Diastereoselective Michael Additions of β-Lactone Enolates to Dimethyl Maleate

Johann Mulzer,*[a] Alexander Chucholowski,[b] Ortrud Lammer,[a] Ibrahim Jibril,[c] and Gottfried Huttner[c]

[a] *Institut für Organische Chemie der Universität Düsseldorf, Universitätsstrasse 1, D-4000 Düsseldorf 1, West Germany*
[b] *Institut für Organische Chemie der Universität München, Karlstrasse 23, D-8000 München 2, West Germany*
[c] *Lehrstuhl für Synthetische Anorganische Chemie, Fakultät für Chemie der Universität Konstanz, Postfach 5560, D-7750 Konstanz, West Germany*

The Michael addition of the β-lactone enolates (**4**) to dimethyl maleate (**5**) proceeds with efficient stereocontrol of both of the newly formed chiral centres.

In many aldol type additions, enolate anions exhibit remarkably high diastereo- and enantiofacial stereo-selectivity.[1] However, no such stereocontrol has been achieved in the corresponding Michael additions. For instance, the formation of (**3**)

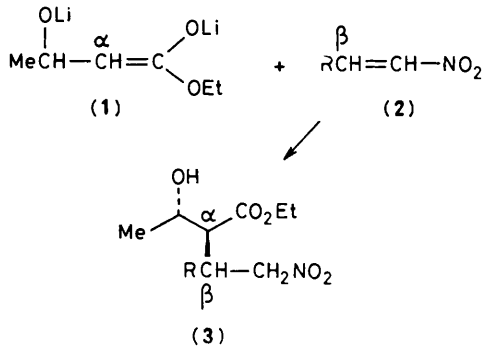


Table 1. Selected data for the addition of (**4**) to (**5**).[a]

(4)	R^1	R^2	Ratio of (6):(7)	Isolated yield of (6), % (m.p., °C)
a	Ph	Bu^t	89:11	73 (159—160)
b	Ph	Pr^i	82:18	68 (128—129)
c	Ph	Me	85:15	50 (oil)
d	Me	Bu^t	1:0[b]	45 (98—99)

[a] Compounds (**4a**—**e**) were prepared as previously described (refs. 3 and 6) treated with (**5**) (1 mol. equiv.) in tetrahydofuran at −78 °C for 1 h. After aqueous work-up the crude product was analysed by ^1H n.m.r. spectroscopy ($CDCl_3$, Me_4Si, 60 MHz). The (**6**):(**7**)-ratio was determined by machine integration of the 4′-H signals with an estimated accuracy of 5%. According to the n.m.r. spectra the additions were quantitative. Compounds (**6**) were isolated by crystallization from ether–pentane [(**6a,b,d**)] and by t.l.c. [(**6c**), silica gel, ether–pentane 1:1] respectively. At −78 °C the addition was irreversible; however, on warming the reaction mixture to room temperature prior to hydrolysis, dissociation into (**4**) and (**5**) was observed. [b] No (**7d**) could be detected.

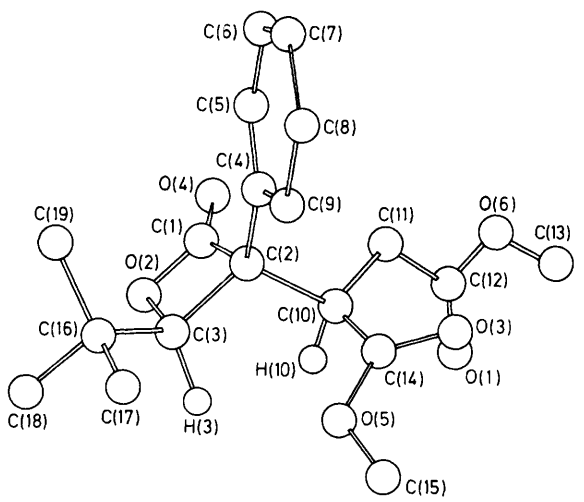
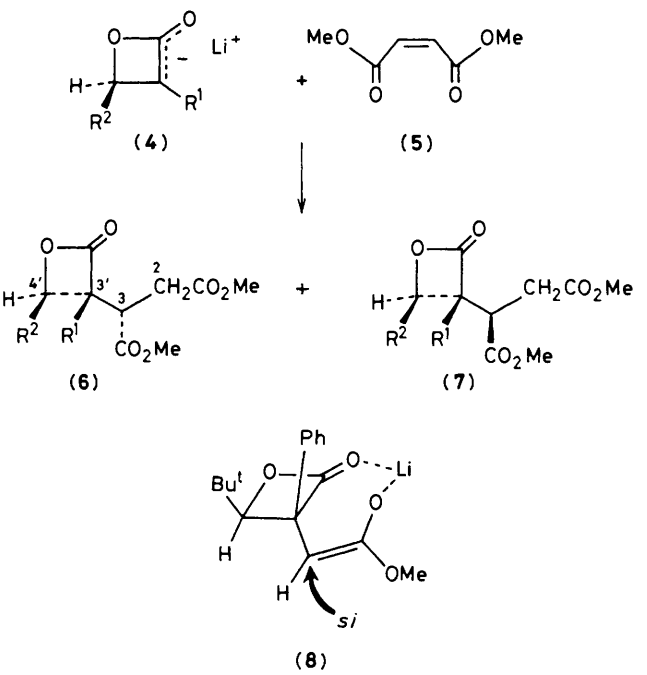


Figure 1. The molecular structure of (**6a**). Note the planar four-membered ring.

and (**1**) and (**2**) proceeds with high (95:5 and 85:15) stereoselectivity only with respect to attack at C_α, whereas the chiral centre at C_β is formed stereorandomly.[2]

We report that the β-lactone enolate (**4**), quite in analogy to their behaviour in aldol type additions,[3] undergo Michael additions to dimethyl maleate (**5**) to furnish (**6**) and (**7**) in quantitative yield (Table 1). The predominant formation of one [*i.e.*, (**6**)] out of four possible diastereoisomers indicates that the reaction proceeds with efficient stereocontrol of both of the newly formed chiral centres at C-3 and C-3′ relative to that already existing at C-4′. We call this phenomenon 'three



centre diastereoselectivity'.[3] The configuration of (**6a**) (Figure 1) was confirmed by an *X*-ray structural determination.† Compound (**7a**) was also prepared independently by *si*-[4] selective addition of methyl bromoacetate to the β-lactone ester enolate (**8**).‡

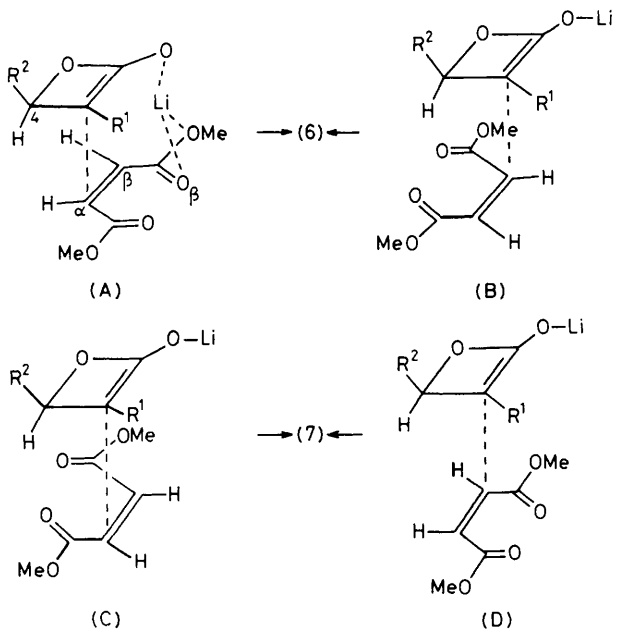
According to the Seebach–Prelog nomenclature[5] the topicity of the addition of (**4**) to (**5**) is *ul* with respect to the 3,3′- and *lk* with respect to the 3′,4′-bonds. The diastereofacial *lk*-stereocontrol is practically complete (>95%); it may be explained by the planarity of (**4**) which for steric reasons is attacked from the ring face opposite to R^2.[6] The enantiofacial *ul*-selectivity is reflected numerically in the (**6**):(**7**)-ratio (Table 1) which may be interpreted in terms of the transition states (A)—(D) (Scheme 1).

With regard to the double bond units in (**4**) and (**5**), (A) and (C) have *cis*- and (B) and (D) *trans*-geometries. In analogy with the aldolization reaction[1] a pericyclic mechanism may be envisaged; the lithium cation resides at C_β first, from where it may migrate to O_β subsequently. Alternatively a HOMO–LUMO complex may be postulated[7] between (**5**) and the enolate moiety of (**4**). On the basis of these two arguments the

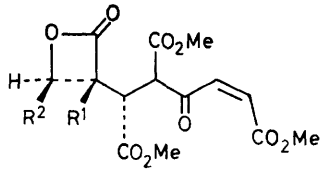
† *Crystal data:* $C_{19}H_{24}O_6$, M = 348.38, monoclinic, space group $P2_1/c$, a = 8.937(8), b = 22.51(2), c = 14.27(1) Å, β = 140.67(4)°, U = 1819 Å^3, Z = 4, D_c = 1.27 g cm^{-3}, $F(000)$ = 744, μ(Mo-K_α) = 1.0 cm^{-1}. Intensity data were recorded at −30 °C on a Nicolet *P*3 diffractometer (graphite monochromated Mo-K_α *X*-radiation, λ = 0.71069 Å) using an ω-scan with 2.0 < $\dot{\omega}$ < 29.3° min^{-1} and 2 < 2θ <42°. Of the 1958 reflections collected 1644 with $I > 2\sigma(I)$ were used in the structure determination. The structure was solved by direct methods using the SHELXTL program system and refined by least-squares. The final refinement converged to R_1 0.048 and R_w 0.057. To our knowledge, this is the first *X*-ray structural determination of a β-lactone derivative.

The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

‡ *si*-Selective additions to (**8**) (>85:15) have been observed for methyl iodide, methyl bromo- and iodo-acetate, and benzyl- and allyl-bromide: A. Chucholowski, Ph.D. Thesis, University of Munich, in preparation.



Scheme 1



(9)

trans-arrangements (B) and (D) have to be discarded. On comparing (A) and (C) the twofold advantage of (A) becomes evident. Firstly, it lacks the steric repulsion between the 4-H of (**4**) and the α-ester group of (**5**). Interactions of this kind determine the steric course of aldol additions to (**4**)[3] and may be the reason why dimethyl fumarate is practically inert towards (**4**) under the conditions described (Table 1, footnote a). Secondly, (A) alone allows the formation of a stable lithium complex between the *exo*-O of (**4**) and the β-ester oxygens of (**5**), thus fixing the reactants in a position suitable for the ensuing pericyclic electron migration.

Interestingly, (**4e**) [R^1 = 3,4-$(OMe)_2C_6H_4$, R^2 = Bu^t] adds to two molecules of (**5**) to give (**9**) [71%, m.p. 207—208 °C (decomp.)]. The reason for this different behaviour of (**4e**) is unclear as yet.

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Received, 16th May 1983; Com. 622

References

1 For some excellent reviews see: D. A. Evans, J. V. Nelson, and T. R. Taber, *Top. Stereochem.*, 1982, **13**, 1; T. Mukaiyama, *Org. React.*, 1982, **28**, 203; C. H. Heathcock in 'Asymmetric Synthesis,' vol. 2, ed. J. D. Morrison, Academic Press, New York, 1983, in the press.
2 M. Zügler, Th. Weller, and D. Seebach, *Helv. Chim. Acta*, 1980, **63**, 2005.
3 J. Mulzer and A. Chucholowski, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 777.
4 V. Prelog and G. Helmchen, *Helv. Chim. Acta*, 1972, **55**, 2581.
5 D. Seebach and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 654.
6 J. Mulzer and Th. Kerkmann, *J. Am. Chem. Soc.*, 1980, **102**, 3620; a similar kind of diastereofacial selectivity has been observed for electrophilic additions to the dianions of β-hydroxyesters: G. Frater, *Helv. Chim. Acta*, 1979, **62**, 2825; 2829; D. Seebach and D. Wasmuth, *ibid.*, 1980, **63**, 197.
7 J. Mulzer, G. Brüntrup, J. Finke, and M. Zippel, *J. Am. Chem. Soc.*, 1979, **101**, 7723.