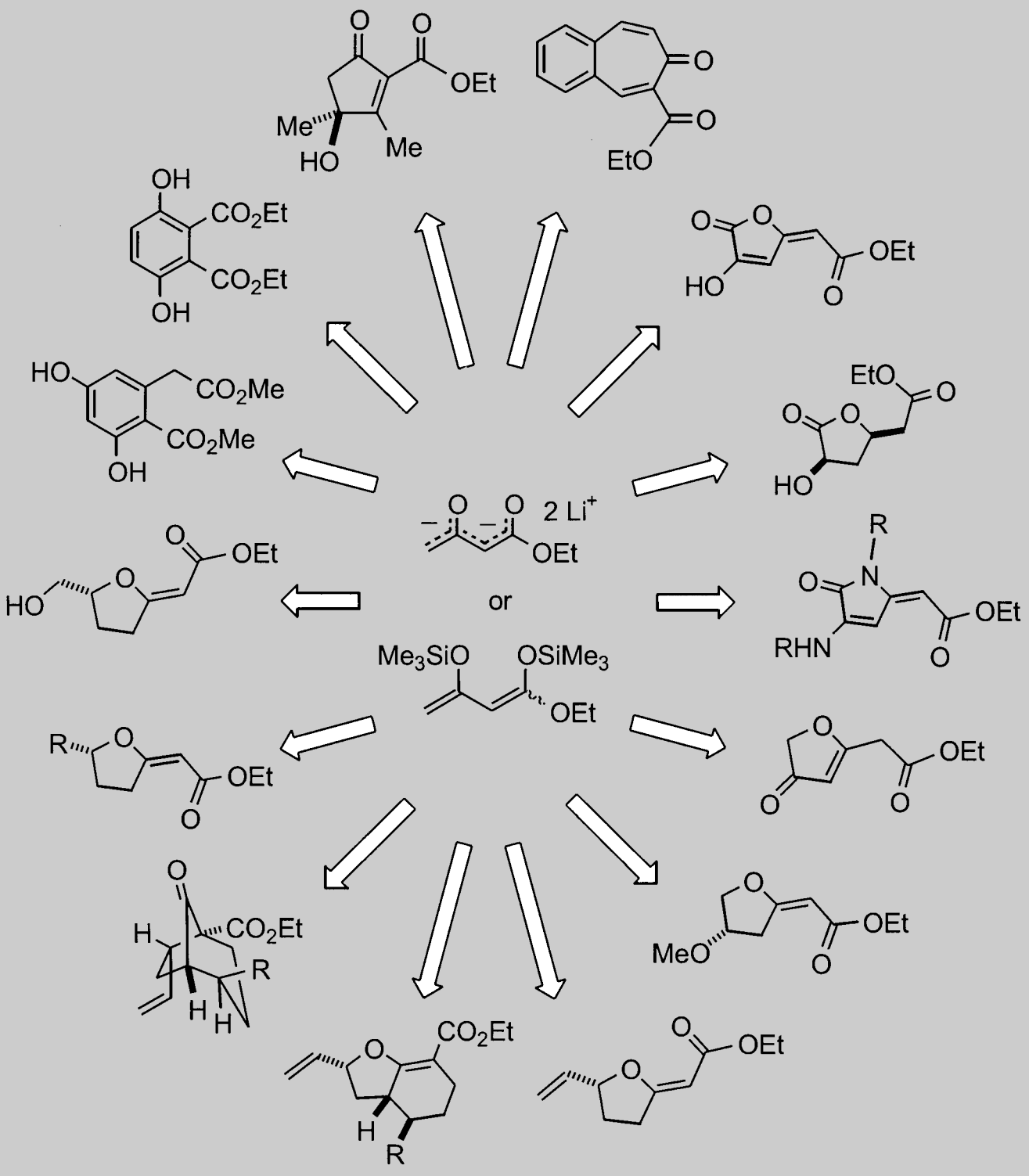
Cyclization Reactions of Free and Masked 1,3-Dicarbonyl Dianions



0947-6539/01/0718-3858 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 18

Regio- and Diastereoselective Cyclization Reactions of Free and Masked 1,3-Dicarbonyl Dianions with 1,2-Dielectrophiles

Peter Langer*[a]

Abstract: Despite their simplicity and synthetic usefulness, cyclisation reactions of 1,3-dicarbonyl dianions with 1,2-dielectrophiles are problematic, since both dianions and 1,2-dielectrophiles are highly reactive compounds (low reactivity matching). In addition, 1,2-dielectrophiles are often rather labile, and reactions with nucleophiles can result in polymerisation, decomposition, formation of open-chained products, elimination or SET-reactions. These intrinsic limitations can be overcome by a proper reactivity tuning and by the use of electroneutral dianion equivalents (masked dianions) in Lewis acid catalysed reactions. The cyclisations reported herein allow for an efficient, regio- and stereoselective one-pot synthesis of biologically relevant ring systems.

Keywords: anions · cyclization · regioselectivity · silyl enol ethers · tetrahydrofurans

Introduction

Ambident dianions are organic substrates containing two delocalised negative charges.[1] The generation of dianions requires strong bases such as lithium diisopropylamide (LDA) or *n*-butyl lithium (*n*BuLi). 1,3-Dicarbonyl compounds can be metallated twice by the action of two equivalents of LDA or by the use of NaH/*n*BuLi.[2] The terminal carbon atom of the dianion can be regioselectively coupled with one equivalent of an electrophile to give a monoanion, which is subsequently trapped by addition of a second electrophile. Monoanions may be alkylated twice by a double deprotonation-alkylation sequence. However, the regioselectivities of the reactions of monoanions and dianions generally differ greatly. For example, 1,3-dicarbonyl monoanions are generally alkylated at the central carbon or at the oxygen atom, whereas the formation of dianions allows for functionalisation of the terminal carbon atom. Exceptions to this are the reactions of highly stabilised 1,3,5-tricarbonyl compounds, which contain two (rather than only one) highly acidic C–H groups. The product obtained by sequential alkylation of a stabilised carbanion can be identical to that prepared from the respective dianion.

Most work in dianion chemistry has been concentrated so far on condensation reactions with monofunctional electrophiles, and the subsequent addition of water to give open-chained products.[1] Despite their simplicity and synthetic usefulness, cyclisation reactions of dianions with dielectrophiles are relatively rare.[3–5] The use of 1,2-dielectrophiles is particularly problematic, since both dianions and 1,2-dielectrophiles are highly reactive compounds (low reactivity matching). In addition, 1,2-dielectrophiles are often rather labile, and reactions with nucleophiles can result in polymerisation, decomposition, formation of open-chained products, elimination, or SET-processes. Two ways of overcoming these intrinsic limitations are viable: a) a proper tuning of the reactivity of the dianion and the dielectrophile and b) the use of electroneutral dianion equivalents (masked dianions) in Lewis acid catalysed reactions.

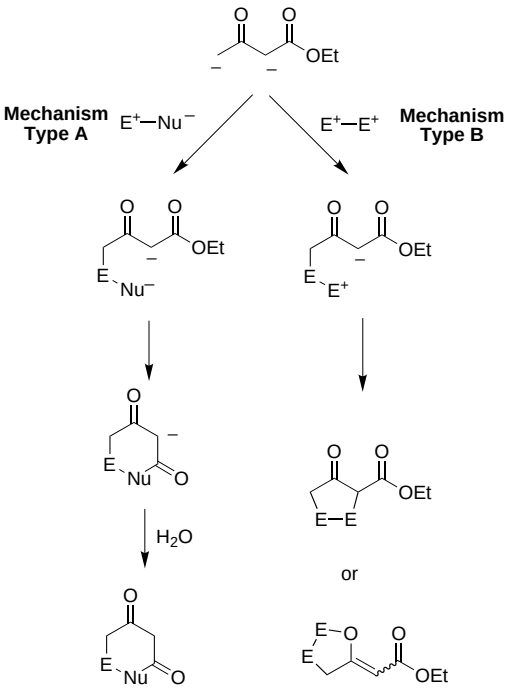
Two general mechanistic pathways can be discussed for cyclisation reactions of dianions (Scheme 1): firstly (mechanism type A), the dianion can react with a monofunctional electrophile with transposition of a negative charge from the dianion to the electrophile. This carbanion attacks an electrophilic centre of the former dianion moiety (e.g. the ester group) to give a monoanion which is subsequently quenched with water. Secondly, the dianion can react as a dinucleophile with a dielectrophile (mechanism type B). This article will mainly focus on cyclisation reactions of 1,3-dicarbonyl dianions following mechanism type B.

Discussion

Oxalic acid dielectrophiles: The reaction of dilithiated ethyl acetoacetate **1a** with oxalyl chloride and oxalic diethyl ester proved unsuccessful and resulted in the formation of complex mixtures.[6] However, we have recently been successful in inducing the desired cyclisation by tuning the reactivity of the dielectrophile: the reaction of the dianion of **1a** with *N*,*N*′-dimethoxy-*N*,*N*′-dimethylethanediamide (a bis-Weinreb amide) **2a**,[6b] which is available from oxalyl chloride in one

[a] Dr. P. Langer
Institut für Organische Chemie, Georg-August-Universität Göttingen
Tammannstr. 2, 37077 Göttingen (Germany)
Fax: (+49) 551-399475
E-mail: planger@gwdg.de

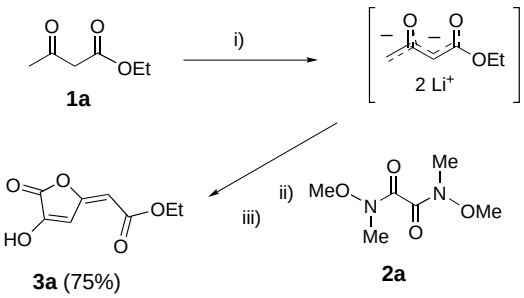
  0947-6539/01/0718-3859 $ 17.50+.50/0



Scheme 1. Possible mechanistic pathways for cyclisation reactions of 1,3-dicarbonyl dianions. Nu = nucleophilic centre, E = electrophilic centre.

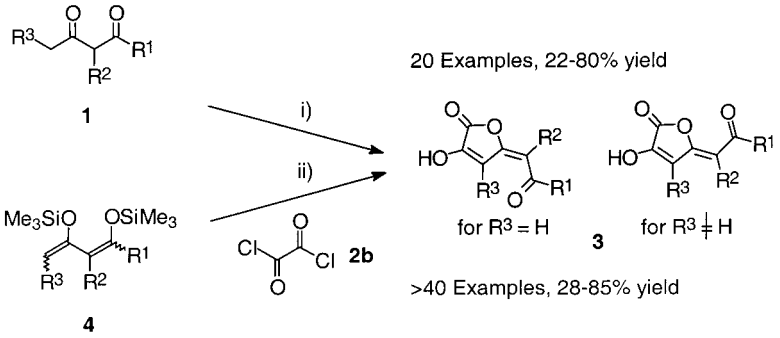
step, resulted in formation of the γ-alkylidenebutenolide **3a** in 75% yield (Scheme 2).[7]

The reaction proceeds by regioselective attack of the terminal carbon of the dianion onto **2a** and subsequent regioselective cyclisation through the oxygen atom of the dianion (mechanism type B). The *O*-regioselectivity can be explained by stereoelectronic considerations.[8] The *E*-diastereoselectivity for the formation of the exocyclic double bond is presumably a result of the dipole–dipole repulsion of the oxygen atoms of a nonchelated enolate intermediate[9] or by the higher thermodynamic stability of the *E*-configured γ-alkylidenebutenolide.[10] From a methodological viewpoint, this reaction represents both the first example of cyclisation of an oxalic acid dielectrophile with an ambident dianion and the first cyclisation of a bis-Weinreb amide.[10, 11]



Scheme 2. Cyclisation of the dianion of ethyl acetoacetate with **2a**.[7] i) 2.3 LDA, THF, −78 °C; ii) **2a**; iii) HCl, H_2O (10%).

Variation of the substituents allowed for the preparation of a variety of γ-alkylidenebutenolides (Scheme 3). All reactions proceeded with very good *E* diastereoselectivity for substrates containing a hydrogen atom at the terminal carbon of the 1,3-dicarbonyl compound ($R^3 = H$). For steric reasons, the selectivity changed from *E* to *Z* configuration for substrates containing a terminal substituent ($R^3 \neq H$). Reactions of sterically hindered, alkoxy-substituted, cyclic and functionalised substrates proved unsuccessful. To overcome these limitations, we have developed an alternative method that relies on the Me_3SiOTf-catalysed cyclisation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes **4**—electroneutral dianion equivalents—with oxalyl chloride (Me_3SiOTf = trimethylsilyl trifluoromethane-sulfonate).[12] The masked 1,3-dicarbonyl dianions **4** are available[13, 14] from the respective 1,3-dicarbonyl compounds in one or two steps and, in most cases, can be stored for several months at −30 °C without decomposition. Although the Me_3SiOTf-catalysed cyclisation is more general than the dianion methodology, the latter has the advantage that the 1,3-dicarbonyl compounds can be used directly. In addition, ester-derived bis(silyl enol) ethers containing a substituent at carbon C(2) are rather labile and readily



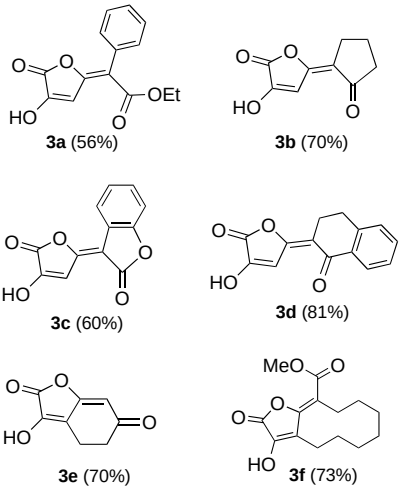
Scheme 3. Cyclisation of 1,3-dicarbonyl dianions and 1,3-bis(trimethylsilyloxy)-1,3-butadienes with oxalic acid dielectrophiles.[7, 12] i) 2.3 LDA, **2a**, THF, −78 °C, then HCl, H_2O; ii) **2b**, 0.3 Me_3SiOTf, CH_2Cl_2, −78 °C.

Abstract in German: *Trotz ihrer bestechenden Einfachheit und potentiellen präparativen Nützlichkeit sind Cyclisierungsreaktionen von ambidenten 1,3-Dicarbonyldianionen mit 1,2-Dielektrophilen schwer zu bewerkstelligen, da sowohl Dianionen als auch viele 1,2-Dielektrophile hochreaktive Verbindungen darstellen (schlechtes Reaktivitätsmatching). Weiterhin sind viele 1,2-Dielektrophile gegenüber starken Nucleophilen relativ labil, was zu einer Reihe von Nebenreaktionen, wie zum Beispiel Polymerisation, Zersetzung, Bildung offenkettiger Produkte, Eliminierungen oder SET-Reaktionen, führen kann. In letzter Zeit konnten durch Anwendung des Konzepts der Reaktivitätsfeinabstimmung und durch Einsatz elektroneutraler Dianion-Äquivalente (maskierter Dianionen) eine Reihe effizienter Cyclisierungsreaktionen entwickelt werden, die eine regio- und diastereoselektive Eintopf-Synthese biologisch relevanter Ringsysteme ermöglichen.*

  0947-6539/01/0718-3860 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 18

undergo 1,5-silyl migration reactions.[15] Amide-derived bis(silyl enol) ethers are particularly prone to such rearrangement reactions.[13]

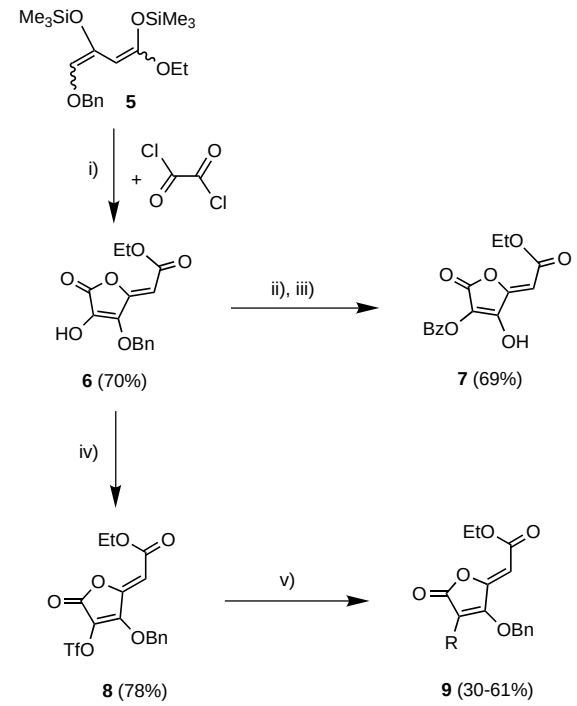
A great variety of γ-alkylidenebutenolides are readily available by reaction of bis(silyl enol) ethers **4** with oxalyl chloride (Schemes 3 and 4). This includes, for example, butenolides **3a** and **3c**, which are analogues of the natural products pulvinic acid and calycin, respectively. Starting with cyclic bis(silyl enol) ethers, a number of biologically relevant bicyclic γ-alkylidenebutenolides were prepared in good yields.[16] For example, the 5,10-bicyclic core structure of **3f** is present in a number of sesquiterpenes.



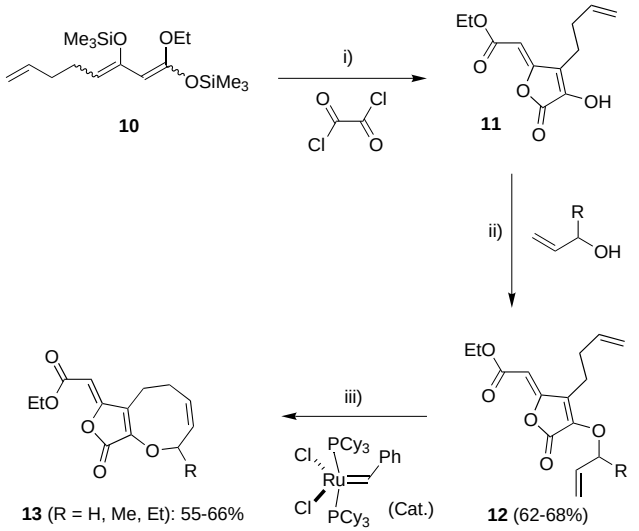
Scheme 4. Selected examples of the γ-alkylidenebutenolides prepared.[12, 16]

Due to their polyketide structure, many natural products contain an oxygen atom at carbon C(4) of the butenolide moiety. The preparation of γ-alkylidenetetronic acids and esters from ascorbic acid derivatives requires several steps and has the disadvantage that no additional substituents can be introduced at the exocyclic double bond or at the butenolide moiety.[17] We have developed a solution to this problem by cyclisation of 4-benzyloxy-1-ethoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**5**) and related bis(silyl enol) ethers with oxalyl chloride, which affords, for example, butenolide **6** in good yield (Scheme 5).[18] The free γ-alkylidenetetronic acid **7** was obtained by orthogonal protection of the C(3) hydroxy group of **6** as a benzoate ester and subsequent chemoselective deprotection of the C(4) hydroxy group.[18] Substituted butenolides, such as **9**, could be prepared by palladium-catalysed cross-coupling reactions via the corresponding enol triflates **8** at carbon C(3) (Scheme 5).[19] The hydrogenation of γ-alkylidenebutenolides proceeded with very good *cis* diastereoselectivity to give γ-lactones in good yields.[20, 21]

Butenolide medium-ring-ether hybrids were efficiently prepared by sequential Me_3SiOTf-catalysed cyclisation, Mitsunobu reaction and ring-closing metathesis (RCM).[22] For example, the 5,8 bicyclic compounds **13** were prepared by cyclisation of bis(silyl enol) ether **10** with oxalyl chloride to give butenolide **11**, which was subsequently alkylated and transformed into **13** by RCM (Scheme 6). The ring size and



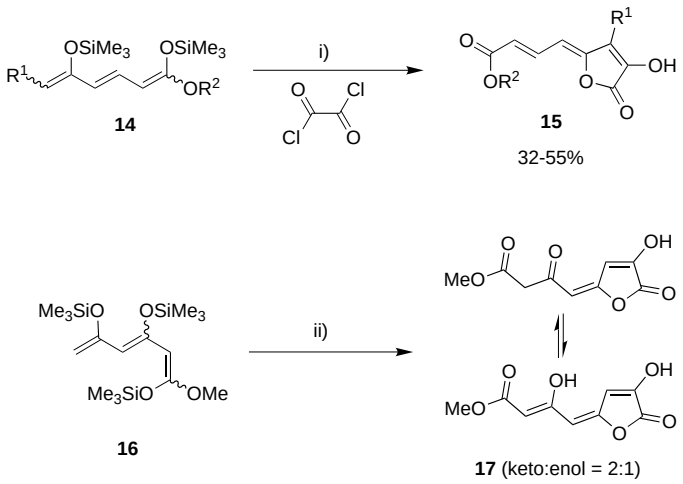
Scheme 5. Synthesis of γ-alkylidenetetronic esters.[18, 19] i) 0.3 Me_3SiOTf, CH_2Cl_2, $-78^\circ C$; ii) BzCl, Pyr; iii) H_2, Pd/C; iv) 1.3 Tf_2O, 2.0 pyridine; iv) 1.2 Bu_3SnR, Pd_2dba_3 (cat.), P(2-furyl)$_3$, LiCl. R = alkinyl, alkenyl, aryl, hetaryl.



Scheme 6. Synthesis of butenolide medium-ring-ether hybrids.[22] i) 0.3 Me_3SiOTf, CH_2Cl_2, $-78^\circ C$, 72%; ii) DEAD, PPh_3, 24 h, 20 °C, THF; iii) Cat. (10 mol %), C_6H_6.

the location of the endocyclic double bond could be efficiently controlled by variation of the length of the two alkenyl chains.

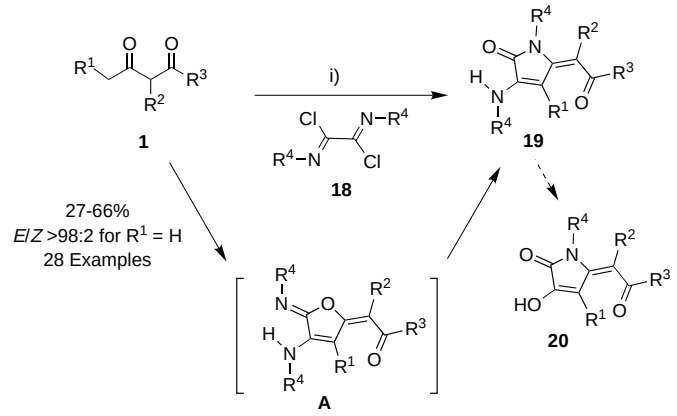
1,5-Bis(trimethylsilyloxy)-1,3,5-hexatrienes **14** can be considered to be vinylogous 1,3-dicarbonyl dianion equivalents. The cyclisation of these compounds with oxalyl chloride allowed for a direct and regioselective synthesis of polyunsaturated γ-alkylidenebutenolides **15**, which are analogues and synthetic precursors of natural products such as lissoclinolide (Scheme 7).[23] The reactions proceed with very good regio-



Scheme 7. Synthesis of polyunsaturated γ-alkylidenebutenolides.[23] i) 0.5 Me_3SiOTf, CH_2Cl_2, $-78^\circ C$. $R^1 = H$, Alkyl, OMe; $R^2 = Me$, Et; $Z/E > 98{:}2$ for $R^1 \neq H$. ii) 0.3 Me_3SiOTf, CH_2Cl_2, 61%; $Z/E < 2{:}98$.

and Z diastereoselectivities for dienes that contain a terminal substituent R^1. Starting with the parent triene ($R^1 = H$), a mixture of geometric isomers was obtained ($E/Z = 1{:}2$) which supports our initial observation (vide supra) that the carbonyl group attached to the exocyclic double bond is a stereodirecting element. In fact, the reaction of oxalyl chloride with 1,3,5-tris(trimethylsilyloxy)-1,3,5-hexatriene **16** afforded the γ-alkylidenebutenolide **17** with very good E diastereoselectivity (Scheme 7).

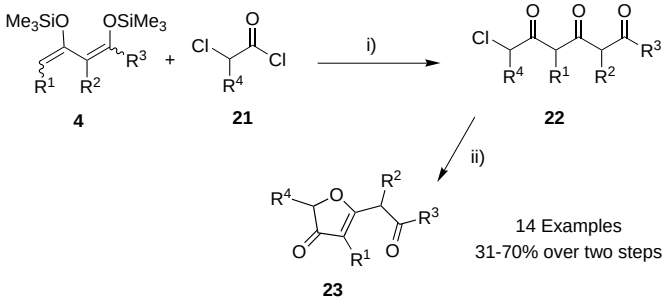
The reaction of dilithiated 1,3-dicarbonyl compounds with oxalic acid-bis(imidoyl)chlorides **18**, aza-analogues of oxalyl chloride, resulted in regioselective formation of a great variety of 5-alkylidene-5*H*-pyrrol-2-ones **19** (Scheme 8).[24]



Scheme 8. Cyclisation of 1,3-dicarbonyl dianions with oxalic acid-bis(imidoyl)chlorides.[24] i) 2.3 LDA, then **18**, THF, $-78^\circ C$.

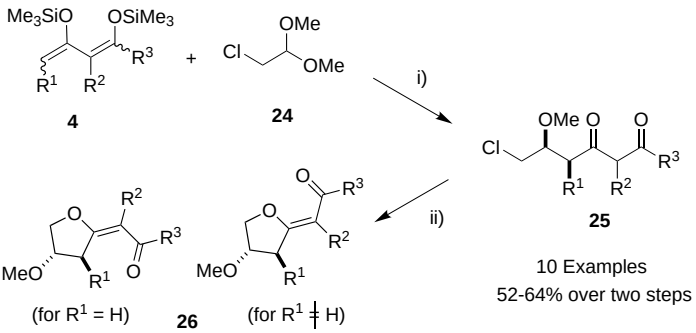
The cyclisation proceeds by regioselective attack of the terminal carbon atom of the dianion onto the dielectrophile and cyclisation through the oxygen atom to give intermediate **A**, which undergoes a Dimroth rearrangement under the reaction conditions (mechanism type B). Due to the stereodirecting effect of R^4, the products were formed with excellent E diastereoselectivity (for $R^1 = H$). The 5-alkylidene-5*H*-pyrrol-2-one system is of biological relevance and occurs in a number of natural products.

α-Chloroacetic chlorides and aldehydes: Reaction of the disodium salt of acetylacetone with the sodium salt of chloroacetic acid was reported to give 4,6-dioxoheptanoic acid by attack of the terminal carbon of the dianion on the carbon attached to the chlorine atom.[25] Although two examples for condensations of 1,3-dicarbonyl dianions with ethyl chloroacetate are known,[26] this reaction has structural limitations. We have recently developed a more general approach which relies on the Me_3SiOTf-catalysed, chemo- and regioselective condensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes **4** with α-chloroacetic chlorides **21** to give the 6-chloro-3,5-dioxoesters **22** (Scheme 9).[27, 28] Upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), these compounds underwent regioselective cyclisation to give a variety of biologically relevant functionalised 3(2*H*)furanones **23** (mechanism type B).



Scheme 9. Cyclisation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with α-chloroacetic chlorides.[27, 28] i) 0.3 Me_3SiOTf, CH_2Cl_2, $-78^\circ C$; ii) 2.0 DBU, THF, 2–12 h. $R^1 = H$, alkyl, OMe; $R^2 = H$, alkyl; $R^3 = O$-alkyl; $R^4 = H$, Me.

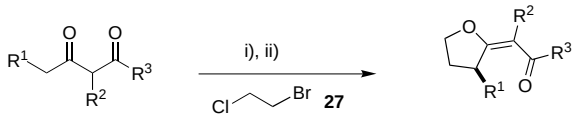
Based on the known Ti^{IV}-mediated reactions of simple silyl enol ethers with glyoxylate esters[29a] and α-bromoacetals,[29b] and on the diastereo- and enantioselective reaction of 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene with α-heterosubstituted aldehydes,[29c] the Me_3SiOTf-catalysed[29d] condensation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with α-chloroacetic aldehyde dimethylacetal **24** was developed (Scheme 10).[28, 30] These reactions chemoselectively afforded the 6-chloro-5-methoxy-3-oxoesters **25**, which were isolated and subsequently transformed into the 2-alkylidene-4-methoxytetrahydrofurans **26** by treatment with DBU (mechanism type B). The products were formed with very good regio- and E/Z diastereoselectivities, and with good 1,2-diastereoselectivities.



Scheme 10. Cyclisation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with α-chloroacetic aldehyde dimethylacetal.[28, 30] i) 0.3 Me_3SiOTf, CH_2Cl_2, $-78^\circ C$; ii) 2.0 DBU, THF, 2 h. R^1, $R^2 = H$, alkyl; $R^3 = O$-alkyl.

0947-6539/01/0718-3862 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 18

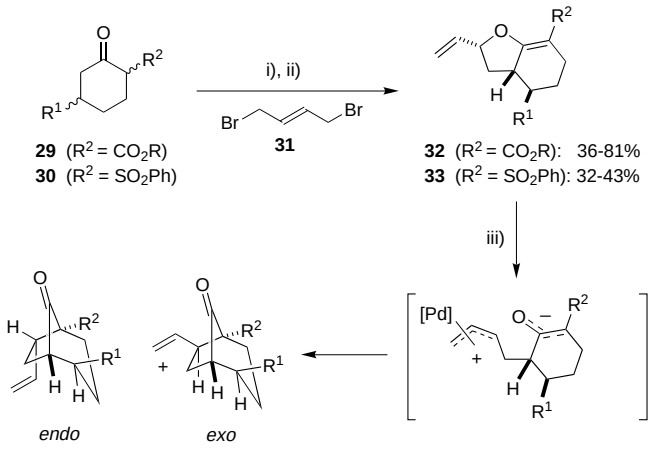
1,2-Dihalides: The reaction of 1,3-dicarbonyl dianions with 1,2-dibromo- or 1,2-diiodoethane resulted in oxidation of the dianion and formation of ethylene.[31] Open-chained condensation products were obtained in the presence of catalytic amounts of CuCl; however, only in 25–33% yield.[32] An elimination reaction was observed when 1,2-dichloroethane was used.[32] The problem was solved by application of the concept of reactivity tuning: cyclisations of 1,3-dicarbonyl dianions **1** with 1,2-dihalides could be successfully induced when 1-bromo-2-chloroethane **27** was employed as the dielectrophile (Scheme 11).[33] The tetrahydrofurans **28** were formed with very good *E* diastereoselectivity. The cyclisation proceeds by attack of the terminal carbon of the dianion on the bromide at low temperature and, upon heating, attack of the enolate oxygen on the less reactive chloride function (mechanism type B).[34]



Scheme 11. Cyclisation of 1,3-dicarbonyl dianions with 1-bromo-2-chloroethane.[33] i) 2.3 LDA; ii) **27**, THF, −78 →20 °C for 14 h, then 68 °C for 14 h. R^1, R^2 = H, alkyl; R^3 = *O*-alkyl, NEt_2.

The reaction of 1,3-dicarbonyl dianions with 1,4-di*chloro*-2-butene has been reported to result in formation of mixtures of open-chained products in low yields.[35] However, cyclisation reactions could be successfully carried out when 1,4-di*bromo*-2-butene **31** was used as the dielectrophile.[36, 37] The products, 2-alkylidene-5-vinyl-tetrahydrofurans, were formed by a S_N/S_N' displacement reaction with very good regio- and *E*/*Z* diastereoselectivity (mechanism type B). The reaction of **31** with dianions of *cyclic* 1,3-dicarbonyl compounds **29** resulted in formation of the 2-vinyl-2,3,3a,4,5,6-hexahydro-2,3-benzofurans **32** with very good 1,2- and 1,3-diastereoselectivity (Scheme 12).[36] These products could be efficiently transformed into the isomeric bicyclo[3.2.1]octan-8-ones **34** by a palladium(0)-catalysed rearrangement. This reaction proceeds by initial ring opening, formation of a π-allyl palladium complex and recyclisation by nucleophilic attack of the carbon atom of the enolate onto the π-allyl palladium complex.[36, 38] Due to π-σ-π isomerisation of the π-allyl palladium complex, the products were obtained as mixtures of *endo*/*exo* diastereomers. One way to overcome this problem was to use a better leaving group: the cyclisation of **31** with dilithiated β-ketosulfones **30** afforded the sulfone-substituted products **33** with very good diastereoselectivity. The palladium-catalysed rearrangement of **33** proceeded with very good stereospecificity to give the *endo*-configured bicyclo[3.2.1]octan-8-ones **35** exclusively and in good yields (Scheme 12).[39]

Epoxides and aziridines: Previous attention in reactions of 1,3-dicarbonyl dianions with epoxides has mainly been focused on the synthesis of open-chained products. For

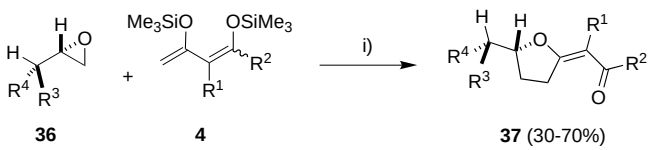


34 (R^2 = CO_2R): 51-92%, *endo*/*exo* = 1.1:1
35 (R^2 = SO_2Ph): 35-81%, *endo*/*exo* > 98:2

Scheme 12. Cyclisation of 1,3-dicarbonyl and β-ketosulfone dianions with 1,4-dibromo-2-butene and palladium catalysed rearrangement of the products.[36, 39] i) 2.3 LDA; ii) **31**, THF, −78 °C, ds > 98:2; iii) DMSO, $Pd(dppe)_2$ (5 mol%), 60–100 °C, 6–24 h.

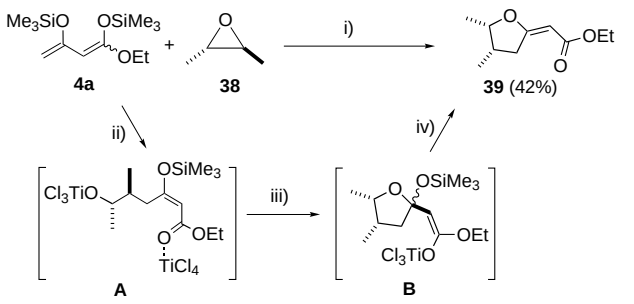
example, a protected seco acid, an open-chained precursor to (*R*,*R*)-(−)-pyrenophorin, has been enantiospecifically prepared by treating the dianion of *tert*-butyl acetoacetate with (*R*)-(+)-propylene oxide and subsequently quenching the reaction with water to give an open-chained product.[40] Cyclisation reactions of epoxides with 1,3-dicarbonyl dianions, which have been carried out in one or two steps, proceed by attack of the terminal carbon atom of the dianion on the sterically less hindered carbon atom of the epoxide.[41] Despite a number of structural and preparative limitations, this type of reaction has been successfully used for the synthesis of (±)-methyl homononactate.[41b] The reaction of 1,3-dicarbonyl dianions with *N*-tosyl aziridines has been reported to give open-chained products, which could be transformed into substituted pyrrolidines by treatment with acidic Amberlyst 15 resin (mechanism type A).[42]

Recently, we reported the first Lewis acid mediated cyclisations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes **4** with epoxides **36** which allowed for the synthesis of 2-alkylidene-tetrahydrofurans **37** with a great variety of substitution patterns and functional groups (Scheme 13).[43] For epoxides containing a base-labile ester, chloride or bromide function, the reaction proceeded with very good chemoselectivity. For all cyclisations, very good regio- and *E*-diastereoselectivities were observed.



Scheme 13. Cyclisation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with epoxides.[43] i) 2.0 $TiCl_4$, CH_2Cl_2, −78 °C, 5 h, 20 °C, 12 h. R^1 = H, alkyl; R^2 = alkyl, Ph, *O*-alkyl; R^3 = H, alkyl, Cl, Br, CO_2Et, CH_2CO_2Et, OBn, $CH_2CH{=}CH_2$; R^4 = H, Me.

The use of 1,2-disubstituted epoxides was equally successful and proceeded with very good stereospecificity. Starting with the *trans*-configured epoxide **38**, the *cis*-configured tetrahydrofuran **39** was obtained and vice versa (Scheme 14). The

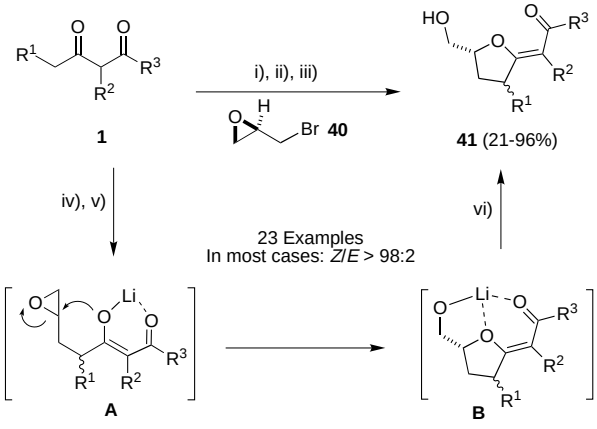


Scheme 14. Mechanism of the cyclisation of dienes **4** with epoxides.[43] i) 2.0 $TiCl_4$, CH_2Cl_2, 4 Å MS, $-78\,^{\circ}C$, 5 h, $20\,^{\circ}C$, 12 h; ii) + 2 $TiCl_4$, $-Me_3SiCl$; iii) $-TiCl_4$; iv) $-$ "$Me_3SiOTiCl_3$".

observed stereoselectivity suggested that formation of 2-alkylidenetetrahydrofurans **37** and **39** can be explained by the following mechanism: the terminal carbon of the diene regioselectively attacks the epoxide **38** to give intermediate **A**, with inversion of configuration. The cyclisation proceeds by $TiCl_4$-mediated attack of the epoxide-derived hydroxy group onto the α,β-unsaturated ester to give intermediate **B**, with retention of configuration (mechanism type A). In fact, the epoxide can be considered as a 1,3-electrophile/nucleophile rather than a 1,2-dielectrophile. Elimination of silanolate subsequently leads to the final product. Attack of the oxygen atom of intermediate **A**, derived from silyl enol ether, onto the hydroxy group would have resulted in inversion of configuration (mechanism type B). The stereoselectivity in favour of products containing *E*-configured exocyclic double bonds can be explained by the W-shaped configuration of intermediate **A**, which allows for minimisation of the dipole–dipole repulsion of the oxygen atoms (vide supra). Attack of the diene onto the sterically more encumbered carbon is observed for epoxides containing a phenyl or vinyl substituent, which more effectively stabilise a carbocationic intermediate.

The SnF_2-mediated reaction of epoxyaldehydes with 3-iodo-2-[(trimethylsilyl)methyl]propene, a trimethylenemethane dianion equivalent, has been reported by Molander and co-workers.[44] This reaction proceeds by attack of the dianion onto the aldehyde and subsequent cyclisation through the terminal carbon of the epoxide to give a six- rather than a five-membered ring. The regioselectivity can be explained by the fact that a *5-exo-tet* cyclisation is stereoelectronically unfavoured, since only carbon but no oxygen atoms are available as nucleophilic centres. The reaction of 1,3-dicarbonyl dianions with carbohydrate-derived epoxy tosylates and triflates has been reported to result in formation of bicyclic systems.[45]

We have recently reported the cyclisation of 1,3-dicarbonyl dianions with 1-bromo-2,3-epoxypropane (**40**).[46, 47] This reaction proceeds by attack of the dianion on the carbon attached to the bromine atom, and subsequent nucleophilic attack of the enolate oxygen on the central carbon atom giving rise to formation of 2-alkylidene-5-hydroxymethyl-tetrahydrofurans (**41**) (mechanism type B; Scheme 15). A thorough optimisation of the conditions (temperature, counter-ions of the dianion, presence of the Lewis acid $LiClO_4$)

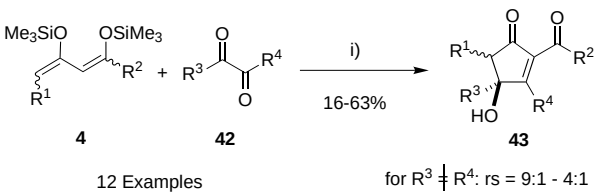


Scheme 15. Cyclisation of 1,3-dicarbonyl dianions with 1-bromo-2,3-epoxypropane.[46, 47] i) NaH, *n*BuLi; ii) **40**; iii) H_2O; THF, $LiClO_4$, $-35\,^{\circ}C$ for 10 h, $20\,^{\circ}C$ for 8 h; iv) NaH, *n*BuLi; v) **40**, $-$NaBr; vi) H_2O. R^1, R^2 = H, alkyl; R^3 = alkyl, Ph, *O*-alkyl, NEt_2.

was important to obtain good yields and high chemo- and regioselectivities. In most cases, the reaction yielded the thermodynamically less stable *Z*-diastereomers which slowly isomerised into the corresponding *E*-configured products. The *Z*-diastereoselectivity can be explained by chelation of the oxygen atoms with a Li^+ ion in intermediates **A** and **B**. This complexation is facilitated by the high concentration of lithium ions in solution.

Hydrogenation of 2-alkylidene-5-hydroxymethyl-tetrahydrofurans by using Pd/C as the catalyst afforded *syn*-configured functionalised tetrahydrofurans in good yields and with good diastereoselectivities.[46b] For steric reasons, the hydrogenation occurred from the sterically less encumbered side of the molecule.

1,2-Dicarbonyl derivatives: In general, cyclisations of 1,3-dianions with enolisable 1,2-dicarbonyl derivatives are not possible, due to competing deprotonation of the latter.[48–50] This problem could be solved by the use of electroneutral dianion equivalents: Molander and co-workers developed the SnF_2-mediated cyclisation of 3-iodo-2-[(trimethylsilyl)-methyl]propene (vide supra) with enolisable 1,2-diketones.[51] Recently, we reported the cyclisation of 1,2-diketones **42** with 1,3-bis(trimethylsiloxy)-1,3-butadienes **4** (Scheme 16).[52] This

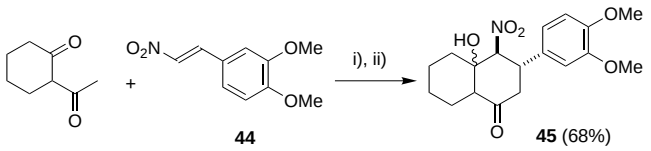


Scheme 16. Cyclisation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 1,2-diketones.[52] i) 2.0 $TiCl_4$, CH_2Cl_2, $-78\,^{\circ}C$, R^1 = H, Me, Et, OMe; R^2 = Me, CH_2OMe, *O*-alkyl; R^3, R^4 = Me, Et.

0947-6539/01/0718-3864 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 18

cyclisation proceeds by a regioselective double Mukaiyama aldol reaction and subsequent elimination of water to give the functionalised cyclopent-2-en-1-ones **43** (mechanism type B). Similarly, the reaction of bis(silyl enol) ethers with 2,2-dimethoxyphenylacetic aldehyde afforded cyclopent-2-en-1-ones by attack of the terminal carbon of the diene on the aldehyde, and subsequent cyclisation by attack of the central carbon atom of the diene on the ketal group.[53]

Nitroalkenes: The cyclisation of 1,3-dicarbonyl dianions with nitroalkenes to give functionalised cyclohexanones was reported by Seebach et al. (Scheme 17).[54] For example, Michael addition of the terminal carbon of the dianion of 2-acetylcyclohexanone with nitroalkene **44** and subsequent aldol reaction gave the decalone **45** with very good 1,2-diastereoselectivity (mechanism type A). In this reaction, the nitroalkene reacts as a 1,2-electrophile/nucleophile. Related reactions of 1,3-dicarbonyl dianions with aldehydes have been reported to give functionalised pyran-4-ones.[55]



Scheme 17. Cyclisation of 1,3-dicarbonyl dianions with nitro-alkenes.[54] i) NaH; ii) *n*BuLi, THF, 0 °C.

A great deal of synthetic interest has been focused on [4+2] cycloaddition reactions of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) and of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with alkenes,[56] alkynes,[57] aldehydes[58] and allenes.[59, 60] The discussion of these reactions is beyond the scope of this article.

Conclusion

Reactions of 1,3-dicarbonyl dianions with electrophiles allow for a functionalisation of the terminal carbon atom of the 1,3-dicarbonyl compound. Despite their simplicity, direct cyclisation reactions of 1,3-dicarbonyl dianions with 1,2-dielectrophiles are problematic. Based on the concept of reactivity tuning and on the use of 1,3-bis(trimethylsilyloxy)-1,3-butadienes (electroneutral dianion equivalents) we have developed a number of cyclisation reactions which allow for a rapid chemo-, regio- and diastereoselective synthesis of a variety of biologically relevant ring systems. The cyclisation of oxalic acid dielectrophiles with free and masked dianions afforded a variety of γ-alkylidenebutenolides. The reaction of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with α-chloroacetic chlorides and α-chloroacetic aldehyde dimethylacetal regioselectively afforded 3(2*H*)furanones and 2-alkylidene-4-methoxytetrahydrofurans, respectively. The reaction of free and masked 1,3-dicarbonyl dianions with 1,4-dibromo-2-butene, 1-bromo-2-chloroethane, epoxides and 1-bromo-2,3-epoxypropane provided a convenient access to functionalised tetrahydrofurans. Cyclopent-2-en-1-ones were prepared by cyclisation of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with 1,2-dicarbonyl derivatives. Further progress is directed towards applications in natural product syntheses and solid-phase methodology.

[1] Reviews: a) A. Maercker, *Methoden Org. Chem.* (Houben-Weyl) 4. Aufl., Bd. E19d, **1993**, 448; b) C. M. Thompson, D. Green, *Tetrahedron* **1991**, *47*, 4223; c) E. M. Kaiser, J. D. Petty, P. L. A. Knutson, *Synthesis* **1977**, 509.

[2] L. Weiler, *J. Am. Chem. Soc.* **1970**, *92*, 6702.

[3] For cyclisations of other than 1,3-dicarbonyl dianions with 1,*n*-dielectrophiles, see for example: a) K. G. Bilyard, P. J. Garratt, R. Hunter, E. Lete, *J. Org. Chem.* **1982**, *47*, 4731; b) R. B. Bates, B. Gordon, T. K. Highsmith, J. J. White, *J. Org. Chem.* **1984**, *49*, 2981; c) K. Tanaka, H. Horiuchi, H. Yoda, *J. Org. Chem.* **1989**, *54*, 63; d) A. Maercker, A. Groos, *Angew. Chem.* **1996**, *108*, 216; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 210.

[4] For cyclisations of other than 1,3-dicarbonyl dianions from our laboratory, see: a) P. Langer, J. Wuckelt, M. Döring, H. Görls, *J. Org. Chem.* **2000**, *65*, 3603; b) P. Langer, M. Döring, *Chem. Commun.* **1999**, 2439; c) P. Langer, *Chem. Commun.* **1999**, 1217; d) P. Langer, J. Wuckelt, M. Döring, R. Beckert, *Eur. J. Org. Chem.* **1998**, 1467; e) P. Langer, M. Döring, *Synlett* **1998**, 396; f) P. Langer, J. Wuckelt, M. Döring, P. R. Schreiner, H. Görls, *Eur. J. Org. Chem.* **2001**, 2245.

[5] For multicomponent cyclisations of dianions from our laboratory, see: a) P. Langer, M. Döring, H. Görls, R. Beckert, *Liebigs Ann./Receuil* **1997**, 2553; b) P. Langer, M. Döring, D. Seyferth, *Chem. Commun.* **1998**, 1927; c) P. Langer, M. Döring, *Synlett* **1998**, 399; d) J. Wuckelt, M. Döring, R. Beckert, P. Langer, *Synlett* **1999**, 1100; e) P. Langer, J. Wuckelt, M. Döring, *J. Org. Chem.* **2000**, *65*, 729; f) P. Langer, J. Wuckelt, M. Döring, H. Görls, *Eur. J. Org. Chem.* **2001**, 1503; g) P. Langer, M. Döring, D. Seyferth, *Synlett* **1999**, 135; h) P. Langer, M. Döring, H. Görls, *Eur. J. Org. Chem.* **2001**, 1511; i) P. Langer, M. Döring, P. R. Schreiner, H. Görls, *Chem. Eur. J.* **2001**, *7*, 2617.

[6] For the extrusion of carbon monoxide in the reaction of glycols with oxalyl chloride, see: a) T. Iida, T. Itaya, *Tetrahedron* **1993**, *49*, 10511; b) M. P. Sibi, M. Marvin, R. Sharma, *J. Org. Chem.* **1995**, *60*, 5016.

[7] P. Langer, M. Stoll, *Angew. Chem.* **1999**, *111*, 1919; *Angew. Chem. Int. Ed.* **1999**, *38*, 1803.

[8] J. E. Baldwin, L. I. Kruse, *J. Chem. Soc. Chem. Commun.* **1977**, 233.

[9] For a review on the structure and reactivity of lithium enolates, see: a) D. Seebach, *Angew. Chem.* **1988**, *100*, 1685; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1624; b) S. J. Rhoads, R. W. Holder, *Tetrahedron* **1969**, *25*, 5443; c) B. Miller, H. Margulies, T. Drabb, Jr., R. Wayne, *Tetrahedron Lett.* **1970**, 3801; d) G. Entenmann, *Tetrahedron Lett.* **1975**, 4241; e) C. Cambillau, P. Sarthou, G. Bram, *Tetrahedron Lett.* **1976**, 281.

[10] For other approaches to γ-alkylidenebutenolides, see for example: a) K. Siegel, R. Brückner, *Chem. Eur. J.* **1998**, *4*, 1116; b) F. Goerth, A. Umland, R. Brückner, *Eur. J. Org. Chem.* **1998**, 1055; c) F. v. d. Ohe, R. Brückner, *Tetrahedron Lett.* **1998**, 1909; d) F. C. Görth, R. Brückner, *Synthesis* **1999**, 1520; e) I. Hanisch, R. Brückner, *Synlett* **2000**, 374; f) E.-i. Negishi, M. Kotora, *Tetrahedron* **1997**, *53*, 6707; g) D. W. Knight, G. Pattenden, *J. Chem. Soc. Perkin Trans. 1* **1979**, 62; h) C. F. Ingham, R. A. Massy-Westropp, G. D. Reynolds, W. D. Thorpe, *Aust. J. Chem.* **1975**, *28*, 2499. For a stereoselective approach to isoascorbic acids, see: i) D. Enders, H. Dyker, F. R. Leusink, *Chem. Eur. J.* **1998**, *4*, 311.

[11] For cyclisations of stabilised carbanions with oxalic acid dielectrophiles, see: a) R. Saalfrank, J. Nachtrab, S. Reck, F. Hampel, *Z. Naturforsch. B*, **1999**, *54*, 179; b) H.-D. Stachel, K. Zeitler, *Arch. Pharm.* (Weinheim, Ger.) **1995**, *328*, 99; c) J. S. Chickos, *J. Org. Chem.* **1973**, *38*, 1231. For the $MgCl_2$ mediated cyclisation of 1,3-dicarbonyl compounds with oxalyl chloride, see: d) R. W. Saalfrank, T. Lutz, *Angew. Chem.* **1990**, *102*, 1064; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1041.

[12] P. Langer, T. Schneider, M. Stoll, *Chem. Eur. J.* **2000**, *6*, 3204.
[13] P. Langer, T. Schneider, *Synlett* **2000**, 497.
[14] a) T. H. Chan, P. Brownbridge, *J. Chem. Soc. Chem. Commun.* **1979**, 578; b) K. Krägeloh, G. Simchen, *Synthesis* **1981**, 30; c) P. Brownbridge, *Synthesis* **1983**, 85; d) B. Simoneau, P. Brassard, *Tetrahedron* **1986**, *14*, 3767; e) G. A. Molander, K. O. Cameron, *J. Am. Chem. Soc.* **1993**, *115*, 830.
[15] G. Anderson, D. W. Cameron, G. I. Feutrill, R. W. Read, *Tetrahedron Lett.* **1981**, 4347.
[16] P. Langer, N. N. R. Saleh, *Org. Lett.* **2000**, 3333.
[17] a) M. A. Khan, H. Adams, *Synthesis* **1995**, 687; b) Y. Nihro, S. Sogawa, A. Izumi, A. Sasanori, T. Sudo, T. Miki, H. Matsumoto, T. Satoh, *J. Med. Chem.* **1992**, *35*, 1618.
[18] P. Langer, T. Eckardt, *Synlett* **2000**, 844.
[19] P. Langer, T. Eckardt, T. Schneider, C. Göbel, R. Herbst-Irmer, *J. Org. Chem.* **2001**, *66*, 2222; for related reactions, see: ref. [10b].
[20] P. Langer, V. Köhler, N. N. R. Saleh, unpublished results.
[21] For the hydrogenation of butenolides, see: a) G. Stork, S. D. Rychnovsky, *J. Am. Chem. Soc.* **1987**, *109*, 1564; b) C. Marino, O. Varela, R. M. de Lederkremer, *Carbohydr. Res.* **1990**, *220*, 145.
[22] P. Langer, T. Eckardt, M. Stoll, *Org. Lett.* **2000**, 2991.
[23] P. Langer, I. Freifeld, *Synlett* **2001**, 523.
[24] P. Langer, M. Döring, *Synlett* **2001**, in press.
[25] R. O. Pendarvis, K. G. Hampton, *J. Org. Chem.* **1974**, *39*, 2289.
[26] M. Yamaguchi, K. Shibato, *Tetrahedron* **1988**, *44*, 4767.
[27] P. Langer, T. Krummel, *Chem. Commun.* **2000**, 967.
[28] P. Langer, T. Krummel, *Chem. Eur. J.* **2001**, *7*, 1720.
[29] a) K. Mikami, S. Matsukawa, *J. Am. Chem. Soc.* **1993**, *115*, 7039; b) T. Mukaiyama, H. Ishihara, K. Inomata, *Chem. Lett.* **1975**, 527; c) D. Enders, F. Burkamp, J. Runsink, *J. Chem. Soc. Chem. Commun.* **1996**, 609. d) For the use of Me_3SiOTf in reactions of simple silyl enol ethers with monofunctional acetals, see: d) S. Murata, M. Suzuki, R. Noyori, *J. Am. Chem. Soc.* **1980**, *102*, 3248.
[30] For an isolated example of a reaction of a 1,3-dicarbonyl dianion with bromoacetic aldehyde, see: a) G. A. Kraus, P. Gottschalk, *J. Org. Chem.* **1983**, *48*, 2111. The $TiCl_4$-mediated condensation of the methyl acetoacetate-derived 1,3-bis(trimethylsilyloxy)-1,3-diene with α-chloroacetic aldehyde dimethylacetal has been reported to proceed with 35% yield: b) P. Brownbridge, T. H. Chan, M. A. Brook, G. J. Kang, *Can. J. Chem.* **1983**, *61*, 688.
[31] K. G. Hampton, R. J. Light, C. R. Hauser, *J. Org. Chem.* **1965**, *30*, 1413.
[32] K. G. Hampton, J. J. Christie, *J. Org. Chem.* **1976**, *41*, 2772.
[33] P. Langer, I. Karimé, *Synlett* **2000**, 743.
[34] For the formation of open-chained products, see: P. H. Lambert, M. Vaultier, R. Carrié, *J. Org. Chem.* **1985**, *50*, 5352.
[35] a) P.-E. Sum, L. Weiler, *Can. J. Chem.* **1977**, *55*, 996. For the formation of open-chained products, see: b) T. R. Hoye, J. C. Suhadolnik, *Tetrahedron* **1986**, *42*, 2855.
[36] P. Langer, E. Holtz, *Angew. Chem.* **2000**, *112*, 3208; *Angew. Chem. Int. Ed.* **2000**, *39*, 3086.
[37] For cyclisations of monoanions, see: a) T. Wang, J. Chen, K. Zhao, *J. Org. Chem.* **1995**, *60*, 2668; b) T. Lavoisier, J. Rodriguez, *Synlett* **1996**, 339.
[38] For π-allyl palladium complexes, see: a) B. M. Trost, *Angew. Chem.* **1989**, *101*, 1199; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1173. For a related reaction, see: b) B. M. Trost, T. A. Runge, *J. Am. Chem. Soc.* **1981**, *103*, 7550.
[39] P. Langer, E. Holtz, N. N. R. Saleh, *Chem. Eur. J.* **2001**, in press.
[40] R. V. Hoffman, T. Patonay, N. K. Nayyar, J. Tao, *Tetrahedron Lett.* **1996**, 2381.
[41] a) T. A. Bryson, *J. Org. Chem.* **1973**, *38*, 3428; b) K. Mori, M. Sasaki, S. Tamada, T. Suguro, S. Masuda, *Tetrahedron* **1979**, *35*, 1601; c) M. Yamaguchi, I. Hirao, *Chem. Lett.* **1985**, 337; d) B. Lygo, *Tetrahedron* **1988**, *44*, 6889.
[42] B. Lygo, *Synlett* **1993**, 765.
[43] P. Langer, T. Eckardt, *Angew. Chem.* **2000**, *112*, 4503; *Angew. Chem. Int. Ed.* **2000**, *39*, 4343.
[44] G. A. Molander, D. C. Shubert, *J. Am. Chem. Soc.* **1986**, *108*, 4683.
[45] T. H. Al-Tel, W. Voelter, *J. Chem. Soc. Chem. Commun.* **1995**, 239; b) T. H. Al-Tel, M. Meisenbach, W. Voelter, *Liebigs Ann.* **1995**, 689.
[46] a) P. Langer, I. Freifeld, E. Holtz, *Synlett* **2000**, 501; b) P. Langer, I. Freifeld, *Chem. Eur. J.* **2001**, *7*, 565.
[47] For a related reaction, see: M. Nakada, Y. Iwata, M. Takano, *Tetrahedron Lett.* **1999**, 9077.
[48] For a review on $TiCl_4$-mediated reactions of simple silyl enol ethers, see: T. Mukaiyama, *Angew. Chem.* **1977**, *89*, 858; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 817.
[49] For base-mediated cyclisations of nonenolisable aromatic 1,2-diones, see for example: a) F. Morgenroth, A. J. Berresheim, M. Wagner, K. Müllen, *Chem. Commun.* **1998**, 1139; b) S. Eguchi, K. Ishiura, T. Noda, T. Sasaki, *J. Org. Chem.* **1987**, *52*, 496.
[50] For reactions of 1,3,5-tricarbonyl compounds with glyoxal in aqueous alkaline solution, see: A. Gawish, R. Mitschka, J. M. Cook, *Tetrahedron Lett.* **1981**, 211.
[51] G. A. Molander, D. C. Shubert, *J. Am. Chem. Soc.* **1986**, *108*, 4683.
[52] a) P. Langer, V. Köhler, *Org. Lett.* **2000**, 1597. For cyclisations with phthalic dialdehyde, see: b) P. Langer, U. Albrecht, *Synlett* **2001**, 526.
[53] a) P. Langer, V. Köhler, B. Kracke, unpublished results; see also: b) T. H. Chan, M. A. Brook, *Tetrahedron Lett.* **1985**, *26*, 2943.
[54] D. Seebach, V. Ehrig, *Angew. Chem.* **1974**, *86*, 446; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 401.
[55] a) J. M. Ansell, A. Hassner, W. E. Burkholder, *Tetrahedron Lett.* **1979**, 2497; b) H. Hagiwara, K. Kimura, H. Uda, *J. Chem. Soc. Chem. Commun.* **1986**, 860.
[56] a) K. Krohn, H.-H. Ostermeyer, K. Tolkiehn, *Chem. Ber.* **1979**, *112*, 2640; b) C. Brisson, P. Brassard, *J. Org. Chem.* **1981**, *46*, 1810, and refernces therein; c) D. W. Cameron, G. I. Feutrill, P. Perlmutter, *Aust. J. Chem.* **1982**, *35*, 1469.
[57] a) S. Danishefsky, R. K. Singh, R. B. Gammill, *J. Org. Chem.* **1978**, *43*, 379; b) J. P. Sestelo, M. del Mar Real, A. Mourino, L. A. Sarandeses, *Tetrahedron Lett.* **1999**, 985, and references therein.
[58] S. Danishefsky, D. F. Harvey, G. Quallich, B. J. Uang, *J. Org. Chem.* **1984**, *49*, 393.
[59] P. Langer, B. Kracke, *Tetrahedron Lett.* **2000**, 4545.
[60] a) W. R. Roush, M. Murphy, *J. Org. Chem.* **1992**, *57*, 6622; b) M. Fink, H. Gaier, H. Gerlach, *Helv. Chim. Acta* **1982**, *65*, 2563.

  0947-6539/01/0718-3866 $ 17.50+.50/0