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# Recent advances in the chemistry of 2-(2-oxoalkylidene)tetrahydrofurans

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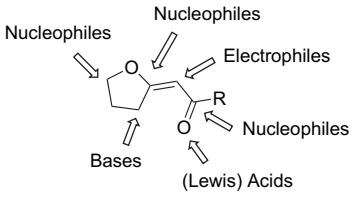
## 1. Introduction

One-pot cyclizations of 1,3-dicarbonyl dianions ('free dianions') and 1,3-bis-silyl enol ethers ('masked dianions') with electrophiles provide a convenient approach to various heterocyclic and carbacyclic ring systems. Cyclizations of free and masked 1,3-dicarbonyl dianions with 1,2-dielectrophiles,[1a,b] one-pot cyclizations of dinucleophiles with oxalic acid-bis(imidoyl)dichlorides,[2] reactions of 1,3-bis-silyl enol ethers in general,[3a] syntheses of butenolides by cyclizations of silyl enol ethers with oxalyl chloride,[3b] syntheses of carbacycles by formal [3+3] cyclizations of 1,3-bis-silyl enol ethers,[3c] and domino reactions of bis-silyl enol ethers with 4-silyloxybenzopyrylium triflates[3d] and iminium salts were previously reviewed.[3e] In some of these reviews[1,3a] specific syntheses of 2-(2-oxoalkylidene)tetrahydrofurans were included.[4–12] The present review provides an overview of recent advances in the synthesis (based on cyclizations of free and masked dianions) and the chemistry of 2-(2-oxoalkylidene)tetrahydrofurans.

2-(2-Oxoalkylidene)tetrahydrofurans are densely functionalized molecules, which combine the structural features of tetrahydrofurans, enol ethers, and α,β-unsaturated carbonyl compounds. Therefore, they can undergo various reactions with nucleophiles, electrophiles, bases or (Lewis) acids (Scheme 1). 2-Alkylidenetetrahydrofurans represent versatile synthetic building blocks for the synthesis of natural products such as macrotetrolide antibiotics and of artificial biologically active substances.[13,14] A variety of synthetic transformations of 2-alkylidenetetrahydrofurans have been reported.[14] These include, for example, cycloadditions,[13a–d] nucleophilic additions,[14e–f] cyclopropanations,[14g] oxidative carbonylations,[14h–j] and hydrogenations.[14k–q] They can be used as direct precursors for the preparation of functionalized tetrahydrofurans[15] and furans.[16,17] In addition, they have been used for the synthesis of nonactates,[18a–c] terpenes,[18d,e] and medium-sized lactones.[18f] 2-Alkylidenetetrahydrofurans are interesting also in their own right as they are of considerable pharmacological relevance[19] and occur in a number of natural products. These include, for example, charlic acid, charolic acid, and terrestric acid, which are metabolites of *Penicillium charlesii* and *Penicillium terrestre*.[19a] Bicyclic 2-alkylidenetetrahydrofurans[19b,c] have been used as direct precursors for the synthesis of the spiroketal chalcogran.[19d–f] The synthesis of 2-alkylidenetetrahydrofurans was first reported in the early 1960s.[20] Since this time, much effort has been devoted to the development of new synthetic methods for their preparation.




**Scheme 1**. Possible reactions of 2-(2-oxoalkylidene)tetrahydrofurans.

## 2. Synthesis of 2-alkylidenetetrahydrofurans

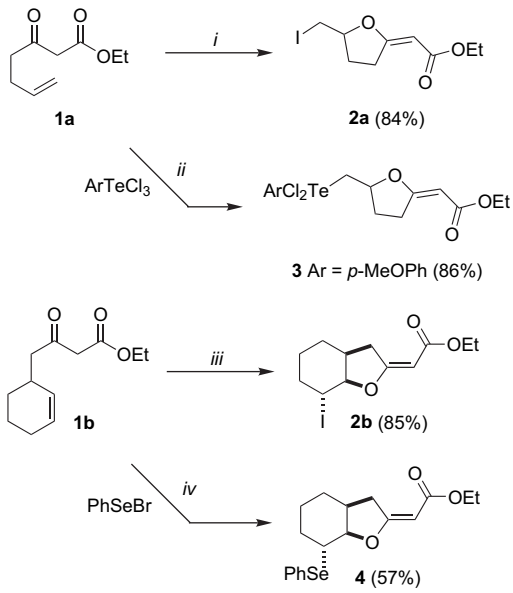
The present review is concentrated on the synthesis of 2-(2-oxoalkylidene)tetrahydrofurans by cyclization reactions of 1,3-dicarbonyl dianions or 1,3-bis-silyl enol ethers.[4–12,21] These reactions can be classified into two types.

(1) One-pot cyclizations (cyclization type A). These reactions proceed by cyclization of the dianion with a 1,2-dielectrophile in one step.
(2) Two-step syntheses (cyclization type B). These transformations proceed by condensation of the dianion with a monofunctional electrophile and subsequent cyclization. These transformations include, for example, selenium [22] or iodine[23] mediated cyclizations of 3-oxohept-6-enoates, which are derived from 1,3-dicarbonyl dianions.

Efficient and elegant base-mediated cyclization reactions, which do not involve the use of true 1,3-dicarbonyl dianions, have been studied in detail by Rodriguez et al. (for references see Section 2.1.3). These reactions are not included in this review. Other syntheses of 2-(2-oxoalkylidene)tetrahydrofurans rely, for example, on Claisen condensations of ester enolates with lactones,[24] Wittig reactions, or transition metal-catalyzed cyclizations.[25] These reactions are also not covered in the present review.

### 2.1. Cyclizations of 1,3-dicarbonyl dianions ('free dianions')

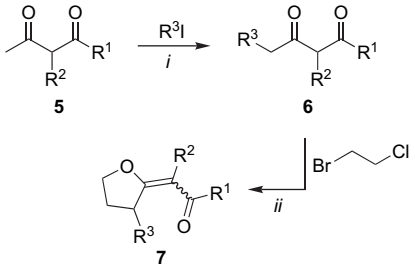
**2.1.1. Cyclizations via 3-oxohept-6-enoates.** 2-Alkylidenetetrahydrofurans were prepared by iodo-, telluro-, and selenocyclization of 3-oxohept-6-enoates (Scheme 2).[23] These syntheses (cyclization type B) are carried out in two steps. In the first step, 3-oxohept-6-enoates (such as **1a** or **1b**) are prepared by the reaction of 1,3-dicarbonyl dianions with allylic bromides. The addition of iodine and aryltellurium trichloride afforded 2-alkylidenetetrahydrofurans **2a** and **3**, respectively. The cyclizations proceed by attack of the electrophile onto the double bond and subsequent




**Scheme 2**. Synthesis of 2-alkylidenetetrahydrofurans by iodo-, telluro- and selenocyclization of 3-oxohept-6-enoates. (i) $I_2$, $Na_2CO_3$, $CH_2Cl_2$, 20 °C, 9 h; (ii) $CHCl_3$, reflux, 45 min; (iii) $I_2$, $Na_2CO_3$, $CH_2Cl_2$, 20 °C, 4 h; (iv) THF, 20 °C, 2 h.

cyclization via the oxygen atom of the 1,3-dicarbonyl moiety. The addition of iodine and phenylselenium bromide to **1b** afforded the bicyclic 2-alkylidenetetrahydrofurans **2b** and **4**, respectively.

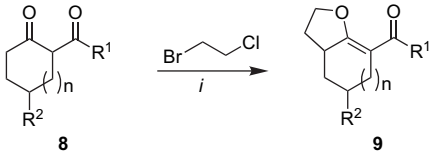
**2.1.2. 1,2-Dihaloethanes and 2-haloethanols.** The regioselective alkylation of the dianions of simple β-ketoesters **5** with alkyl iodides provides a convenient access to a variety of higher homologues **6**.[11] These include branched, non-branched, and ω-chloroalkyl-substituted derivatives. The one-pot cyclization of the dianions[26] of 1,3-dicarbonyl compounds **5** and **6** with 1-bromo-2-chloroethane[27,28] afforded a variety of 2-alkylidenetetrahydrofurans **7**[6,11] in good yields with very good regio- and *E*/*Z*-diastereoselectivity (cyclization type A, Scheme 3, Table 1).[29,30] Notably, the synthesis of 2-alkylidenetetrahydrofurans containing a remote chloro group proceeded with very good chemoselectivity. In fact, the chloro group proved to be compatible with the LDA-mediated generation of the dianions and the LDA-mediated cyclization.[11] Lindqvist and Brandänge earlier reported base-mediated intramolecular cyclizations of ω-halo-β-keto esters to give cyclic ethers or ketones.[29a] The one-pot cyclization of dilithiated ethyl 4-chloroacetoacetate with 1-bromo-2-chloroethane afforded, albeit in low yield, 3-chloro-2-alkylidenetetrahydrofuran **7ak** as a separable mixture of *E*/*Z*-isomers.




**Scheme 3**. Cyclization of 1,3-dicarbonyl dianions with 1-bromo-2-chloroethane. (i) (1) LDA (2.3 equiv), THF, 0 °C, 1 h, (2) $R^3I$; −78→20 °C, 14 h, (3) 20 °C, 2 h; (ii) (1) LDA (2.3 equiv), THF, 0 °C, 1 h, (2) $BrCH_2CH_2Cl$, −78→20 °C, 14 h, (3) 20 °C, 24 h or 68 °C, 9 h.

Bicyclic 2-alkylidenetetrahydrofurans **9** were prepared by cyclization of dilithiated cyclic 1,3-dicarbonyl compounds **8** with 1-bromo-2-chloroethane (Scheme 4, Table 2).[31,32] Again, all cyclizations proceeded in one pot (cyclization type A), except for the 5,5-bicyclic 2-alkylidenetetrahydrofuran **9a**, which had to be prepared over two steps via **9a′**. All reactions proceeded with excellent regioselectivity in moderate to very good yields.

Bryson reported the condensation of the dianion of **6b** with the tetrahydropyranyl (THP) ether of iodoethanol to give




**Scheme 4**. Synthesis of bicyclic 2-alkylidenetetrahydrofurans **9**. (i) (1) LDA (2.3 equiv), THF, 0 °C, 1 h, (2) $BrCH_2CH_2Cl$, −78→−20 °C, 6 h, (3) −20 °C, 12 h, (4) −20→20 °C, 12 h, (5) 20 °C, 12 h.

**Table 1**. Products and yields

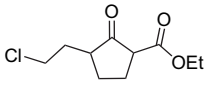
| **6**,**7** | $R^1$ | $R^2$ | $R^3$ | Yield,[a] % | | *E*/*Z*[b] (**7**) |
|---|---|---|---|---|---|---|
| | | | | **6** | **7** | |
| **a** | OMe | H | H | —[c] | 86 | >98:2 |
| **b** | OEt | H | H | —[c] | 79 | >98:2 |
| **c** | O$^i$Pr | H | H | —[c] | 64 | >98:2 |
| | | | | | 13 | <2:98 |
| **d** | $O(CH_2)_2OMe$ | H | H | —[c] | 70 | 10:1 |
| **e** | O$^t$Bu | H | H | —[c] | 63 | 10:1 |
| **f** | O$^t$Bu | H | H | —[c] | 77 | >98:2 |
| **g** | OBn | H | H | —[c] | 60 | 10:1 |
| **h** | $NEt_2$ | H | H | —[c] | 80 | >98:2 |
| **i** | Ph | H | H | —[c] | 82 | >98:2 |
| **j** | OMe | H | Me | —[c] | 72 | >98:2 |
| **k** | OEt | H | Et | —[c] | 82 | >98:2 |
| **l** | OMe | H | OMe | —[c] | 49 | >98:2 |
| **m** | OEt | H | $^n$Pr | 93 | 42 | >98:2 |
| | | | | | 17 | <2:98 |
| **n** | O$^t$Bu | H | $^n$Pr | 90 | 49 | <2:98 |
| **o** | OEt | H | $^n$Bu | 100 | 69 | >98:2 |
| **p** | OEt | H | $^n$Hex | 95 | —[d] | — |
| **q** | O$^t$Bu | H | $^n$Hex | 71 | —[d] | <2:98 |
| **r** | OEt | H | $^n$Hept | 100 | —[d] | — |
| **s** | O$^t$Bu | H | $^n$Hept | 77 | —[d] | <2:98 |
| **t** | OEt | H | $^n$Oct | 96 | —[d] | — |
| **u** | O$^t$Bu | H | $^n$Oct | 87 | —[d] | <2:98 |
| **v** | OEt | H | $^n$Non | 100 | —[d] | — |
| **w** | OEt | H | $^n$Dec | 100 | —[d] | — |
| **x** | O$^t$Bu | H | $^n$Dec | 60 | 41 | <2:98 |
| **y** | O$^t$Bu | H | $^{iso}$Bu | 44 | 45 | <2:98 |
| **z** | O$^t$Bu | H | $^{iso}$Pent | 98 | 48 | <2:98 |
| **aa** | OEt | H | Allyl | 95 | —[d] | — |
| **ab** | OEt | H | Bn | 100 | —[d] | — |
| **ac** | O$^t$Bu | H | Bn | 57 | 40 | <2:98 |
| **ad** | OMe | H | $(CH_2)_3Cl$ | 77 | 44 | >98:2 |
| **ae** | OEt | H | $(CH_2)_3Cl$ | 55 | —[d] | — |
| **af** | OMe | H | $(CH_2)_5Cl$ | 50 | —[d] | — |
| **ag** | OEt | H | $(CH_2)_5Cl$ | 56 | —[d] | — |
| **ah** | OEt | H | $(CH_2)_6Cl$ | 88 | —[d] | — |
| **ai** | O$^t$Bu | H | $(CH_2)_6Cl$ | 80 | 91 | <2:98 |
| **aj** | OEt | H | OBn | —[c] | 46 | >98:2 |
| **ak** | OEt | H | Cl | —[c] | 23 | >98:2 |
| | | | | | 10 | <2:98 |
| **al** | OEt | Me | H | —[c] | 70 | >98:2 |
| **am** | OEt | Et | H | —[c] | 68 | >98:2 |
| **an** | OEt | Bu | H | —[c] | 60 | >98:2 |
| **ao** | $-OCH_2CH_2-$ | | H | —[c] | 58 | >98:2 |
| **ap** | $-OCH(Et)CH_2-$ | | H | —[c] | 62 | >98:2 |

[a] Yields of isolated products.
[b] *E*/*Z* ratio of the exocyclic double bond of **7**, determined by $^1H$ and $^{13}C$ NMR shifts.
[c] Commercially available 1,3-dicarbonyl compounds **5**.
[d] Experiment not carried out.

**Table 2**. Products and yields

| **8**,**9** | *n* | $R^1$ | $R^2$ | Yield,[a] % (**9**) |
|---|---|---|---|---|
| **a** | 0 | OEt | H | 67[b] |
| **b** | 1 | OEt | H | 42 |
| **c** | 1 | OMe | Me | 47[c] |
| **d** | 3 | OEt | H | 43 |
| **e** | 7 | OEt | H | 90 |

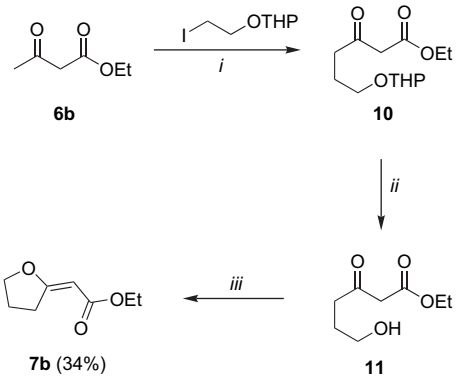
[a] Yields of isolated products.
[b] Yield over two steps (via **9a′**) by DBU (THF, 20 °C, 3 h).




**9a'**

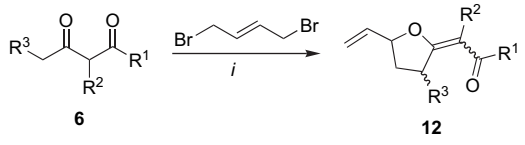
[c] Diastereoselectivity=5:2.

product **10**, which was deprotected and transformed (by treatment with *p*-toluenesulfonic acid) into 2-alkylidenetetrahydrofuran **7b** (cyclization type B, Scheme 5).[20b]




**Scheme 5**. Synthesis of 2-alkylidenetetrahydrofuran **7b**. (i) (1) NaH, *n*BuLi, THF, (2) $ICH_2CH_2OTHP$; (ii) $H_2O$, $H^+$, EtOH; (iii) *p*-TsOH, benzene.

**2.1.3. 1,4-Dibromo-2-butene.** The one-pot cyclization of dilithiated 1,3-dicarbonyl compounds with 1,4-dibromo-2-butene[33] provides a convenient approach to 2-alkylidene-5-vinyltetrahydrofurans **12** (Scheme 6, Table 3).[6] The formation of products **12** can be explained by a domino $S_N/S_N'$ reaction (cyclization type A). The products are formed as separable mixtures of *E*/*Z*-isomers. The ratio strongly depends on the reaction time and on the substituents. The exocyclic double bond is initially formed with *Z*-configuration. By stirring the reaction mixture at room temperature, an isomerization of the exocyclic double bond to the thermodynamically more stable *E*-configuration is observed. However, the isomerization could not be efficiently carried out after isolation of the *Z*-isomer, since the rearrangement was accompanied by decomposition. Weiler and Sum reported that the reaction of 1,3-dicarbonyl dianions with 1,4-dichloro-2-butene (rather than 1,4-dibromo-2-butene) resulted in the formation of mixtures of open-chain products in low yields.[33a] Elegant and efficient cyclizations of 1,4-dibromo-2-butene with the stabilized carbanions of dimethyl acetone-1,3-dicarboxylate and of various other 1,3,5-tricarbonyl compounds were reported by Rodriguez.[33c] These reactions are not covered in the present review.




**Scheme 6**. Synthesis of 2-alkylidene-5-vinyltetrahydrofurans **12**. (i) (1) LDA (2.3 equiv), THF, 0 °C, 1 h, (2) 1,4-dibromobut-2-ene, −78→20 °C, 14 h, (3) 20 °C, 24 h.

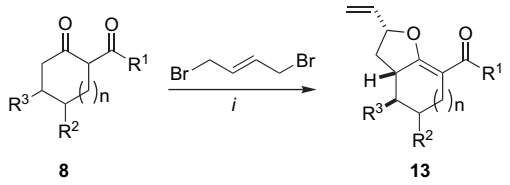
The cyclization of the dianions of cyclic 1,3-dicarbonyl compounds **8** with 1,4-dibromobut-2-ene afforded the 5,6- and 5,7-bicyclic 2-alkylidene-5-vinyltetrahydrofurans **13** in good yields and with very good 1,2- and 1,3-diastereoselectivities (cyclization type A, Scheme 7, Table 4).[5,6,31,32]

**2.1.4. Epoxides and cyclic sulfates.** The first cyclizations of 1,3-dicarbonyl dianions with epoxides were reported by

**Table 3**. Products and yields

| 12 | 6 | $R^1$ | $R^2$ | $R^3$ | Yield,[a] % (12) | *E*/*Z*[b] (12) |
|---|---|---|---|---|---|---|
| **a** | **a** | OEt | H | H | 40 | >98:2 |
| | | | | | 35 | <2:98 |
| **b** | **f** | O$^t$Bu | H | H | 58 | <2:98 |
| **c** | **h** | $NEt_2$ | H | H | 73 | <2:98 |
| **d** | **aq** | Me | H | H | 47 | <2:98 |
| **e** | **i** | Ph | H | H | 57 | >98:2 |
| | | | | | 35 | <2:98 |
| **g** | **j** | OMe | H | Me | 61[c] | 8:1 |
| **h** | **k** | OEt | H | Et | 53[c] | <2:98 |
| **i** | **al** | OEt | Me | H | 64 | <2:98 |
| **j** | **am** | OEt | Et | H | 61 | <2:98 |
| **k** | **an** | OEt | Bu | H | 32 | <2:98 |
| **l** | **ao** | $-OCH_2CH_2-$ | | H | 32 | >98:2 |
| **m** | **ap** | $-OCH(Et)CH_2-$ | | H | 46 | >98:2 |

[a] Yields of isolated products.
[b] *E*/*Z* ratio of the exocyclic double bond of **12**, determined by $^1H$ and $^{13}C$ NMR shifts.
[c] Diastereoselectivities: for **12g**, dr=5:6 and for **12h**, dr=2:1.




**Scheme 7**. Synthesis of bicyclic 2-alkylidene-5-vinyltetrahydrofurans **13**. (i) (1) LDA (2.3 equiv), THF, 0 °C, 1 h, (2) 1,4-dibromobut-2-ene, −78→−20 °C, 6 h, (3) −20 °C, 12 h, (4) −20→20 °C, 12 h, (5) 20 °C, 12 h.

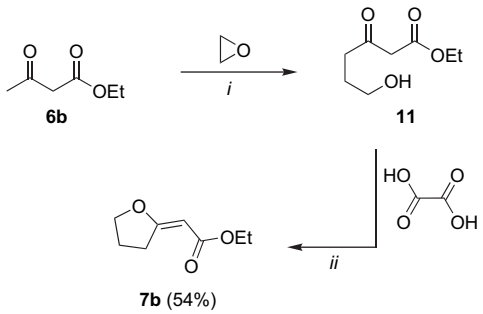
**Table 4**. Synthesis of bicyclic 2-alkylidene-5-vinyltetrahydrofurans **13**

| 13 | 8 | *n* | $R^1$ | $R^2$ | $R^3$ | Yield,[a,b] % (13) |
|---|---|---|---|---|---|---|
| **a** | **b** | 1 | OEt | H | H | 81 |
| **b** | **f** | 1 | O$^i$Pr | H | H | 77 |
| **c** | **g** | 1 | $O(CH_2)_2OMe$ | H | H | 78 |
| **d** | **h** | 1 | H | H | H | 37 |
| **e** | **c** | 1 | OMe | Me | H | 63 |
| **f** | **i** | 1 | OEt | $^t$Bu | H | 53 |
| **g** | **j** | 1 | OMe | Ph | H | 65 |
| **h** | **k** | 1 | OEt | Ph | H | 65 |
| **i** | **l** | 1 | OEt | H | Me | 74 |
| **j** | **m** | 1 | OMe | H | Et | 72 |
| **k** | **n** | 1 | OMe | H | Bu | 35 |
| **l** | **o** | 1 | OEt | H | H | 63[c] |
| **m** | **p** | 2 | $^t$Bu | H | H | 66[c] |

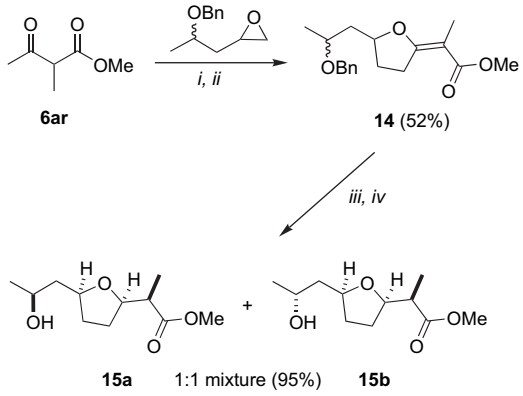
[a] Yields of isolated products.
[b] Double bond of all compounds **13** *E*/*Z*<2:98, and diastereoselectivity: dr>98:2 in favor of the drawn diastereomer.
[c] Diastereoselectivities: for **13l**, dr=7:3 and for **13m**, dr=9:1.

Bryson (Scheme 8).[20b] The reaction of the dianion of ethyl acetoacetate with ethylene oxide afforded product **11**, which was transformed, by acid-mediated cyclization, into 2-alkylidenetetrahydrofuran **7b** (cyclization type B).

Lygo et al. reported the synthesis of (±)-methyl homononactate (**15a**) and methyl 8-*epi*-homononactate (**15b**) (Scheme 9).[13h,18a] 2-Alkylidenetetrahydrofuran **14** was prepared from dianion **6ar** (cyclization type B). Hydrogenation of **14** afforded products **15a** and **15b**, which are subunits of the nactins—a biologically important class of macrotetrolide antibiotics isolated from a variety of *Streptomyces* cultures.[13]




**Scheme 8**. Cyclization of the dianion of **6b** with ethylene oxide; (i) (1) NaH, *n*BuLi, THF, (2) oxirane, 0→20 °C; (ii) oxalic acid, $CH_2Cl_2$, reflux, 2 h.

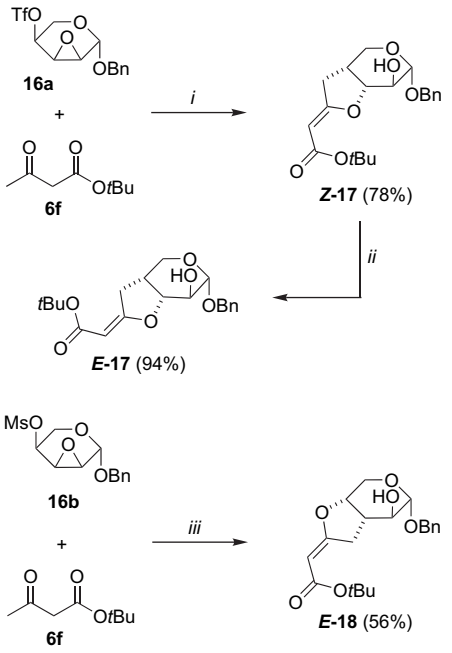



**Scheme 9**. Synthesis of (±)-methyl homononactate (**15a**) and methyl 8-*epi*-homononactate (**15b**) via 2-alkylidenetetrahydrofuran **14**. (i) (1) NaH, *n*BuLi, THF, 20 °C; (ii) oxalic acid, $CH_2Cl_2$, reflux; (iii) 10% Pd/C, MeOH, $H_2$, 1 atm; (iv) 5% $Rh/Al_2O_3$, MeOH, $H_2$, 65 psi.

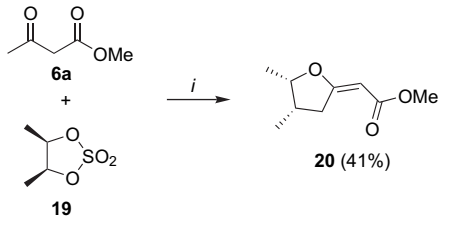
A variety of cyclizations of 1,3-dicarbonyl dianions with carbohydrate-derived epoxytriflates, -mesylates and -tosylates were reported by Voelter et al. (cyclization type A, Scheme 10).[19b,c] The regioselective cyclization of the dianion of **6f** with epoxytriflate **16a** at −78 °C afforded the *Z*-configured bicyclic 2-alkylidenetetrahydrofuran *Z*-**17** (kinetic reaction control), which underwent an isomerization into the thermodynamically more stable *E*-configured isomer *E*-**17** upon treatment with TFA. The formation of *Z*-**17** proceeded by attack of the terminal carbon atom of the dianion onto the triflate and subsequent cyclization by attack of the oxygen atom onto the epoxide. The reaction of the dianion of **6f** with mesylate **16b**, carried out at 0 °C, afforded product *E*-**18** by attack of the dianion onto the epoxide and subsequent cyclization by attack of the oxygen atom onto the mesylate. The cyclization of the dianion of **6f** with the corresponding epoxytosylate was carried out at room temperature and gave a mixture of both regioisomers in 75% yield (**18**/**17**=2.5:1).

The cyclization of the dianion of **6a** with cyclic sulfate **19** afforded 2-alkylidenetetrahydrofuran **20** (Scheme 11).[21i,j] The reaction proceeds by attack of the carbon atom of the dianion onto **19** and subsequent cyclization via the oxygen atom of the dianion (cyclization type A). A number of related cyclizations were reported.

The cyclization of 1,3-dicarbonyl dianions with epibromohydrin was reported to afford 2-alkylidene-5-hydroxymethyltetrahydrofurans **21** (Scheme 12, Table 5).[8a,b] The

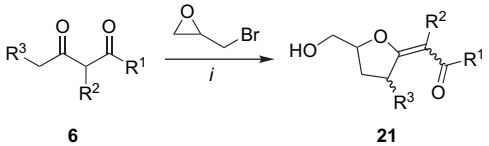



**Scheme 10**. Cyclizations of carbohydrate-derived epoxytriflate and -mesylate **16a**,**b** with the dianion of **6f**. (i) NaH, *n*BuLi, THF, −78→20 °C; (ii) (1) TFA (1%), $CH_2Cl_2$, 0 °C, 1.5 h, (2) 20 °C 3 h; (iii) NaH, *n*BuLi, THF, R=Ms, 0 °C, 6 h, R=Ts, 20 °C, 12 h.




**Scheme 11**. Cyclization of 1,3-dicarbonyl dianions with cyclic sulfates. (i) LDA, THF, 0→20 °C.

reaction may proceed by attack of the terminal carbon atom of the dianion onto the bromide and subsequent attack of the oxygen atom onto the epoxide (cyclization type A). Alternatively, the reaction may proceed by attack of the dianion onto the epoxide, Payne rearrangement, and subsequent cyclization (cyclization type A). The success of this cyclization reaction strongly depends on a proper tuning of the temperature, on the use of the sodium–lithium rather than the dilithium salt of the 1,3-dicarbonyl compound, and on the use of over-stoichiometric amounts of the Lewis acid $LiClO_4$. In most cases, *Z*-configured diastereomers were initially formed, which slowly underwent an isomerization into the thermodynamically more stable *E*-configured isomers. Takano et al. reported the cyclization of 1,3-dicarbonyl dianions with substituted epibromohydrins.[8c]



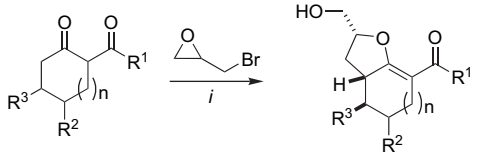

**Scheme 12**. Synthesis of 2-alkylidene-5-hydroxymethyltetrahydrofurans **21**. (i) (1) NaH, *n*BuLi, THF, 0 °C, 1 h, (2) epibromohydrin, $LiClO_4$, −78→−40 °C, (3) −40 °C, 8 h, (4) −40→20 °C, (5) 20 °C, 10 h.

**Table 5**. Products and yields

| 21 | 6 | $R^1$ | $R^2$ | $R^3$ | Yield,[a] % (**21**) | *E*/*Z*[b] (**21**) |
|---|---|---|---|---|---|---|
| **a** | **a** | OMe | H | H | 74 | <2:98 |
| **b** | **b** | OEt | H | H | 74 | <2:98 |
| **c** | **c** | O$^i$Pr | H | H | 92 | 1:10 |
| **d** | **d** | O(CH$_2$)$_2$OMe | H | H | 57 | <2:98 |
| **e** | **e** | O$^i$Bu | H | H | 68 | <2:98 |
| **f** | **f** | O$^t$Bu | H | H | 71 | <2:98 |
| **g** | **g** | Obn | H | H | 78 | <2:98 |
| **h** | **h** | NEt$_2$ | H | H | 96 | <2:98 |
| **i** | **aq** | Me | H | H | 73 | 3:4 |
| **j** | **as** | $^t$Bu | H | H | 70 | >98:2 |
| **k** | **i** | Ph | H | H | 61 | >98:2 |
| **l** | **at** | OEt | H | Me | 62[c] | <2:98 |
| **m** | **k** | OEt | H | Et | 65[c] | <2:98 |
| **n** | **aa** | OEt | H | Allyl | 78[c] | <2:98 |
| **o** | **au** | Me | Me | H | 72 | 3:4 |
| **p** | **al** | OEt | Me | H | 71 | <2:98 |
| **q** | **am** | OEt | Et | H | 75 | <2:98 |
| **r** | **an** | OEt | Bu | H | 72 | <2:98 |

[a] Yields of isolated products.
[b] *E*/*Z* ratio of the exocyclic double bond of **21**, determined by $^1$H and $^{13}$C NMR shifts.
[c] Diastereoselectivities: for **21l**, dr=5:6; for **21m**, dr=2:1; and for **21n**, dr=4:3.

The cyclization of the dianions of cyclic 1,3-dicarbonyl compounds **8** with epibromohydrin gave the 5,6- and 5,7-bicyclic 2-alkylidene-5-hydroxymethyltetrahydrofurans **22** with moderate diastereoselectivity (cyclization type A, Scheme 13, Table 6).[8b]




**8** **22**

**Scheme 13**. Synthesis of bicyclic 2-alkylidene-5-hydroxymethyltetrahydrofurans **22**. (i) (1) NaH, *n*BuLi, THF, 0 °C, 1 h, (2) epibromohydrin, $LiClO_4$, −78→−40 °C, (3) −40 °C, 8 h, (4) −40→20 °C, (5) 20 °C, 10 h.

**Table 6**. Products and yields

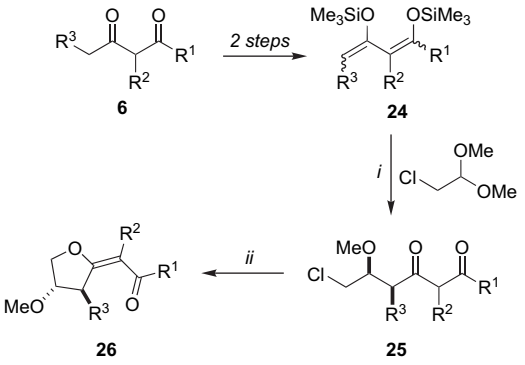
| 22 | 8 | *n* | $R^1$ | $R^2$ | $R^3$ | Yield,[a] % (**22**) | dr[b] (**22**) |
|---|---|---|---|---|---|---|---|
| **a** | **a** | 1 | OEt | H | H | 72 | 4:1 |
| **b** | **k** | 1 | OEt | Ph | H | 42 | 4:1 |
| **c** | **r** | 1 | OMe | H | Me | 30 | 4:1 |
| **d** | **p** | 2 | OEt | H | H | 21 | 3:1 |

[a] Yields of isolated products.
[b] Diastereomeric ratio.

## 2.2. Cyclizations of 1,3-bis-silyl enol ethers ('masked dianions')

1,3-Bis-silyl enol ethers can be regarded as masked 1,3-dicarbonyl dianions. Their chemistry has been reviewed.[3] Similar to reactions of 1,3-dicarbonyl dianions, the cyclizations of 1,3-bis-silyl enol ethers can proceed in one step (cyclization type A) or in two steps (cyclization type B).

**2.2.1. 1-Chloro-2,2-dimethoxyethane.** The reaction of 1,3-bis-silyl enol ethers with aldehydes and acetals is of considerable synthetic importance.[34,35] Numerous cyclization reactions of 1,3-bis-silyl enol ethers and of 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) with functionalized aldehydes are known (hetero-Diels–Alder reaction).[36] Chan and co-workers[34b] reported an early example of a $TiCl_4$-mediated condensation of a 1,3-bis-silyl enol ether with 1-chloro-2,2-dimethoxyethane.[7,12] The reaction could be improved by the employment of trimethylsilyl-trifluoromethanesulfonate ($Me_3SiOTf$). The $Me_3SiOTf$-catalyzed[37] reaction of 1,3-bis-silyl enol ethers **24** with 1-chloro-2,2-dimethoxyethane afforded the open-chain condensation products **25** (Scheme 14, Table 7).[12] Treatment



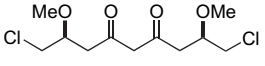

**6** **24** **26** **25**

**Scheme 14**. Synthesis of 2-alkylidene-4-methoxytetrahydrofurans **26**. (i) $Me_3SiOTf$, $CH_2Cl_2$, −78→20 °C; (ii) DBU, THF, 20 °C.

**Table 7**. Products and yields

| 24–26 | 6 | $R^1$ | $R^2$ | $R^3$ | Yield,[a] % | | *E*/*Z*[b] (**26**) |
|---|---|---|---|---|---|---|---|
| | | | | | **25** | **26** | |
| **a** | **a** | OMe | H | H | 72 | 86 | >98:2 |
| **b** | **b** | OEt | H | H | 66 | 74 | >98:2 |
| **c** | **c** | O$^i$Pr | H | H | 70 | 80 | >98:2 |
| **d** | **d** | O(CH$_2$)$_2$OMe | H | H | 67 | 68 | >98:2 |
| **e** | **e** | O$^i$Bu | H | H | — | 60[f] | >98:2 |
| **f** | **g** | OBn | H | H | 51 | 94 | >98:2 |
| **g** | **i** | Ph | H | H | 51 | —[d] | — |
| **h** | **aq** | Me | H | H | 24[c] | —[e] | — |
| **i** | **j** | OMe | H | Me | 63 | 90 | >98:2 |
| **j** | **k** | OEt | H | Et | 83 | 99 | >98:2 |
| **k** | **l** | OMe | H | OMe | 64 | 49 | >98:2 |
| | | | | | | 33 | <2:98 |
| **l** | **aa** | OEt | H | Allyl | 57 | 80 | >98:2 |
| **m** | **m** | OEt | H | $^n$Pr | 87 | 79 | >98:2 |
| **n** | **o** | OEt | H | $^n$Bu | 85 | 73 | >98:2 |
| **o** | **p** | OEt | H | $^n$Hex | 88 | 76 | >98:2 |
| **p** | **t** | OEt | H | $^n$Oct | 53 | 97 | >98:2 |
| **q** | **v** | OEt | H | $^n$Non | 79 | 87 | >98:2 |
| **r** | **w** | OEt | H | $^n$Dec | 86 | 70 | >98:2 |
| **s** | **ah** | OEt | H | (CH$_2$)$_6$Cl | 78 | 93 | >98:2 |
| **t** | **al** | OEt | Me | H | — | 58[f] | >98:2 |
| **u** | **ao** | –OCH$_2$CH$_2$– | | H | 97 | 92 | >98:2 |

[a] Yields of isolated products. For compounds **26i–s**: *trans*/*cis*>98:2. Compounds **25** were obtained as mixtures of keto–enol-tautomers.
[b] *E*/*Z* ratio of the exocyclic double bond of **26**, determined by $^1$H and $^{13}$C NMR shifts, confirmed by crystal structure analyses.
[c] Besides, double condensation product **25h′** (19%) was isolated.

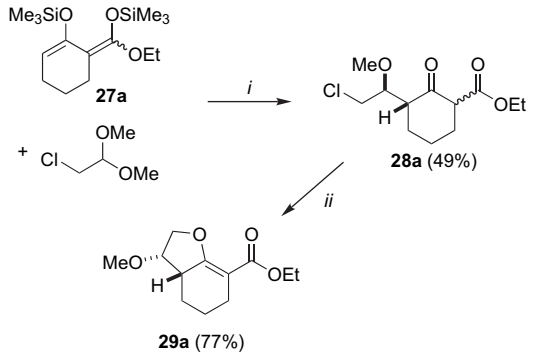



**25h'**

[d] Treatment with DBU gave the corresponding furan (see Section 3.7).
[e] Reaction resulted in decomposition.
[f] Yields over two steps.

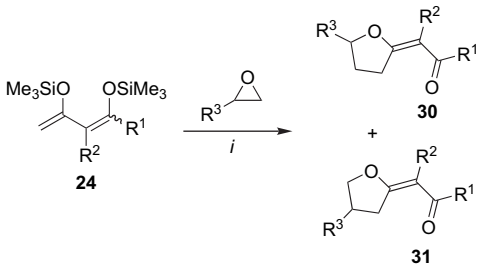
of **25** with DBU resulted in regioselective cyclization and formation of a variety of 2-alkylidene-4-methoxytetrahydrofurans **26** in good to excellent yields with excellent *E*-diastereoselectivity (cyclization type B).[7,12]

The reaction of cyclic 1,3-bis-silyl enol ether **27a**[38] with 1-chloro-2,2-dimethoxyethane afforded the condensation products **28a**.[12] Treatment of the latter with DBU gave 2-alkylidene-4-methoxytetrahydrofuran **29a** (Scheme 15). A number of related products were prepared (Table 8).[12,31,32]



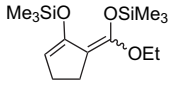
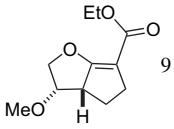
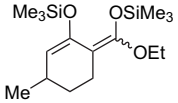
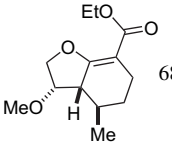
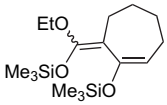
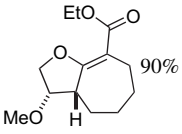
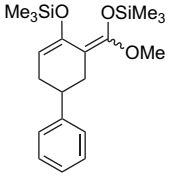
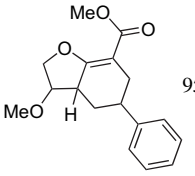
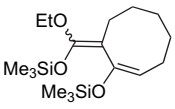
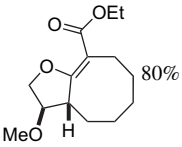
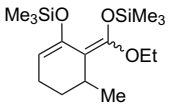
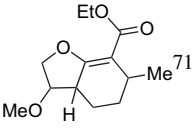
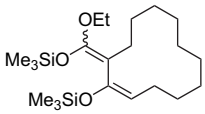
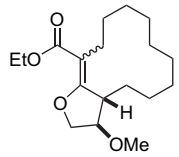
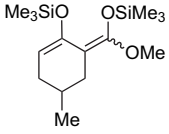
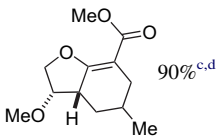

**Scheme 15**. Synthesis of bicyclic 2-alkylidene-4-methoxytetrahydrofuran **29a**. (i) $Me_3SiOTf$, $CH_2Cl_2$, −78→20 °C; (ii) DBU, THF, 20 °C.

**2.2.2. Epoxides.** The reaction of 1,3-dicarbonyl dianions with epoxides (Section 2.1.4) is limited to epoxides containing no base-labile functional groups. As a result of the basic reaction conditions, the cyclizations have to be carried out, in most cases, in two steps (cyclization type B) rather than as one-pot reactions (cyclization type A). The $TiCl_4$-mediated one-pot cyclization of 1,3-bis-silyl enol ethers with epoxides provides an alternative method, which allows for the synthesis of 2-alkylidenetetrahydrofurans containing base-labile functional groups. The cyclization of 1,3-bis-silyl enol ethers **24** with epoxides afforded a variety of 2-alkylidenetetrahydrofurans **30** and **31** (cyclization type A, Scheme 16, Table 9).[4,9] In most cases, the reactions proceed by attack of the terminal carbon atom of the bis-silyl enol ether onto the sterically less hindered carbon of the epoxide, cyclization by attack of the epoxide-derived oxygen atom onto the carbonyl group, and subsequent formation of the double bond. The formation of regioisomers **31** strongly depends on the reaction




**Scheme 16**. Cyclization of 1,3-bis-silyl enol ethers with epoxides. (i) $TiCl_4$, $CH_2Cl_2$, 4 Å MS (in several cases), −78→20 °C.

**Table 8**. Products and yields

| Entry | 27[b] | Yield,[a] % | | Entry | 27[b] | Yield,[a] % | |
|---|---|---|---|---|---|---|---|
| | | 28 | 29 | | | 28 | 29 |
| **b** |  | 42% |  91% | **f** |  | 86% |  68% |
| **c** |  | 90% |  90% | **g** |  | 89% |  95%[d] |
| **d** |  | 65% |  80% | **h** |  | — |  71%[c,d] |
| **e** |  | 76% |  60% (*Z*); 38% (*E*) | **i** |  | — |  90%[c,d] |

[a] Yields of isolated products. For products **29a–f**: dr>98:2 in favor of the drawn diastereomer.
[b] All bis-silyl enol ethers were prepared in one step, except for **27e** (two steps).
[c] Yields over two steps.
[d] Combined yields of the separated diastereomers; for **29g**, three isomers (dr>98:2 for each); for **29h**, two fractions (inseparable 2:1 mixture of diastereomers for each); for **29i**, two isomers (dr>98:2 for each).

**Table 9**. Products and yields

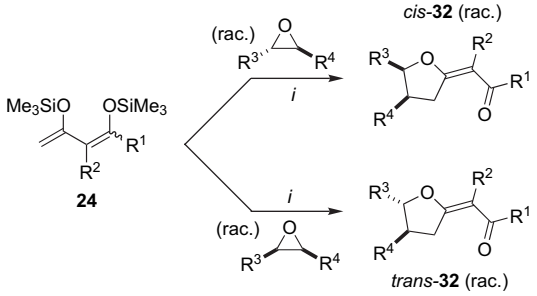
| 30,31 | 24 | $R^1$ | $R^2$ | $R^3$ | Yield,[a,b] % | |
|---|---|---|---|---|---|---|
| | | | | | **30** | **31** |
| **a** | **a** | OMe | H | Me | 42 | 18 |
| **b** | **a** | OMe | H | Et | 57 | 13 |
| **c** | **a** | OMe | H | $^n$Bu | 36 | 23 |
| **d** | **a** | OMe | H | $CH_2Cl$ | 66 | — |
| **e** | **a** | OMe | H | $(CH_2)_2CO_2Et$ | 51 | — |
| **g** | **b** | OEt | H | Me | 70 | — |
| **h** | **b** | OEt | H | Et | 62 | — |
| **i** | **b** | OEt | H | $^n$Bu | 44 | — |
| **j** | **b** | OEt | H | $(CH_2)_2CH{=}CH_2$ | 30 | — |
| **k** | **b** | OEt | H | $CH_2OBn$ | 58 | — |
| **l** | **b** | OEt | H | $CH_2Cl$ | 52 | — |
| **m** | **b** | OEt | H | $CH_2Br$ | 48 | — |
| **n** | **b** | OEt | H | CH(Me)Br | 41 | — |
| **o** | **b** | OEt | H | Ph | — | 30 |
| **p** | **t** | OEt | Me | Et | 58 | — |
| **q** | **t** | OEt | Me | $(CH_2)_2CH{=}CH_2$ | 32 | — |
| **r** | **t** | OEt | Me | $CH_2Cl$ | 45 | — |
| **s** | **t** | OEt | Me | $CH_2CO_2Et$ | 50 | — |
| **t** | **v** | OEt | Et | Me | 50 | — |
| **u** | **v** | OEt | Et | $CH_2Br$ | 44 | — |
| **v** | **w** | $CH_2OMe$ | H | Me | — | 42 |
| **w** | **w** | $CH_2OMe$ | H | Et | 40 | — |
| **x** | **w** | $CH_2OMe$ | H | $CH_2Cl$ | 45 | — |
| **y** | **h** | Me | H | Me | 36[c] | — |
| **z** | **h** | Me | H | Et | 6 | 15 |
| **aa** | **g** | Ph | H | Me | 6 | 62 |
| **ab** | **g** | Ph | H | Et | 9 | 65 |
| **ac** | **g** | Ph | H | $CH{=}CH_2$ | — | 38 |
| **ad** | **g** | Ph | H | $CH_2Cl$ | 54 | — |
| **ae** | **g** | Ph | H | $CH_2Br$ | 56 | — |
| **af** | **g** | Ph | H | $CH_2CO_2Et$ | 41 | — |
| **ag** | **u** | $-OCH_2CH_2-$ | | Me | 60 | — |
| **ah** | **u** | $-OCH_2CH_2-$ | | Et | 45 | — |
| **ai** | **u** | $-OCH_2CH_2-$ | | $^n$Bu | 37 | — |
| **aj** | **u** | $-OCH_2CH_2-$ | | $(CH_2)_2CH{=}CH_2$ | 36 | — |
| **ak** | **u** | $-OCH_2CH_2-$ | | $CH_2Cl$ | 66 | — |
| **al** | **u** | $-OCH_2CH_2-$ | | $CH_2Br$ | 62 | — |
| **am** | **x** | $-OCH(Et)CH_2-$ | | Et | 57 | — |
| **an** | **x** | $-OCH(Et)CH_2-$ | | $CH_2Br$ | 82 | — |

[a] Yields of isolated products.
[b] *E*/*Z*>98:2 for all products (by $^1$H and $^{13}$C NMR).
[c] Inseparable 3:1 mixture of regioisomers (C-5/C-4).

conditions and on the type and quality of the starting materials. The exocyclic double bond of all products was formed with very good *E*-diastereoselectivity. The reaction of epoxyaldehydes with 3-iodo-2-[(trimethylsilyl)methyl]-propene, which can be regarded as a masked trimethylenemethane dianion, was reported by Molander and Shubert.[39]

The $TiCl_4$-mediated cyclization of (racemic) cis- and trans-configured 1,2-disubstituted epoxides with 1,3-bis-silyl enol ethers afforded the *trans*- and *cis*-4,5-dialkyl-functionalized 2-alkylidenetetrahydrofurans **32**, respectively, with excellent *E*-diastereoselectivity (Scheme 17, Table 10).[9]

The $TiCl_4$-mediated cyclization of 1,3-bis-silyl enol ethers with commercially available (*R*)-(−)- and (*S*)-(+)-epichlorohydrin afforded the enantiomerically pure methyl (5-chloromethyldihydrofuran-2(3*H*)-ylidene)acetates (*R*)-(−)-**30d** and (*S*)-(+)-**30d**, respectively (Scheme 18).[40] The excellent enantiospecificity can be explained by the fact that the stereogenic center is not involved in the reaction and no racemization occurred.

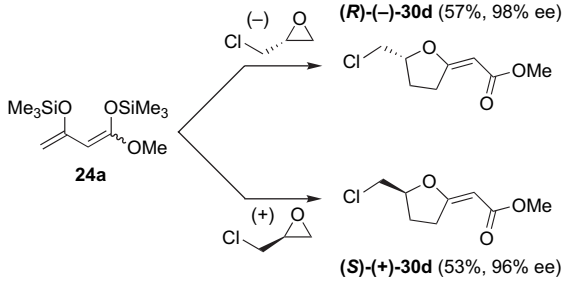



**Scheme 17**. Synthesis of 4,5-substituted 2-alkylidenetetrahydrofurans **32**. (i) $TiCl_4$, $CH_2Cl_2$, 4 Å MS (in several cases), −78→20 °C.

**Table 10**. Products and yields

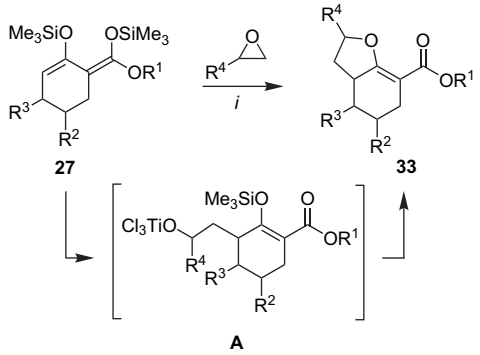
| 32 | 24 | Configuration | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield,[a,b] % (**32**) |
|---|---|---|---|---|---|---|---|
| **a** | **b** | trans | OEt | H | Me | Me | 45 |
| **a** | **b** | cis | OEt | H | Me | Me | 42 |
| **b** | **t** | cis | OEt | Me | Me | Me | 37 |
| **c** | **u** | trans | $-OCH_2CH_2-$ | | Me | Me | 37 |
| **d** | **a** | trans | OMe | H | $-CH_2(CH_2)_2CH_2-$ | | 30 |
| **e** | **b** | trans | OEt | H | $-CH_2(CH_2)_2CH_2-$ | | 26 |
| **f** | **c** | trans | O$^i$Pr | H | $-CH_2(CH_2)_2CH_2-$ | | 32 |
| **g** | **e** | trans | O$^i$Bu | H | $-CH_2(CH_2)_2CH_2-$ | | 31 |
| **h** | **g** | trans | Ph | H | $-CH_2(CH_2)_2CH_2-$ | | 24 |
| **i** | **u** | trans | $-OCH_2CH_2-$ | | $-CH_2(CH_2)_2CH_2-$ | | 26 |

[a] Yields of isolated products.
[b] *E*/*Z*>98:2 for all products (by $^1$H and $^{13}$C NMR).




**Scheme 18**. Synthesis of enantiomerically pure 2-alkylidene-5-chloromethyltetrahydrofuran **30d**. (i) $TiCl_4$, $CH_2Cl_2$, −78→20 °C.

The cyclization of cyclic 1,3-bis-silyl enol ethers **27** with epoxides afforded, via the trichlorotitanium(IV) alkoxide intermediate **A**, the 5,6-bicyclic 2-alkylidene-5-alkyltetrahydrofurans **33** (Scheme 19, Table 11).[31,32]




**Scheme 19**. Synthesis of 5,6- and 5,7-bicyclic 2-alkylidene-5-alkyltetrahydrofurans **33**. (i) (1) Epoxide, $TiCl_4$ (2.0 equiv), 4 Å MS, $CH_2Cl_2$, −78 °C, 4 h, (2) −78→20 °C, 14 h, (3) 20 °C, 12 h.

**Table 11**. Products and yields

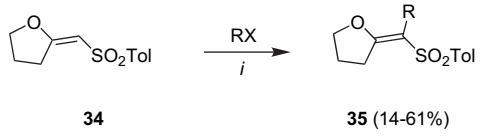
| 33 | 27 | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield,[a,b] % (33) |
|---|---|---|---|---|---|---|
| **a** | **a** | Et | H | H | Me | 28[c] |
| **b** | **a** | Et | H | H | $CH_2Cl$ | 46[c] |
| **c** | **a** | Et | H | H | $CH_2Br$ | 42[c] |
| **d** | **i** | Me | Me | H | Me | 30[c] |
| **e** | **i** | Me | Me | H | Et | 21[c] |
| **f** | **i** | Me | Me | H | $CH_2Cl$ | 40[d] |
| **g** | **g** | Me | Ph | H | Me | 32[c] |
| **h** | **g** | Me | Ph | H | $CH_2Cl$ | 42[d] |
| **i** | **g** | Me | Ph | H | $CH_2Br$ | 37[c] |
| **j** | **f** | Et | H | Me | $CH_2Cl$ | 57[c] |

[a] Yields of isolated products.
[b] *E*/*Z*<2:98 for all products.
[c] Inseparable mixture of diastereomers.
[d] Combined yields of separated diastereomers.

## 3. Reactions of 2-alkylidenetetrahydrofurans

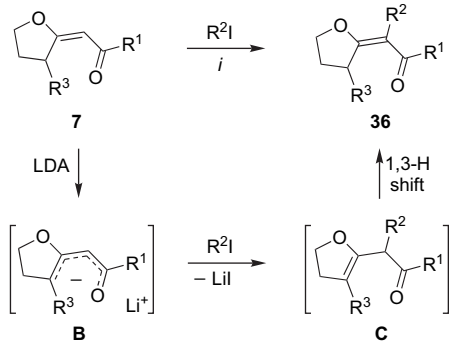
### 3.1. Alkylations

Deprotonation of 2-(tosylmethylidene)tetrahydrofuran (**34**) with *n*BuLi and subsequent alkylation in the presence of hexamethylphosphoramide (HMPA) was reported to give 2-(1-tosylalkylidene)tetrahydrofurans **35** (Scheme 20).[41]




**Scheme 20**. Alkylation of 2-(tosylmethylidene)tetrahydrofuran **34**. (i) (1) *n*BuLi, THF, HMPA, (2) RX, −78→20 °C (R=alkyl, X=I).

The LDA/HMPA-mediated alkylation of ester-substituted 2-alkylidenetetrahydrofurans **7** afforded the substituted 2-alkylidenetetrahydrofurans **36** via **B** and **C** (Scheme 21, Table 12).[11] The alkylations proceed with very good regio- and *E*/*Z*-diastereoselectivity.




**Scheme 21**. Alkylation of 2-alkylidenetetrahydrofurans **7**. (i) (1) LDA (2.0 equiv), THF, HMPA, (2) RI, −78→20 °C, 14 h, (3) 20 °C, 5 h.

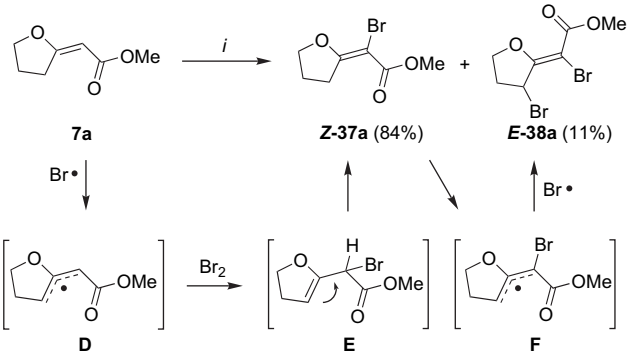
### 3.2. Brominations

The reaction of 2-alkylidenetetrahydrofurans **7** with *N*-bromosuccinimide (NBS) afforded a variety of brominated 2-alkylidenetetrahydrofurans via **D**, **E**, and **F** (Scheme 22, Table 13).[42–44] This includes the synthesis of mono- and dibrominated products, such as 1′-bromo-2-alkylidenetetrahydrofurans **37**, 1′,3-dibromo-2-alkylidenetetrahydrofurans **38**, 3-bromo-2-alkylidenetetrahydrofurans **39**, and 3,3-dibromo-2-alkylidenetetrahydrofurans **40**. The formation of the products can be explained by a radical mechanism (Scheme 22). The regioselectivity depends on the substitution pattern of the products. The use of an excess of NBS (3.0 equiv) resulted in the selective formation of 1′,3-dibromo-2-alkylidenetetrahydrofurans **38**.

**Table 12**. Products and yields

| 36 | 7 | $R^1$ | $R^2$ | $R^3$ | Yield,[a] % (36) | *E*/*Z*[b] (36) |
|---|---|---|---|---|---|---|
| **a** | **b** | OEt | $^n$Hex | H | 57 | >98:2 |
| **b** | **b** | OEt | $^n$Hept | H | 49 | >98:2 |
| **c** | **b** | OEt | $^n$Oct | H | 51 | >98:2 |
| **d** | **b** | OEt | $^n$Dec | H | 48 | >98:2 |
| **e** | **f** | O$^t$Bu | Et | H | 51 | >98:2 |
| **f** | **f** | O$^t$Bu | $^n$Pr | H | 45 | >98:2 |
| **g** | **f** | O$^t$Bu | $^n$Hept | H | 91 | >98:2 |
| **h** | **f** | O$^t$Bu | $^{iso}$Bu | H | 40 | >98:2 |
| **i** | **f** | O$^t$Bu | Allyl | H | 25 | >98:2 |
| **j** | **f** | O$^t$Bu | Bn | H | 32 | >98:2 |
| **k** | **f** | O$^t$Bu | $(CH_2)_6Cl$ | H | 79 | >98:2 |
| **l** | **f** | O$^t$Bu | $CH_2CO_2Me$ | H | 38 | >98:2 |
| **m** | | O$^t$Bu | H | $CH_2CO_2Me$ | 43 | >98:2 |
| **n** | **a** | OMe | $^{iso}$Pent | H | 41 | >98:2 |
| **o** | **a** | OMe | Bn | H | 45 | >98:2 |
| **p** | | OMe | Bn | Bn | 43 | >98:2 |
| **q** | **a** | OMe | $(CH_2)_3Cl$ | H | 41 | >98:2 |
| **r** | **a** | OMe | $(CH_2)_5Cl$ | H | 45 | >98:2 |
| **s** | **j** | OMe | Me | Me | 43 | >98:2 |
| **t** | **j** | OMe | $^n$Hex | Me | 42 | 2:1 |
| **u** | **k** | OEt | $^n$Pr | Et | 38 | 2:1 |
| **v** | **1q** | O$^t$Bu | $^n$Dec | $^n$Hex | 92 | >98:2 |
| **w** | **l** | OMe | $^n$Hex | OMe | 74 | >98:2 |
| **x** | **z** | O$^t$Bu | $^n$Hex | $^{iso}$Pent | 74 | >98:2 |
| **y** | **11ao** | | –$OCH_2CH_2$– | Bn | 36 | 2:1 |

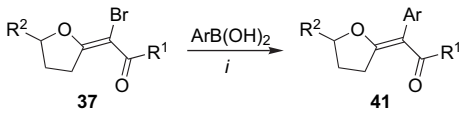
[a] Yields of isolated products.
[b] *E*/*Z* ratio of the exocyclic double bond (by $^{13}C$ NMR).




**Scheme 22**. Bromination of 2-alkylidenetetrahydrofuran **7a**. (i) NBS, $CCl_4$, reflux, 3 h.

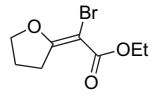
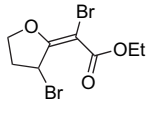
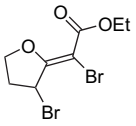
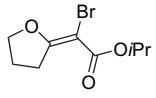
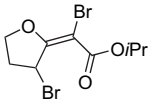
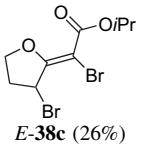
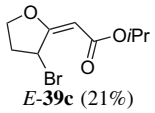
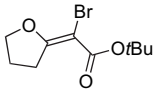
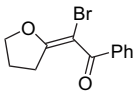
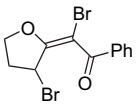
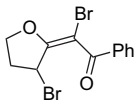
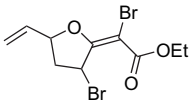
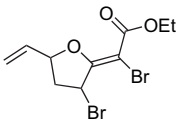
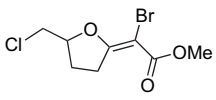
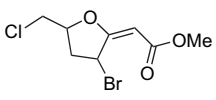
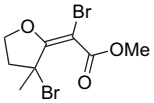
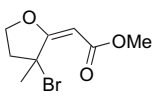
### 3.3. Palladium(0)-catalyzed cross-coupling reactions

**3.3.1. Suzuki reactions.** The Suzuki cross-coupling reaction of 2-alkylidene-1′-bromotetrahydrofurans **37** with aryl boronic acids, catalyzed by $Pd(PPh_3)_4$ (3 mol %), afforded the aryl-substituted 2-alkylidenetetrahydrofurans **41** (Scheme 23, Table 14).[42,43] All Suzuki reactions proceeded in good to very good yields and with excellent *E*-diastereospecifity.



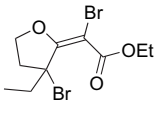
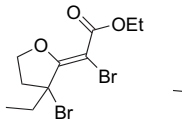
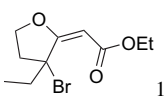
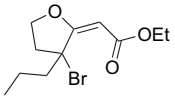
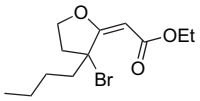
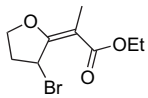
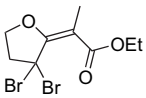
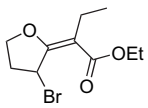
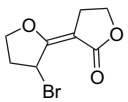
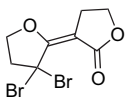

**Scheme 23**. Suzuki reactions of 2-alkylidene-1′-bromotetrahydrofurans **37**. (i) $ArB(OH)_2$ (3 equiv), $Pd(PPh_3)_4$ (3 mol %), $K_3PO_4$ (6.0 equiv), 1,4-dioxane, reflux, 6 h.

**Table 13**. Products and yields

| Educt | Products[a] (%) | | | NBS (equiv) |
|---|---|---|---|---|
| **7b** |  *Z*-**37b** (41%) |  *Z*-**38b** (26%) |  *E*-**38b** (15%) | 1.3 |
| **7b** | *Z*-**38b** (70%) | | *E*-**38b** (23%) | 3.0 |
| **7c** |  *Z*-**37c** (19%) |  *Z*-**38c** (27%) |  *E*-**38c** (26%) | 1.3 |
| **7c** | *Z*-**37c** (65%) | *E*-**38c** (12%) |  *E*-**39c** (21%) | 1.1 |
| **7f** |  *Z*-**37d** (73%) | | | 1.3 |
| **7i** |  *Z*-**37e** (53%) |  *Z*-**38e** (12%) | | 1.3 |
| **7i** |  *Z*-**38e** (63%) | | | 2.3 |
| **12a** |  *Z*-**38f** (50%) |  *E*-**38f** (26%) | | 1.6 |
| **30d** |  *Z*-**37g** (35%) |  *E*-**39g** (48%) | | 1.3 |
| **7j** |  *Z*-**38h** (44%) |  *E*-**39h** (47%) | | 1.5 |

(*continued*)

**Table 13**. (*continued*)

| Educt | Products[a] (%) | | | NBS (equiv) |
|---|---|---|---|---|
| **7k** |  *Z*-**38i** (60%) |  *E*-**38i** (6%) |  *E*-**39i** (31%) | 1.8 |
| **7m** |  *E*-**39j** (87%) | | | 1.3 |
| **7o** |  *E*-**39k** (91%) | | | 1.3 |
| **7al** |  *E*-**39l** (56%) |  *E*-**40l** (12%) | | 1.1 |
| **7am** |  *E*-**39m** (80%) | | | 1.1 |
| **7ao** |  *E*-**39n** (76%) |  *E*-**40n** (22%) | | 1.2 |

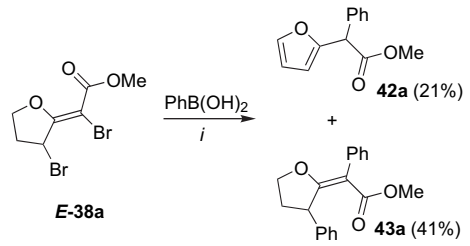
[a] Yields of isolated products.

**Table 14**. Products and yields

| **41** | Substrate | $R^1$ | $R^2$ | Ar | Yield,[a,b] % (**41**) |
|---|---|---|---|---|---|
| **a** | *Z*-**37a** | OMe | H | Ph | 79 |
| **b** | *Z*-**37a** | OMe | H | 4-$MeC_6H_4$ | 91 |
| **c** | *Z*-**37a** | OMe | H | 4-$(MeO)C_6H_4$ | 91 |
| **d** | *Z*-**37a** | OMe | H | 4-$ClC_6H_4$ | 92 |
| **e** | *Z*-**37a** | OMe | H | 2-Thienyl | 62 |
| **f** | *Z*-**37a** | OMe | H | 2-$(MeO)C_6H_4$ | 96 |
| **g** | *Z*-**37a** | OMe | H | 2,5-$(MeO)_2C_6H_3$ | 87 |
| **h** | *Z*-**37b** | OEt | H | 2-$(MeO)C_6H_4$ | 93 |
| **i** | *Z*-**37b** | OEt | H | 2,4-$(MeO)_2C_6H_3$ | 96 |
| **j** | *Z*-**37b** | OEt | H | 2,6-$(MeO)_2C_6H_3$ | 87 |
| **k** | *Z*-**37e** | Ph | H | 2-$(MeO)C_6H_4$ | 77 |
| **l** | *Z*-**37g** | OMe | $CH_2Cl$ | 2-$(MeO)C_6H_4$ | 96 |
| **m** | *Z*-**37d** | O$^t$Bu | H | Ph | 87 |
| **n** | *Z*-**37d** | O$^t$Bu | H | 4-$MeC_6H_4$ | 88 |
| **o** | *Z*-**37d** | O$^t$Bu | H | 4-$(MeO)C_6H_4$ | 77 |
| **p** | *Z*-**37d** | O$^t$Bu | H | 4-$ClC_6H_4$ | 87 |
| **q** | *Z*-**37d** | O$^t$Bu | H | 2-Thienyl | 48 |
| **r** | *Z*-**37o** | OH | H | 4-$(HO)C_6H_4$ | 80[c] |

[a] Yields of isolated products.
[b] *E*/*Z*>98:2 for all products.
[c] Prepared from **40c**; (ii) (1) $BBr_3$, $CH_2Cl_2$, 0→20 °C, (2) MeOH; (iii) KOH, $H_2O$/THF (1:1), reflux.

The Suzuki reaction of 2-alkylidene-1′,3-dibromotetrahydrofurans **38** with aryl boronic acids allowed an efficient synthesis of 2-alkylidene-1′,3-diaryltetrahydrofurans **43** and furans **42** (Scheme 24, Table 15).[43] The formation of products **43** can be explained by a double-Suzuki reaction. The formation of furans **42a**,**e** proceeds by Suzuki reaction of the alkenyl bromide, thermal elimination of hydrogen bromide, and subsequent aromatization. For **42e**, the elimination is more favored than a double-Suzuki reaction, due to steric reasons.



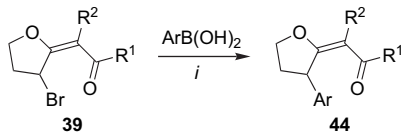

**Scheme 24**. Double-Suzuki reactions of 2-alkylidene-1′,3-dibromotetrahydrofuran *E*-**38a**. (i) $PhB(OH)_2$ (6.0 equiv), $Pd(PPh_3)_4$ (3 mol %), $K_3PO_4$ (6.0 equiv), 1,4-dioxane, reflux, 6 h.

**Table 15**. Products and yields

| Substrate | Product[a] (%) |
|---|---|
| *E*-**38a** | **43b**[b] (92%) |
| *Z*-**38b** | **43c**[b] (66%) |
| *Z*-**38e** | **43d**[b] (62%) |
| *Z*-**38i** | **42e** (60%) |

[a] Yields of isolated products.
[b] *E*/*Z*>98:2.

The Suzuki reaction of 2-alkylidene-3-bromotetrahydrofurans **39** with aryl boronic acids afforded the *E*-configured 2-alkylidene-3-aryltetrahydrofurans **44** in good yields (Scheme 25, Table 16).[43]



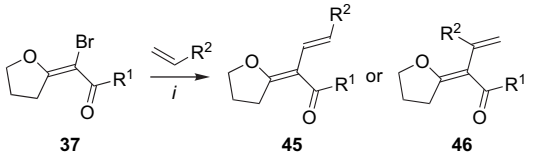

**Scheme 25**. Suzuki reactions of 2-alkylidene-3-bromotetrahydrofurans **39**. (i) $ArB(OH)_2$ (3.0 equiv), $Pd(PPh_3)_4$ (3 mol %), $K_3PO_4$ (6.0 equiv), 1,4-dioxane, reflux, 6 h.

**Table 16**. Products and yields

| **44** | Educt | $R^1$ | $R^2$ | Ar | Yield,[a] % (**44**) |
|---|---|---|---|---|---|
| **a** | *E*-**39l** | OEt | Me | 4-$ClC_6H_4$ | 52 |
| **b** | *E*-**39m** | OEt | Et | 4-$ClC_6H_4$ | 76 |
| **c** | *E*-**39n** | –$OCH_2CH_2$– | | Ph | 55 |

[a] Yields of isolated products, *E*/*Z*>98:2.

**3.3.2. Heck reactions.** Heck reactions of 2-alkylidene-1′-bromotetrahydrofurans **37** with acrylates and styrenes afforded the alkenyl-substituted 2-alkylidenetetrahydrofurans **45** and **46**, respectively (Scheme 26, Table 17).[42,43] The regiochemical outcome of the reactions was different for styrenes and for acrylonitrile and *tert*-butyl acrylate.




**Scheme 26**. Heck reactions of 2-alkylidene-1′-bromotetrahydrofurans **37**. (i) $CH_2{=}CHR^2$, $Pd(PPh_3)_4$ (3 mol %), $NEt_3$, DMF, 100 °C, 25 h.

**Table 17**. Products and yields

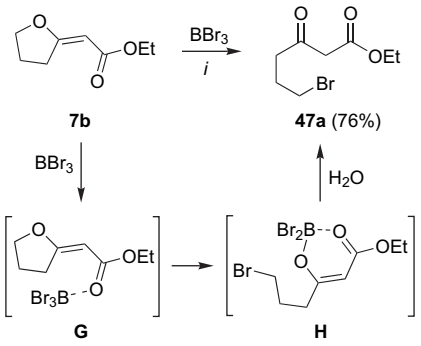
| Product | Substrate | $R^1$ | $R^2$ | Yield[a] (%) |
|---|---|---|---|---|
| **45a** | *Z*-**37a** | OMe | $CO_2{}^tBu$ | 85 |
| **45b** | *Z*-**37a** | OMe | CN | 47 |
| **45c** | *Z*-**37b** | OEt | $CO_2{}^tBu$ | 51 |
| **46a** | *Z*-**37a** | OMe | Ph | 56 |
| **46b** | *Z*-**37a** | OMe | 4-(MeO)$C_6H_4$ | 45 |
| **46c** | *Z*-**37c** | O$^i$Pr | 4-(MeO)$C_6H_4$ | 58 |

[a] Yields of isolated products.

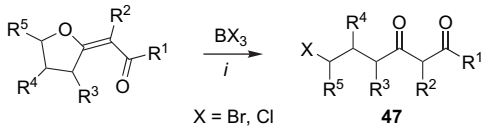
## 3.4. Boron tribromide-mediated ether cleavage

The reaction of 2-alkylidenetetrahydrofuran **7b** with boron tribromide ($BBr_3$) afforded ethyl 6-bromo-3-oxohexanoate (**47a**) in good yield (Scheme 27). The reaction proceeds by activation of **7b** (intermediate **G**), ring cleavage (intermediate **H**) and subsequent protonation of the enolate. The reaction of substituted 2-alkylidenetetrahydrofurans with boron tribromide or boron trichloride afforded a variety of 6-bromo- and 6-chloro-3-oxoalkanoates **47** in good to very good yields and with excellent chemo- and regioselectivity (Scheme 28, Table 18).[45,46] These reactions are of interest also from a methodology viewpoint. Whereas the $BBr_3$-mediated cleavage of methylaryl ethers is well known and widely used,[47] reactions of other ethers are more rare. Known examples include the formation of ω-bromoalkanols

by ring opening of cyclic ethers with $BBr_3$/MeOH,[47c] or the transformation of lactones into ω-halocarboxylic acids.[47d] Functionalized carbonyl compounds, which contain a halide group at a remote position, represent versatile synthetic building blocks.[48] Notably, 6-bromo-3-oxoalkanoates are not directly available by the reaction of dianions with 1,2-dibromoethane, due to reduction of the dielectrophile.[29b]

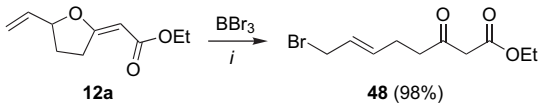



**Scheme 27**. Possible mechanism for the ether cleavage of 2-alkylidenetetrahydrofurans. (i) (1) $BBr_3$ (4.0 equiv), $CH_2Cl_2$, 0→20 °C, 12 h, (2) 20 °C, 6 h, (3) $H_2O$.



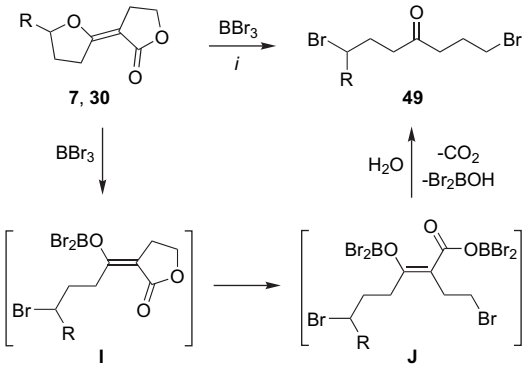

**Scheme 28**. Ether cleavage of 2-alkylidenetetrahydrofurans with boron trihalides. (i) (1) $BX_3$ (4.0 equiv), $CH_2Cl_2$, 0→20 °C, 12 h, (2) 20 °C, 6 h, (3) $H_2O$.

The reaction of $BBr_3$ with 2-alkylidene-5-vinyltetrahydrofuran **12a** gave ethyl 8-bromo-3-oxooct-6-enoate (**48**) by cleavage of the tetrahydrofuran moiety and migration of the double bond (Scheme 29).[46] A direct synthesis of **48** by the reaction of dilithiated ethyl acetoacetate with 1,4-dibromobut-2-ene was not possible.




**Scheme 29**. Ether cleavage of 2-alkylidene-5-vinyltetrahydrofuran **12a**. (i) (1) $BBr_3$ (4.0 equiv), $CH_2Cl_2$, 0→20 °C, 12 h, (2) 20 °C, 6 h, (3) $H_2O$.

The reaction of tetrahydro[2,3′]bifuranyliden-2′-ones **7** and **30** with $BBr_3$ afforded the 1,7-dibromoheptan-4-ones **49** (Scheme 30, Table 19).[45,46] The formation of **49** can be explained by $BBr_3$-mediated ring opening of the cyclic enol (intermediate **I**), cleavage of the lactone, decarboxylation, and final protonation of the enolate **J**. 1,7-Dibromoheptan-4-ones represent useful synthetic building blocks.[49] Notably, unsymmetrical 1,7-dibromoheptan-4-ones are not readily available by other methods.[49f]




**Scheme 30**. Ether cleavage of tetrahydro[2,3′]bifuranyliden-2′-ones **7** and **30**. (i) (1) $BBr_3$ (4.0 equiv), $CH_2Cl_2$, 0→20 °C, 12 h, (2) 20 °C, 6 h, (3) $H_2O$.

**Table 18**. Products and yields

| 47 | Substrate | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | X | Yield,[a] % (**47**) |
|---|---|---|---|---|---|---|---|---|
| **a** | **7b** | OEt | H | H | H | H | Br | 76 |
| **b** | **36c** | OEt | $^n$Oct | H | H | H | Br | 95 |
| **c** | **36d** | OEt | $^n$Dec | H | H | H | Br | 81 |
| **d** | **36q** | OMe | $(CH_2)_3Cl$ | H | H | H | Br | 84 |
| **e** | **36o** | OMe | Bn | H | H | H | Br | 96 |
| **f** | **41a** | OMe | Ph | H | H | H | Cl | 84 |
| **g** | **41b** | OMe | 4-$MeC_6H_4$ | H | H | H | Br | 89 |
| **h** | **41c** | OMe | 4-$(MeO)C_6H_4$ | H | H | H | Br | 72 |
| **i** | **41d** | OMe | 4-$ClC_6H_4$ | H | H | H | Br | 77 |
| **j** | **43a** | OMe | Ph | Ph | H | H | Br | 96 |
| **k** | **7k** | OEt | H | Et | H | H | Br | 83 |
| **l** | **7m** | OEt | H | $^n$Pr | H | H | Br | 96 |
| **m** | **7ad** | OMe | H | $(CH_2)_3Cl$ | H | H | Br | 86 |
| **n** | **30a** | OMe | H | H | H | Me | Br | 80 |
| **o** | **30b** | OMe | H | H | H | Et | Br | 91 |
| **p** | **30c** | OMe | H | H | H | $^n$Bu | Br | 75 |
| **q** | **30d** | OMe | H | H | H | $CH_2Cl$ | Br | 80 |
| **r** | **30m** | OEt | H | H | H | $CH_2Br$ | Br | 93 |
| **s** | **31b** | OMe | H | H | Et | H | Br | 82 |
| **t** | **31o** | OEt | H | H | Ph | H | Br | 83 |
| **u** | **7i** | Ph | H | H | H | H | Br | 98 |
| **v** | **9e** | OEt | –$(CH_2)_9$– | | H | H | Br | 87 |

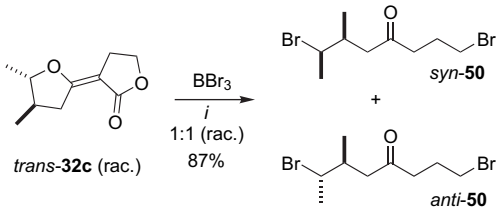
[a] Yields of isolated products.

**Table 19**. Products and yields

| 49 | Substrate | R | 49[a] (%) |
|---|---|---|---|
| **a** | **7ao** | H | 73 |
| **b** | **30ag** | Me | 88 |
| **c** | **30ah** | Et | 68 |
| **d** | **30ak** | $CH_2Cl$ | 85 |

[a] Yields of isolated products.

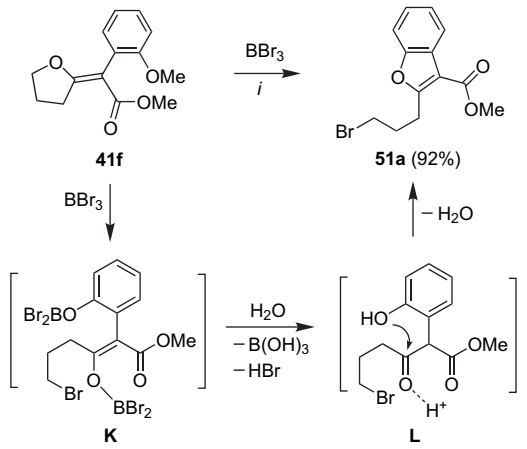
Treatment of *trans*-4,5-dimethyltetrahydro[2,3′]bifuranyliden-2′-one **32c** with $BBr_3$ afforded a 1:1 diastereomeric mixture of *syn*- and *anti*-1,7-dibromo-6-methyloctan-4-one (**50**) (Scheme 31).[46]




**Scheme 31**. Ether cleavage of *trans*-4,5-dimethyltetrahydro[2,3′]bifuranyliden-2′-one (**32c**). (i) (1) $BBr_3$ (4.0 equiv), $CH_2Cl_2$, 0→20 °C, 12 h, (2) 20 °C, 6 h, (3) $H_2O$.

### 3.5. Boron tribromide-mediated ring transformations

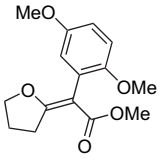
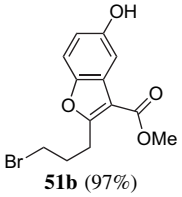
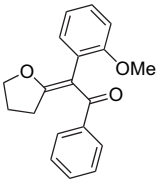
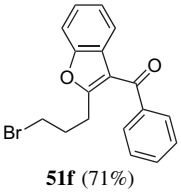
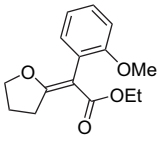
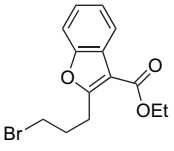
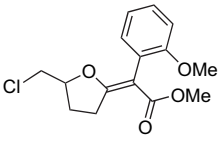
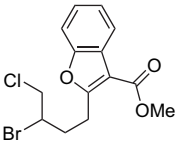
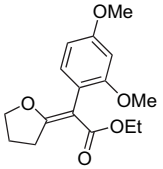
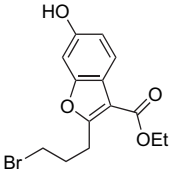
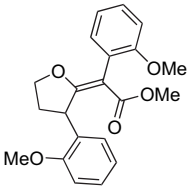
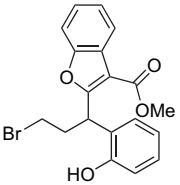
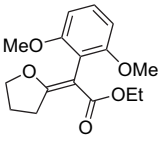
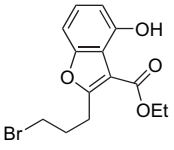
The reaction of 1′-(2-methoxyphenyl)-2-alkylidenetetrahydrofurans **41** (or **43**) with $BBr_3$ afforded the 2-(3-bromopropyl)benzofurans **51** in very good yields and with excellent chemoselectivity (Scheme 32, Table 20).[50] The mechanism presumably involves the formation of **51** by $BBr_3$-mediated ring opening of **41** and cleavage of the arylmethyl ether to give intermediate **K**. Addition of water results in hydrolysis of the boronic ester to give intermediate **L**. The product is formed by acid-mediated cyclization (upon aqueous work-up with water) and aromatization by extrusion of water. Functionalized benzofurans[51,52] represent important synthetic building blocks and occur in a variety of pharmacologically relevant natural products. The related synthetic drug amiodarone, shows antiarrhythmic and antianginal properties and is used in the clinic.[53]



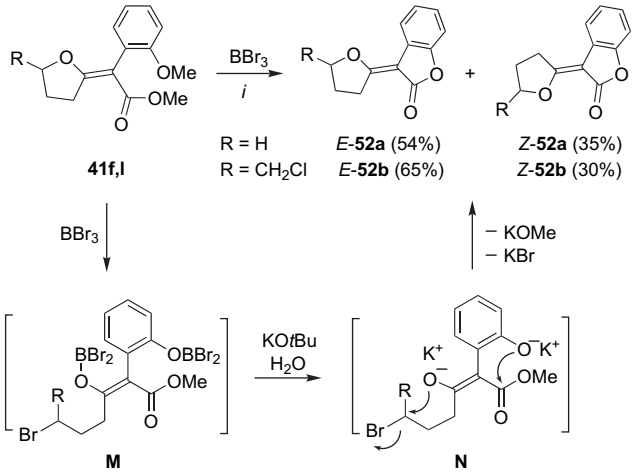

**Scheme 32**. Domino 'ring-cleavage–deprotection–cyclization' reactions of 1′-(2-methoxyphenyl)-2-alkylidenetetrahydrofurans. (i) (1) $BBr_3$ (4.0 equiv), $CH_2Cl_2$, 0→20 °C, 12 h, (2) 20 °C, 6 h, (3) $H_2O$.

Treatment of 1′-(2-methoxyphenyl)-2-alkylidenetetrahydrofurans **41f**,**l** and subsequent addition of an aqueous solution of KO$^t$Bu (1 M) afforded 3-(dihydrofuran-2-ylidene)-3*H*-benzofuran-2-ones **52a**,**b** as separable mixtures of *E*/*Z*-isomers (Scheme 33).[50] The reaction involves the formation of **52** by $BBr_3$-mediated ring cleavage of **41** and cleavage of the arylmethyl ether (intermediate **M**). Addition of an aqueous solution of KO$^t$Bu (KO$^t$Bu+ $H_2O$→KOH+$^t$BuOH) results in hydrolysis of the boronic ester to give intermediate **N** and subsequent base-mediated recyclization of the tetrahydrofuran moiety and lactonization. Product **52** was isolated as a mixture of *E*/*Z*-isomers.

**Table 20**. Products and yields

| Entry | Substrate | Product[a] (%) | Entry | Substrate | Product[a] (%) |
|---|---|---|---|---|---|
| 1 |  **41g** |  **51b** (97%) | 5 |  **41k** |  **51f** (71%) |
| 2 |  **41h** |  **51c** (84%) | 6 |  **41l** |  **51g** (80%) |
| 3 |  **41i** |  **51d** (97%) | 7 |  **43b** |  **51h** (58%) |
| 4 |  **41j** |  **51e** (92%) | | | |

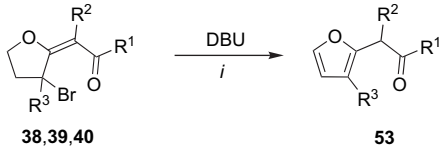
[a] Yields of isolated products.




**Scheme 33**. Lactonization of 1′-(2-methoxyphenyl)-2-alkylidenetetrahydrofurans **41f,l**. (i) (1) (4.0 equiv), $BBr_3$ (4.0 equiv), $CH_2Cl_2$, 0→20 °C, 12 h, (2) 20 °C, 6 h, (3) KO$^t$Bu, $H_2O$ (1 M), 20 °C, 1 h.

## 3.6. Eliminations

**3.6.1. 2-Alkylidene-3-bromotetrahydrofurans.** Treatment of 2-alkylidene-3-bromotetrahydrofurans with DBU resulted in the elimination of hydrogen bromide and subsequent aromatization to give furans **53** (Scheme 34, Table 21).[44] Furans represent important synthetic building blocks and occur in many natural products.[54–56] The DBU-mediated dehydroiodination of 5-iodomethyl 2-alkylidenetetrahydrofurans is known to give 5-methylene-2-alkylidenetetrahydrofurans.[23a]



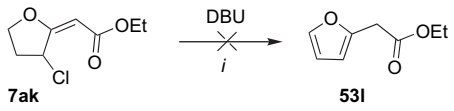

**Scheme 34**. Elimination reactions of 2-alkylidene-3-bromotetrahydrofurans **38–40**. (i) DBU (2.0 equiv), THF, 20 °C, 12 h.

**Table 21**. Products and yields

| **53** | Substrate | $R^1$ | $R^2$ | $R^3$ | Yield,[a] % (**53**) |
|---|---|---|---|---|---|
| **a** | *E*-**39c** | O$^i$Pr | H | H | 72 |
| **b** | *E*-**39h** | OMe | H | Me | 75 |
| **c** | *E*-**39i** | OEt | H | Et | 64 |
| **d** | *E*-**39j** | OEt | H | $^n$Pr | 55 |
| **e** | *E*-**39k** | OEt | H | $^n$Bu | 53 |
| **f** | *E*-**39l** | OEt | Me | H | 52 |
| **g** | *E*-**39m** | Et | Et | H | 66 |
| **h** | *E*-**39n** | –$OCH_2CH_2$– | | H | 63 |
| **i** | *Z*-**38i** | OEt | Br | Et | 61 |
| **j** | *E*-**40l** | OEt | Me | Br | 76 |
| **k** | *E*-**40n** | –$OCH_2CH_2$– | | Br | 83 |

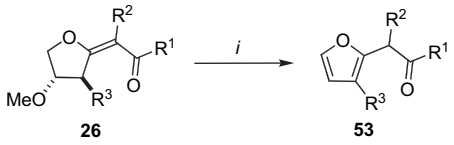
[a] Yields of isolated products.

Treatment of 2-alkylidene-3-chlorotetrahydrofuran **7ak** with DBU gave a complex mixture rather than furan **53l** (Scheme 35).




**Scheme 35**. Treatment of 2-alkylidene-3-chlorotetrahydrofuran **7ak** with DBU. (i) DBU (2.0 equiv), THF, 20 °C, 12 h.

**3.6.2. 2-Alkylidene-4-methoxytetrahydrofurans.** 2-Alkylidene-4-methoxytetrahydrofurans **26** (see Section 2.2.1) could be efficiently transformed into various furans **53** by treatment with trifluoroacetic acid (TFA) (method A) or, alternatively, by simple reflux (method B) (Scheme 36, Table 22).[12,32] The formation of furans **53** proceeds by elimination of methanol and subsequent aromatization by migration of the exocyclic double bond. A related synthesis of pyrroles from 2-alkylidenepyrrolidines is known.[57]



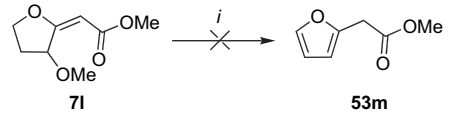

**Scheme 36**. Synthesis of furans **53** from 2-alkylidene-4-methoxytetrahydrofurans **26**. (i) Method A: TFA, $CH_2Cl_2$, 20 °C; method B: $CH_2Cl_2$, reflux.

**Table 22**. Products and yields

| **53** | Substrate | $R^1$ | $R^2$ | $R^3$ | Yield,[a] % (**53**) |
|---|---|---|---|---|---|
| **a** | **26c** | O$^i$Pr | H | H | 61 |
| **b** | **26i** | OMe | H | Me | 84 |
| **c** | **26j** | OEt | H | Et | 79 |
| **d** | **26m** | OEt | H | $^n$Pr | 100 |
| **e** | **26n** | OEt | H | $^n$Bu | 100 |
| **h** | **26u** | –$OCH_2CH_2$– | | H | 98[c] |
| **l** | **26b** | OEt | H | H | 100 |
| **m** | **26a** | OMe | H | H | 80 |
| **n** | **26d** | $O(CH_2)_2OMe$ | H | H | 100 |
| **o** | **26f** | OBn | H | H | 100 |
| **p** | **25g** | Ph | H | H | 70[b] |
| **q** | **26k** | OMe | H | OMe | 98[c] |
| **r** | **26l** | OEt | H | Allyl | 100 |
| **s** | **26o** | OEt | H | $^n$Hex | 100 |
| **t** | **26p** | OEt | H | $^n$Oct | 100 |
| **u** | **26q** | OEt | H | $^n$Non | 100 |
| **v** | **26r** | OEt | H | $^n$Dec | 100 |
| **w** | **26s** | OEt | H | $(CH_2)_6Cl$ | 76 |

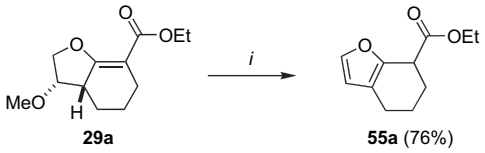
[a] Yields of isolated products.
[b] By treatment of **25g** with DBU.
[c] By reflux of a $CH_2Cl_2$ solution.

Treatment of 2-alkylidene-3-methoxytetrahydrofuran **7l** with TFA resulted in the formation of a complex mixture rather than **53m** (Scheme 37).[12] This result and the regioselective formation of furan **53q** from **26k** showed that the presence of a methoxy group at carbon C-4 is mandatory for the efficient formation of a furan.




**Scheme 37**. Attempted reaction of 2-alkylidene-3-methoxytetrahydrofuran **7l** with TFA. (i) Method A: TFA, $CH_2Cl_2$, 20 °C; method B: $CH_2Cl_2$, reflux.

Treatment of a $CH_2Cl_2$ solution of bicyclic 2-alkylidenetetrahydrofuran **29a** with TFA or, alternatively, simple reflux of a 1,4-dioxane solution afforded tetrahydrobenzofuran **55a** (Scheme 38, Table 23).[12,31,32] A number of related products were also prepared (Table 23).




**Scheme 38**. Synthesis of bicyclic furan **55a**. (i) Method A: TFA, $CH_2Cl_2$, 20 °C; method B: 1,4-dioxane, reflux.

### 3.7. Dehydrogenations

Dehydrogenation and oxidation reactions have been employed for the synthesis of furans and benzofurans.[58] The dehydrogenation of 2-alkylidenetetrahydrofurans provides a convenient approach to (furan-2-yl)acetates, 7-(alkoxycarbonyl)benzofurans, and 7-(alkoxycarbonyl)-2,3-dihydrobenzofurans.[31,32] The reaction of **7** and **9e** with 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ) afforded (furan-2-yl)acetates **53** and **55d**, respectively, by dehydrogenation and subsequent migration of the exocyclic double bond (Scheme 39, Table 24).[12]

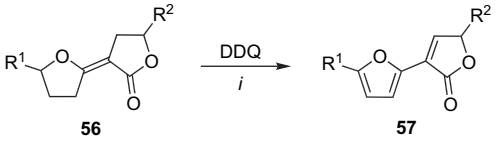

**Scheme 39**. Oxidation of 2-alkylidenetetrahydrofurans **7** and **9**. (i) DDQ, 1,4-dioxane, reflux, 48 h.

**Table 24**. Products and yields

| Product | Substrate | $R^1$ | $R^2$ | $R^3$ | Yield,[a] % |
|---|---|---|---|---|---|
| **53a** | **7c** | $^i$Pr | H | H | 52 |
| **53b** | **7j** | Me | H | Me | 41 |
| **53c** | **7k** | Et | H | Et | 53 |
| **53f** | **7al** | Et | Me | H | 52 |
| **53l** | **7b** | Et | H | H | 59 |
| **53m** | **7a** | Me | H | H | 57 |
| **53x** | **7f** | $^t$Bu | H | H | 55 |
| **53y** | **7z** | $^t$Bu | H | $^{iso}$Pent | 54 |
| **53z** | **7ai** | $^t$Bu | H | $(CH_2)_6Cl$ | 67 |
| **55d** | **9e** | Et | | $-(CH_2)_9-$ | 80 |

[a] Yields of isolated products.

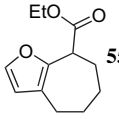
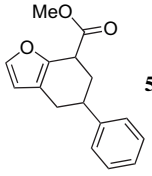
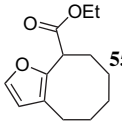
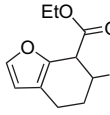
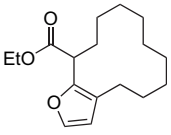
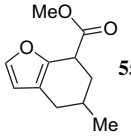
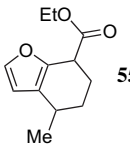
The DDQ-mediated dehydrogenation of tetrahydro[2,3′]-bifuranyliden-2′-ones **56** afforded the 5′*H*-[2,3′]bifuranyl-2′-ones **57** (Scheme 40, Table 25).[31,32] The formation of **57** can be explained by oxidation of both the tetrahydrofuran and the lactone moiety.




**Scheme 40**. Dehydrogenation of tetrahydro[2,3′]bifuranyliden-2′-ones **56**. (i) DDQ (2.2 equiv), 1,4-dioxane, reflux, 48 h.

The DDQ-mediated reaction of 5,6-bicyclic 2-alkylidenetetrahydrofurans **9**, **13**, and **33** afforded separable mixtures of 7-(alkoxycarbonyl)benzofurans **58** and 7-(alkoxycarbonyl)-2,3-dihydrobenzofurans **59** (Scheme 41, Table 26).[31,32] The formation of side products **58b′**,**k′** and **59d′**,**k** can be

**Table 23**. Products and yields

| Entry | Substrate | Product[a] (%) | Entry | Substrate | Product[a] (%) |
|---|---|---|---|---|---|
| 1 | **29c** |  **55b** (100%) | 5 | **29g** |  **55f**[c] (98%) |
| 2 | **29d** |  **55c** (84%) | 6 | **29h** |  **55g**[b] (100%) |
| 3 | **29e** |  **55d** (100%) | 7 | **29i** |  **55h**[c] (97%) |
| 4 | **29f** |  **55e**[b] (100%) | | | |

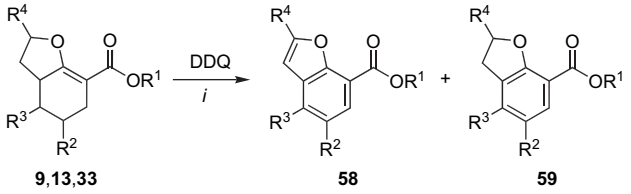
[a] Yields of isolated products.
[b] Isolated as a single diastereomer.
[c] Isolated as an inseparable 1:1 mixture of diastereomers.

**Table 25**. Products and yields

| 56,57 | $R^1$ | $R^2$ | Yield,[a] % (57) |
|---|---|---|---|
| **a** | H | H | 56 |
| **b** | H | Et | 42 |
| **c** | Me | H | 48 |

[a] Yields of isolated products.

explained by DDQ-mediated chlorination of the methyl group of the substrates. The formation of **58c′** can be explained by [4+2] cycloaddition of **58c** with DDQ and subsequent fragmentation. 7-Alkanoylbenzofurans and 7-alkanoyl-2,3-dihydrobenzofurans occur in a number of pharmacologically relevant natural products.[59,60]



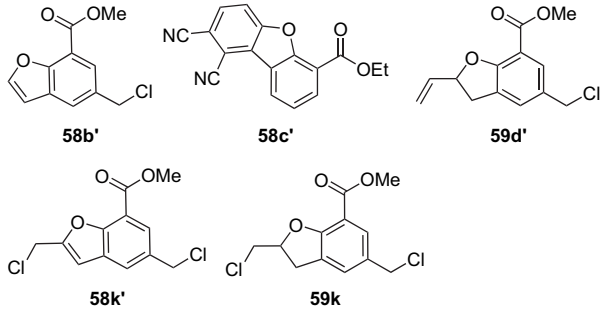

**Scheme 41**. Oxidation of 5,6-bicyclic 2-alkylidenetetrahydrofurans **9**, **13**, and **33**. (i) DDQ, 1,4-dioxane, reflux, 24 h.

The reaction of 5,6-bicyclic 2-alkylidene-4-methoxytetrahydrofurans **29** with DDQ (method A) afforded the 2,3-unsubstituted benzofurans **58** by thermal elimination of methanol

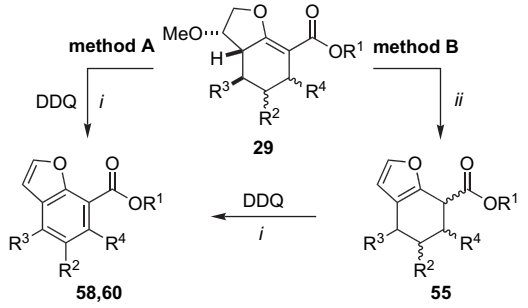
**Table 26**. Products and yields

| 58,59 | Substrate | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield,[a] % | | DDQ (equiv) |
|---|---|---|---|---|---|---|---|---|
| | | | | | | 58 | 59 | |
| **a** | **9b** | Et | H | H | H | 0 | 57 | 3.0 |
| **b** | **9c** | Me | Me | H | H | 30[b] | 0 | 5.0 |
| **c** | **13a** | Et | H | H | Vinyl | 18[c] | 63 | 3.0 |
| **d** | **13e** | Me | Me | H | Vinyl | — | 36[d] | 3.0 |
| **e** | **13g** | Me | Ph | H | Vinyl | 18 | 43 | 3.0 |
| **f** | **13i** | Et | H | Me | Vinyl | 22 | 50 | 3.0 |
| **g** | **33a** | Et | H | H | Me | 60 | 0 | 5.0 |
| **h** | **33b** | Et | H | H | $CH_2Cl$ | 30 | 52 | 5.0 |
| **i** | **33c** | Et | H | H | $CH_2Br$ | 18 | 42 | 3.0 |
| **j** | **33d** | Me | Me | H | Me | 65 | 0 | 5.0 |
| **k** | **33f** | Me | Me | H | $CH_2Cl$ | 20[e] | 20[f] | 5.0 |
| **l** | **33g** | Me | Ph | H | Me | 63 | 0 | 5.0 |
| **m** | **33h** | Me | Ph | H | $CH_2Cl$ | 15 | 80 | 3.0 |
| **n** | **33i** | Me | Ph | H | $CH_2Br$ | 31 | 40 | 5.0 |
| **o** | **33j** | Et | H | Me | $CH_2Cl$ | 20 | 38 | 3.0 |

[a] Yields of isolated products.
[b] Compound **58b′** (26%) was isolated as a side product.
[c] Compound **58c′** (4%) was isolated as a side product.
[d] Compound **59d′** (18%) was isolated as a side product.
[e] Compound **58k′** (10%) was isolated as a side product.
[f] The structure of **59k** is given below.




and subsequent dehydrogenation (Scheme 42, Table 27).[31,32] The transformation of **29** into **58** could be successfully carried out also in two steps (method B): heating of a 1,4-dioxane solution of **29** (in the absence of DDQ) afforded the 4,5,6,7-tetrahydrobenzofurans **55**, which were subsequently transformed into benzofurans **58** (or **60**) by treatment with DDQ.

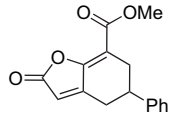



**Scheme 42**. Oxidation of 5,6-bicyclic 2-alkylidene-4-methoxytetrahydrofurans **29**. (i) DDQ, 1,4-dioxane, reflux, 24 h; (ii) 1,4-dioxane, reflux, 6 h.

**Table 27**. Products and yields

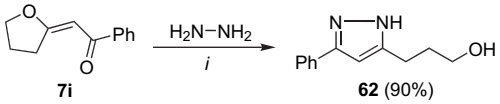
| Product | Substrate | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield,[a] % (58,60) | Method | DDQ (equiv) |
|---|---|---|---|---|---|---|---|---|
| **58b** | **29i** | Me | Me | H | H | 53 | A | 5.0 |
| **58p** | **29g** | Me | Ph | H | H | 46[b] | A | 4.0 |
| | | | | | | 66[c] | B | 3.0 |
| **58q** | **29f** | Et | H | Me | H | 62 | A | 5.0 |
| **58r** | **29a** | Et | H | H | H | 53 | A | 5.0 |
| | | | | | | 53 | B | 4.0 |
| **60** | **29h** | Et | H | H | Me | 75 | B | 3.0 |

[a] Yields of isolated products.
[b] Compound **61** (30%) was isolated as a side product.
[c] Compound **61** (7%) was isolated as a side product.



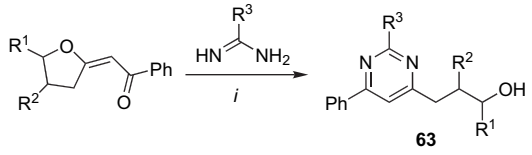

## 3.8. Ring transformations with dinucleophiles

Detty reported the synthesis of pyrazole **62** by reaction of 2-alkylidenetetrahydrofuran **7i** with hydrazine (Scheme 43).[14e] The ring transformation proceeds by nucleophilic attack of hydrazine onto **7i**, cyclization, and cleavage of the tetrahydrofuran moiety.




**Scheme 43**. Synthesis of pyrazole **62**. (i) EtOH, 50 °C, 0.5 h.

Functionalized 6-phenyl-4-(3′-hydroxypropyl)pyrimidines **63** were prepared by the reaction of 2-alkylidenetetrahydrofurans with amidines or *N*,*N*-dimethylguanidine (Scheme 44, Table 28).[61] The products contain a remote alcohol functionality and are not readily available by other methods.[62,63]



**Scheme 44**. Ring transformation reactions of 2-alkylidenetetrahydrofurans. (i) $NEt_3$, EtOH, reflux, 12 h.

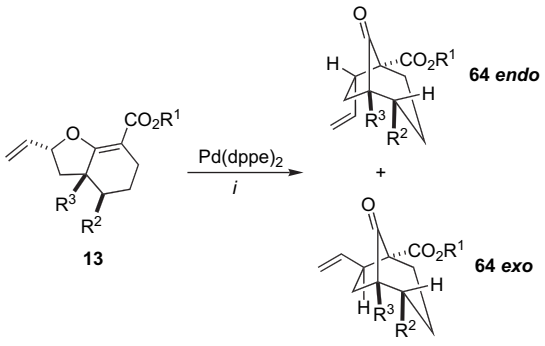
**Table 28**. Products and yields

| 63 | Substrate | $R^1$ | $R^2$ | $R^3$ | Yield,[a] % (**63**) |
|---|---|---|---|---|---|
| **a** | **7i** | H | H | Ph | 60 |
| **b** | **7i** | H | H | Me | 41 |
| **c** | **7i** | H | H | $NMe_2$ | 56 |
| **d** | **12e** | Vinyl | H | Ph | 76 |
| **e** | **12e** | Vinyl | H | Me | 51 |
| **f** | **12e** | Vinyl | H | $NMe_2$ | 51 |
| **g** | **30aa** | Me | H | Ph | 45 |
| **h** | **30aa** | Me | H | Me | 41 |
| **i** | **30ab** | Et | H | Ph | 55 |
| **j** | **30ad** | $CH_2Cl$ | H | Ph | 85 |
| **k** | **30ae** | $CH_2Br$ | H | Ph | 79 |
| **l** | **31aa** | H | Me | Ph | 50 |
| **m** | **31aa** | H | Me | Me | 47 |
| **n** | **31ab** | H | Et | Ph | 57 |
| **o** | **31ab** | H | Et | Me | 42 |

[a] Yields of isolated products.

## 3.9. Palladium(0)-catalyzed rearrangements

Trost and Runge were the first to report the palladium(0)-catalyzed 1,3-oxygen-to-carbon alkyl shift of 2-alkylidene-5-vinyltetrahydrofurans to give functionalized cyclopentanones.[64] These reactions proceed by ring opening to give an enolate and a π-allylpalladium complex and subsequent recyclization by nucleophilic attack of the carbon atom of the enolate onto the π-allylpalladium complex. The palladium(0)-catalyzed rearrangement of bicyclic 2-alkylidene-5-vinyltetrahydrofurans **13** afforded the functionalized bicyclo[3.2.1]octan-8-ones **64** (Scheme 45, Table 29).[5,10] The products were isolated as separable mixtures of diastereomers (*endo*/*exo*=1.2:1–1.1:1), due to a π–σ–π-isomerization of the π-allylpalladium complex. The reaction proceeded with very good stereospecificity when sulfone, rather than ester, derivatives were employed.



**Scheme 45**. Palladium(0)-catalyzed rearrangement of bicyclic 2-alkylidene-5-vinyltetrahydrofurans **13**. (i) $Pd(dppe)_2$ (5 mol %), DMSO, 60 °C, 6–24 h.

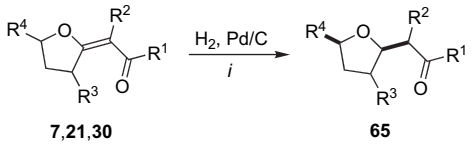
**Table 29**. Products and yields

| 64 | Substrate | $R^1$ | $R^2$ | $R^3$ | Yield,[a] % (**64**) |
|---|---|---|---|---|---|
| **a** | **13a** | Et | H | H | 95 |
| **b** | **13b** | $^i$Pr | H | H | 92 |
| **c** | **13c** | $(CH_2)_2OMe$ | H | H | 91 |
| **d** | **13i** | Et | Me | H | 93 |
| **e** | **13l** | Et | H | $CO_2Et$ | 95 |

[a] Yields of isolated products; for all reactions: *endo*/*exo*=1.2:1–1.1:1.

## 3.10. Hydrogenations

The hydrogenation of 2-alkylidenetetrahydrofurans has been applied to the synthesis of natural products, such as methyl nonactate and nonactin.[14k–m,18] The Pd/C-catalyzed hydrogenation of 2-alkylidenetetrahydrofurans **7**, **21**, and **30** afforded the (tetrahydrofuran-2-yl)acetates **65** (Scheme 46, Table 30).[65,66] The diastereoselectivity of the hydrogenation strongly depends on the substitution pattern of the starting material.



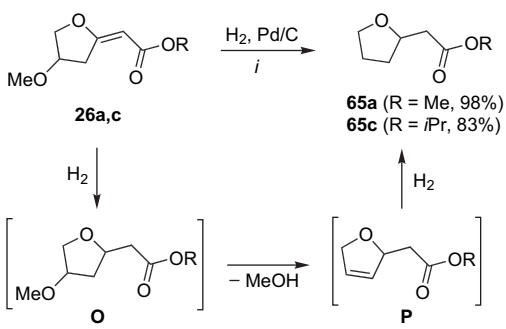
**Scheme 46**. Hydrogenation of 2-alkylidenetetrahydrofurans **7**, **21**, and **30**. (i) $H_2$ Pd/C (0.5 equiv), MeOH or EtOH, 20 °C, 48 h.

**Table 30**. Products and yields

| 65 | Substrate | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Yield,[a] % (**65**) | *syn*/*anti*[b] |
|---|---|---|---|---|---|---|---|
| **a** | **7a** | OMe | H | H | H | 97 | — |
| **b** | **7b** | OEt | H | H | H | 100 | — |
| **c** | **7c** | O$^i$Pr | H | H | H | 100 | — |
| **d** | **7f** | O$^t$Bu | H | H | H | 83 | — |
| **e** | **7j** | OMe | H | Me | H | 89 | 6:5[c] |
| **f** | **7k** | OEt | H | Et | H | 95 | 6:5[c] |
| **g** | **7ao** | $-OCH_2CH_2-$ | | H | H | 86 | 3:2[c] |
| **h** | **30h** | OEt | H | H | Et | 70 | 3:1 |
| **i** | **30d** | OMe | H | H | $CH_2Cl$ | 100 | >10:1 |
| **j** | **21a** | OMe | H | H | $CH_2OH$ | 67 | 7:1 |
| **k** | **21f** | O$^t$Bu | H | H | $CH_2OH$ | 87 | 10:1 |
| **l** | **21h** | $NEt_2$ | H | H | $CH_2OH$ | 86 | 5:1 |

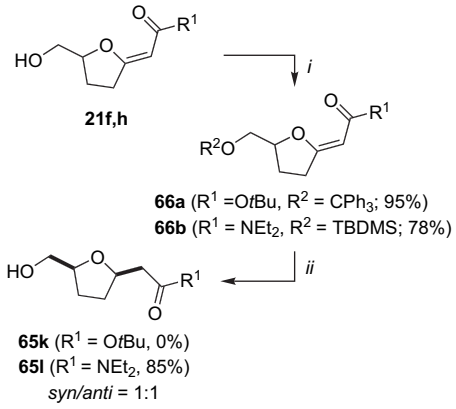
[a] Yields of isolated products.
[b] Diastereoselectivity (by $^1$H NMR).
[c] Diastereomeric ratio, assignment arbitrary.

The hydrogenation of 2-alkylidene-4-methoxytetrahydrofurans **26a**,**c** afforded the (tetrahydrofuran-2-yl)acetates **65a**,**c** by elimination of methanol and subsequent hydrogenation of the double bond thus formed (Scheme 47).[65]



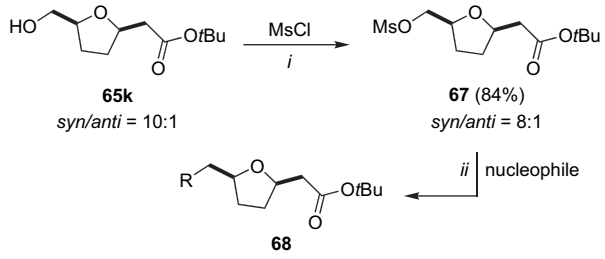
**Scheme 47**. Hydrogenation of 2-alkylidene-4-methoxytetrahydrofurans **26a**,**c**. (i) $H_2$ Pd/C (0.5 equiv), MeOH 20 °C, 48 h.

The influence of hydroxyl protective groups on the diastereoselectivity of hydrogenation was studied: 5-hydroxymethyl-2-alkylidenetetrahydrofurans **21f**,**h** were protected with trityl and TBDMS groups to give **66a**,**b** (Scheme 48).[66] The hydrogenation of trityl-substituted 2-alkylidenetetrahydrofuran **66a** failed. (5-Hydroxymethyltetrahydrofuran-2-yl)acetamide **65l** was formed as an inseparable 1:1 mixture of diastereomers by hydrogenation of **66b** and subsequent hydrolytic cleavage of the silyl ether. These experiments show that the presence of a free hydroxyl group is mandatory to obtain a good stereoselectivity.




**Scheme 48**. Synthesis of tetrahydrofurans **65k**,**l**. (i) (1) $NEt_3$, $Ph_3CCl$ (or TBDMSCl), $CH_2Cl_2$, 0→20 °C, (2) 20 °C, 24 h; (ii) $H_2$, Pd/C (0.5 equiv), EtOH, 20 °C, 48 h.

Tetrahydrofuran **65k** was transformed into mesylate **67**. The reaction of **67** with a variety of nucleophiles afforded the functionalized tetrahydrofurans **68** in 33–93% yields and with moderate to good diastereoselectivities (Scheme 49, Table 31).[66]

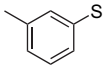
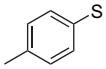



**Scheme 49**. Nucleophilic substitution reactions of methanesulfonyloxy-functionalized (tetrahydrofuran-2-yl)acetate **67**. (i) (1) MsCl, $NEt_3$, $CH_2Cl_2$, 0→20 °C, (2) 20 °C, 18 h; (ii) nucleophiles and conditions (see Table 31).

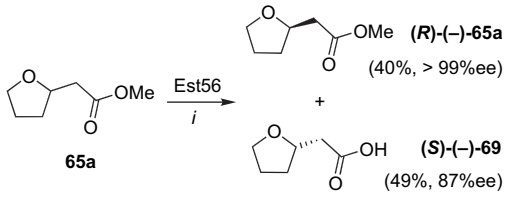
### 3.11. Enzymatic kinetic resolutions

The kinetic resolution of esters by enzymatic hydrolysis provides a valuable synthetic tool.[67,68] This concept was applied to the resolution of racemic (tetrahydrofuran-2-yl)acetates, which are readily available by the hydrogenation of 2-alkylidenetetrahydrofurans (see Section 3.10). In one example, the enzymatic kinetic resolution of **65a**, using the recombinant esterase Est56, gave (*R*)-(−)-**65a** (40%, >99% ee) and acid (*S*)-(−)-**69** (49%, 87% ee) (Scheme 50).[65]

**Table 31**. Products and yields

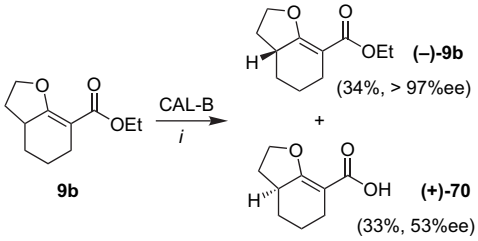
| 68 | R | Yield,[a] % (68) | *syn*/*anti*[b] | Nucleophile | Conditions[d] |
|---|---|---|---|---|---|
| **a** | Br | 51 | 8:1 | LiBr | (1) |
| **b** | I | 48 | 8:1 | NaI | (1) |
| **c** | CN | 58 | 8:1 | NaCN | (2) |
| **d** | $N_3$ | 72 | 8:1 | $NaN_3$ | (2) |
| **e** | $NH_2$ | 93[c] | 7:1 | $H_2$, Pd/C | (3) |
| **f** | $NMe_2$ | 57 | 4:1 | $Me_2NH$ | (2) |
| **g** |  | 63 | 8:1 | pyrrolidine | (4) |
| **h** |  | 65 | 7:1 | morpholine | (4) |
| **i** | S($^n$Pr) | 45 | 4:3 | ($^n$Pr)SH | (5) |
| **j** | S($^t$Bu) | 93 | 1:1 | ($^t$Bu)SH | (5) |
| **k** | $S(CH_2)_2CO_2(^nBu)$ | 57 | 4:1 | $(^nBu)O_2C(CH_2)_2SH$ | (5) |
| **l** | $SCH_2CO_2Me$ | 68 | 5:1 | $MeO_2CCH_2SH$ | (5) |
| **m** | $SCH_2Ph$ | 53 | 5:1 | $PhCH_2SH$ | (5) |
| **n** | SPh | 74 | 6:1 | PhSH | (5) |
| **o** |  | 77 | 4:1 | *o*-TolSH | (5) |
| **p** |  | 76 | 5:1 | *m*-TolSH | (5) |
| **q** |  | 77 | 11:2 | *p*-TolSH | (5) |
| **r** |  | 33 | 3:2 | 2-hydroxypyridine | (5) |

[a] Yields of isolated products.
[b] Diastereoselectivity (by $^1H$ NMR).
[c] Compound **68e** prepared by hydrogenation of **68d**.
[d] (1) acetone, reflux, 12 h; (2) DMF, 60–80 °C, 24–48 h; (3) EtOH, 20 °C, 48 h; (4) 1,4-Dioxane, 60 °C, 48 h; (5) NaO$^t$Bu, THF, reflux.



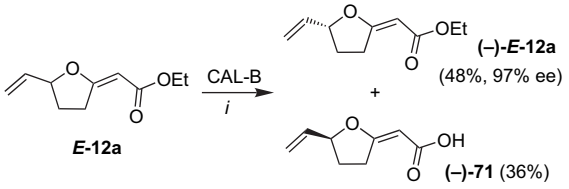

**Scheme 50**. Enzymatic kinetic resolution of tetrahydrofuran **65a**. (i) Recombinant esterase Est56, phosphate buffer (50 mM, pH 7.5), 37 °C, 54 h.

Enzymatic kinetic resolution also provides a convenient approach to enantiomerically pure 2-alkylidenetetrahydrofurans.[40] As an example, the CAL-B (*Candida antarctica* lipase B)[69] catalyzed enantioselective hydrolysis of bicyclic 2-alkylidenetetrahydrofuran **9b** afforded (−)-**9b** (34%, >97% ee) and acid (+)-**70** (33%, 53% ee) (Scheme 51).[40]




**Scheme 51**. Enzymatic kinetic resolution of 5,6-bicyclic 2-alkylidenetetrahydrofuran **9b**. (i) CAL-B, phosphate buffer (50 mM, pH 7.5), toluene (10% v/v), 37 °C, 96 h, assignment of the absolute configuration is arbitrary.

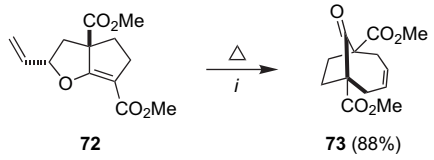
The CAL-B-catalyzed kinetic resolution of *E*-**12a** afforded (−)-*E*-**12a** (48%, 97% ee) and acid (−)-**71** (36%) (Scheme 52).[40] The enantiomeric excess of the acid (−)-**71** could not be determined by GC measurements, due to reaction of the vinyl functionality with diazomethane.[70]




**Scheme 52**. Enzymatic kinetic resolution of 2-alkylidene-5-vinyltetrahydrofuran *E*-**12a**; (i) CAL-B, phosphate buffer (50 mM, pH 7.5), toluene (10% v/v), 37 °C, 200 h, assignment of the absolute configuration is arbitrary.

### 3.12. Thermal Claisen rearrangements

Rodriguez et al. reported an interesting thermal Claisen rearrangement of bicyclic 2-alkylidenetetrahydrofurans into bridged bicyclo[4.2.1] ring systems (Scheme 53).[71] Heating of a xylene solution of **72** (which is readily available by $K_2CO_3$-mediated cyclization of dimethyl acetone-1,3-dicarboxylate with 1,4-dibromobut-2-ene)[72] afforded the product **73** in very good yield.




**Scheme 53**. Thermal Claisen rearrangement. (i) Xylene, reflux, 48 h.

## 4. Summary

The cyclization of 1,3-dicarbonyl dianions ('free dianions') and 1,3-bis-silyl enol ethers ('masked dianions') with various 1,2-dielectrophiles provides an efficient strategy for the synthesis of 2-alkylidenetetrahydrofurans, which represent useful synthetic building blocks. 2-Alkylidenetetrahydrofurans can be functionalized by lithiation and subsequent alkylation, NBS-mediated bromination and subsequent palladium-catalyzed cross-coupling, $BBr_3$-mediated ring cleavage, elimination, dehydrogenation, palladium-catalyzed rearrangement, hydrogenation, Claisen rearrangements, and enzymatic kinetic resolution.

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**Biographical sketch**

**Esen Bellur** was born in Adana, Turkey in 1980. In 2002, she completed her undergraduate studies, ranked as the best student in chemistry, at Middle East Technical University (Ankara, Turkey), where she carried out her undergraduate research on the synthesis of symmetric trimethine and pentamethine carboxyl-functionalized cyanine dyes under supervision of Professor E. U. Akkaya. During her undergraduate studies, she worked in the pharmaceutical R&D laboratories of Roche AG Pharmaceuticals (Basel, Switzerland) on the synthesis of biologically active organic compounds (antidepressants) (2001), and in the R&D laboratories of Bayer AG (Leverkusen, Germany) on the synthesis of organic and organometallic compounds for data storage tools (2002). Starting from 2002, she carried out her studies directed towards Ph.D. under the supervision of Professor Dr. Peter Langer at the Ernst-Moritz-Arndt University of Greifswald, Germany. During her studies, she developed various syntheses and reactions of 2-alkylidenetetrahydrofurans and 2-alkylidenepyrrolidines based on one-pot cyclizations of free and masked dianions. Her research efforts are included in this review. After completion of her Ph.D. studies in 2006, she moved to Turkey and started to work as a researcher responsible for the development of novel polyurethane syntheses. She is currently a team leader of the pharmaceutical research division at Sandoz-Syntek in Istanbul, Turkey.

**Holger Feist** was born in the former German Democratic Republic (East Germany) in 1959. He received his Diploma degree in chemistry from the University of Rostock (Germany) under the guidance of Professor Helmut Zinner in 1985. After his studies, he moved for six months to the Institute of Organic Chemistry of the Academy of Science of East Germany in Berlin. He returned to the University of Rostock and obtained his Dr. rer. nat. in 1990 under the supervision of Professor Klaus Peseke with a thesis on the synthesis and application of monosaccharides containing electrophilic functionalities. From September 1991 until February 1992 he joined the laboratory of Professor Peter Köll (Oldenburg, Germany) as a post-doctoral fellow in the field of carbohydrate chemistry. In 1992, Dr. Feist took a permanent position at the University of Rostock and worked on the synthesis of various types of unusual monosaccharides under the supervision of Professor Peseke. In 2005 he joined the group of Professor Peter Langer as a senior research associate.

**Peter Langer** was born in Hannover (Germany) in 1969. He studied chemistry at the University of Hannover and at the Massachusetts Institute of Technology (MIT) and received his Diploma under the guidance of Prof. Dietmar Seyferth in March 1994. In February 1997 he obtained his Dr. rer. nat. for a synthetic work on Cinchona alkaloids under the supervision of Professor H. Martin R. Hoffmann at the University of Hannover (Germany). During a postdoctoral period with Professor Steven V. Ley, FRS (Cambridge, UK) he worked on the synthesis of oligosaccharides. In 1998 he moved to the University of Göttingen where he started his independent research (related to cyclization reactions of dianions) associated to Professor Armin de Meijere. He completed his habilitation in July 2001 and was appointed Privatdozent. In April 2002 he took a permanent position as a full professor (C4) at the University of Greifswald. In December 2004 Peter Langer moved to a new position as a full professor (C4) at the University of Rostock, which is located in the North-East of Germany at the Baltic Sea. Since July 2005 he is also associated to the Leibniz-Institute of Catalysis e. V. at the University of Rostock. Professor Langer is coauthor of currently ca. 215 research papers. His research is focussed on the development of new synthetic methods and their application to the synthesis of biologically relevant ring systems and natural products. This includes one-pot cyclizations, domino reactions, catalysis, azide and isothiocyanate chemistry, arene and heterocyclic chemistry, carbohydrate chemistry, medicinal chemistry, natural products, and new materials. Awards and scholarships: Studienstiftung des deutschen Volkes (1992–94), Fonds der Chemischen Industrie (1995–96), Feodor-Lynen scholarship (1997–98), Liebig scholarship (1999–2001), Heisenberg scholarship (2001).