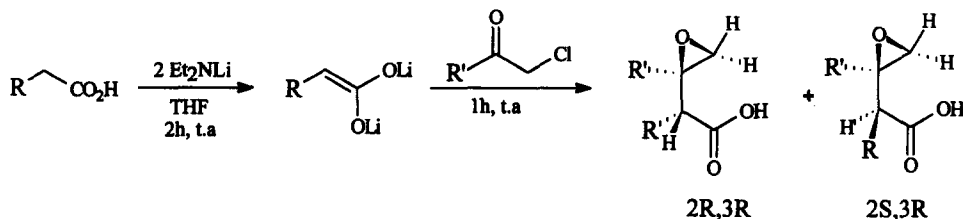
Received 12 September 1997; revised 21 November 1997; accepted 28 November 1997

Abstract: Lithium dienolates of saturated or α,β -unsaturated acids react with α -chloroketones provide a convenient method for preparation of highly substituted β,γ -epoxyacids. These highly reactive compounds lead in most cases to variable amounts of the corresponding β -lactones and allylic alcohols. © 1998 Elsevier Science Ltd. All rights reserved.

Chemical components of pheromones are unstable on exposure to air and sunlight, a feature which constitutes a serious drawback for their application in pest control. This problem can be surmounted by slow release formulations which provide physical protection to the unstable volatile components of the pheromone or other semiochemicals. Release from a propheromone providing chemical protection to the reactive sites of the pheromone would constitute a substantial improvement.¹ A likely convenient system for chemical protection and slow release of unsaturated semiochemicals could be based on a *retro* Diels-Alder process where the corresponding cyclo-adducts should be cleaved slowly by light or heat as natural activating agents at the crop fields.²

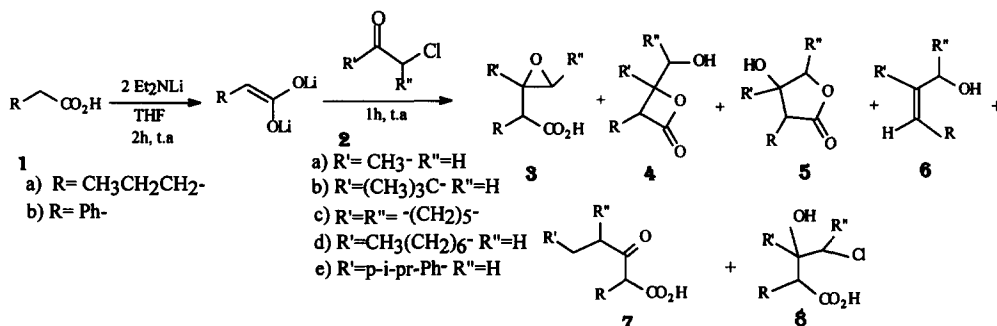
During our studies on the synthesis of this adducts through butenolides³ we were interested in the preparation of β,γ -epoxyacids as key intermediate in this process. These important intermediate compounds in organic synthesis⁴ are normally prepared from α,β -unsaturated ester by double bond deconjugation and oxidation.⁵

We describe here a convenient method to prepare highly substituted β,γ -epoxyacids from lithium dienolates of saturated or α,β -unsaturated acids and α -chloroketones. Ketones **2** are either commercially available or prepared by standard methods.^{6,7} Generation of lithium dienolate of acids **1a** and **1b** was best



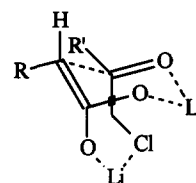
performed by reaction with 2.2 equivalents of LDE for 2 h at room temperature and were allowed to react with ketones **2** for 1 hour at room temperature. The results are summarized in Table 1.

TABLE 1
Addition of lithium diolates of saturated acids to α -chloroketones



Entry	Acid	α -chloroketone	Yield	Conversion	% 3	% 4	% 5	% 6	% 7	% 8
1	1a	2a	71%	74%	74	26	—	—		
2	1a	2b	71%	82%	89	—	—	11		
3	1a	2c	62%	71%	—	—	100	—		
4	1a	2d	50%	53%	50	—	50	—		
5	1a	2e	68%	68%				100		
6	1b	2a	86%	91%	72	28				
7	1b	2b	73%	81%	82				18	
8	1b	2c	85%	87%	72					28
9	1b	2d	61%	74%	65	35				

As shown in Table 1, the major product is in most cases the corresponding β,γ -epoxyacid **3** as a mixture of diastereoisomers ranging from a 7:3 to 100:0 ratio. Two chair-like conformations are possible for the addition transition state, and that leading to the R*,R* diastereoisomer would be favored, although configurations have not been unambiguously determined.



Other reaction products **4** to **8** come, either from a different reaction pathway as explained below, or from transformation of the β,γ -epoxyacids during work up. The β,γ -epoxyacids could undergo conversion into β -lactones **4** (as diastereoisomeric mixtures) through an S_N1 or S_N2 intramolecular process. In fact, when a crude mixture from the reaction of **1b** and **2a** was stirred overnight in acidic aqueous solution, the corresponding β -lactone was obtained in 55 % yield. Allylic alcohols **6** may result from the β,γ -epoxyacids **3**, either through an intramolecular process or a syn thermal cycloelimination from **4**. For entries 2 and 5 a Z geometry for the double bond of the allylic alcohol **6** was established by NOE experiments. In both cases direct decarboxylation from **3** is more likely to occur as no β -lactones have been observed even at trace level. On the other side R*,R* epoxyacids should lead to *cis* β -lactones through an S_N2 process which in turn would have delivered allylic alcohols with an E geometry for the double bond.

According to Baldwin cyclization rules γ -lactones should not be expected from β,γ -epoxyacids and their formation when **1a** reacts with **2d** and **2c** should be the result of an increasing hindrance for an *anti* orientation of alkoxide and chlorine groups, which gives a better chance to substitution of chlorine by the carboxylate group. Accordingly, when chlorine is highly hindered halohydrine results (entry 8). When the carbonyl group is highly hindered substitution of chlorine by the carboxylate group is observed (entry 7).

The study was extended to unsaturated acids (**9a** to **9c**) because its dienolate chemistry is more familiar to us.^{8,9} In this case quantitative generation of lithium diendiolates is achieved at low temperature and its reactions with ketones **2a** and **2b** are summarized in Table 2. As before β,γ -epoxyacids **10** are the major products that led again to β -lactones **11**.

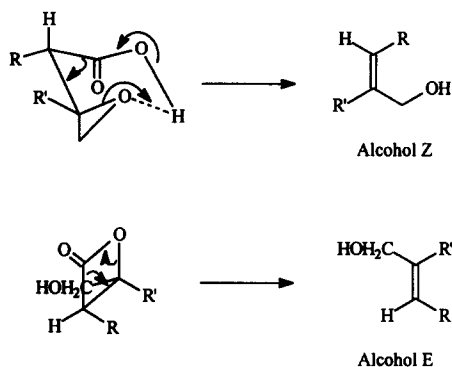
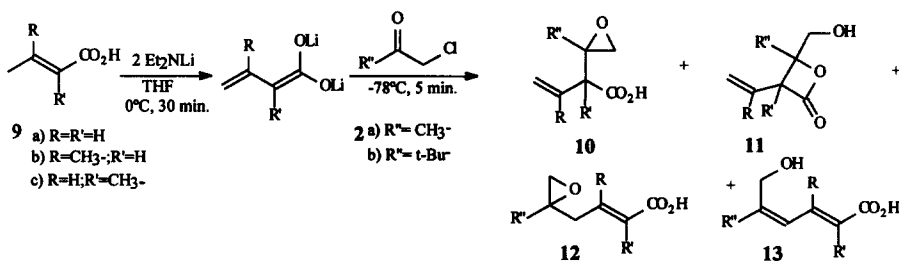
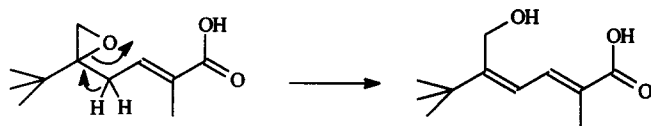


TABLE 2

Addition of lithium diendiolates of unsaturated acids to α -chloroketones



Entry	Acid	α -chloroketone	Yield	% 10	% 11	% 12	% 13
1	9a	2a	70%	45	55	—	—
2	9a	2b	90%	100	—	—	—
3	9b	2a	86%	63	37	—	—
4	9b	2b	79%	50	50	—	—
5	9c	2a	79%	58	42	—	—
6	9c	2b	82%	—	—	71	29



Only the bulky ketone **2b** under the severe steric control shown by tiglic acid (**9c**) led to γ -position attack, product **12** that rearranges in part to the highly conjugated system **13**.

As a conclusion, the addition of carboxylic acid dianions to α -chloroketones led to β,γ -epoxyacid carboxylates which on work-up afford the corresponding epoxyacids and partly evolve to β -lactones or allylic alcohols. Amounts of these side products critically depend on the starting material and work up conditions.

Acknowledgment. The present research has been financed by CICYT (PB89-0421).

REFERENCES

1. Jutsum, A.R. and Gordon, F.S. (Eds.), "Insect pheromones in plant protection", J. Wiley and sons 1989.
2. a) Carruthers, W.; "Cycloaddition reactions in Organic Synthesis"; Pergamon Press 1990. b) Ripoll, J. L.; Rouessac, A. and Rouessac, F. *Tetrahedron* **1978**, *34*, 19-40. c) Lasne, M. C. and Ripoll, J. L. *Synthesis*, **1985**, 121-143. c) Gustafsson, J. And Sterner, O.; *J. Org. Chem.* **1994**, *59*, 3994-3997.
3. a) Marshall, J.A. and Dubay, N.J.; *J. Org. Chem.* **1993**, *58*, 3602-3603. b) Krasnoslobodskaya, L.D. and Gol'dfab, Ya.L. ; *Russ. Chem. Reviews* **1969**, *38*, 389-406. c) Schmit, C. ; Sahraoui-Taleb, S. ; Differding, E. ; Dehasse-De lombart, C.G. and Ghosez, L.; *Tetrahedron Letters* **1984**, *25*, 5043-5046. d) Jansen, B.J.M. ; Bouwman, C.T. and Groot, A.de ; *Tetrahedron Letters* **1994**, *35*, 2977-2980. e) Trost, B.M. and McIntosh, M.C. ; *J. Am. Chem. Soc.* **1995**, *117*, 7255-7256.
4. a) Cormnier, R.A., Grosshans, C.A. and Skibbe, S.L., *Synth. Commun.* **1988**, *18*, 677-679. b) Roberts, S.M. in Barton, D. and Ollis, W.D., "Comprehensive Organic Chemistry, The Synthesis and Reactions of Organic Compounds" Vol. 2, 1979 p. 739-778.
5. Cory, R.M., Ritchie, B.M. and Shrier, A.M., *Tetrahedron Lett.* **1990**, *31*, 6789-6792.
6. Raina, S. and Singh, V. K., *Tetrahedron* **1995**, *51*, 2467-2476.
7. Leiserson, J.L. and Weissberger, A., Organic Synthesis Collect., Vol. III, 183 1955.
8. a) Parra, M., Mestres, R., Aparicio, D., Durana, N. and Rubiales, G., *J. Chem. Soc. Perkin Trans I* **1989**, 327-332. b) Aurell, M.J. ; Gil, S. ; Mestres, R. ; Parra, M. and Tortajada A.; *Tetrahedron* **1994**, *50*, 5109-5118. c) Aurell, M.J. ; Gil, S. ; Mestres, R. ; Parra, M. and Tortajada A. ; *J. Chem. Res., Synop.* **1994**, 276-277. d) Aurell, M.J. ; Ceita, L. ; Mestres, R. ; Parra, M. and Tortajada A.; *Tetrahedron* **1995**, *51*, 3915-3928.
9. BuLi in hexane (5 mmol) was concentrated by a flush of Ar and the residue dissolved in THF (2 ml) at -78°C. After 10 min at 0°C, Et₂NH (0.5 ml) was added dropwise at -78°C and the solution was stirred for 15 min. at 0°C. The carboxylic acid (2.25 mmol) in THF (2 ml) was then added dropwise at -78°C. After 30 min. at 0°C the solution was cooled at -78°C and the corresponding α-chloroketone (2'25 mmol) in THF (2 ml) was added slowly and stirring was continued for 1h. Water (15 mL) was added and the resulting mixture was extracted with ethyl ether (3x15 ml). After acidification with conc. HCl at 0°C (ice-water bath), the aqueous phase was extracted with ethyl acetate (3x15 ml). The solution was washed with brine and dried (MgSO₄). Evaporation of solvent, gave the crude acidic fraction.