# Domino Reaction of 1,3-Bis(trimethylsilyloxy)-1,3-dienes with Oxalyl Chloride: General and Stereoselective Synthesis of γ-Alkylidenebutenolides

**Peter Langer,*[a] Toni Schneider,[a] and Martin Stoll[a]**

*Dedicated to Professor H. Martin R. Hoffmann on the occasion of his 65th birthday*

**Abstract:** The Lewis acid catalyzed cyclization of oxalyl chloride with 1,3-bis(trimethylsilyloxy)-1,3-dienes **3**, derived from 1,3-dicarbonyl compounds **1**, provides a new and general approach for the synthesis of γ-alkylidenebutenolides **4**, a pharmacologically and synthetically important class of substances. A variety of butenolides were efficiently prepared in good yields and with very good regio- and stereoselectivities. An up-scaling of the reaction was possible. The use of the Lewis acid trimethylsilyl-trifluoromethanesulfonate (TMSOTf) proved to be superior to other activation conditions. Sterically undemanding γ-alkylidenebutenolides could be prepared alternatively by reaction of the corresponding 1,3-dicarbonyl dianions with *N*,*N*′-dimethoxy-*N*,*N*′-dimethylethanediamide (**2d**). In contrast to the dianion method, the Lewis acid catalyzed reaction also facilitated the cyclization of sterically hindered, base-labile, cyclic and functionalized substrates. From a methodology viewpoint, the dianion reaction represents the first cyclization of a bis-Weinreb amide and the first cyclization of an oxalic acid-synthon with an ambident dianion. The TMSOTf-catalyzed reactions are both the first cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-dienes with a $C_2$ dielectrophile and the first cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-dienes with a carboxylic acid dichloride or a related dielectrophile.

**Keywords:** butenolides · catalysts · cycloadditions · 1,3-dienes · stereoselective synthesis

## Introduction

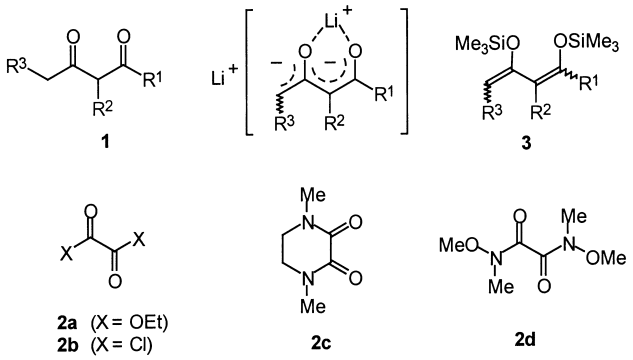
Many natural products, such as the prominent compounds freelingyne, tetrenolin, dihydroxerulin and patulin, belong to the pharmacologically important group of γ-alkylidenebutenolides.[1] In particular, α-hydroxy-γ-alkylidenebutenolides[2] and the related isotetronic acids[3] are currently of great interest since they are key intermediates in several natural product syntheses. In this context, transition metal catalyzed coupling or reduction reactions via enol triflates have been used to transform γ-alkylidenebutenolides into natural products.[2] It was only recently that an efficient stereoselective route was introduced to obtain a specific member of the class of γ-alkylidenebutenolides, namely 5-(2-hydroxyethylidene)-2(5*H*)-furanone, by stereospecific elimination of L- and D-gulono-1,4-lactone.[2] Since a carbohydrate derivative is used as the substrate for this reaction, this method cannot be employed for the direct preparation of substituted butenolides. However, many naturally occurring γ-alkylidenebutenolides contain substituents at both the α- and the β-position or at the exocyclic double bond. Unfunctionalized, *z*-configured γ-alkylidenebutenolides have been stereoselectively prepared by $Ag^I$-catalyzed isomerization of (*Z*)-2-en-4-ynoic acids.[4] Other known methods for the preparation of γ-alkylidenebutenolides proceed with low[5] or no[6] stereoselectivity or with undesired regiochemistry.[7] To the best of our knowledge, no method was available which provided a direct and stereoselective approach to functionalized γ-alkylidenebutenolides with a wide range of substitution patterns.

To fill this gap, we have investigated the concept of direct cyclization of 1,3-dicarbonyl compounds with oxalic acid dielectrophiles. Despite the simplicity of this idea, the cyclization of 1,3-dicarbonyl compounds that contain a terminal hydrogen atom (e.g. acetylacetone) with oxalyl chloride in the presence of Lewis acids was not achieved until 1990.[8] The cyclization proceeds through the *central* carbon atom and an oxygen atom of the 1,3-diketone. Recently, we developed the first cyclization reactions of 1,3-dicarbonyl compounds **1** with oxalic acid dielectrophiles which proceed by attack of a *terminal* carbon atom of the nucleophile.[9] To achieve the desired regioselectivity, the 1,3-dicarbonyl com-

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

  0947-6539/00/0617-3204 $ 17.50+.50/0 

pounds were used in the corresponding ambident dianionic form.[10, 11] The use of *N,N′*-dimethoxy-*N,N′*-dimethylethanediamide (**2d**)[12] as the dielectrophile was mandatory to induce a cyclization reaction rather than polymerization.[13] Although this reaction provided convenient access to a variety of γ-alkylidenebutenolides, there is still the need for the development of a more general method which also allows the use of base-labile, sterically hindered, cyclic and functionalized substrates. Herein, we report full details of our dianion methodology and the development of a completely new and general method for the preparation of γ-alkylidenebutenolides. Based on the Mukaiyama aldol reaction,[14] we have developed the first Lewis acid catalyzed cyclization of 1,3-bis(trimethylsilyloxy)-1,3-dienes **3** with oxalyl chloride (**2b**),



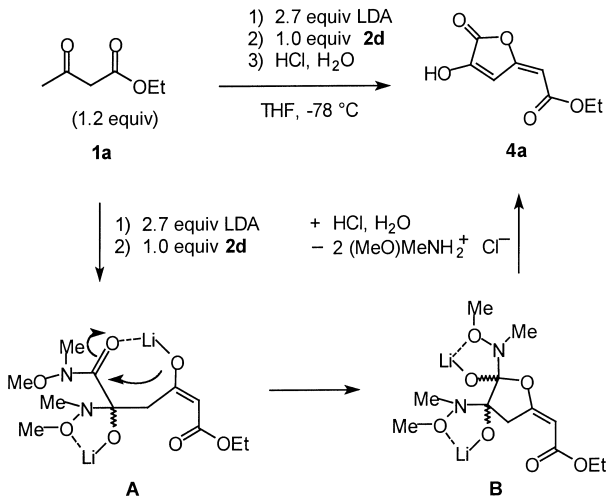

which provides direct access to a great variety of γ-alkylidenebutenolides.

**Abstract in German:** *Die Lewis Säure katalysierte Cyclisierung von Oxalylchlorid mit 1,3-Bis(trimethylsilyloxy)-1,3-dienen **3** bietet einen neuartigen und generellen Zugang zu der pharmakologisch und für die Naturstoffsynthese wichtigen Substanzklasse der γ-Alkylidenbutenolide **4**. Die benötigten Diene **3** wurden ausgehend von 1,3-Dicarbonylverbindungen **1** dargestellt. Eine große Bandbreite von Butenoliden **4** konnte in guten Ausbeuten und mit sehr guten Regio- und Stereoselektivitäten hergestellt werden, wobei an zwei Beispielen gezeigt wurde, daß ein Up-Scaling der Reaktion möglich ist. Als optimale Lewis Säure hat sich Trimethylsilyl-trifluormethansulfonat (TMSOTf) erwiesen. Sterisch weniger anspruchsvolle γ-Alkylidenebutenolide konnten durch direkte Umsetzung dilithiierter 1,3-Dicarbonyl-Dianionen mit N,N′-Dimethoxy-N,N′-dimethylethandiamid (**2d**) hergestellt werden. Im Unterschied zu der Dianion-Methode erlaubt die Lewis Säure katalysierte Variante darüber hinaus eine erfolgreiche Cyclisierung von sterisch gehinderten, basenlabilen, cyclischen und funktionalisierten Substraten. Aus methodischem Blickwinkel stellt die Dianion-Methode die bisher erste Cyclisierungsreaktion eines Bis-Weinrebamids und die erste Cyclisierung eines Oxalsäure-Dielektrophils mit einem ambidenten Dianion dar. Bei der TMSOTf-katalysierten Reaktion handelt es sich sowohl um die erste Cyclisierung eines 1,3-Bis(trimethylsilyloxy)-1,3-diens mit einem $C_2$-Dielektrophil als auch um die erste Cyclisierung eines 1,3-Bis(trimethylsilyloxy)-1,3-diens mit einem Dicarbonsäuredichlorid.*

1,3-Bis(trimethylsilyloxy)-1,3-dienes (**3**) represent synthons of 1,3-dianions that have been treated with monofunctional electrophiles in the presence of Lewis acids.[15] Cyclization reactions of 1,3-bis(trimethylsilyloxy)-1,3-dienes with $C_3$, $C_4$, and $C_5$ dielectrophiles (ketones, aldehydes or acetals) have been reported and proceed generally with participation of the terminal and the central carbon atom of the 1,3-bis(trimethylsilyloxy)-1,3-diene.[16] Despite the synthetic potential of these building blocks, to the best of our knowledge, no cyclization reactions of 1,3-bis(trimethylsilyloxy)-1,3-dienes with $C_2$ dielectrophiles, such as oxalyl chloride, have been reported so far.[17] Presumably, this can be attributed to the relative lability of the oxalic acid substructure which can give rise to several drawbacks in the reaction with nucleophiles.[18] In addition, to the best of our knowledge, no cyclization reactions of 1,3-bis(trimethylsilyloxy)-1,3-dienes with carboxylic acid dichlorides or related dielectrophiles have yet been reported.[19]

## Results and Discussion

**Cyclization of 1,3-dianions with *N,N′*-dimethoxy-*N,N′*-dimethylethanediamide (2d)**: 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). The reaction of the dianion of **1a** with 1,4-dimethylpiperazine-2,3-dione (**2c**)[20] was also unsuccessful, although **2c** had previously been reported to undergo condensation reactions with two equivalents of monofunctional organolithium compounds. Fortunately, the problem could be finally solved with the use of *N,N′*-dimethoxy-*N,N′*-dimethylethanediamide (**2d**). This compound was first reported in 1995 and was used only in condensation reactions with simple monolithium compounds such as phenyllithium.[12] Exposure of this Weinreb oxalic amide to the dianion of ethyl acetoacetate (**1a**) induced a cyclization reaction, and the γ-alkylidenebutenolide **4a** was obtained in 75% yield (Scheme 1). The product was formed




Scheme 1. Possible mechanism for the reaction of 1,3-dianions with *N,N′*-dimethoxy-*N,N′*-dimethylethanediamide (**2d**).

  0947-6539/00/0617-3205 $ 17.50+.50/0 

both regioselectively (by cyclization of the terminal carbon and the neighboring oxygen atom of the dianion) and with complete stereoselectivity. Optimized yields were obtained by the use of 1.2 equivalents of the dianion, addition of **2d** at $-78\,^{\circ}C$, and warming of the reaction mixture to room temperature within a period of six hours, followed by treatment with hydrochloric acid.

According to Harris et al., the reaction of the bis(*N*-methoxy-*N*-methylamide) of a glutaric acid derivative with the dianion of *tert*-butylacetoacetate **1b** led to formation of an open-chain product.[21a] No conversion was observed, however, in the reaction of the simple *N*-methoxy-*N*-methylacetamide with the monoanion of acetophenone.[21b] For the cyclization reaction reported herein, 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 on the substrate and a subsequent cyclization step that also proceeds regioselectively at the neighboring oxygen atom. Our working hypothesis to explain the regioselectivity of the ring closure is based on the complexation of the lithium atom by both the amide and the enolate functionalities (intermediate **A**; Scheme 1). This chelation step brings the amide and the enolate functionalities close to each other, thus favoring a regioselective ring closure and formation of intermediate **B**.[22] Both five-membered chelate complexes are subsequently cleaved with hydrochloric acid to form the carbonyl groups. The preparative scope and the limitations of the dianion methodology are discussed in the next section in order to directly compare it with the new Lewis acid mediated cyclization reaction reported herein.

**Cyclization of 1,3-bis(trimethylsilyloxy)-1,3-dienes (3) with oxalyl chloride (2b)**: Our first attempts to induce a cyclization reaction between the 1,3-bis(trimethylsilyloxy)-1,3-diene **3a** and oxalic acid dielectrophiles were unsuccessful: reaction of **3a** with diethyl oxalate (**2a**) in dichloromethane in the presence of stoichiometric amounts of titanium(IV) chloride resulted in a complex mixture. In contrast, reaction of the diene **3a** with oxalyl chloride (**2b**) in the absence of a Lewis acid gave the *E*-configured butenolide **4a**, however, in only 22% yield. Our first attempts to improve the yield by the use of tin(IV) chloride or zinc(II) bromide as the Lewis acid were unsuccessful (Table 1). Interestingly, significantly improved yields were obtained by using stoichiometric or catalytic amounts of trifluoroacetic acid (TFA). However, the stereoselectivities decreased to 11:1 and 15:1, respectively. Low yields of **4a** were also obtained when pyridinium hydrochloride was employed. Fortunately, use of the Lewis acid trimethylsilyl-trifluoromethanesulfonate (TMSOTf)[16e] led to a dramatic improvement: butenolide **4a** was isolated in 88% yield with excellent regio- and stereoselectivity when stoichiometric amounts of TMSOTf were employed. Much to our satisfaction, the use of substoichiometric amounts (0.3 equiv) of TMSOTf resulted in the stereoselective formation of **4a** in 87% yield. Optimized yields were obtained when a solution of the catalyst in $CH_2Cl_2$ was added to a solution of **2b** and 1,3-bis(trimethylsilyloxy)-1,3-diene **3a** in $CH_2Cl_2$ at $-78\,^{\circ}C$. The reaction mixture was allowed to warm to $20\,^{\circ}C$ over 6 h.

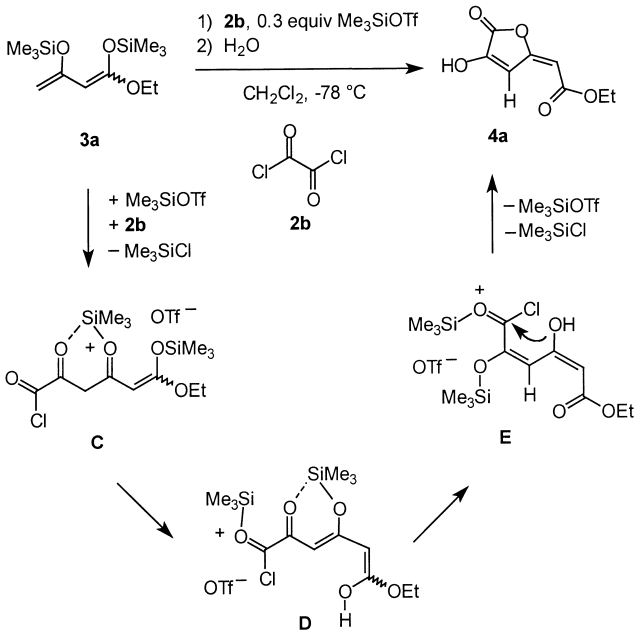
Table 1. Optimization of the reaction of 1,3-bis(trimethylsiloxy)-1,3-diene **3a** with oxalyl chloride.

| Entry | Lewis acid | Equiv | $t$[h][a] | $E$:$Z$[b] | [%][c] |
|---|---|---|---|---|---|
| 1 | none | | 6 + 14 | > 98:2 | 22 |
| 2 | $TiCl_4$ | 2 | 6 + 14 | > 98:2 | 18 |
| 3 | $TiCl_4$ | 0.3 | 6 + 14 | > 98:2 | 20 |
| 4 | $SnCl_4$ | 2 | 6 + 14 | > 98:2 | 24 |
| 5 | $ZnBr_2$ | 0.3 | 6 + 14 | > 98:2 | 33 |
| 6 | $CF_3COOH$ | 2 | 6 + 14 | 11:1 | 58 |
| 7 | $CF_3COOH$ | 0.3 | 6 + 14 | 15:1 | 56 |
| 8 | $C_5H_6NCl$ | 2 | 6 + 14 | 14:1 | 27 |
| 9 | TMSOTf | 2 | 6 + 1 | > 98:2 | 74 |
| 10 | TMSOTf | 2 | 6 + 14 | > 98:2 | 88 |
| 11 | TMSOTf | 0.3 | 6 + 1 | > 98:2 | 70 |
| 12 | TMSOTf | 0.3 | 6 + 14 | > 98:2 | 87 |

[a] Reaction time ($-78 \rightarrow 20\,^{\circ}C$) + reaction time at $20\,^{\circ}C$. [b] Integration of the $^1H$ NMR spectra of the crude products. [c] Yields of isolated products.

Importantly, in contrast to the dianion method, an up-scaling of the reaction to 40 mmol was possible to give the butenolide **4a** in excellent yield and with a very high stereoselectivity (vide infra).

The formation of the butenolide **4a** can be explained by the following working hypothesis (Scheme 2): attack of the terminal carbon atom of the 1,3-bis(trimethylsilyloxy)-1,3-diene on oxalyl chloride (which is activated by TMSOTf) followed by expulsion of trimethylchlorosilane (TMSCl) gives intermediate **C**. Intramolecular silyl migration results in formation of intermediate **D** and in the generation of an ester function (intermediate **E**). The product is finally formed by attack of the oxygen atom on the activated carboxylic acid chloride, expulsion of TMSCl, and regeneration of the catalyst. The lactonization under formation of the five-membered ring must be preferred over the formation of any




Scheme 2. Possible mechanism for the TMSOTf-mediated reaction of 1,3-bis(trimethylsilyloxy)-1,3-dienes **3** with oxalyl chloride (**2b**).



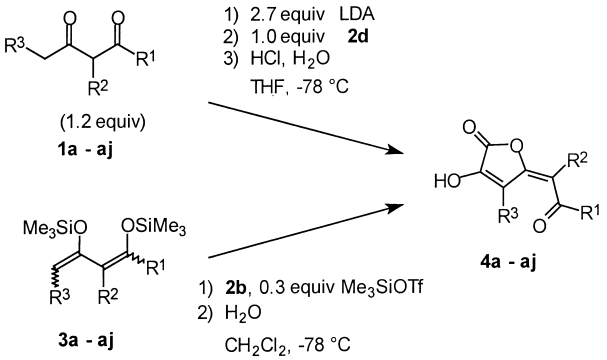
0947-6539/00/0617-3206 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 17

open-chain 1:2-products. The regioselective cyclization that involves the oxygen atom suggests that the latter was deprotected during the cyclization and that the silyl groups were transferred from their original positions to the oxygen atoms of the oxalic acid subunit to result in an activation of the second carboxylic acid chloride function.

An attempt to prepare *E*-configured γ-alkylidenebutenolides by stereospecific elimination at insufficiently low temperatures led to a mixture of geometric isomers.[2c] This also occurred upon treatment of *E*-configured γ-alkylidenebutenolides with chlorosulfonic acid.[7c] These observations strongly support the assumption that the stereoselectivity observed in this study to preferentially give γ-alkylidenebutenolides with an *E*-configuration is not thermodynamically but kinetically controlled. In fact, the formation of the *E*-configured products obtained by the use of both this and the dianion method can be explained by the formation of a stabilizing intramolecular hydrogen bond C–H···O or by the W-shaped configurations of intermediates **A** and **E** which allow a minimization of the dipole–dipole repulsion of the oxygen atoms.

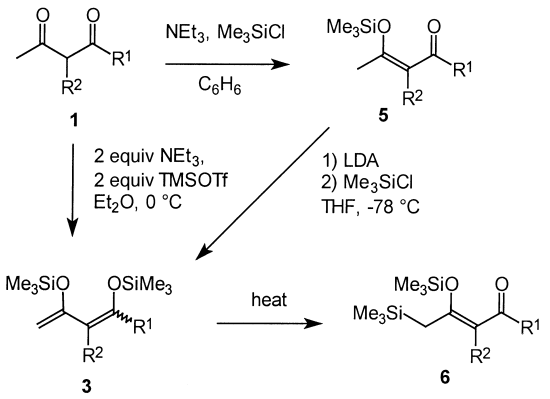
From a methodology viewpoint, the TMSOTf-mediated reaction reported herein represents, to the best of our knowledge, both the first cyclization of a 1,3-bis(trimethylsilyloxy)-1,3-diene with a $C_2$ dielectrophile and the first cyclization of a 1,3-bis(trimethylsilyloxy)-1,3-diene with a carboxylic acid dichloride or a related dielectrophile. In addition, a cyclization reaction that involves the terminal carbon and the neighboring oxygen atom of a 1,3-bis(trimethylsilyloxy)-1,3-diene has not been reported to date.

To investigate the preparative scope and the limitations of the two methods for the preparation of γ-alkylidenebutenolides, the substituents of the substrates were systematically varied (Scheme 3, Table 2). The starting materials were




Scheme 3. Synthesis of γ-alkylidenebutenolides **4a–aj**.

prepared as follows: bis-silyl enol ethers (**3**) derived from 1,3-keto esters were obtained in two steps. The 1,3-dicarbonyl compounds were converted into the corresponding silyl enol ethers **5**, generally high yields, by reaction with TMSCl in the presence of triethylamine (Scheme 4).[23] The desired 1,3-bis(trimethylsilyloxy)-1,3-dienes **3** were obtained by treatment of the silyl enol ethers **5** with lithium diisopropylamide (LDA) at −78 °C and subsequent treatment with TMSCl (method A).[16e] A variety of bis-silyl enol ethers were conven-

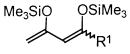
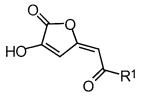
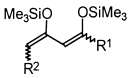
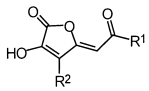
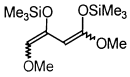
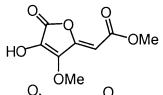
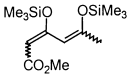
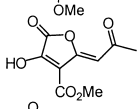
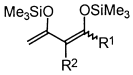
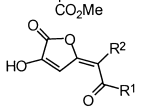
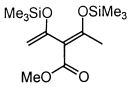
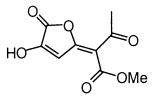
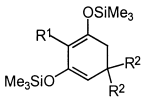
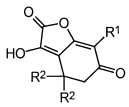
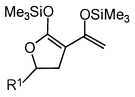
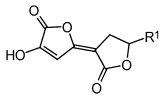
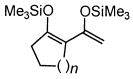
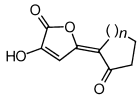
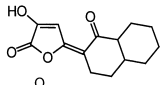
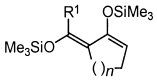
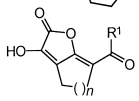
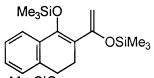
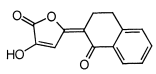
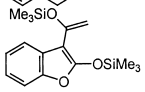
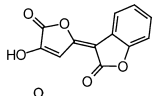
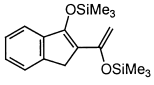
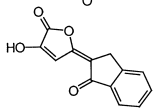



Scheme 4. Synthesis of 1,3-bis(trimethylsilyloxy)-1,3-dienes **3**.

iently prepared in only one step by treatment of the 1,3-diketones with two equivalents of TMSOTf (method B).[24] It is noteworthy, that 1,3-bis(trimethylsilyloxy)-1,3-dienes **3** are not accessible by reaction of 1,3-dicarbonyl dianions with TMSCl (owing to attack of the chlorosilane at the carbon atom of the dianions to give the C-silylated silyl enol ethers **6**). We observed that, upon heating, the ester-derived 1,3-bis(trimethylsilyloxy)-1,3-dienes that contain a substituent at C2 readily underwent a 1→5 silyl migration reaction to give the silyl enol ethers **6**.[25] To avoid this rearrangement, the respective bis-silyl enol ethers had to be used within two days of their preparation. In some cases, it was advantageous to remove the solvent at 0 °C rather than at room temperature. In spite of the precautions, amide-derived 1,3-bis(trimethylsilyloxy)-1,3-dienes could not be obtained (owing to rearrangement of the silyl group from the oxygen to the terminal carbon atom). However, most of the 1,3-bis(trimethylsilyloxy)-1,3-dienes prepared were stable for months when stored under an inert atmosphere at −20 °C.

Reaction of **2d** with the dianions of ethyl acetoacetate, *tert*-butyl acetoacetate, benzoylacetone, 5,5-dimethyl-2,4-hexanedione, and acetylacetone afforded the γ-alkylidenebutenolides **4a–e** in good yields and with excellent stereoselectivities (Table 2). The TMSOTf-catalyzed reaction of oxalyl chloride with the 1,3-bis(trimethylsilyloxy)-1,3-dienes **3a** and **3c–e** afforded the butenolides **4a** and **4c–e** in significantly improved yields. Reaction of the dianion of *S-tert*-butyl thioacetoacetate[26a] and of *N,N*-diethyl acetoacetamide[26b] with the bis-Weinreb amide **2d** afforded the butenolides **4f** and **4g** in good yields and with very good stereoselectivities. Butenolide **4g** could not be prepared by the Lewis acid mediated cyclization reaction, since the required amide-derived bis-silyl enol ether could not be prepared (see above). Starting with 1,3-bis(trimethylsilyloxy)-1,3-dienes **3h–k**, containing a methyl, ethyl, butyl, and benzyl group, respectively, at the terminal carbon atom, the corresponding *Z*-configured butenolides **4h–k** could be isolated in good yields and with very good stereoselectivities. The change of the stereoselectivity from *E*- to *Z*-configuration can be explained by the steric influence of the substituents $R^2$ and by the absence of the stereodirecting hydrogen bonds. Importantly, the use of the dianion method gave the butenolides **4h–k** in significantly lower yields or did not generate them at all.

Table 2. Synthesis of the $\gamma$-alkylidenebutenolides **4a–aj**.

| | **3** | Conditions[a] | $R^1$ | $R^2$ | **4** | Dianion method yield [%][b] | TMSOTf method yield [%][b] |
|---|---|---|---|---|---|---|---|
| **a** |  | A | OEt | – |  | 75 | 87 |
| **b** | | – | O(*t*Bu) | – | | 73 | – |
| **c** | | B | Ph | – | | 57 | 80 |
| **d** | | B | *t*Bu | – | | 80 | 84 |
| **e** | | B | Me | – | | 56 | 74 |
| **f** | | – | S(*t*Bu) | – | | 67 | – |
| **g** | | – | $NEt_2$ | – | | 63 | – |
| **h** |  | A | OMe | Me |  | 70 | 80 |
| **i** | | A | OEt | Et | | 54 | 76 |
| **j** | | A | OEt | Bu | | 0 | 70 |
| **k** | | A | OEt | Bn | | 0 | 68 |
| **l** |  | A | – | – |  | 0 | 85 |
| **m** |  | C | – | – |  | 0 | 43 |
| **n** |  | B | Me | Me |  | 72 | 77 |
| **o** | | A | OEt | Me | | 71 | 71 |
| **p** | | A | OEt | Et | | 43 | 66 |
| **q** | | A | OEt | Bu | | 0 | 62 |
| **r** | | A | Ph | Allyl | | 0 | 45 |
| **s** | | A | OEt | Ph | | 0 | 56 |
| **t** | | A | Ph | Bn | | 0 | 62 |
| **u** |  | C | – | – |  | 0 | 48 |
| **v** |  | B | H | H |  | 0 | 70 |
| **w** | | B | Me | H | | 0 | 64 |
| **x** | | B | H | Me | | 0 | 66 |
| **y** |  | A | H | – |  | 73 | – |
| **z** | | A | Me | | | 60 | 41 |
| **aa** |  | A | – | $n=1$ |  | 75 | – |
| **ab** | | D | – | $n=2$ | | 23[c] | 22[c] |
| **ac** | | – | – | – |  | 61 | – |
| **ad** |  | D | Me | $n=2$ | | [c] | [c] |
| **ae** | | A | OEt | $n=2$ |  | 0 | 71 |
| **af** | | B | Ph | $n=2$ | | 0 | 50 |
| **ag** | | A | OEt | $n=1$ | | 0 | 26 |
| **ah** |  | B | – | – |  | 74 | 81 |
| **ai** |  | B | – | – |  | 52 | 60 |
| **aj** |  | B | – | – |  | 22 | 28 |

[a] Reaction conditions for the preparation of the dienes **3**: A = 1) $NEt_3$, TMSCl, 2) LDA, TMSCl; B = $NEt_3$, TMSOTf; C = TMSCl (2 equiv), $ZnCl_2$, $NEt_3$; D = 1) $NEt_3$, TMSCl, 2) $NEt_3$, TMSOTf. [b] Yields of isolated products. In all cases, the stereoselectivity was >98:2 in favor of the drawn isomers. For the butenolides **4e**, **4f**, **4n**, **4r**, **4s** and **4t** the *E*:*Z*-ratios were 5:1, 10:1, 3.5:1, 1:3, 7:1 and 1:3, respectively. [c] A 3:1 mixture of the regioisomers **4ab** and **4ad** was obtained in 72% yield from which a sample of **4ab** was separated in 23% yield.



0947-6539/00/0617-3208 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 17

On account of their polyketide structure, many natural products contain a methoxy- or a related group in the β-position of the butenolide.[27] The synthesis of butenolide **4l**, which contains a methoxy group in the β-position and an unprotected hydroxy group in the α-position,[28] was therefore of special interest. This compound was prepared in good yield and with very good stereoselectivity by reaction of diene **3l**[29] with oxalyl chloride. Importantly, starting with the corresponding dianion, butenolide **4l** could *not* be prepared. Silylation of methyl triacetate afforded the diene **3m**.[30] Reaction of **3m** with oxalyl chloride gave the *Z*-configured ester-functionalized butenolide **4m**. This compound could not be prepared by the dianion method. Starting with the 1,3-bis(trimethylsilyloxy)-1,3-dienes **3n–t**, substituted at the central carbon atoms, the butenolides **4n–t** were isolated in good yields. Despite the fact that these butenolides bear substituents at their exocyclic double bonds, good to excellent stereoselectivities were observed. Starting with the corresponding dianions, the methyl- and the ethyl-substituted butenolides **4n–p** were obtained, in moderate to good yields. The butyl, allyl-, phenyl-, and the benzyl-substituted butenolides, **4q–t** respectively, could *not* be prepared at all.

Silylation of methyl 2-acetylacetoacetate afforded the 1,3-bis(trimethylsilyloxy)-1,3-diene **3u**.[31] Reaction of **3u** with oxalyl chloride afforded the butenolide **4u**, which proved to be very sensitive towards hydrolysis. Butenolide **4u** could not be obtained from the reaction of the corresponding dianion with **2d**. Reaction of oxalyl chloride with the cyclic 1,3-bis(trimethylsilyloxy)-1,3-dienes **3v–x**[24] afforded the interesting γ-alkylidenebutenolides **4v–x** in good yields. It is again noteworthy that these butenolides could *not* be prepared by the reaction of the corresponding dianions[32] with **2d**. The bicyclic core structure of the butenolides **4v–x** is present in a variety of natural products, such as xylerythrine, peniophorine, or peniosanguine.[33] Treatment of oxalyl chloride with the 1,3-bis(trimethylsilyloxy)-1,3-diene of 2-acetyl-γ-butyrolactone **3z** gave the butenolide **4z** in moderate yield with very good stereoselectivity. Butenolides **4y–z** could be prepared in better yields by the dianion methodology. Butenolide **4aa** could not be prepared by the TMSOTf method on account of problems associated with the preparation of the required diene **3aa**. In contrast, butenolide **4aa** could be prepared in good yield from the dianion[34] of 2-acetylcyclopentanone. The 1,3-bis(trimethylsilyloxy)-1,3-diene **3ab** could be prepared in pure form for the first time by a new regioselective two-step procedure:[35] reaction of 2-acetylcyclohexanone with TMSCl/$NEt_3$ in benzene regioselectively afforded 2-acetyl-1-trimethylsiloxycyclohexene which was cleanly converted into **3ab** by treatment with one equivalent of TMSOTf/$NEt_3$ in ether. However, reaction of oxalyl chloride with **3ab** afforded a 3:1 mixture of the regioisomeric butenolides **4ab** and **4ad**. Similar results were obtained when the dianion of 2-acetylcyclohexanone[36] was employed. Reaction of the dianion of 2-acetyldecalone with **2d** regio- and stereoselectively afforded the butenolide **4ac** in good yield.

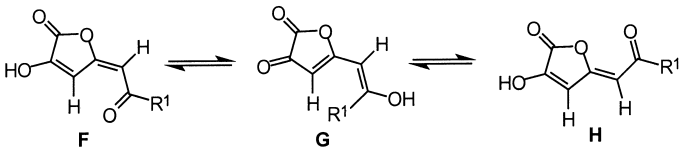
The new 1,3-bis(trimethylsilyloxy)-1,3-diene **3ae** was prepared from ethyl cyclohexanone-2-carboxylate in two steps (method A). Reaction of **3ae** with oxalyl chloride afforded the bicyclic butenolide **4ae** which contains a 5,6-ring system. The related phenyl-substituted diene **3af** was prepared from the corresponding 1,3-dione in one step (method B). Reaction of **3af** with oxalyl chloride afforded the butenolide **4af**. Reaction of oxalyl chloride with the diene **3ag**, which was prepared from ethyl cyclopentanone-2-carboxylate in two steps, afforded the butenolide **4ag** which contains a 5,5-ring system. Importantly, the bicyclic butenolides **4ae–ag** could *not* be prepared by the use of the dianion method although the required dianions have been previously reported.[37] Reaction of oxalyl chloride with the 1,3-bis(trimethylsilyloxy)-1,3-diene **3ah**, prepared in one step from 2-acetyltetralone, afforded the butenolide **4ah** in good yield and with very good stereoselectivity. This product could be equally successfully prepared from the corresponding dianion. The 1,3-bis(trimethylsilyloxy)-1,3-diene **3ai** was prepared in one step from 3-acetyl-2,3-dihydrobenzofuran-2-one in good yield. Reaction of oxalyl chloride with the diene **3ai** gave the γ-alkylidenebutenolide **4ai**, a derivative of the natural product calycine,[38] in good yield and with very good stereoselectivity. The yield of this product was much lower when the corresponding dianion was employed. Reaction of oxalyl chloride with the 1,3-bis(trimethylsilyloxy)-1,3-diene **3aj**, which was obtained from 2-acetylbenzopentan-1-one in one step, stereoselectively afforded the γ-alkylidenebutenolide **4aj**. This product was also obtained with the dianion methodology. The 1,3-bis(trimethylsilyloxy)-1,3-dienes which lead to butenolides **4ae–4aj** have not been previously reported.

All reactions presented herein were carried out on a 1.5 to 3.5 mmol scale. Importantly, an up-scaling is possible for the TMSOTf-catalyzed cyclization reaction. For example, the γ-alkylidenebutenolides **4a** and **4l** were conveniently prepared with excellent stereoselectivities on a 40 mmol scale in 83% and 84% yields, respectively. Depending on the substrate, an extension of the reaction times from 2 to 14 h was necessary in order to obtain good yields. The yields decreased when the reaction mixtures were stirred at 20 °C for longer than 20 h because of decomposition.

## Conclusions

The TMSOTf-catalyzed cyclization of oxalyl chloride with 1,3-bis(trimethylsilyloxy)-1,3-dienes provides a new and *general* approach to a variety of γ-alkylidenebutenolides which are of pharmacological relevance and of importance for natural product syntheses. Although several side-reactions are, in principle, possible (owing to the labile nature of the oxalic acid substructure)[18] the butenolides **4a–aj** could be prepared in good yields and with very good regio- and stereoselectivities. In most cases, the yields were higher than in the corresponding cyclization reactions of 1,3-dianions with *N*,*N*′-dimethoxy-*N*,*N*′-dimethylethanediamide (**2d**). Both methods are comparable in terms of the regio- and stereoselectivities achieved. In those cases where the dianion method performs well it has the advantage that the 1,3-dicarbonyl compounds can be directly used. In contrast to the dianion methodology, the Lewis acid catalyzed cyclization allows the use of sterically hindered, base-labile, cyclic and functionalized substrates. For unsubstituted butenolides and

for butenolides containing a substituent at the exocyclic double bond, very good *E*-selectivities were generally obtained. The best stereoselectivities were observed in the case of ester-derived butenolides. In contrast, only moderate selectivities were obtained in the case of acetylacetone-derived butenolides **4e** and **4n** ($R^1 = Me$). On the other hand, very good stereoselectivities were observed for the ketone-derived butenolides **4c** and **4d** that contain a phenyl and a *tert*-butyl group, respectively. For most of the butenolides prepared, the tautomeric form **F** is adopted exclusively which




accounts for the excellent stereoselectivities obtained. In contrast, tautomer **G** is present in the case of the butenolide that contains an aldehyde group ($R^1 = H$).[39] For the butenolides **4e** and **4n**, relatively broad signals ($^1$H NMR) were observed for the CH-hydrogen atoms of the two geometric isomers. The tautomeric ester form **G** could not be detected in solution. A rapid equilibrium between the structures **F**, **G**, and **H** presumably accounts for the moderate stereoselectivities obtained for butenolides **4e** and **4n**. Surprisingly good *E*-selectivities were observed for ester-derived butenolides that contain a substituent at the exocyclic double bond. In the case of butenolides that contain a substituent at the ring system, very good *Z*-selectivities were generally obtained owing to steric reasons.

From a methodology viewpoint, the dianion reaction represents both the first cyclization of an oxalic acid dielectrophile with an ambident dianion as well as the first cyclization of a bis-Weinreb amide. To the best of our knowledge, the Lewis acid-catalyzed reactions reported herein represent both the first cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-dienes with a $C_2$ dielectrophile and the first cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-dienes with a carboxylic acid dichloride or a related dielectrophile. These reactions also represent the first examples of cyclizations which involve the terminal carbon and the neighboring oxygen atom of a 1,3-bis(trimethylsilyloxy)-1,3-diene. In conclusion, the Lewis acid mediated cyclization reaction of oxalyl chloride with 1,3-bis(trimethylsilyloxy)-1,3-dienes represents a new and general method for the synthesis of $\gamma$-alkylidenebutenolides and constitutes a significant expansion of the methods known today for the preparation of this important type of compound. We are currently working towards the application of this methodology to the synthesis of natural products.

## Experimental Section

**General comments**: All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere in oven-dried (150 °C) glassware. THF was freshly distilled from Na, and $CH_2Cl_2$ from $CaH_2$. *N*,*N*′-Dimethoxy-*N*,*N*′-dimethylethanediamide (**2d**) was prepared according to a literature procedure.[12] For the $^1$H and $^{13}$C NMR spectra ($^1$H NMR: 200 or 300 MHz, $^{13}$C NMR: 50 or 75 MHz) the deuterated solvents indicated were used. The multiplicity of the $^{13}$C NMR signals were determined with the DEPT 135 technique and quoted as: $CH_3$, $CH_2$, CH, and C for primary, secondary, tertiary and quaternary carbon atoms. Yields refer to analytically pure samples. Isomer ratios were derived from suitable $^1$H NMR integrals. Mass spectral data (MS) were obtained by means of electron ionization (70 eV) or chemical ionization (CI, $H_2O$). For preparative-scale chromatography, silica gel (Merck, 60–200 mesh) was used. Melting points were measured on a Dr. Tottoli apparatus (Büchi) and are uncorrected. Elemental analyses were performed at the microanalytical laboratory of the Universität Göttingen. IR spectra were recorded on a Perkin–Elmer 1600 Series FT-IR spectrometer. The configurations of the exocyclic double bonds of several butenolides were proven by NOE measurements. For *E*-configured butenolides, the signals ($^1$H NMR) of both the ring and the exocyclic CH groups are shifted downfield relative to the respective signals of the *Z* isomers. This observation, which has already been previously made,[2a] was also useful for determining the configuration of the products.

**General procedure for the two-step preparation of 1,3-bis(trimethylsilyloxy)-1,3-dienes (3) (method A)**: First step: To a solution of the 1,3-keto ester (49 mmol) in benzene (100 mL) was added $NEt_3$ (64 mmol) and TMSCl (64 mmol) at 20 °C. The suspension was stirred for 14 h; the precipitated salts were removed by filtration, and the solvent was removed in vacuo. The residue was distilled in vacuo to give the silylenolethers **5** in 80–90% yields. Second step: To a solution of LDA in THF, prepared by addition of *n*BuLi (39 mmol, 2.35 M in *n*-hexane) to a solution of diisopropylamine (39 mmol) in THF (50 mL) at 0 °C, was added a solution of the silylenolether **5** (22 mmol) in THF at −78 °C. After the mixture had been stirred for 1 h at −78 °C, TMSCl (48 mmol) was added. The solution was allowed to warm to ambient temperature over a period of 2 h and the solution was stirred for 1 h at 20 °C. The solvent was removed in vacuo and petrol ether was added to the residue. The precipitated lithium chloride was removed by filtration under inert conditions and the solvent of the filtrate was removed in vacuo to give a yellow oil which was distilled in vacuo in a bulb-to-bulb distillation apparatus.

**General procedure for the one-step preparation of 1,3-bis(trimethylsilyloxy)-1,3-dienes (3) (method B)**: To a solution of the 1,3-diketone (10 mmol) and of triethylamine (2.84 mL, 20.40 mmol) in diethyl ether (20 mL), was slowly added TMSOTf (3.54 mL, 19.6 mmol ) at 0 °C. The suspension was stirred for 2 h and the organic layer was separated from the salt with a syringe. After addition of a small amount of sodium triphenylmethoxide, the solvent was removed and the residue was distilled in vacuo.

**General procedure for the preparation of $\gamma$-alkylidenebutenolides (4) by cyclization of 1,3-dianions with *N*,*N*′-dimethoxy-*N*,*N*′-dimethylethanediamide (2d)**: A solution of LDA in THF was prepared by addition of *n*BuLi (1.44 mL, 3.4 mmol, 2.35 M in *n*-hexane) to a solution of diisopropylamine (0.44 mL, 3.4 mmol) in THF (20 mL) at 0 °C. After the mixture had been stirred for 15 min at 0 °C, the 1,3-dicarbonyl compound **1** (1.47 mmol) was added and the solution was stirred for 45 min at 0 °C. The mixture was cooled to −78 °C and a solution of **2d** (220 mg, 1.25 mmol) in THF (4 mL) was added. The solution was allowed to warm to 0 °C over a period of 5.5 h. The cooling bath was removed and the solution was stirred for 30 min at 20 °C. An aqueous solution of HCl (10%, 4 mL) was added and the mixture was stirred for 10 min. Additional HCl solution (20 mL) was added and the aqueous layer was repeatedly extracted with diethyl ether/THF (1:1). The combined organic layers were dried ($MgSO_4$), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, ether/petrol ether).

**4a**: Prepared from ethyl acetoacetate (0.19 mL, 1.47 mmol). Colorless solid; yield: 170 mg (75%); m. p. 58 °C; $^1$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*$CO_2$Et), 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*H$CO_2$Et), 108.76 (ring-*C*H), 150.34, 160.74, 164.22, 166.10 (C); MS (EI, 70 eV): 184 ([$M^+$], 17), 156 (20), 139 (69), 69 (100); IR (KBr): $\tilde{\nu} = 3229, 3149, 3082, 2986, 1776, 1694, 1626, 1384, 1268, 1146, 1088, 1038$ cm$^{-1}$; elemental analysis calcd for $C_8H_8O_5$: C 52.18, H 4.38; found: C 52.41, H 4.65.

**4b**: Prepared from *tert*-butyl acetoacetate (0.25 mL, 1.51 mmol). Colorless solid; yield: 193 mg (73%); m.p. 60 °C; $^1$H NMR ([D$_6$]acetone, 200 MHz):



0947-6539/00/0617-3210 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 17

$\delta = 1.50$ (s, 9H; $C(CH_3)_3$), 5.56 (s, 1H; C*H*$CO_2t$Bu), 7.13 (s, 1H; ring-CH); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $\delta = 28.29$ ($C(CH_3)_3$), 81.39 ($C(CH_3)_3$), 100.65 (*C*H$CO_2t$Bu), 108.94 (ring-CH), 150.05, 160.03, 164.28, 165.48 (C); MS (EI, 70 eV): 212 ([$M^+$], 24), 157 (89), 139 (85), 57 (100); elemental analysis calcd for $C_{10}H_{12}O_5$: C 56.60, H 5.70; found: C 56.59, H 5.77.

**4c**: Prepared from benzoylacetone (239 mg, 1.48 mmol). Colorless solid; yield: 182 mg (57%); m.p. 56 °C; $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta =$ 7.02 (s, 1H; CH), 7.37 (s, 1H; ring-CH), 7.65 (m, 3H; Ph), 8.08 (m, 2H; Ph); $^{13}$C NMR ([D$_6$]acetone, 75 MHz): $\delta = 102.20$ (CO*C*H), 109.68 (ring-CH), 128.81 (CH, Ph), 129.56 (CH, Ph), 133.85 (CH, Ph), 139.44 (C, Ph), 151.87, 161.27, 164.39 (C), 189.94 (CO); MS (EI, 70 eV): 216 ([$M^+$], 58), 188 (16), 160 (27), 139 (35), 105 (100); IR (KBr): $\tilde{\nu} = 3419$, 3160, 2684, 2434, 1765, 1662, 1606, 1451, 1397, 1255, 1174, 1089, 1043 cm$^{-1}$; elemental analysis calcd for $C_{12}H_8O_4$: C 66.67, H 3.73; found: C 66.60, H 3.84.

**4d**: Prepared from 5,5-dimethyl-2,4-hexanedione (210 mg, 1.48 mmol). Colorless solid; yield: 232 mg (80%); m.p. 65 °C; $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta = 1.20$ (s, 9H; $C(CH_3)_3$), 6.46 (s, 1H; CCHCO), 7.21 (s, 1H; ring-CH); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $\delta = 26.37$ ($C(CH_3)_3$), 44.67 ($C(CH_3)_3$), 101.77 (*C*HCO), 109.59 (ring-CH), 151.14, 160.04, 164.46 (C), 204.98 (CO); MS (EI, 70 eV): 196 ([$M^+$], 11), 168 (20), 140 (100), 112 (17), 69 (41), 57 (55); IR (KBr): $\tilde{\nu} = 3243$, 3148, 2965, 2688, 2362, 1776, 1677, 1610, 1464, 1366, 1243, 1218, 1180, 1067, 1017 cm$^{-1}$; elemental analysis calcd for $C_{10}H_{12}O_4$: C 61.22, H 6.16; found: C 61.20, H 6.35.

**4e**: Prepared from acetylacetone (220 mg, 2.21 mmol). Colorless solid; yield: 190 mg (56%, $E$:$Z = 5$:1); m. p. 60 °C; $^1$H NMR ([D$_4$]MeOH, 200 MHz): $\delta = 2.20$ (s, 3H; $CH_3$), 6.34 (s, 1H; C*H*COCH$_3$), 6.96 (s, 1H; ring-CH); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $\delta = 19.74$ ($CH_3$), 115.95 (*C*HCOCH$_3$), 118.26 (ring-CH), 156.15, 162.39, 169.85 (C), 182.62 (CO); MS (EI, 70 eV): 154 ([$M^+$], 69), 126 (31), 81 (32), 69 (100); IR (KBr): $\tilde{\nu} =$ 3433, 3121, 2979, 2880, 2805, 2729, 2622, 2534, 2466, 1790, 1669, 1646, 1588, 1385, 1240, 1196, 1163, 1062 cm$^{-1}$; elemental analysis calcd for $C_7H_6O_4$: C 54.55, H 3.92; found: C 54.47, H 3.91.

**4f**: Prepared from S-*tert*-butyl-3-oxo-thiobutanoate (258 mg, 1.48 mmol). Colorless solid; yield: 226 mg (67%, $E$:$Z = 10$:1); m. p. 64 °C; $E$ isomer: $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta = 1.56$ (s, 9H; $C(CH_3)_3$), 5.99 (s, 1H; COCH), 7.13 (s, 1H; ring-CH); $^{13}$C NMR ([D$_6$]acetone, 75 MHz): $\delta = 29.54$ ($C(CH_3)_3$), 48.97 (C), 105.48 (ring-CH), 109.21 (CO*C*H), 151.27, 157.12 (C), 164.41 (O*C*OC), 189.56 (COS). $Z$ isomer: $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta = 1.55$ (s, 9H; $C(CH_3)_3$), 5.66 (s, 1H; COCH), 6.57 (s, 1H; ring-CH); $^{13}$C NMR ([D$_6$]acetone, 75 MHz): $\delta = 29.54$ ($C(CH_3)_3$), 48.58 (SC), 105.34 (ring-CH), 111.31 (CO*C*H), 149.57, 153.51 (C), 165.22 (O*C*OC), 186.33.56 (COS); MS (EI, 70 eV): 228 ([$M^+$], 10), 139 (100), 69 (37), 57 (42); IR (KBr): $\tilde{\nu} = 3425$, 3202, 2961, 2361, 1777, 1657, 1611, 1453, 1365, 1216, 1180, 1129, 1039 cm$^{-1}$; elemental analysis calcd for $C_{10}H_{12}O_4S$: C 52.62, H 5.30; found: C 52.47, H 5.60.

**4g**: Prepared from *N*,*N*-diethyl-acetoacetamide (0.23 mL, 1.48 mmol). Colorless oil; yield: 196 mg (63%); $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta = 1.18$ (m, $J = 6$ Hz, 6H; $CH_3$), 3.44 (m, $J = 6$ Hz, 4H; $CH_2$), 6.15 (s, 1H; COC*H*), 7.07 (s, 1H; ring-CH); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $\delta =$ 13.41, 14.97 ($CH_3$), 42.00, 44.04 ($CH_2$), 99.41 (CH), 109.42 (ring-CH), 150.40, 159.69 (C) , 165.68, 166.62 (CO); MS (EI, 70 eV): 211 ([$M^+$], 17), 166 (15), 139 (26), 100 (16), 72 (73), 58 (100), 44 (24); elemental analysis calcd for $C_{10}H_{13}O_4N$: C 56.87, H 6.20; found: C 56.62, H 6.32.

**4h**: Prepared from methyl 3-oxopentanoate (430 mg, 3.29 mmol). Colorless solid; yield: 423 mg (70%); m.p. 67 °C; $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta = 2.04$ (s, 3H; $CH_3$), 3.75 (s, 3H; $OCH_3$), 5.47 (s, 1H; CH); $^{13}$C NMR ([D$_6$]DMSO, 50 MHz): $\delta = 6.97$ (*C*$CH_3$), 51.20 ($OCH_3$), 93.98 (CH), 119.91, 144.03, 157.87, 163.35, 164.04 (C); MS (EI, 70 eV): 184 ([$M^+$], 92), 153 (100), 101 (31), 83 (98), 69 (64); IR (KBr): $\tilde{\nu} = 3423$, 3157, 2588, 2362, 1781, 1693, 1666, 1443, 1412, 1365, 1300, 1146, 1039, 1012 cm$^{-1}$; elemental analysis calcd for $C_8H_8O_5$: C 52.18, H 4.38; found: C 52.36, H 4.50.

**4i**: Prepared from ethyl 3-oxo-hexanoate (0.23 mL, 1.48 mmol). Colorless solid; yield: 170 mg (54%); m.p. 74 °C; $^1$H NMR ([D$_4$]MeOH, 200 MHz): $\delta = 1.16$ (t, $J = 6$ Hz, 3H; $CCH_2CH_3$), 1.30 (t, $J = 6$ Hz, 3H; $OCH_2CH_3$), 2.41 (q, $J = 6$ Hz, 2H; $CCH_2CH_3$), 4.20 (q, $J = 6$ Hz, 2H; $OCH_2CH_3$), 5.44 (s, 1H; CH); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $\delta = 12.89$ ($CCH_2CH_3$), 14.52 ($OCH_2CH_3$), 16.05 ($CCH_2CH_3$), 60.62 ($OCH_2CH_3$), 95.89 (CH), 126.78, 144.04, 157.71, 163.64, 164.84 (C); MS (EI, 70 eV): 212 ([$M^+$], 41), 167 (79), 138 (58), 110 (37), 97 (66), 69 (100); IR (KBr): $\tilde{\nu} = 3548$, 3161, 2978, 2362, 1784, 1665, 1464, 1399, 1368, 1280, 1171, 1140, 1092, 1031 cm$^{-1}$; elemental analysis calcd for $C_{10}H_{12}O_5$: C 56.60, H 5.70; found: C 56.65, H 5.64.

**4n**: Prepared from 3-methyl-2,4-pentanedione (0.20 mL, 1.48 mmol). Yellow solid; yield: 180 mg (72%, $E$:$Z = 3.5$:1); m.p. 71 °C; $E$ isomer: $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta = 2.18$ (s, 3H; $CH_3$), 2.38 (s, 3H; $COCH_3$), 7.16 (s, 1H; ring-CH); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $\delta =$ 13.37 ($CH_3$), 29.68 (CO*C*H$_3$), 111.01 (CH), 115,63, 149.42, 153.53 (C), 164.47 (O*C*OC), 199.80 (CO); $Z$ isomer: $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta = 1.91$ (s, 3H; $CH_3$), 2.53 (s, 3H; $COCH_3$), 6.96 (s, 1H; ring-CH); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $\delta = 12.50$ ($CH_3$), 31.95 (CO*C*H$_3$), 110.24 (CH), 115.57, 147.87, 152.77 (C), 164.46 (O*C*OC), 196.74 (CO); MS (EI, 70 eV): 168 ([$M^+$], 100), 153 (89), 139 (11), 112 (25), 83 (63), 69 (31); IR (KBr): $\tilde{\nu} = 3560$, 3433, 3099, 2970, 2831, 2645, 2487, 1784, 1687, 1619, 1437, 1421, 1369, 1330, 1268, 1109, 1075 cm$^{-1}$; elemental analysis calcd for $C_8H_8O_4$: C 57.14, H 4.80; found: C 56.92, H 4.66.

**4o**: Prepared from ethyl 3-methyl-acetoacetate (192 mg, 1.48 mmol). Colorless solid; yield: 206 mg (71%); m.p. 74 °C; $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta = 1.35$ (t, $J = 6$ Hz, 3H; $CH_2CH_3$), 2.03 (s, 3H; $CH_3$), 4.24 (q, $J = 6$ Hz, 2H; $CH_2$), 7.23 (s, 1H; ring-CH); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $\delta = 11.86$ ($CH_2CH_3$), 13.72 ($CH_3$), 60.70 ($CH_2$), 108.16 (*C*$CH_3$), 110.29 (ring-CH), 147.91, 154.61, 163.56, 166.30 (C); MS (EI, 70 eV): 198 ([$M^+$], 58), 153 (100), 124 (40), 83 (76), 69 (54), 55 (32); elemental analysis calcd for $C_9H_{10}O_5$: C 54.55, H 5.09; found: C 55.12, H 5.40.

**4p**: Prepared from ethyl 3-ethyl-acetoacetate (0.24 mL, 1.48 mmol). Colorless solid; yield: 135 mg (43%); m.p. 78 °C; $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta = 1.11$ (t, $J = 6$ Hz, 3H; $CCH_2CH_3$), 1.37 (t, $J = 6$ Hz, 3H; $OCH_2CH_3$), 2.55 (q, $J = 5$ Hz, 2H; $CCH_2CH_3$), 4.29 (q, $J = 5$ Hz, 2H; $OCH_2CH_3$), 7.24 (s, 1H; ring-CH); $^{13}$C NMR ([D$_6$]acetone, 75 MHz): $\delta =$ 14.19 ($CCH_2CH_3$), 14.46 ($CCH_2CH_3$), 20.82 ($OCH_2CH_3$), 61.43 ($OCH_2CH_3$), 111.06 (CH), 115.08, 148.70, 155.17, 165.34, 166.81 (C); MS (EI, 70 eV): 212 ([$M^+$], 63), 201 (22), 166 (100), 139 (89), 110 (31), 97 (37), 69 (94); IR (KBr): $\tilde{\nu} = 3518$, 3332, 3121, 2975, 2488, 2343, 1760, 1707, 1635, 1458, 1404, 1367, 1331, 1234, 1133, 1081, 1028 cm$^{-1}$; elemental analysis calcd for $C_{10}H_{12}O_5$: C 56.60, H 5.70; found: C 56.46, H 5.82.

**4y**: Prepared from α-acetyl-γ-butyrolactone (190 mg, 1.48 mmol). Colorless oil; yield: 196 mg (73%); $^1$H NMR ([D$_4$]MeOH, 200 MHz): $\delta = 3.13$ (t, $J = 6$ Hz, 2H; $CCH_2CH_2O$), 4.45 (t, $J = 6$ Hz, 2H; $CCH_2CH_2O$), 7.05 (s, 1H; ring-CH); $^{13}$C NMR ([D$_4$]MeOH, 50 MHz): $\delta = 26.47$ (*C*$CH_2$), 67.55 ($OCH_2$), 104.72 (CH), 107.46 (O*C*C), 149.59, 155.39, 165.31, 172.73 (C); MS (EI, 70 eV): 182 ([$M^+$], 100), 124 (48), 79 (45), 69 (17); IR (KBr): $\tilde{\nu} =$ 3410, 3140, 2675, 2285, 1881, 1801, 1724, 1685, 1611, 1478, 1441, 1384, 1322, 1226, 1043, 1009 cm$^{-1}$; elemental analysis calcd for $C_8H_6O_5$: C 52.76, H 3.32; found: C 52.54, H 3.30.

**4z**: Prepared from 3-acetyl-5-methyl-dihydro-furan-2-one (210 mg, 1.48 mmol). Colorless solid; yield: 174 mg (60%); m.p. 82 °C; $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta = 1.46$ (d, $J = 6$ Hz, 3H; $CH_3$), 2.76 (m, 1H; $CH_2$), 3.35 (m, 1H; $CH_2$), 4.83 (m, $J = 5$ Hz, 1H; OCH), 7.18 (s, 1H; ring-CH); $^{13}$C NMR ([D$_6$]acetone, 75 MHz): $\delta = 18.26$ ($CH_3$), 29.77 ($CH_2$), 71.42 ($CH_2$*C*H), 102.32 (C), 104.19 (ring-CH), 144.73, 149.99, 160.59, 166.30 (C); MS (EI, 70 eV): 196 ([$M^+$], 30), 152 (67), 124 (100), 79 (58), 69 (27); elemental analysis calcd for $C_9H_8O_5$: C 55.11, H 4.11; found: C 55.35, H 4.23.

**4aa**: Prepared from 2-acetyl-cyclopentanone (0.18 mL, 1.48 mmol). Colorless solid; yield: 200 mg (75%); m.p. 80 °C; $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta = 1.87$ (m, 2H; $CH_2CH_2CH_2CO$), 2.42 (t, $J = 7$ Hz, 2H; $CH_2(CH_2)_2CO$), 2.88 (t, $J = 7$ Hz, 2H; $CH_2CO$), 7.23 (s, 1H; ring-CH); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $\delta = 21.63$ ($CH_2CH_2CH_2CO$), 28.73 ($CH_2(CH_2)_2CO$), 41.78 ($CH_2CO$), 109.14 (CH), 117.24, 151.01, 154.10 (C), 166.64 (O*C*OC), 210.53 (CO); MS (EI, 70 eV): 180 ([$M^+$], 100), 138 (48), 124 (66), 82 (20), 79 (46); IR (KBr): $\tilde{\nu} = 3369$, 3170, 2970, 2675, 2338, 1801, 1687, 1620, 1460, 1435, 1404, 1313, 1284, 1206, 1042 cm$^{-1}$; elemental analysis calcd for $C_9H_8O_4$: C 60.03, H 4.48; found: C 59.89, H 4.74.

**4ab**: This reaction gave a mixture of two regioisomeric products **4ab** and **4ad** in 71% yield (205 mg). Starting from 2-acetyl-cyclohexanone (0.20 mL, 1.48 mmol), pure **4ab** was isolated as a colorless oil from the mixture of regioisomers by repeated column chromatography. Yield: 66 mg (23%); $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta = 1.87$ (m, 4H; C=C$CH_2$), 2.47 (t, $J = 7$ Hz, 2H; $CH_2(CH_2)_2CH_2CO$), 2.77 (t, 2H; $CH_2CO$), 7.12 (s, 1H; ring-CH); $^{13}$C NMR ([D$_6$]acetone, 75 MHz): $\delta = 23.51$, 23.86 ($CH_2(CH_2)_2$-$CH_2CO$), 26.66 ($CH_2(CH_2)_3CO$), 41.87 ($CH_2CO$), 111.23 (CH), 116.92,

149.64, 152.64 (C), 164.50 (O*C*OC), 200.45 (CO); MS (EI, 70 eV): 194 ([$M^+$], 86), 166 (52), 138 (36), 125 (100), 110 (23), 82 (30); IR (KBr): $\tilde{\nu}$ = 3423, 3129, 2950, 2879, 2685, 2361, 1798, 1651, 1620, 1579, 1343, 1316, 1268, 1239, 1154, 1058 cm$^{-1}$; elemental analysis calcd for $C_{10}H_{10}O_4$: C 61.85, H 5.19; found: C 61.57, H 5.23.

**4ac**: Prepared from 2-acetyl-decalone (287 mg, 1.48 mmol). Colorless oil; yield: 224 mg (61%, mixture of *cis* and *trans* isomers); $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta$ = 1.87 (m, 8H), 1.32 (m, 4H), 2.23 (m, 1H), 3.09 (m,1H), 6.98 (s, 1H; ring-CH); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $\delta$ = 26.15, 26.30, 26.41, 28.82, (CH(*C*H$_2$)$_4$CH), 34.71 (C=*C*CH$_2$CH$_2$), 40.92 (C=C*C*H$_2$CH$_2$), 55.87 (*C*HCHCO), 62.17 (CH*C*HCO), 111.03 (ring-CH), 117.34 (COH), 148.91, 151.73(C=C), 164.64 (C) 201.69 (CO); MS (EI, 70 eV): 248 ([$M^+$], 43), 220 (34), 126 (28), 95 (100), 79(20).

**4ah**: Prepared from 2-acetyl-tetralone (278 mg, 1.48 mmol). Yellow solid; yield: 265 mg (74%); m.p. 90 °C; $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta$ = 3.10 (s, 4H; CH$_2$CH$_2$), 7.43 (m, $J$ = 6 Hz, 2H; Ar ), 7.46 (s, 1H; ring-CH ), 7.60 (t, $J$ = 6 Hz, 1H; Ar), 8.04 (m, $J$ = 6 Hz, 1H; Ar); $^{13}$C NMR ([D$_6$]acetone, 75 MHz): $\delta$ = 25.72, 28.83 (CH$_2$), 111.15 (ring-CH), 127.71, 128.00, 129.37, 134.12 (CH, Ar), 135.00, 144.37, 150.01, 150.11, 154.09, 164.40 (C), 187.67 (C*C*OC); MS (EI, 70 eV): 242 ([$M^+$], 100), 186 (30), 141 (29), 115 (33), 90 (16), 69 (10); IR (KBr): $\tilde{\nu}$ = 3430, 3098, 2962, 2686, 2362, 1804, 1647, 1620, 1562, 1456, 1342, 1251, 1158, 1057 cm$^{-1}$; elemental analysis calcd for $C_{14}H_{10}O_4$: C 69.42, H 4.16; found: C 69.77, H 4.34.

**4ai**: Prepared from 3-acetyl-3*H*-benzofuran-2-one (260 mg, 1.47 mmol). Isolated as a yellow solid by repeated chromatography; yield: 176 mg (52%); m.p. 94 °C; $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta$ = 6.43 (s, 1H; ring-CH), 7.07 (m, 3H; Ar), 7.60 (m, 1H; Ar); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $\delta$ = 92.39, 99.21 (C), 110.23 (CH), 122.75, 124.15, 125.33, 126.72 (CH, Ar), 151.63 (C), 163.20, 166.33 (C), 166.42, 168.70 (CO); MS (EI, 70 eV): 230 ([$M^+$], 21), 195 (8), 161 (21), 64 (25), 46 (100); IR (KBr): $\tilde{\nu}$ = 3412, 3060, 2927, 2362, 1720, 1635, 1458, 1351, 1288, 1241, 1199, 1151, 1097, 1018 cm$^{-1}$; elemental analysis calcd for $C_{12}H_6O_5$: C 62.62, H 2.63; found: C 62.80, H 2.55.

**4aj**: Prepared from 2-acetyl-indan-1-one (257 mg, 1.48 mmol). Yellow solid; yield: 74 mg (22%); $^1$H NMR ([D$_8$]THF, 300 MHz): $\delta$ = 3.88 (s, 2H; CH$_2$), 7.36 (s, 1H; ring-CH), 7.40, 7.59, 7.73 (m, 4H; CH, Ar); $^{13}$C NMR ([D$_8$]THF, 75 MHz): $\delta$ = 25.54 (CH$_2$), 108.33 (ring-CH), 114.71 (C), 123.96, 127.16, 128.22, 135.02 (CH, Ar), 140.70, 149.09, 150.27, 153.88 (C), 164.69, 193.28 (CO); MS (EI, 70 eV): 228 ([$M^+$], 100), 172 (12), 155 (23), 144 (29), 131 (34), 102 (18), 77 (11).

**General procedure for the preparation of γ-alkylidenebutenolides by reaction of 1,3-bis(trimethylsilyloxy)-1,3-dienes with oxalyl chloride**: To a solution of a mixture of oxalyl chloride (1.5 mmol, 0.13 mL) and the 1,3-bis(trimethylsilyloxy)-1,3-diene **3** (1.5 mmol) in $CH_2Cl_2$ (30 mL) was added a solution of TMSOTf (0.45 mmol) in $CH_2Cl_2$ (7 mL) at −78 °C. The reaction mixture was allowed to warm to 20 °C over a period of 6 h. After the mixture had been stirred for 2 h at 20 °C, a saturated solution of NaCl was added, the organic layer was separated, and the aqueous layer was repeatedly extracted with diethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, diethyl ether/petrol ether).

**4a**: Prepared from 1-ethoxy-1,3-bis(trimethylsilyloxy)-buta-1,3-diene **3a** (410 mg, 1.50 mmol). Colorless solid; yield: 277 mg (87%).

**4c**: Prepared from 1-phenyl-1,3-bis(trimethylsilyloxy)-1,3-butadiene **3c** (552 mg, 1.80 mmol). Colorless solid; yield: 310 mg (80%).

**4d**: Prepared from 5,5-dimethyl-2,4-bis(trimethylsilyloxy)-1,3-hexadiene **3d** (430 mg, 1.50 mmol). Colorless solid; yield: 247 mg (84%).

**4e**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3e** (368 mg, 1.50 mmol). Colorless solid; yield: 170 mg (74%, $E$:$Z$ = 5:1).

**4h**: Prepared from 1,3-bis(trimethylsilyloxy)-1-methoxy-1,3-pentadiene **3h** (494 mg, 1.80 mmol). Colorless solid; yield: 264 mg (80%).

**4i**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3i** (454 mg, 1.50 mmol). Colorless solid; yield: 242 mg (76%).

**4j**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3j** (496 mg, 1.50 mmol). Colorless solid; yield: 252 mg (70%); m.p. 86 °C; $^1$H NMR ([D$_6$]-acetone, 200 MHz): $\delta$ = 0.92 (t, $J$ = 6 Hz, 3H; CH$_3$), 1.25 (t, $J$ = 6 Hz, 3H; CH$_3$), 1.40 (m, 2H; CH$_2$), 1.54 (m, 2H; CH$_2$), 2.46 3.31 (t, $J$ = 6 Hz, 2H; CH$_2$), 2.88 (br, OH), 4.16 (q, $J$ = 6 Hz, 2H; OCH$_2$), 5.45 (s, 1H; CC*H*CO); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $\delta$ = 13.94, 14.46 (CH$_3$), 22.31, 22.95, 30.82 (CH$_2$), 60.63 (OCH$_2$), 95.73 (C*C*HCO), 125.32, 144.45, 158.06 (C), 163.72, 164.69 (CO); MS (EI, 70 eV): 240 ([$M^+$], 100), 212 (16), 194 (39), 166 (58); elemental analysis calcd for $C_{12}H_{16}O_5$: C 59.99, H 6.71; found: C 59.24, H 6.67.

**4k**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3k** (656 mg, 1.80 mmol). Colorless solid; yield: 334 mg (68%); m.p. 92 °C; $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta$ = 1.22 (t, $J$ = 5 Hz, 3H; CH$_3$), 3.83 (s, 2H;C*H*$_2$Ph), 4.08 (q, $J$ = 5 Hz, 2H; OC*H*$_2$CH$_3$), 5.38 (s, 1H; CC*H*CO), 7.25 (m, 5H; Ph); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $\delta$ = 14.46 (CH$_3$), 28.14 (CH$_2$), 60.64 (O*C*H$_2$CH$_3$), 96.63 (C*C*HCO), 123.68 (C), 127.40, 129.01, 129.44 (CH, Ph), 138.38, 145.41, 157.71 (C), 163.53, 164.63 (CO); MS (EI, 70 eV): 274 ([$M^+$], 100).

**4l**: Prepared from 1,4-dimethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene **3l** (436 mg, 1.50 mmol). Colorless solid; yield: 255 mg (85%); m.p. 87 °C; $^1$H NMR ([D$_4$]MeOH, 200 MHz): $\delta$ = 3.75 (s, 3H; OCH$_3$), 4.18 (t, 3H; COOCH$_3$), 5.44 (s, 1H; CH); $^{13}$C NMR ([D$_4$]MeOH, 50 MHz): $\delta$ = 52.14 (OCH$_3$), 59.86 (COO*C*H$_3$), 94.29 (CH), 126.31, 142.53, 154.34 (C), 165.57, 165.70 (OCO); IR (KBr): $\tilde{\nu}$ = 3208, 3082, 2877, 2362, 1795, 1682, 1466, 1442, 1372, 1348, 1302, 1195, 1119, 1089, 1024 cm$^{-1}$; MS (EI, 70 eV): 200 ([$M^+$], 61), 169 (50), 140 (30), 113 (64), 85 (42), 69 (100); elemental analysis calcd for $C_8H_8O_6$: C 48.01, H 4.03; found: C 47.71, H 4.28.

**4m**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3m** (544 mg, 1.80 mmol). Colorless solid; yield: 163 mg (43%); m.p. 102 °C; $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta$ = 2.40 (s, 3H; CH$_3$), 3.79 (s, 3H; OCH$_3$), 6.36 (s, 1H; CC*H*CO); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $\delta$ = 19.62 (CH$_3$), 52.79 (OCH$_3$), 115.68 (C*C*HCO), 127.14 (C), 160.62, 164.07, 167.72 (C), 175.97 (*C*OCH$_3$); MS (EI, 70 eV): 212 ([$M^+$], 80), 181 (100), 154 (92); elemental analysis calcd for $C_9H_8O_6$: C 50.95, H 3.80; found: C 50.70, H 3.62.

**4n**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3n** (388 mg, 1.50 mmol). Colorless solid; yield: 194 mg (77%, $E$:$Z$ = 3.5:1).

**4o**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3o** (518 mg, 1.80 mmol). Colorless solid; yield: 253 mg (71%).

**4p**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3p** (544 mg, 1.80 mmol). Colorless solid; yield: 252 mg (66%).

**4q**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3q** (594 mg, 1.80 mmol). Colorless solid; yield: 268 mg (62%); m.p. 78 °C; $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta$ = 0.89 (t, $J$ = 6 Hz, 3H; CCH$_2$C*H*$_3$), 1.30 (t, $J$ = 6 Hz, 3H; OCH$_2$C*H*$_3$), 1.38 (m, 4H; CH$_2$), 2.48 (t, $J$ = 6 Hz, 2H; CH$_2$), 4.22 (q, $J$ = 6 Hz, 2H; OCH$_2$), 7.17 (s, 1H; CH); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $\delta$ = 14.06, 14.40 (CH$_3$), 23.04, 27.00, 32.17 (CH$_2$), 61.29 (OCH$_2$), 110.89 (CH), 113.66, 148.67, 155.39, 164.36 (C), 166.86 (CO); MS (EI, 70 eV): 240 ([$M^+$], 17), 213 (100), 171 (72), 69 (64); elemental analysis calcd for $C_{12}H_{16}O_5$: C 59.99, H 6.71; found: C 60.29, H 6.83.

**4r**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3r** (624 mg, 1.80 mmol). Yellow solid; yield: 208 mg (45%, $E$:$Z$ = 1:3); m.p. 70 °C; $Z$ isomer: $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta$ = 3.38 (m, 2H; CCH$_2$C*H*$_3$), 4.90 – 5.20 (m, 2H; =CH$_2$), 5.83 (m, 1H; C*H*=CH$_2$), 6.02 (s, 1H; CH), 7.45 – 7.90 (m, 5H; Ph); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $\delta$ = 37.34 (CH$_2$), 114.51 (CH), 121.63 (=CH$_2$), 123.90 (C), 133.75, 134.41, 138.13 (CH), 139.52, 144.17, 151.87, 157.08, 168.81 (C), 200.25 (CO); $E$ isomer: $^1$H NMR ([D$_6$]acetone, 200 MHz): 3.35 (m, 2H; CCH$_2$C*H*$_3$), 4.90 – 5.20 (m, 2H; =CH$_2$), 5.83 (m, 1H; C*H*=CH$_2$), 6.98 (s, 1H; CH), 7.45 – 7.90 (m, 5H; Ph); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): 37.87 (CH$_2$), 113.20 (CH), 121.42 (=CH$_2$), 121.95 (C), 133.61, 134.32, 138.32 (CH), 139.98, 143.41, 152.87, 157.08, 168.80 (C), 199.44 (CO); MS (EI, 70 eV): 256 ([$M^+$], 2), 202 (8), 105 (100); elemental analysis calcd for $C_{15}H_{12}O_4$: C 70.31, H 4.72; found: C 70.97, H 5.14.

**4s**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3s** (631 mg, 1.80 mmol). Yellow solid; yield: 263 mg (56%, $E$:$Z$ = 7:1); m.p. 68 °C; $^1$H NMR ([D$_6$]acetone, 200 MHz): 1.25 (t, $J$ = 6 Hz, 3H; CH$_3$), 3.05 (br, OH), 4.25 (q, $J$ = 6 Hz, 2H; OCH$_2$), 6.40 (s, 1H; CH, $Z$ isomer), 7.25 (s, 1H; CH, $E$ isomer), 7.38 (m, 5H; Ph); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $E$ isomer: $\delta$ = 14.32 (CH$_3$), 61.68 (CH$_2$), 110.97 (CH), 113.78 (C), 128.35, 128.47, 131.26 (CH), 133.90, 148.93, 155.13, 164.47 (C), 166.60 (CO); MS (EI, 70 eV): 260 ([$M^+$], 100), 215 (21), 187 (19); elemental analysis calcd for $C_{14}H_{12}O_5$: C 64.61, H 4.65; found: C 64.48, H 4.73.

**4t**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3t** (715 mg, 1.80 mmol). Yellow solid; yield: 342 mg (62%, $E$:$Z$ = 1:3); m.p. 82 °C; $^1$H NMR ([D$_6$]acetone, 200 MHz): 2.85 (br, OH), 3.93 (s, 2H; CH$_2$, $E$



0947-6539/00/0617-3212 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 17

isomer), 4.02 (s, 2H; $CH_2$, *Z* isomer), 5.97 (s, 1H; CH, *Z* isomer), 7.21 (s, 1H; CH, *E* isomer), 7.10–7.70 (m, 10H; Ph); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): *Z* Isomer: $\delta = 34.44$ ($CH_2$), 109.97 (CH), 120.50 (C), 127.08, 129.22, 129.37, 129.85, 133.64 (CH), 139.46, 139.92, 147.75, 152.82, 164.51 (C), 195.87 (CO); MS (EI, 70 eV): 306 ([$M^+$], 100); elemental analysis calcd for $C_{19}H_{14}O_4$: C 74.50, H 4.61; found: C 74.33, H 4.84.

**4u**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3u** (544 mg, 1.80 mmol). Yellow oil; yield: 183 mg (48%); $^1$H NMR ([D$_4$]MeOH, 200 MHz): 2.40 (s, 3H; $CH_3$), 3.80 (s, 3H; $OCH_3$), 6.93 (s, 1H; CH); $^{13}$C NMR ([D$_4$]MeOH, 50 MHz): $\delta = 18.89$ ($CH_3$), 53.34 ($OCH_3$), 119.34 (CH), 123.61 (C), 154.23, 161.03, 165.73 (C), 169.46, 177.65 (CO); MS (EI, 70 eV): 212 ([$M^+$], 6), 172 (100); elemental analysis calcd for $C_9H_8O_6$: C 50.95, H 3.80; found: C 50.82, H 3.57.

**4v**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-cyclohexadiene **3v** (386 mg, 1.50 mmol). Colorless solid; yield: 174 mg (70%); m.p. 104 °C; $^1$H NMR ([D$_4$]MeOH, 200 MHz): $\delta = 2.60$ (t, $J = 6$ Hz, 2H; CC$H_2$CH$_2$CO), 2.93 (t, $J = 6$ Hz, 2H; CCH$_2$C$H_2$CO), 5.76 (s, 1H; CH); $^{13}$C NMR ([D$_4$]MeOH, 50 MHz): $\delta = 18.57$ (C*C*H$_2$CH$_2$CO), 36.26 (CCH$_2$*C*H$_2$CO), 105.50 (CH), 119.00 (*C*CH$_2$CH$_2$CO), 143.00 (O*C*CHCO), 164.84 (OCO-*C*OH), 166.13 (O*C*OCOH), 199.98 (CO); MS (EI, 70 eV): 166 ([$M^+$], 100), 138 (18), 110 (58), 82 (28), 69 (62); IR (KBr): $\tilde{\nu} = 3431$, 3063, 2973, 2902, 2694, 1804, 1616, 1434, 1383, 1312, 1218, 1194, 1130, 1053 cm$^{-1}$; elemental analysis calcd for $C_8H_6O_4$: C 57.84, H 3.64; found: C 57.72, H 3.82.

**4w**: Prepared from 2-methyl-1,3-bis(trimethylsilyloxy)-1,3-cyclohexadien **3w** (406 mg, 1.50 mmol). Colorless solid; yield: 173 mg (64%); m.p. 120 °C; $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta = 1.82$ (s, 3H; $CH_3$), 2.57 (t, $J = 5$ Hz, 2H; CC$H_2$CH$_2$CO), 2.93 (t, $J = 5$ Hz, 2H; CCH$_2$C$H_2$CO); $^{13}$C NMR ([D$_6$]acetone, 75 MHz): $\delta = 8.35$ ($CH_3$), 18.26 (C*C*H$_2$CH$_2$CO), 35.66 (CCH$_2$*C*H$_2$CO), 114.81 (*C*CH$_2$CH$_2$CO), 120.81, 140.47 (C), 159.12 (O*C*C), 164.32 (OCO), 196.96 (CO); MS (EI, 70 eV): 180 ([$M^+$], 100), 152 (4), 124 (16), 96 (14), 69 (10), 44 (47); IR (KBr): $\tilde{\nu} = 3552$, 3198, 2646, 2365, 1783, 1682, 1622, 1432, 1400, 1376, 1341, 1206, 1096, 1053 cm$^{-1}$; elemental analysis calcd for $C_9H_8O_4$: C 60.00, H 4.48; found: C 59.78, H 4.62.

**4x**: Prepared from 1,1-dimethyl-2,4-bis(trimethylsilyloxy)-cyclohexa-2,4-diene **3x** (426 mg, 1.50 mmol). Colorless solid; yield: 192 mg (66%); m.p. 105 °C; $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta = 1.39$ (s, 6H; C($CH_3$)$_2$), 2.44 (s, 2H; $CH_2$), 5.78 (s, 1H; CH); $^{13}$C NMR ([D$_6$]acetone, 50 MHz): $\delta = 27.44$ (C($CH_3$)$_2$), 33.80 (*C*($CH_3$)$_2$), 52.68 ($CH_2$), 105.42 (CH), 127.28 (C, *C*($CH_3$)$_2$), 141.58 (C), 163.22 [=*C*(OH)], 164.68, 196.56 (CO); MS (EI, 70 eV): 194 ([$M^+$], 100), 179 (42), 151 (62), 109 (27), 69 (33); IR (KBr): $\tilde{\nu} = 3421$, 2957, 2869, 26803, 2528, 1906, 1812, 1747, 1575, 1467, 1412, 1351, 1303, 1221, 1147 cm$^{-1}$; elemental analysis calcd for $C_{10}H_{10}O_4$: C 61.85, H 5.19; found: C 61.62, H 5.43.

**4z**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3z** (537 mg, 1.50 mmol). Colorless solid; yield: 165 mg (41%).

**4ab**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3ab** (511 mg, 1.80 mmol) to give a 3:1 mixture of the two regioisomeric products **4ab** and **4ad** which was isolated as a light yellow oil. Yield: 250 mg (72%). The pure butenolide **4ab** was isolated in 22% yield (77 mg).

**4ae**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3ae** (566 mg, 1.80 mmol). Light yellow oil; yield: 286 mg (71%); $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta = 1.28$ (t, $J = 6$ Hz, 3H; $CH_3$), 1.80 (quintet, $J = 5$ Hz, 2H; $CH_2$), 2.52 (t, $J = 5$ Hz, 2H; $CH_2$), 2.58 (t, $J = 5$ Hz, 2H; $CH_2$), 4.18 (q, $J = 6$ Hz, 2H; $OCH_2$); $^{13}$C NMR ([D$_6$]acetone, 75 MHz): $\delta = 14.57$ ($CH_3$), 21.16, 22.53, 25.14 ($CH_2$), 60.99 ($OCH_2$), 107.91, 123.13, 139.97, 152.72 (C), 165.08, 165.37 (CO); MS (EI, 70 eV): 224 ([$M^+$], 35), 178 (100), 150 (61); elemental analysis calcd for $C_{11}H_{12}O_5$: C 58.93, H 5.39; found: C 58.76, H 5.50.

**4af**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3af** (622 mg, 1.80 mmol). Light yellow oil; yield: 230 mg (50%); $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta = 1.90$ (quintet, $J = 5$ Hz, 2H; $CH_2$), 2.66 (m, $J = 5$ Hz, 4H; $CH_2$), 5.80 (br, OH), 7.40–7.85 (m, 5H; Ph); $^{13}$C NMR ([D$_6$]acetone, 75 MHz): $\delta = 19.23$ ($CH_3$), 20.74, 21.33, 22.77 ($CH_2$), 115.34, 122.51 (C), 128.93, 129.93, 133.43 (CH, Ph), 139.54, 149.96 (C), 164.79, 194.14 (CO); MS (EI, 70 eV): 256 ([$M^+$], 100), 227 (46), 105 (58), 77 (56).

**4ag**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3ag** (540 mg, 1.80 mmol). Colorless solid; yield: 98 mg (26%); $^1$H NMR ([D$_6$]acetone, 200 MHz): $\delta = 1.25$ (t, $J = 5$ Hz, 3H; $CH_3$), 2.75 (m, 2H; $CH_2$), 2.75 (m, 2H; $CH_2$), 4.19 (q, 2H; $OCH_2$); MS (EI, 70 eV): 210 ([$M^+$], 100).

**4ah**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3ah** (600 mg, 1.80 mmol). Colorless solid; yield: 352 mg (81%).

**4ai**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3ai** (575 mg, 1.80 mmol). Isolated as a yellow solid by repeated chromatography; yield: 250 mg (60%).

**4aj**: Prepared from 1,3-bis(trimethylsilyloxy)-1,3-diene **3aj** (477 mg, 1.50 mmol). Yellow solid; yield: 96 mg (28%).

## Acknowledgements

P.L. thanks Professor Dr. A. de Meijere for his support. Financial support from the Fonds der Chemischen Industrie (Liebig scholarship and funds for P.L.) is gratefully acknowledged.

[1] Reviews: a) 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; E.-i. Negishi, M. Kotora, *Tetrahedron* **1997**, *53*, 6707–6738.

[2] 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**.

[3] a) D. Enders, H. Dyker, F. R. Leusink, *Chem. Eur. J.* **1998**, *4*, 311–320; b) for the use of isotetronic acids in the synthesis of nonactinic acids, see: A. G. M. Barrett, H. G. Sheth, *J. Org. Chem.* **1983**, *48*, 5017–5022; c) For the synthesis of erythronolide A, see: G. Stork, S. D. Rychnovsky, *J. Am. Chem. Soc.* **1987**, *109*, 1564–1565.

[4] M. Kotora, E.-i. Negishi, *Synthesis* **1997**, 121–128.

[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) 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] a) D. W. Knight, G. Pattenden, *J. Chem. Soc. Perkin Trans 1* **1979**, 62–69; b) C. F. Ingham, R. A. Massy-Westropp, G. D. Reynolds, W. D. Thorpe, *Aust. J. Chem.* **1975**, *28*, 2499–2510; c) R. A. Massy-Westropp, M. F. Price, *Aust. J. Chem.* **1980**, *33*, 333–341; d) I. Bell, E. R. H. Jones, M. C. Whiting, *J. Chem. Soc.* **1958**, 1313–1322; e) G. Struve, S. Seltzer, *J. Org. Chem.* **1982**, *47*, 2109–2113.

[8] R. W. Saalfrank, T. Lutz, *Angew. Chem.* **1990**, *102*, 1064–1066; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1041–1043.

[9] P. Langer, M. Stoll, *Angew. Chem.* **1999**, *111*, 1919–1922; *Angew. Chem. Int. Ed.* **1999**, *38*, 1803–1805.

[10] a) 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.

[11] 1,3-Dicarbonyl dianions have been previously used in natural product syntheses: a) R. W. Hoffmann, W. Ladner, K. Steinbach, W. Massa, R. Schmidt, G. Snatzke, *Chem. Ber.* **1981**, *114*, 2786–2801; b) P. G. Willard, L. A. Grab, S. E. de Laszlo, *J. Org. Chem.* **1983**, *48*, 1123–1125; c) T. Clarke, S. V. Ley, *J. Chem. Soc. Perkin Trans. 1* **1987**, 131–135; d) B. Lygo, *Tetrahedron* **1988**, *44*, 6889–6896; e) S. G. Gilbreath, C. M. Harris, T. M. Harris, *J. Am. Chem. Soc.* **1988**, *110*, 6172–6179.

[12] M. P. Sibi, M. Marvin, R. Sharma, *J. Org. Chem.* **1995**, *60*, 5016–5023.

[13] Cyclization reactions of dianions with dielectrophiles are much less common than condensations with simple 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.

[14] T. Mukaiyama, *Angew. Chem.* **1977**, *89*, 858–866; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 817–825.

[15] a) T.-H. Chan, P. Brownbridge, *J. Chem. Soc. Chem. Commun.* **1979**, 578–579; b) T.-H. Chan, P. Brownbridge, *J. Am. Chem. Soc.* **1980**, *102*,

3534 – 3538; c) R. P. Attrill, A. G. M. Barrett, P. Quayle, J. Van der Westhuizen, M. Betts, *J. Org. Chem.* **1984**, *49*, 1679 – 1682; d) H. Hagiwara, K. Kimura, H. Uda, *J. Chem. Soc. Chem. Commun.* **1986**, 860 – 861.

[16] a) D. W. Cameron, G. I. Feutrill, P. Perlmutter, *Aust. J. Chem.* **1982**, *35*, 1469 – 1480; b) G. J. Kang, T.-H. Chan, *J. Org. Chem.* **1985**, *50*, 452 – 457; c) G. J. O'Malley, R. A. Murphy, Jr., M. P. Cava, *J. Org. Chem.* **1985**, *50*, 5533 – 5537; d) S. D. Lee, T.-H. Chan, *Tetrahedron* **1984**, *40*, 3611 – 3626; e) G. A. Molander, K. O. Cameron, *J. Am. Chem. Soc.* **1993**, *115*, 830 – 846.

[17] For [4+2] cycloaddition reactions of 1,3-bis(trimethylsilyloxy)-1,3-dienes, see: a) K. Krohn, H.-H. Ostermeyer, K. Tolkiehn, *Chem. Ber.* **1979**, *112*, 2640 – 2649; b) C. Brisson, P. Brassard, *J. Org. Chem.* **1981**, *46*, 1810 – 1814, and references therein.

[18] For the decarbonylation during the cyclization of glycols with oxalyl chloride, see: T. Iida, T. Itaya, *Tetrahedron* **1993**, *49*, 10511 – 10530.

[19] For reactions with monofunctional carboxylic acid chlorides, see: a) T. H. Chan, D. Stössel, *J. Org. Chem.* **1986**, *51*, 2423 – 2428; b) T. H. Chan, D. Stössel, *J. Org. Chem.* **1988**, *53*, 4901 – 4908.

[20] U. T. Mueller-Westerhoff, M. Zhou, *J. Org. Chem.* **1994**, *59*, 4988 – 4992.

[21] 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.

[22] For a review on the structure and reactivity of lithium enolates, see: D. Seebach, *Angew. Chem.* **1988**, *100*, 1685 – 1715; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1624 – 1654.

[23] H. O. House, L. J. Czuba, M. Gall, H. D. Olmstead, *J. Org. Chem.* **1969**, *34*, 2324 – 2336.

[24] K. Krägeloh, G. Simchen, *Synthesis* **1981**, 30 – 32.

[25] G. Anderson, D. W. Cameron, G. I. Feutrill, R. W. Read, *Tetrahedron Lett.* **1981**, 4347 – 4348.

[26] a) T. Clarke, S. V. Ley, *J. Chem. Soc. Perkin Trans 1* **1987**, 131 – 135; b) J. S. Hubbard, T. M. Harris, *Tetrahedron Lett.* **1978**, 4601 – 4602.

[27] a) See [1]; b) D. W. Knight, G. Pattenden, *J. Chem. Soc. Perkin Trans 1* **1979**, 62 – 69; c) Butenolide **4l** represents a potential starting material for the synthesis of chlorothricolide (by cycloaddition reactions at the exocyclic double bond): R. E. Ireland, M. D. Varney, *J. Org. Chem.* **1986**, *51*, 635 – 648; d) K. Okumura, K. Okazaki, K. Takeda, E. Yoshii, *Tetrahedron Lett.* **1989**, 2233 – 2236; e) J. E. Wrobel, B. Ganem, *J. Org. Chem.* **1983**, *48*, 3761 – 3764.

[28] The chemoselective differentiation between the two hydroxy groups of ascorbic acid derivatives is problematic: a) M. G. Kulkarni, S. R. Thopate, *Tetrahedron* **1996**, 1293 – 1302; b) for a regioselective approach, see U. Beifuss, O. Kunz, G. P. Aguado, *Synlett* **1999**, 147 – 149.

[29] B. Simoneau, P. Brassard, *Tetrahedron* **1986**, *14*, 3767 – 3774.

[30] T.-H. Chan, D. Stossel, *J. Org. Chem.* **1986**, *51*, 2423 – 2428.

[31] P. Alleri, M. Anstasia, S. Bingham, P. Ciuffreda, A. Fiecchi, G. Cigetti, M. Muir, A. Scala, J. Tyman, *J. Chem. Soc. Perkin Trans. 1* **1998**, 575 – 582.

[32] N. M. Berry, *Synthesis* **1986**, 476 – 480.

[33] a) J. Gripenberg, J. Martikkala, *Acta Chem. Scand.* **1969**, *23*, 2583 – 2588; b) J. Gripenberg, J. Martikkala, *Acta Chem. Scand.* **1970**, *24*, 3444 – 3448; c) J. Gripenberg, *Acta Chem. Scand.* **1970**, *24*, 3449 – 3454; d) J. Gripenberg, *Acta Chem. Scand.* **1971**, *25*, 2999 – 3005.

[34] Previously, this compound could only be obtained as the minor component in a 1:4 mixture of the regioisomers **3ab** and **3ad**: L. Hansson, R. Carlson, *Acta Chem. Scand.* **1989**, *43*, 304 – 306.

[35] K. Hintzer, R. Weber, V. Schurig, *Tetrahedron Lett.* **1981**, 55 – 58.

[36] D. Seebach, V. Ehrig, *Chem. Ber.* **1975**, *108*, 1961 – 1973.

[37] R. H. Schlessinger, J. L. Wood, A. J. Poss, R. A. Nugent, W. H. Parsons, *J. Org. Chem.* **1983**, *48*, 1146 – 1147.

[38] B. Åkermark, *Acta Chem. Scand.* **1961**, *15*, 1695 – 1701.

[39] P. Langer, T. Schneider, unpublished results.

Received: September 20, 1999 [F2043]

  0947-6539/00/0617-3214 $ 17.50+.50/0 