[14] Crystal data for **2** at 168 K: $C_{40}H_{60}Nd_2Se_2$, monoclinic, $P2_1/n$, $a=8.5323(8)$, $b=20.5232(11)$, $c=11.6385(7)$ Å, $\beta=103.329(5)^\circ$, $V=1983.1(2)$ Å^3, $Z=2$. At convergence, $wR2=0.1261$ and GOF = 1.371 for 182 variables refined against all 4559 unique data (as a comparison for refinement on F, $R1=0.0505$ for those 4068 data with $(F>4\sigma(F))$.

[15] a) P. A. Böttcher, *Z. Anorg. Allg. Chem.* **1977**, *432*, 167–172; b) P. A. Böttcher, *Z. Anorg. Allg. Chem.* **1980**, *461*, 13–21; c) F. Hulliger, T. Z. Sigrist, *Z. Naturforsch. B* **1981**, *36*, 14–15; d) M. A. Ansari, J. A. Ibers, *Coord. Chem. Rev.* **1990**, *100*, 223–266, and references therein.

[16] W. J. Evans, S. E. Foster, *J. Organomet. Chem.* **1992**, *433*, 79–94.

[17] a) Crystal data for **3** at 168 K: $C_{40}H_{60}Sm_2Se_2$, monoclinic, $P2_1/n$, $a=8.5307(4)$, $b=20.4855(10)$, $c=11.5805(5)$ Å, $\beta=103.762(1)^\circ$, $V=1967.7(2)$ Å^3, $Z=2$. At convergence, $wR2=0.1530$ and GOF = 1.324 for 181 variables refined against all 4778 unique data (as a comparison for refinement on F, $R1=0.0510$ for those 4574 data with $(F>4\sigma(F))$. b) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-112873 and CCDC-112874. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Regio- and Stereoselective Synthesis of γ-Alkylidenebutenolides by Cyclization of Dilithiated 1,3-Dicarbonyl Compounds with *N,N′*-Dimethoxy-*N,N′*-dimethylethanediamide**

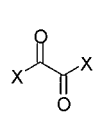
Peter Langer* and Martin Stoll

Dedicated to Professor Armin de Meijere on the occasion of his 60th birthday

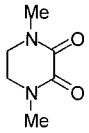
Numerous natural products, including prominent compounds such as dihydroxerulin, tetrenolin, freelingyne, or pulvinic acid, belong to the pharmacologically important category of γ-alkylidenebutenolides.[1] Dihydroxerulin, for instance, has proven to be an important nontoxic inhibitor in the biosynthesis of cholesterol,[2] while tetrenolin exhibits antibiotic activity against gram-positive bacteria.[3] α-Hydroxy-γ-alkylidenebutenolides are particularly suitable building blocks for natural product synthesis (by means of transition metal-catalyzed coupling and reduction reactions of the corresponding enol triflates). However, it was only recently that an efficient stereoselective route was introduced to obtain a specific member of this class, 5-(2-hydroxyethylidene)-2(5*H*)-furanone, by stereospecific elimination of L- and D-gulono-1,4-lactone.[4] Since a carbohydrate derivative is used as the substrate for this reaction, this method cannot be used to synthesize other substituted butenolides. Previously reported β-eliminations for the synthesis of α-alkyl-substituted or unsubstituted γ-alkylidenebutenolides proceed with low[5] stereoselectivity or no stereoselectivity at all.[6] Wittig reactions of suitable phosphorylides with methoxymaleic anhydrides proceed with undesired regiochemistry and generally unsatisfactory stereoselectivity.[7] Wittig reactions of alkyl-substituted maleic anhydrides[8] or other methods[9] lead only to *E*/*Z* mixtures of α-alkyl-substituted or unsubstituted γ-alkylidenebutenolides. To our knowledge, no method exists which provides a direct and stereoselective approach to γ-alkylidenebutenolides with a wide range of substitution patterns.

To fill this gap, we investigated the concept of direct cyclization of 1,3-dicarbonyl compounds with the oxalic acid dielectrophiles **2**. Despite the simplicity of this idea, the cyclization of 1,3-dicarbonyl compounds containing a terminal hydrogen atom (e.g. acetylacetone) with oxalyl chloride in the presence of Lewis acids was not successfully carried out until 1990.[10] The cyclization in this case proceeds through the *central* carbon atom and an oxygen atom of the 1,3-diketone under formation of 4-acyl-5-alkyl-2,3-dioxo-2,3-dihydrofurans. To the best of our knowledge, we present herein the first cyclizations of 1,3-dicarbonyl compounds with oxalic acid dielectrophiles which proceed by attack of a *terminal* carbon atom of the nucleophile. This method allows for a simple regio- and stereoselective route to a series of γ-alkylidenebutenolides. To achieve the desired regioselectivity, the 1,3-dicarbonyl compounds are used in the corresponding ambident dianionic form.[11, 12]

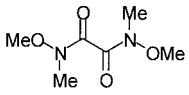
Initial experiments showed that reactions of the dianion of ethyl acetoacetate (**1a**) with diethyl oxalate (**2a**) or oxalyl chloride (**2b**) led to the formation of complex, inseparable mixtures (owing to overaddition, polymerization, or decomposition; Table 1). The reaction of the dianion of **1a** with 1,4-



2a (X = OEt)
2b (X = Cl)



2c

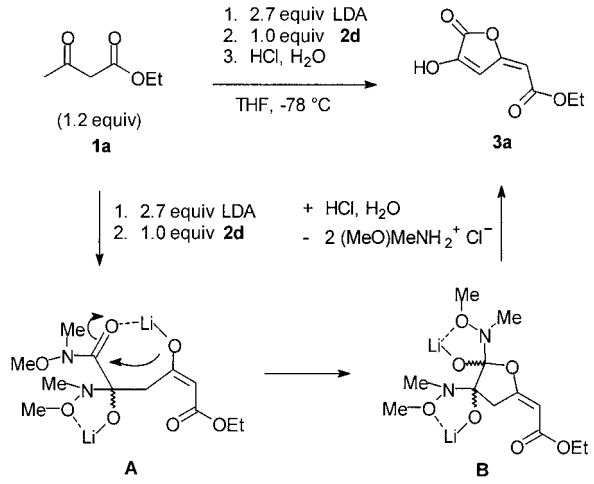


2d

dimethylpiperazine-2,3-dione (**2c**)[13] also remained unsuccessful, although **2c** had previously been reported to undergo condensation reactions with two equivalents of monofunctional organolithium compounds. Fortunately, the problem could be solved with the use of the Weinreb amide[14] *N,N′*-dimethoxy-*N,N′*-dimethylethanediamide (**2d**), which was reported in 1995 and which until now has been used only in condensation reactions with simple monolithium compounds such as phenyllithium.[14a] Exposure of this Weinreb oxalic amide to the dianion of **1a** induced a cyclization reaction, and the γ-alkylidenebutenolide **3a** was obtained in 75% yield (Scheme 1). The product was formed both regioselectively (by cyclization of the terminal carbon and the neighboring oxygen atom of the dianion) and with complete stereoselectivity. The *E* configuration of the semicyclic double bond was unequivocally proven with NOE NMR studies of the γ-alkylidenebutenolide **3b**, which was obtained in 73% yield from the

[*] Dr. P. Langer, M. Stoll
Institut für Organische Chemie der Universität
Tammannstrasse 2, D-37077 Göttingen (Germany)
Fax: (+49) 551-399475
E-mail: planger@uni-goettingen.de

[**] This work was supported by the Fonds der Chemischen Industrie (Liebig scholarship and funds for P.L.). P.L. thanks Prof. Dr. A. de Meijere for his support and Dr. P. R. Schreiner for critical comments.



Scheme 1. A possible mechanism for the reaction of the dianion of **1a** with **2d**. LDA = lithium diisopropylamide.

Table 1. Optimization of the reaction of the dianion of **1a** with the oxalic acid dielectrophiles **2a–d**.

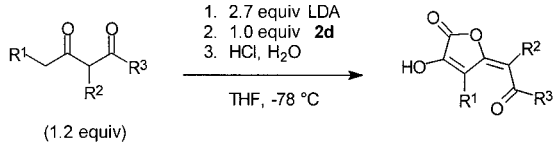
Entry	**2**	*T* [°C]	*t* [h]	Equiv (**1a**)	Yield (**3a**) [%]
1	**a**	−78→20	6	1.0	0
2	**b**	−78→20	6	1.0	0
3	**c**	−78→20	6	1.0	0
4	**d**	−78→20	6	1.0	69
5	**d**	−78→20	6	2.0	52
6	**d**	−78→20	6	1.2	75
7	**d**	−78→−40	5	1.2	64
8	**d**	0→20	4	1.2	0

reaction of **2d** with the dianion of *tert*-butyl acetoacetate (**1b**, Table 2). Optimized yields were obtained by use of 1.2 equivalents of the dianion, addition of the Weinreb oxalamide **2d** to the solution of the dianion at −78 °C, and warming of the reaction solution to room temperature within a period of six hours, followed by subsequent treatment with hydrochloric acid (Table 1). When two equivalents of the dianion were used, **3a** was still obtained in 52% yield.

According to Harris et al., the reaction of the bis(*N*-methoxy-*N*-methylamide) of a glutaric acid derivative with the dianion of **1b** led to the formation of an open-chain product.[15a] No conversion was observed, however, in the reaction of the simple *N*-methoxy-*N*-methylacetamide with the *mono*anion of acetophenone.[15b] In the case of the cyclization of the bis-Weinreb amide presented here, which we believe is the first reported cyclization of this type, the intramolecular formation of the five-membered ring must be preferred over the formation of any open-chain 1:2 product. The product is probably formed by a regioselective attack of the terminal carbon atom of the dianion onto the substrate and a subsequent cyclization step that also proceeds regioselectively at the neighboring oxygen atom. Our working hypothesis for explaining the regioselectivity of the ring closure is based on the complexation of the lithium atom by both the amide and the enolate oxygen atoms as ilustrated in intermediate **A** (Scheme 1). This chelation step brings the amide and the enolate functionalities close together, thus favoring a regioselective ring closure under formation of intermediate **B**.[16] Both five-membered chelate complexes of intermediate **B** are subsequently cleaved with hydrochloric acid to form the carbonyl group. An attempt to prepare *E*-configured γ-alkylidenebutenolides by stereospecific elimination at insufficently low temperatures[4c] led to a mixture of geometric isomers. The same happens upon treatment of *E*-configured γ-alkylidenebutenolides with chlorosulfonic acid.[8] These observations strongly support the assumption that the stereoselectivity observed in this study to preferentially form γ-alkylidenebutenolides with *E* configuration is not thermodynamically but instead kinetically controlled.

The reaction of the Weinreb oxalamide **2d** with the dianions of acetylacetone (**1c**), *N*,*N*-diethyl acetoacetamide (**1d**), and benzoylacetone (**1e**) gave rise to the γ-alkylidenebutenolides **3c**, **3d**, and **3e**, respectively, in generally good yields and with very good stereoselectivities (Table 2).

Table 2. Synthesis of the γ-alkylidenebutenolides **3a–q**.[a]



3	R^1	R^2	R^3	Yield [%]
a	H	H	OCH_2CH_3	75
b	H	H	$OC(CH_3)_3$	73
c	H	H	CH_3	56
d	H	H	$N(CH_2CH_3)_2$	63
e	H	H	C_6H_5	57
f	CH_3	H	OCH_3	70
g	CH_2CH_3	H	OCH_2CH_3	54
h	H	CH_3	OCH_2CH_3	71
i	H	CH_2CH_3	OCH_2CH_3	43
j	H	$-CH_2CH_2O-$		73
k	H	$-CH_2CH(CH_3)O-$		60
l	H	$-CH_2CH(CH_2CH_3)O-$		38
m	CH_3	$-CH_2CH_2O-$		20
n	H	$-CH_2CH_2CH_2-$		75
o	H	$-CH_2CH_2CH_2CH_2-$		23
p	H	$-CH_2CH_2(C_6H_4)-$		74
q	H	$-(C_6H_4)O-$		52

[a] The *E*:*Z* ratio was >98:2 for **3a–e** and **3h–q**. In the cases of **3f** and **3g** the *E*:*Z* ratio was 1:40 and <2:98, respectively.

Although *E*/*Z* selectivities of greater than 98:2 were obtained in three experiments to synthesize the butenolide **3c**, there was one experiment in which an isomeric mixture (5:1) was isolated (probably because higher temperatures were used when adding **2d**). This result provides independent evidence for the *E* configuration of the semicyclic double bond: Analogous to the ^{1}H NMR data of similar compounds,[4] the main component (*E*)-**3c** shows a larger chemical shift for the two CH signals than the corresponding signals of the minor component (*Z*)-**3c**. Starting from the R^1- or R^2-substituted methyl and ethyl acetoacetates **1f–i** the corresponding substituted butenolides **3f–i** were prepared in good yields and with very high stereoselectivities. In the case of **3f** and **3g** the *Z*-configured butenolides were formed with efficient stereoselectivities. The *Z* configuration of **3g** was unequivocally proven by NOE NMR studies. The change of the

  1433-7851/99/3812-1804 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **1999**, *38*, No. 12

stereoselectivity from *E* to *Z* configuration can be explained by the steric influence of the alkyl substituents in the β-position of the butenolide.

The interesting γ-alkylidenebutenolides **3j**–**o** could be synthesized easily by using the cyclic 1,3-dicarbonyl compounds **1j**–**o**: The conversion of the oxalamide **2d** with the dianions of the 2-acetyl-γ-butyrolactones **1j**–**m** yielded the butenolides **3j**–**m** in generally good yields and with very high stereoselectivities in favor of the *E* isomers. Likewise, the butenolide **3n** was prepared in good yield starting from 2-acetylcyclopentanone (**1n**). Furthermore, the butenolide **3o** was prepared from 2-acetylcyclohexanone (**1o**). The low yield in this case can be explained by the necessary separation of the regioisomeric minor product, which was formed by the cyclization of the secondary α-carbon atom in the six-membered ring of 2-acetylcyclohexanone. The reaction of **2d** with the dianion of 2-acetyltetralone (**1p**) yielded the butenolide **3p** in good yield and with very high stereoselectivity. Reaction of **2d** with the dianion of 3-acetyl-2,3-dihydrobenzofuran-2-one (**1q**), which to our knowledge has not been reported to date, led to the γ-alkylidenebutenolide **3q**, an analogue of the natural product calycin,[17] in good yield and with very high stereoselectivity.

Cyclization of the dianions of the dicarbonyl compounds **1a**–**q** with the Weinreb amide **2d** allowed the regio- and stereoselective preparation of a series of substituted α-hydroxy-γ-alkylidenebutenolides. The yields obtained for the butenolides **3a**–**q** are quite satisfactory considering that a series of side reactions (e.g. decarbonylation[14a]) are possible due to the unstable nature of the oxalic acid structure of **2d**.[18] The reaction presented herein constitutes a significant expansion of the methods known today for the synthesis of γ-alkylidenebutenolides, which are of pharmacological relevance and of importance for natural product synthesis. Moreover, this reaction is convenient to carry out.

Experimental Section

Typical procedure: **3a**: A solution of lithium diisopropylamide (LDA) in THF was prepared by dropwise addition of *n*BuLi (1.44 mL, 3.4 mmol, 2.35 M solution in *n*-hexane) to a solution of diisopropylamine (0.44 mL, 3.4 mmol) in THF (20 mL) at 0 °C. After 15 min of stirring at 0 °C, **1a** (0.19 mL, 1.47 mmol) was added, and the solution was stirred for 45 min at 0 °C. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA; 0.5 mL, 3.4 mmol) was then added at −78 °C followed by a solution of **2d** (220 mg, 1.25 mmol) in THF (4 mL). The temperature of the reaction solution was increased to 0 °C over a period of 5.5 h. The cooling bath was removed, and the reaction mixture was stirred for 30 min at 20 °C. Then 4 mL of a 10% aqueous HCl solution were added and the solution stirred for 10 min, after which another 20 mL of a 10% aqueous HCl solution were added. The aqueous layer was extracted multiple times with THF/diethyl ether (1/3). The combined organic layers were dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo. Purification of the residue by preparative chromatography (silica gel, diethyl ether/petroleum ether, 1/10 → 1/3) yielded 170 mg of a colorless solid. ^{1}H NMR ([D$_6$]acetone, 200 MHz): $\delta = 1.32$ (t, $J = 8$ Hz, 3H, CH_3), 4.22 (q, $J = 8$ Hz, 2H, CH_2), 5.71 (s, 1H, C*H*CO_2Et), 7.20 (s, 1H, ring CH); ^{13}C NMR ([D$_6$]acetone, 50 MHz): $\delta = 14.43$ (CH_3), 60.94 (CH_2), 98.68 (*C*HCO_2Et), 108.76 (ring CH), 150.34, 160.74, 164.22, 166.10 (C); MS (EI, 70 eV): 184 (M^+, 17), 156 (20), 139 (69), 69 (100). All new compounds were characterized by spectroscopic methods and high-resolution mass spectra and/or elemental analyses.

Received: January 25, 1999 [Z12954]
German version: *Angew. Chem.* **1999**, *111*, 1919–1922

Keywords: butenolides · C–C coupling · dianions · lactones · stereoselective syntheses

[1] a) Reviews: Y. S. Rao, *Chem. Rev.* **1976**, *76*, 625–694; b) G. Pattenden, *Prog. Chem. Nat. Prod.* **1978**, *35*, 133–198; c) D. W. Knight, *Contemp. Org. Synth.* **1994**, *1*, 287–315.
[2] D. Kuhnt, T. Anke, H. Besl, M. Bross, R. Herrmann, U. Mocek, B. Steffan, W. Steglich, *J. Antibiot.* **1990**, *43*, 1413–1420.
[3] a) C. G. Gallo, C. Coronelli, A. Vigevani, G. C. Lancini, *Tetrahedron* **1969**, *25*, 5677–5680; b) H. Pagani, G. Lancini, G. Tamoni, C. Coronelli, *J. Antibiot.* **1973**, *26*, 1–6.
[4] a) K. Siegel, R. Brückner, *Chem. Eur. J.* **1998**, *4*, 1116–1122; b) F. Goerth, A. Umland, R. Brückner, *Eur. J. Org. Chem.* **1998**, 1055–1062; c) K. Siegel, Diplomarbeit, Universität Göttingen, **1996**.
[5] a) F. Bohlmann, C. Zdero, *Chem. Ber.* **1966**, *99*, 1226–1228; b) J. B. Jones, J. M. Young, *J. Med. Chem.* **1968**, *11*, 1176; c) K. Yamada, Y. Togawa, T. Kato, Y. Hirata, *Tetrahedron* **1971**, *27*, 5445–5451; d) S. Tsuboi, H. Wada, S. Mimura, A. Takeda, *Chem. Lett.* **1987**, 937–938; e) there is one report in which good stereoselectivities were observed for the preparation of α,β-dimethoxy-γ-alkylidenebutenolides by β-elimination: M. A. Khan, H. Adams, *Synthesis* **1995**, 687–692.
[6] a) M. Ito, Y. Hirata, Y. Shibata, K. Tsukida, *J. Chem. Soc. Perkin Trans. 1* **1990**, 197–199; b) C. Di Nardo, L. O. Jeronic, R. M. Lederkremer, O. Varela, *J. Org. Chem.* **1996**, *61*, 4007–4013.
[7] D. W. Knight, G. Pattenden, *J. Chem. Soc. Perkin Trans 1* **1979**, 62–69.
[8] a) C. F. Ingham, R. A. Massy-Westropp, G. D. Reynolds, W. D. Thorpe, *Aust. J. Chem.* **1975**, *28*, 2499–2510; b) R. A. Massy-Westropp, M. F. Price, *Aust. J. Chem.* **1980**, *33*, 333–341.
[9] a) I. Bell, E. R. H. Jones, M. C. Whiting, *J. Chem. Soc.* **1958**, 1313–1322; b) G. Struve, S. Seltzer, *J. Org. Chem.* **1982**, *47*, 2109–2113; c) ref. [1].
[10] R. W. Saalfrank, T. Lutz, *Angew. Chem.* **1990**, *102*, 1064–1066; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1041–1043.
[11] a) For the preparation of dianions from 1,3-dicarbonyl compounds, see L. Weiler, *J. Am. Chem. Soc.* **1970**, *92*, 6702–6704; b) D. Seebach, V. Ehrig, *Angew. Chem.* **1974**, *86*, 446–448; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 401–403; c) reviews of dianions: A. Maercker, *Methoden Org. Chem.* (Houben-Weyl), 4th ed., Vol. E19d, **1993**, 448–566; d) C. M. Thompson, D. Green, *Tetrahedron* **1991**, *47*, 4223–4285.
[12] Cyclizations of dianions with dielectrophiles are significantly less common than condensation reactions with monofunctional electrophiles: a) K. G. Bilyard, P. J. Garratt, R. Hunter, E. Lete, *J. Org. Chem.* **1982**, *47*, 4731–4736; b) R. B. Bates, B. Gordon, T. K. Highsmith, J. J. White, *J. Org. Chem.* **1984**, *49*, 2981–2987; c) K. Tanaka, H. Horiuchi, H. Yoda, *J. Org. Chem.* **1989**, *54*, 63–70; d) A. Maercker, A. Groos, *Angew. Chem.* **1996**, *108*, 216–218; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 210–212.
[13] U. T. Mueller-Westerhoff, M. Zhou, *J. Org. Chem.* **1994**, *59*, 4988–4992.
[14] a) M. P. Sibi, M. Marvin, R. Sharma, *J. Org. Chem.* **1995**, *60*, 5016–5023; b) review of Weinreb amides: M. Mentzel, H. M. R. Hoffmann, *J. Prakt. Chem.* **1997**, *339*, 517–524.
[15] a) S. G. Gilbreath, C. M. Harris, T. M. Harris, *J. Am. Chem. Soc.* **1988**, *110*, 6172–6179; b) T. A. Oster, T. M. Harris, *Tetrahedron Lett.* **1983**, 1851–1854.
[16] Review of the structure and reactivity of lithium enolates: D. Seebach, *Angew. Chem.* **1988**, *100*, 1685–1715; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1624–1654.
[17] B. Åkermark, *Acta Chem. Scand.* **1961**, *15*, 1695–1701.
[18] For decarbonylation reactions that occur during the cyclization of glycols with oxalyl chloride, see T. Iida, T. Itaya, *Tetrahedron* **1993**, *49*, 10511–10530.

  1433-7851/99/3812-1805 $ 17.50+.50/0