# 3-Alkoxy-2,5-dihydrofurans by Gold-Catalyzed Allenyl Cyclizations and Their Transformation into 1,4-Dicarbonyl Compounds, Cyclopentenones, and Butenolides

Malte Brasholz, Branislav Dugovič, Hans-Ulrich Reissig*

Institut für Chemie und Biochemie, Freie Universität Berlin, Takustr. 3, 14195 Berlin, Germany
Fax +49(30)83855367; E-mail: hans.reissig@chemie.fu-berlin.de

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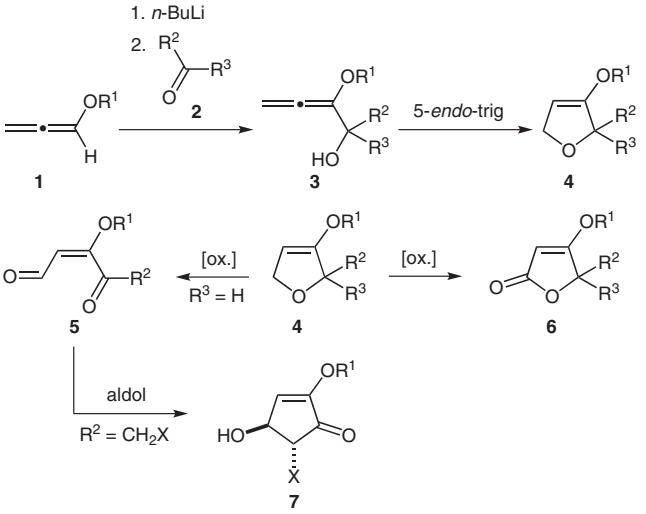
Dedicated to Prof. Grzegorz Mlostoń (Łódź) on the occasion of his 60th birthday

**Abstract:** The addition of lithiated alkoxyallenes to carbonyl compounds furnishes allenyl alcohols, which undergo a highly efficient and chemoselective 5-*endo*-trig cyclization to 3-alkoxy-2,5-dihydrofurans catalyzed by gold(I) chloride. The dihydrofurans produced can be either oxidized to β-alkoxy butenolides by a manganese(III) acetate catalyzed radical oxidation with *tert*-butyl hydroperoxide, or transformed into α,β-unsaturated γ-keto aldehydes by an oxidative ring cleavage using DDQ in the presence of water. Treatment of the γ-keto aldehydes with sodium methoxide in methanol promotes a diastereoselective intramolecular aldol addition furnishing alkoxy-substituted cyclopentenone derivatives in good yield.

**Key words:** allenes, dihydrofurans, cyclopentenones, gold catalysis, allylic oxidation

The synthesis of heterocycles with lithiated alkoxyallenes and varied electrophilic components opens access to a great diversity of small- and medium-sized ring systems.[1] In the past, we and others have developed efficient two- or multi-component coupling protocols, leading to furan,[2] pyrrole,[3] or 1,2-oxazine derivatives,[4] as well as to highly functionalized pyridines,[5] imidazoles,[6] and oxazoles.[7] The diverse classes of alkoxyallene-based heterocycles are often versatile synthetic intermediates and have found numerous applications as key building blocks in the synthesis of natural products, small molecule libraries, and components for supramolecular chemistry. As we keep exploring the synthetic potential of lithiated alkoxyallenes, our synthetic procedures continue to evolve, and one example is the [3+2] cyclization of alkoxyallenes **1** with carbonyl compounds **2** leading to 3-alkoxy-2,5-dihydrofurans **4** (Scheme 1). This method for the preparation of 2,5-dihydrofurans is not new, since the 5-*endo*-trig cyclization of the key intermediates, alkoxyallenyl alcohols **3**, has first been described by Brandsma and Arens in 1969.[8] However, the investigation of different reagent systems suitable to promote this transformation has been ongoing, and we have just recently found a general, chemoselective, and widely applicable set of conditions for this important reaction employing a gold(I) catalyst.[9]




**Scheme 1** Preparation and oxidation reactions of alkoxyallene-derived 3-alkoxy-2,5-dihydrofurans **4** and their subsequent transformations into γ-keto aldehydes **5**, aldol products **7**, and butenolides **6**

The [3+2] cyclization approach to dihydrofurans **4** allows for the introduction of various substituents $R^2$ and $R^3$ in the 2-position of the heterocyclic product by choice of the aldehyde or ketone **2**, and therefore it is a fairly flexible and rapid method to obtain products with this particular substitution pattern, which complements other established methods[10] like the Birch reduction of furans,[11] allylic substitutions of 2,3-dihydrofurans,[12] the conversion of furanoses by elimination,[13] ring-closing metathesis of diallylalcohols,[14] or the dehydration of *cis*-1,4-dihydroxyalkenes.[15]

The value of 3-alkoxy-2,5-dihydrofurans as synthetic intermediates is also based on their potential to undergo oxidative transformations. As they formally are progenitors of furans, the same type of oxidation reactions could potentially occur,[16] for example, the oxidative ring opening of furans to dicarbonyl compounds. This is a well-known process that can be induced by many oxidants including nitric acid,[17] bromine,[18] hydroperoxides with transition metal catalysts,[19] chromium(VI) reagents,[20] *N*-bromosuccinimide,[21] and *meta*-chloroperbenzoic acid.[22] Other important classes of compounds that may be obtained from furans by oxidation are butenolides[23] and tetronic acids,[24] that is, by oxidation of 2-trimethylsilylfurans or the corresponding 2-boryl derivatives.[25]

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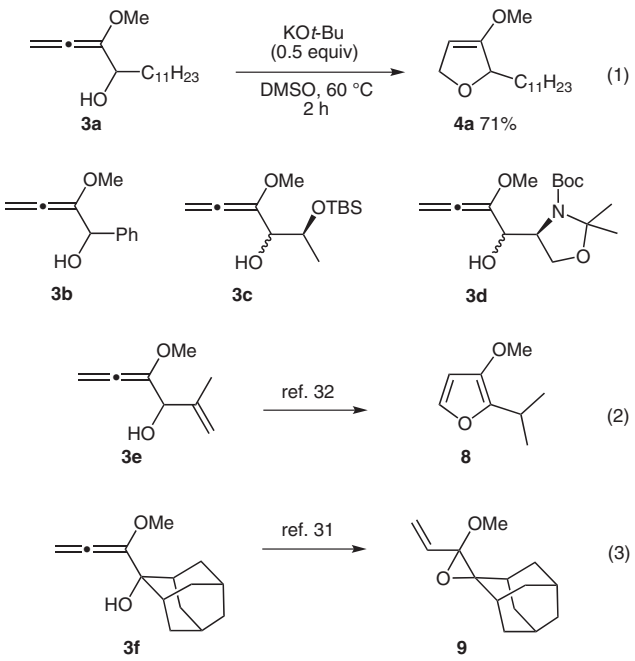
We have been investigating the oxidation chemistry of 3-alkoxy-2,5-dihydrofurans **4**, and were able to transfer some of the oxidation modes of furans onto our substrates. As shown in Scheme 1, substrates **4** could be oxidized to α,β-unsaturated γ-keto aldehydes **5**,[26] or alternatively, to β-alkoxy butenolide derivatives **6**[9] by choice of the reaction conditions. In this account, we describe the full details and improved protocols for the preparation of dihydrofurans **4** and their selective oxidation reactions leading to product classes **5** and **6**. In addition, we report the intramolecular aldol reaction of γ-keto aldehydes **5** to alkoxy-substituted *trans*-cyclopentenones **7** that are useful precursors for further transformations.[26d]

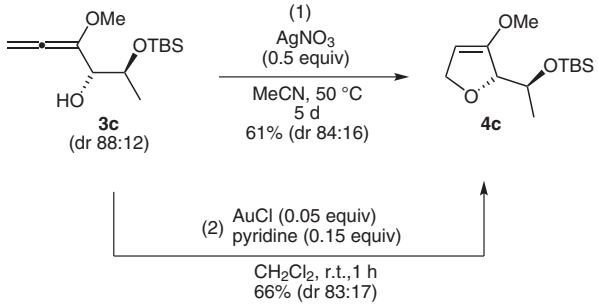
## Synthesis of 3-Alkoxy-2,5-dihydrofurans from Lithiated Alkoxyallenes and Carbonyl Compounds

The cycloisomerization of allenyl alcohols to 2,5-dihydrofurans is a well-known type of reaction, and over the past decades, a number of different reagents were found to promote these transformations, including Brønsted acids,[27] transition metals like silver(I)[28] and gold salts,[29] and other electrophilic species.[29b,30] The choice of reagent is considerably limited for alkoxy-substituted allenyl alcohols **3**, due to their acid sensitive enol ether moiety. Brandsma and co-workers have described the first 5-*endo*-trig cyclizations of these substrates using a substoichiometric amount of potassium *tert*-butoxide (0.1 to 0.5 equiv) in DMSO at 50–60 °C.[8] These basic reaction conditions often provide good yields of dihydrofurans **4** in the range of 40–80%. In a subsequent report, it has been suggested by Magnus et al. that the reaction proceeds via a radical mechanism.[31] However, the method is limited to fairly simple substrates such as allenyl alcohol **3a**, which was converted into dihydrofuran **4a** as shown in Scheme 2 (transformation 1). Aryl-substituted allenyl alcohols like **3b** as well as substrates bearing sensitive protecting groups, for example, compounds **3c** and **3d**, tend to undergo decomposition under the reaction conditions. Moreover, base-promoted isomerization processes may occur during the reaction, as exemplified by the cyclization of allenyl alcohol **3e** to furan derivative **8** (Scheme 2, transformation 2),[32] and sterically demanding substrates such as adamantanone-derived adduct **3f** may react to vinyl epoxide products like **9** (Scheme 2, transformation 3).[31]

As part of our ongoing interest in alkoxyallene-derived 2,5-dihydrofurans **4** and 2,5-dihydropyrroles as useful intermediates in natural product synthesis,[1] we kept searching for more general reaction conditions for cyclization of the allenic precursors. As we have previously reported, many functionalized alkoxyallenyl alcohols **3** and alkoxyallenyl amines undergo cyclization with silver(I) salts in acetone or acetonitrile,[3] a protocol which is complementary to Brandsma's method. Usually, a substoichiometric amount of silver(I) (0.1 to 0.3 equiv) is required, and heating may be necessary to achieve full conversion. This method allows for the cyclization of some substrates that are incompatible with KO*t*-Bu in DMSO, as shown for allenyl alcohol **3c** in Scheme 3 (transformation 1), but its drawbacks are the high loading of catalyst and the sluggish conversion in some cases. The use of a base additive like potassium carbonate along with silver(I) has an accelerating effect on cyclizations of various alkoxyallenyl amines,[3] but is not effective in case of alkoxyallenyl alcohols **3**.

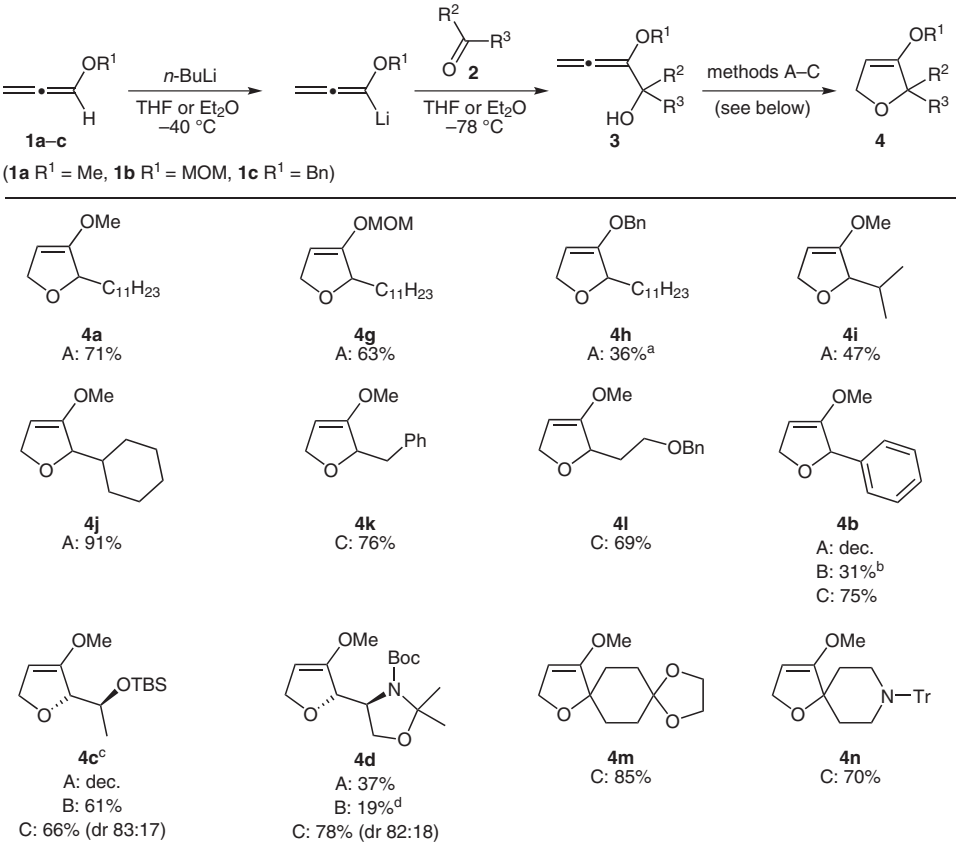



**Scheme 2** Cyclization of allenyl alcohols **3** to 3-alkoxy-2,5-dihydrofurans **4** with KO*t*-Bu and DMSO




**Scheme 3** Cyclization of allenyl alcohol **3c** to 3-alkoxy-2,5-dihydrofuran **4c** with Ag(I) or Au(I)

Gold catalysts have been extensively studied in the activation of carbon–carbon multiple bonds,[33] and the intramolecular hydroamination and hydroalkoxylation of allenic double bonds proceed readily with gold(I) and gold(III) species in many examples.[29,33] Our own investigations showed that for the cyclization of alkoxy-substituted substrates **3**, gold(III) chloride as well as cationic gold(I) complexes were too reactive, and we observed mostly decomposition of the starting materials. However, the reagent system of gold(I) chloride and pyridine previously reported by Gockel and Krause[34] turned out to be the ideal and most general catalyst for substrates **3**. These conditions left the sensitive enol ether moiety intact, and many




**Scheme 4** Scope of dihydrofuran synthesis from alkoxyallenes **1** and carbonyl compounds **2**. Method A: 0.5 equiv KO*t*-Bu, DMSO, 60 °C, 1–2 h. Method B: 0.3–0.5 equiv $AgNO_3$, MeCN, r.t. or 50 °C. Method C: 0.05 equiv AuCl, 0.15 equiv pyridine, $CH_2Cl_2$, r.t., 30 min to 1 h. [a] Allenyl alcohol **3h** used in the cyclization step contained benzyloxyallene (**1c**). [b] Result taken from ref. 26a. [c] Yield of the crude allenyl alcohol **3c** was 89%. [d] $AgBF_4$ was used instead of $AgNO_3$ and the reaction was stopped after 72 h with incomplete conversion.

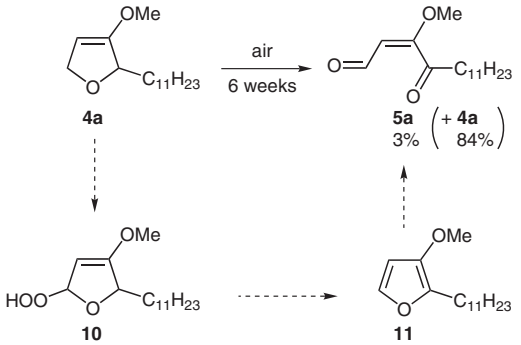
functional groups were tolerated. Complete conversion was achieved with 5% of catalyst loading and in short reaction times, as shown for substrate **3c** in Scheme 3 (transformation 2).

A summary of the described transformations is given in Scheme 4. Alkoxyallenes **1** (typically 3.5 equiv) were deprotonated at –40 °C with *n*-butyllithium (3.0 equiv) in THF or diethyl ether and then treated with aldehydes and ketones **2** (1.0 equiv) at –78 °C. α-Chiral aldehydes preferentially led to the *anti*-adducts in all cases.[35] After extractive workup and removal of the excess of alkoxyallene **1** in vacuo, crude allenyl alcohols **3** were mostly obtained in quantitative yield and were directly cyclized under different reaction conditions. When diastereomeric mixtures of allenyl alcohols **3** were employed in the cyclization step, the *syn*/*anti* ratio was essentially retained under all reaction conditions employed.

The examples **4a** and **4g–j** show that cyclizations with KO*t*-Bu and DMSO (method A) smoothly proceeded with allenyl substrates **3** that bear simple aliphatic substituents $R^2/R^3$ and different alkoxy substituents $R^1$ are also well tolerated. In the case of product **4h**, the yield was lowered to 36% due to the presence of nonvolatile benzyloxyallene (**1c**) in the cyclization step, leading to the formation of unknown side products. The examples **4b–d** illustrate that AuCl and pyridine (method C) is the reagent of choice for substrates that earlier could only be cyclized with moderate success employing Brandsma's conditions or $AgNO_3$ (method B). Cyclizations of allenic precursors **3** derived from ketones also proceeded efficiently using AuCl, as shown by examples **4m** and **4n**.

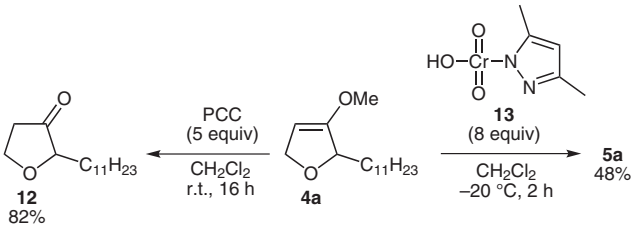
## Oxidative Cleavage to α,β-Unsaturated γ-Keto Aldehydes

Alkoxy-substituted 2,5-dihydrofurans **4** are prone to oxidative degradation. An early observation we made was the oxidative ring cleavage of compound **4a** when kept in the open air, slowly generating α,β-unsaturated γ-keto aldehyde **5a** (Scheme 5).



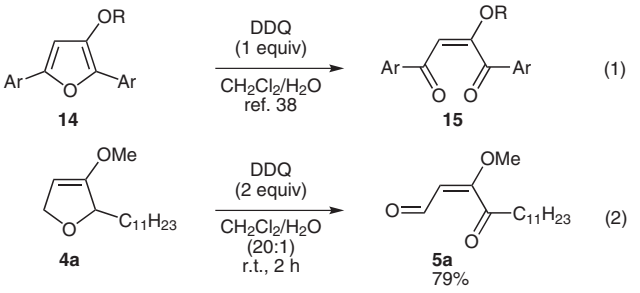

**Scheme 5** Aerobic oxidation of 2,5-dihydrofuran **4a**

The oxidation had most likely proceeded via the hydroperoxide **10** and furan **11** as intermediates, and in order to verify this assumption, we tried to prepare a sample of furan **11** by oxidation of substrate **4a** in the presence of various oxidants. To our surprise, we were unable to deliberately induce this oxidation. While reagents like manganese(IV) oxide and DDQ gave only minimal conversion even at reflux temperature in anhydrous dichloromethane or chlorobenzene, other reagents like the acidic pyridinium chlorochromate or platinum on carbon exclusively led to cleavage of the enol ether moiety of **4a** yielding 3-furanone **12** (Scheme 6). On the other hand, the chromium(VI) oxide dimethylpyrazole complex **13**,[36] a reagent known for allylic oxidation of 2,5-dihydrofurans,[37] gave γ-keto aldehyde **5a** as the sole product in 48% yield (Scheme 6).



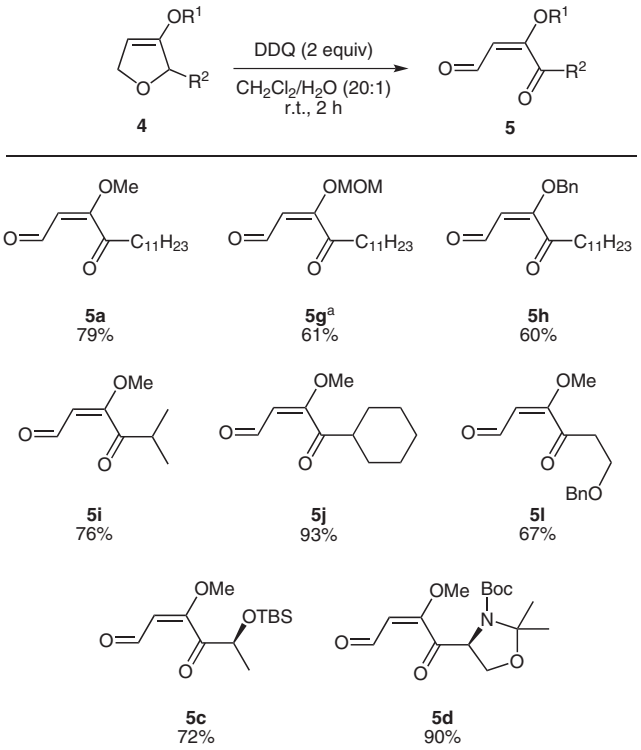

**Scheme 6** Reactions of 3-alkoxy-2,5-dihydrofuran **4a** with chromium(VI) reagents

While we could not selectively oxidize substrate **4a** to the 3-alkoxyfuran **11**, we recognized the oxidation to γ-keto aldehyde **5a** as the transformation of much higher synthetic value, and this process was studied in detail.[26] Prior to our investigations, DDQ in wet dichloromethane had been used as a reagent for the oxidation of 2,5-diaryl-substituted 3-alkoxyfurans **14** to 1,4-diketones **15** (Scheme 7, transformation 1).[38] When 2,5-dihydrofuran **4a** was reacted under the same conditions, γ-keto aldehyde **5a** and unconsumed starting material **4a** were obtained in a ratio of approximately 1:1. This experiment showed that the presumed intermediate furan species **11** is too short-lived to be isolated. Treatment of **4a** with a total of two equivalents of DDQ in the presence of water resulted in complete conversion of dihydrofuran **4a** into γ-keto aldehyde **5a** (transformation 2).



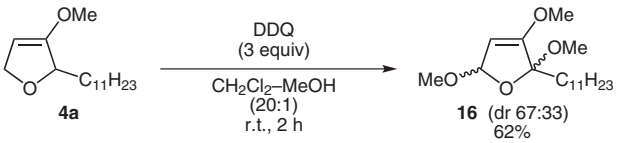

**Scheme 7** DDQ-promoted oxidations of furans **14** and 3-methoxy-2,5-dihydrofuran **4a**

The formal four-electron oxidation of 2,5-dihydrofurans **4** to γ-keto aldehydes **5** with DDQ in the presence of water is applicable to a wide range of substrates **4** and a scope of the method is shown in Scheme 8.




**Scheme 8** Oxidative cleavage of 2,5-dihydrofurans **4** leading to α,β-unsaturated γ-keto aldehydes **5**. [a] Reaction mixture buffered at pH 7 with aqueous phosphate buffer.

The method is well compatible with different acid-sensitive protecting groups such as TBS ethers as well as oxazolidinyl groups, and oxidation-prone benzyl ethers are also left intact. Only in case of MOM ether **5g**, buffering of the reaction mixture at pH 7 was necessary to avoid hydrolysis of the protective group. When employing chiral dihydrofuran substrates in the reaction, γ-keto aldehyde products were obtained without noticeable racemization.[39] It should be noted that the transformations leading to compounds such as **5c** and **5d** resemble the Achmatowicz reaction, the oxidation of α-hydroxy or α-amino furan derivatives to 4-enuloses,[40] which in turn are versatile building blocks in the *de novo* synthesis of carbohydrates and other functionalized six-membered-ring structures.[41] Finally, water could be replaced by methanol as co-solvent in the DDQ-mediated oxidation, leading to cyclic bis-acetals such as compound **16** in Scheme 9.



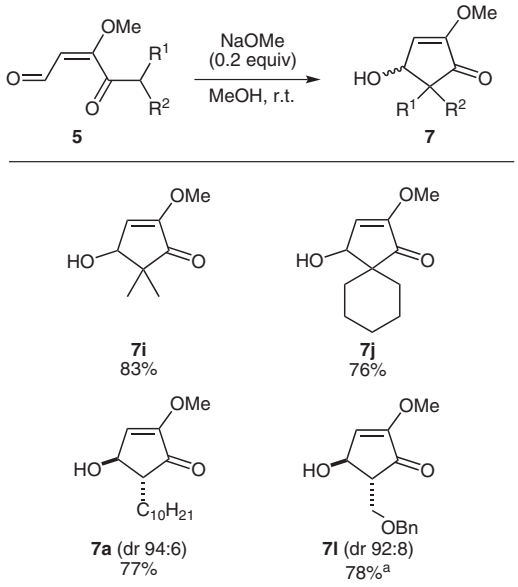

**Scheme 9** DDQ-mediated oxidation in the presence of methanol to cyclic bis-acetal **16**

We already demonstrated the synthetic utility of dicarbonyl compounds **5** by converting them into heterocyclic products like pyridazine and tetronic acid derivatives,[26a] as well as their use as templates for the synthesis of rare carbohydrates.[26b,c] A more recent application of these versatile intermediates is the intramolecular aldol addition leading to cyclopentenone derivatives.[26d] As shown in Scheme 10, the primary product of the DDQ-mediated oxidation of dihydrofuran **4k** readily cyclized during chromatography on silica gel, to give cyclopentenone derivative **7k** with high diastereoselectivity (*trans*/*cis* = 94:6).


**4k** **7k** 76% (dr 94:6)

**Scheme 10** Oxidation of 3-methoxy-2,3-dihydrofuran **4k** and subsequent silica gel promoted intramolecular aldol addition to cyclopentenone **7k**

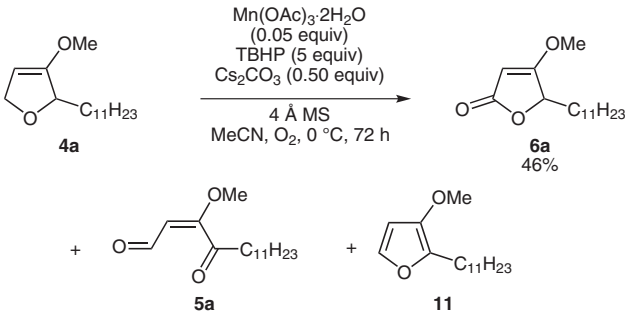
A number of different enolizable γ-keto aldehydes **5** were deliberately converted into cyclopentenone products, and the reactions proceeded readily using a catalytic amount of sodium methoxide in methanol as the base. As shown in Scheme 11, dialkyl-substituted **7i** and **7j** were obtained in good yields. In cases with an α-methylene substructure, the aldol addition gave the *trans*-configured products with high preference (examples **7a** and **7l**), very likely as a result of thermodynamic control.[42]




**Scheme 11** Intramolecular aldol reactions yielding cyclopentenones **7**. [a] Reaction performed with aq $Na_2CO_3$ in THF.

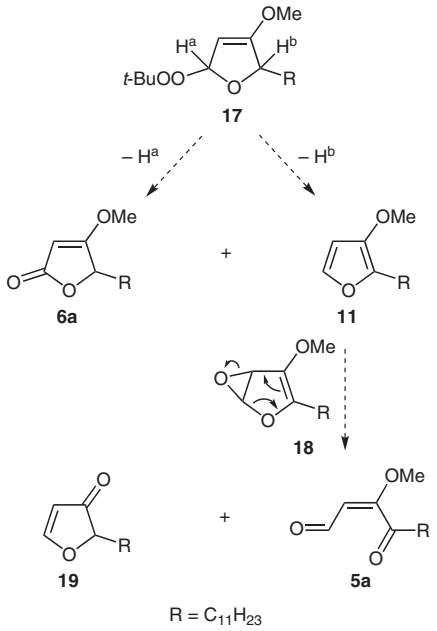
## Allylic Oxidation of Dihydrofurans to β-Alkoxybutenolides

The oxidation of 2,5-dihydrofurans in allylic position can lead to butenolides, however, the only example of this transformation known in the literature[37] employs chromium(VI) oxide dimethylpyrazole complex **13**[36] as the oxidizing reagent. As shown in Scheme 6, 3-alkoxy-2,5-dihydrofurans **4** react with complex **13** via a different mechanism and undergo oxidative cleavage to γ-keto aldehydes **5**. We continued investigating alternative oxidation methods for the desired allylic oxidation, and reaction conditions reported by Shing and co-workers using *tert*-butyl hydroperoxide and catalytic amounts of manganese(III) acetate[43] led to the formation of butenolide **6a** from dihydrofuran **4a** in a moderate yield of 36%. In an attempt to improve this result, the influence of the solvent, the reaction temperature, and of various acidic and basic additives were investigated. As shown in Scheme 12, we could improve the yield of butenolide **6a** to 46%, by using 0.5 molar equivalents of cesium carbonate[44] as a basic additive, and performing the reaction at 0 °C under an atmosphere of oxygen. Along with the desired product **6a**, we isolated trace amounts of γ-keto aldehyde **5a** and furan **11**. When no base was added, the yields of **5a** and **11** were much higher (20–40%).

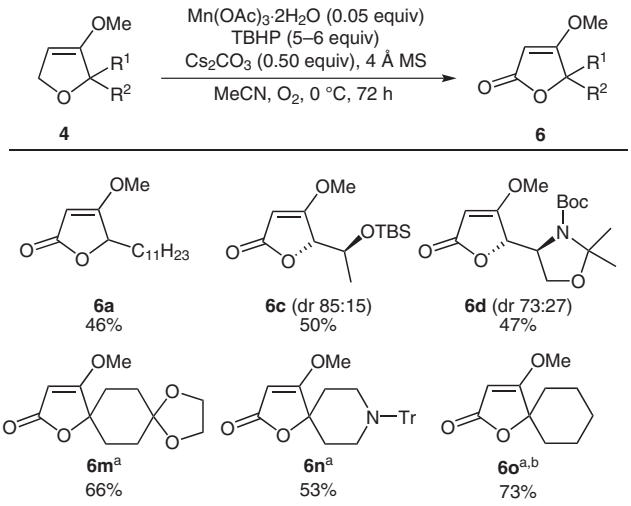



**Scheme 12** Allylic oxidation of 3-methoxy-2,5-dihydrofuran **4a** to butenolide **6a**

A mechanistic rationale for these observations is depicted in Scheme 13. The dihydrofuran substrate is first converted into peroxide **17**, which may undergo rearrangement to butenolide **6a** by abstraction of $H^a$ or, alternatively, elimination to furan **11** by abstraction of $H^b$. Furan **11** may then react to epoxide **18**, which rearranges to γ-keto aldehyde **5a**. The amount and strength of the basic additive was critical for balancing the reaction and we used $K_3PO_4$, $Cs_2CO_3$, NaOAc, and $NaH_2PO_4$ at 0.5–3.0 molar equivalents. However, temperature had the greatest impact on the yield of **6a**. Carrying out the reaction at 0 °C for 72 hours increased the yield by 10% compared to the reaction at room temperature. Peroxide **17** may also undergo 1,4-elimination to furan-3(2*H*)one **19** and we could isolate this intermediate in one case. This side reaction becomes increasingly important at elevated temperatures, and as enolizable compounds like **19** are prone to oligomerization,[45] it may account for the observed loss of material in the overall process.



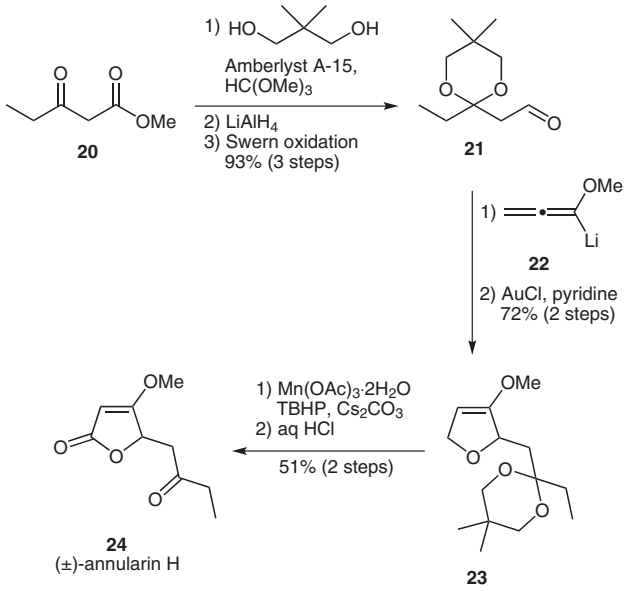

**Scheme 13** Mechanistic rationale for the fragmentation of hydroperoxide **17**




**Scheme 14** Scope of allylic oxidation of 3-methoxy-2,5-dihydrofurans **4** leading to β-alkoxybutenolides **6**. [a] Reaction performed at room temperature for 48 h. [b] No base was used.

A small scope of the allylic oxidation of substrates **4** is shown in Scheme 14. Yields of butenolides **6** ranged from 45–50% (examples **6a**, **6c**, **6d**). In the case of compound **6d**, a minor shift of the original ratio of diastereomers was observed, after chromatographic purification. When spirodihydrofurans were employed as precursors, yields of up to 73% were obtained (examples **6m**, **6n**, **6o**), and the reaction could well be performed at room temperature without a noticeable difference in yield.

The utility of our new protocols for the preparation of dihydrofurans and their allylic oxidation could be demonstrated by a short synthesis of the natural product (±)-annularin H (**24**)[46] as shown in Scheme 15. Methyl 3-oxovalerate (**20**) was readily converted into aldehyde **21** by




**Scheme 15** Synthesis of the natural product annularin H (**24**)

acetal protection of the keto group, reduction with lithium aluminum hydride and Swern oxidation[47] of the resulting alcohol. Addition of lithiated methoxyallene **22** to aldehyde **21** and subsequent cyclization of the allenyl alcohol with gold(I) chloride and pyridine led to dihydrofuran **23** in good overall yield. Allylic oxidation of this substrate and subsequent hydrolysis of the acetal protecting group furnished the natural product with good overall efficiency.

By way of their reactions with diverse electrophilic species, lithiated alkoxyallenes deliver heterocyclic products of high synthetic value. While the known preparation of 3-alkoxy-2,5-dihydrofurans has been re-shaped employing gold catalysis, the examination of 2,5-dihydrofurans in oxidation reactions led to new procedures for their oxidative cleavage to γ-keto aldehydes and their allylic oxidation to butenolides. The intramolecular aldol reactions of suitably substituted γ-keto aldehydes readily furnished highly functionalized cyclopentenone derivatives, which could be versatile intermediates for further synthetic elaborations.

Reactions were performed under exclusion of air and moisture, in flame-dried glassware and under an atmosphere of argon (oxygen, respectively). Anhydrous solvents were prepared by standard procedures, and commercial reagents were used without further purification, with the exception of aldehydes which were either distilled freshly or chromatographed prior to use. AuCl (99.9%) was purchased from Sigma Aldrich. Column chromatography was performed using silica gel 60 (230–400 mesh, 40–63 μm, Merck). $^1$H and $^{13}$C NMR spectra were recorded on JEOL (Eclipse 500) and Bruker (AMX 500 and AC 250) instruments. Chemical shifts are reported relative to the resonances of $CHCl_3$ at δ = 7.25 ppm ($^1$H NMR) and δ = 77.0 ppm ($^{13}$C NMR). IR spectra were recorded with a Nicolet 5SXC FTIR spectrometer, EI mass spectra with Finnigan MAT 711 (80 eV, 8 kV) and Finnigan MAT CH7A (80 eV, 3 kV) instruments. FAB mass spectra were obtained using a Finnigan CH5DF instrument (3 kV) and ESI mass spectra with an Agilent ESI-TOF 6210 instrument (4 μL/min, 1 bar, 4000 V). Elemental analyses were obtained from Perkin-Elmer and Vario EL analyzers.

Melting points were measured with a Büchi MP 510 apparatus and are uncorrected. Optical rotation values were determined using Perkin-Elmer (241-P) and IBZ (POLAR-LμP) polarimeters (λ = 589 nm, sodium D-emission, quartz cuvette, thickness 10 cm).

**Addition of Lithiated Alkoxyallenes to Aldehydes and Ketones and Gold-Catalyzed Cyclization to 2,5-Dihydrofurans; Preparation of Compound *anti*/*syn*-4c; Typical Procedure 1**

Methoxyallene[48] (**1a**; 0.90 mL, 756 mg, 10.8 mmol) was dissolved in $Et_2O$ (15 mL) and *n*-BuLi (3.70 mL, 2.50 M in hexanes, 9.25 mmol) was added at –40 °C. After 30 min, the mixture was cooled to –78 °C and a solution of (*S*)-2-(*tert*-butyldimethylsiloxy)propanal[49] (590 mg, 3.13 mmol) in $Et_2O$ (7 mL) was added. The mixture was stirred for 3 h, $H_2O$ (20 mL) was added, and after warming to r.t., the layers were separated. The aqueous layer was extracted with $Et_2O$ (3 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to dryness to provide the intermediate allenyl alcohol *anti*/*syn*-**3c** (721 mg, 89%, *anti*/*syn* = 88:12) as a yellowish oil, which was directly used in the next step.

*anti*-**3c**

$^1$H NMR (500 MHz, $CDCl_3$): δ = 0.01, 0.03 (2 s, 2 × 3 H, $SiMe_2t$-Bu), 0.81 (s, 9 H, $SiMe_2t$-Bu), 1.13 (d, *J* = 6.0 Hz, 3 H, 1-H), 2.39 (d, *J* = 5.8 Hz, 1 H, OH), 3.37 (s, 3 H, OMe), 3.91–3.99 (m, 2 H, 2-H, 3-H), 5.50 ($m_c$, 2 H, 6-H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = –5.1, –4.6 (2 q, $SiMe_2t$-Bu), 17.9 (q, C-1), 18.5, 26.7 (s, q, $SiMe_2t$-Bu), 55.9 (q, OMe), 69.5 (d, C-2), 75.0 (d, C-3), 91.8 (t, C-6), 133.6 (s, C-4), 198.4 (s, C-5).

*syn*-**3c**

$^1$H NMR (500 MHz, $CDCl_3$): δ (characteristic signals) = 1.23 (d, *J* = 6.9 Hz, 3 H, 1-H), 2.55 (d, *J* = 8.0 Hz, 1 H, OH).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ (characteristic signals) = 56.0 (q, OMe), 68.7 (d, C-2), 74.2 (d, C-3), 92.5 (t, C-6), 135.0 (s, C-4), 198.3 (s, C-5).

The allenyl alcohol *anti*/*syn*-**3c** (721 mg, max. 2.79 mmol) was dissolved in $CH_2Cl_2$ (40 mL) and pyridine (40 μL, 39 mg, 0.49 mmol) was added, followed by AuCl (33 mg, 0.14 mmol). After stirring for 1 h at r.t., conversion was complete as indicated by TLC, and the mixture was concentrated in vacuo and chromatographed (silica gel, EtOAc–hexanes, 1:8) to provide 2,5-dihydrofuran *anti*/*syn*-**4c** (533 mg, 66% over 2 steps, *anti*/*syn* = 83:17) as a yellowish liquid. The diastereomers could not be separated.

**(*S*)-2-[(*S*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-3-methoxy-2,5-dihydrofuran (*anti*-4c)**

$^1$H NMR (500 MHz, $CDCl_3$): δ = 0.06 ($m_c$, 6 H, $SiMe_2t$-Bu), 0.88 (s, 9 H, $SiMe_2t$-Bu), 1.11 (d, *J* = 6.4 Hz, 3 H, 2′-H), 3.63 (s, 3 H, OMe), 3.94 (dq, *J* = 2.3, 6.4 Hz, 1 H, 1′-H), 4.50–4.53 (m, 1 H, 2-H), 4.60–4.65 (m, 3 H, 4-H, 5-H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = –4.9, –4.6 (2 q, $SiMe_2t$-Bu), 17.3 (q, C-2′), 18.2, 25.9 (s, q, $SiMe_2t$-Bu), 57.4 (q, OMe), 70.2 (d, C-1′), 73.5 (t, C-5), 85.7 (d, C-2), 91.3 (d, C-4), 156.5 (s, C-3).

**(*R*)-2-[(*S*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-3-methoxy-2,5-dihydrofuran (*syn*-4c)**

$^1$H NMR (500 MHz, $CDCl_3$): δ (characteristic signals) = 0.85 (s, 9 H, $SiMe_2t$-Bu), 1.21 (d, *J* = 6.5 Hz, 3 H, 2′-H), 3.63 (s, 3 H, OMe), 3.90 (dq, *J* = 2.0, 6.5 Hz, 1 H, 1′-H), 4.28-4.32 (m, 1 H, 2-H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ (characteristic signals) = 20.0 (q, C-2′), 25.7 (q, $SiMe_2t$-Bu), 57.1 (q, OMe), 68.3 (d, C-1′), 73.7 (t, C-5), 85.6 (d, C-2), 91.4 (d, C-4), 155.8 (s, C-3).

*anti*/*syn*-**4c**

IR (film): 2960–2855 (=C–H, C–H), 1665 $cm^{-1}$ (C=C).

MS (EI, 50 °C): *m*/*z* (%) = 258 ($[M]^+$, 2), 157 ($[C_8H_{17}OSi]^+$, 100), 115 ($[C_6H_{15}Si]^+$, 25).

HRMS (EI, 40 °C): *m*/*z* calcd for $[C_{13}H_{26}O_3Si]^+$: 258.1651; found: 258.1672.

**DDQ-Mediated Oxidative Cleavage of 2,5-Dihydrofurans to γ-Keto Aldehydes; (*S*,*E*)-5-*tert*-Butyldimethylsiloxy-3-methoxy-4-oxohex-2-enal (5c); Typical Procedure 2**

$H_2O$ (0.11 mL) was added to a solution of dihydrofuran *anti*/*syn*-**4c** (150 mg, 0.58 mmol) in $CH_2Cl_2$ (2.30 mL) followed by DDQ (264 mg, 1.16 mmol). The mixture was stirred at r.t. for 2 h, then aq $NaHCO_3$ (2 mL) and $H_2O$ (2 mL) were added. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated in vacuo and chromatographed (silica gel, EtOAc–hexanes, 1:4) to provide keto aldehyde **5c** (114 mg, 72%) as a yellowish liquid; $[\alpha]_D^{22}$ –6.8 (*c* = 0.22, $CHCl_3$).

IR (film): 2955–2860 (=C–H, C–H), 1730, 1670, 1605 $cm^{-1}$ (C=O, C=C).

$^1$H NMR (500 MHz, $CDCl_3$): δ = 0.04 (s, 6 H, $SiMe_2t$-Bu), 0.84 (s, 9 H, $SiMe_2t$-Bu), 1.34 (d, *J* = 6.8 Hz, 3 H, 6-H), 3.75 (s, 3 H, OMe), 4.69 (q, *J* = 6.8 Hz, 1 H, 5-H), 5.53 (d, *J* = 7.3 Hz, 1 H, 2-H), 9.66 (d, *J* = 7.3 Hz, 1 H, 1-H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = –5.1, –4.9 (2 q, $SiMe_2t$-Bu), 19.5 (q, C-6), 18.0, 25.6 (s, q, $SiMe_2t$-Bu), 56.4 (q, OMe), 71.8 (d, C-5), 108.3 (d, C-2), 170.0 (s, C-3), 190.2 (d, C-1), 199.0 (s, C-4).

MS (pos. FAB): *m*/*z* (%) = 295 ($[M + Na]^+$, 1), 273 ($[M + H]^+$, 7), 215 ($[M – C_4H_9]^+$, 5), 159 ($[C_8H_{19}OSi]^+$, 56), 115 ($[C_6H_{15}Si]^+$, 14), 73 ($[C_3H_9Si]^+$, 100).

Anal. Calcd for $C_{13}H_{24}O_4Si$ (272.4): C, 57.32; H, 8.88. Found: C, 57.32; H, 8.90.

**Intramolecular Aldol Reaction of γ-Keto Aldehydes; *cis*/*trans*-5-Decyl-4-hydroxy-2-methoxycyclopent-2-enone (7a); Typical Procedure 3**

A mixture of keto aldehyde **5a** (100 mg, 0.37 mmol) and NaOMe (0.5 M in MeOH, 0.14 mL, 0.07 mmol) in MeOH (5 mL) was stirred at r.t. for 2 h. The mixture was concentrated to dryness and the residue was chromatographed (silica gel, EtOAc–hexanes, 1:1) to provide cyclopentenone **7a** (77 mg, 77%, *trans*/*cis* = 94:6) as a colorless solid; mp 44 °C.

**Major Isomer, *trans*-7a**

IR (KBr): 3410 (OH), 3080–2850 (=C–H, C–H), 1705 (C=O), 1635 $cm^{-1}$ (C=C).

$^1$H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3 H, 10′-H), 1.26–1.36, 1.41–1.49 (2 m, 18 H, 9 × $CH_2$), 1.79–1.87 (m, 1 H, 5-H), 2.15 (br s, 1 H, OH), 3.75 (s, 3 H, OMe), 4.60 (br s, 1 H, 4-H), 6.23 (d, *J* = 2.9 Hz, 1 H, 3-H).

$^{13}$C NMR (125 MHz, $CDCl_3$): δ = 14.1 (q, C-10′), 22.6, 27.1, 29.0, 29.3, 29.4, 29.5, 29.6, 31.9 (8 t, 9 × $CH_2$), 55.0 (d, C-5), 57.1 (q, OMe), 72.1 (d, C-4), 125.0 (d, C-3), 157.6 (s, C-2), 201.4 (s, C-1).

MS (EI, 50 °C): *m*/*z* (%) = 268 (67, $[M]^+$), 253 (7, $[M – CH_3]^+$), 239 (10) $[M – C_2H_5]^+$, 128 (100).

Anal. Calcd for $C_{16}H_{28}O_3$ (268.4): C, 71.60; H, 10.52. Found: C, 71.13; H, 10.21.

**Manganese(III) Acetate Catalyzed Allylic Oxidation of 2,5-Dihydrofurans with *tert*-Butyl Hydroperoxide; Preparation of Compound *anti*/*syn*-6c: Typical Procedure 4**

Molecular sieves (4 Å, powder, 570 mg) were suspended in a solution of dihydrofuran *anti*/*syn*-**4c** (302 mg, 1.17 mmol) and $Cs_2CO_3$ (190 mg, 0.58 mmol) in MeCN (13 mL). TBHP solution (1.15 mL,

5.50 M in nonane, 6.33 mmol) was added at 0 °C, followed by $Mn(OAc)_3 \cdot 2H_2O$ (16 mg, 60 μmol) and the mixture was stirred at this temperature, under an atmosphere of $O_2$, for 72 h. The mixture was poured into an aqueous solution of $FeSO_4 \cdot 7H_2O$ (3.00 g in 30 mL $H_2O$) and diluted with EtOAc (20 mL). After filtration of the mixture through Celite (with EtOAc), the layers were separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated in vacuo, and chromatographed (silica gel, EtOAc–hexanes, 1:2 → 1:1) to provide butenolide *anti*/*syn*-**6c** (158 mg, 50%, *anti*/*syn* = 85:15) as a yellowish oil. HPLC separation afforded analytical samples of the single diastereomers.

**(*S*)-5-[(*S*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-4-methoxyfuran-2(5*H*)-one (*anti*-6c)**

Yellowish oil; $[\alpha]_D^{22}$ +65.0 (*c* = 0.80, $CHCl_3$).

$^1$H NMR (500 MHz, $CDCl_3$): δ = 0.043, 0.046 (2 s, 2 × 3 H, $SiMe_2t$-Bu), 0.84 (s, 9 H, $SiMe_2t$-Bu), 1.23 (d, *J* = 6.6 Hz, 3 H, 2′-H), 3.85 (s, 3 H, OMe), 4.17 (dq, *J* = 2.5, 6.6 Hz, 1 H, 1′-H), 4.62 (dd, *J* = 0.8, 2.5 Hz, 1 H, 5-H), 5.06 (d, *J* = 0.8 Hz, 1 H, 3-H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = –5.1, –4.9 (2 q, $SiMe_2t$-Bu), 18.6 (q, C-2′), 20.1, 25.6 (s, q, $SiMe_2t$-Bu), 59.2 (q, OMe), 67.9 (d, C-1′), 82.5 (d, C-5), 90.0 (d, C-3), 172.5 (s, C-2), 180.5 (s, C-4).

**(*R*)-5-[(*S*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-4-methoxyfuran-2(5*H*)-one (*syn*-6c)**

Colorless solid; mp 57–58 °C; $[\alpha]_D^{22}$ –9.5 (*c* = 0.75, $CHCl_3$).

$^1$H NMR (500 MHz, $CDCl_3$): δ = –0.02, 0.04 (2 s, 2 × 3 H, $SiMe_2t$-Bu), 0.82 (s, 9 H, $SiMe_2t$-Bu), 1.31 (d, *J* = 6.4 Hz, 3 H, 2′-H), 3.85 (s, 3 H, OMe), 4.12 (dq, *J* = 2.1, 6.4 Hz, 1 H, 1′-H), 4.56 (dd, *J* = 0.9, 2.1 Hz, 1 H, 5-H), 5.07 (d, *J* = 0.9 Hz, 1 H, 3-H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = –5.4, –4.4 (2 q, $SiMe_2t$-Bu), 17.9 (q, C-2′), 17.8, 25.5 (s, q, $SiMe_2t$-Bu), 59.0 (q, OMe), 66.2 (d, C-1′), 82.5 (d, C-5), 89.9 (d, C-3), 172.7 (s, C-2), 179.9 (s, C-4).

***anti*/*syn*-6c**

IR (film): 3020–2860 (=C–H, C–H), 1760, 1630 $cm^{-1}$ (C=O, C=C).

MS (EI, 50 °C): *m*/*z* (%) = 257 ($[M - CH_3]^+$, 10), 228 (12), 215 ($[M - C_4H_9]^+$, 100), 143 ($[M + H - CH_3 - C_6H_{15}Si]^+$, 62), 73 ($[C_3H_9Si]^+$, 46).

Anal. Calcd for $C_{13}H_{24}O_4Si$ (272.4): C, 57.32; H, 8.88. Found: C, 57.43; H, 9.01.

**Synthesis of (±)-Annularin H**

**(2-Ethyl-5,5-dimethyl[1,3]dioxane-2-yl)acetaldehyde (21)**

Amberlyst A-15 ($SO_3H$-form, 0.98 g, 1.1 mmol/g) was added at r.t. to a solution of methyl 3-oxovalerate (2.28 g, 17.5 mmol), 2,2-dimethylpropanediol (2.63 g, 25.3 mmol) and $HC(OMe)_3$ (4.00 mL, 3.88 g, 36.6 mmol) in $CH_2Cl_2$ (30 mL). The suspension was stirred for 16 h, then filtered, and evaporated to dryness to provide the crude intermediate ketal (4.55 g) as a colorless liquid.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 0.89 (s, 3 H, Me), 0.94 (t, *J* = 7.5 Hz, 3 H, 5-H), 0.97 (s, 3 H, Me), 1.86 (q, *J* = 7.5 Hz, 2 H, 4-H), 2.77 (s, 2 H, 2-H), 3.45, 3.56 (2 d, *J* = 11.6 Hz, 2 × 2 H, 4′-H, 6′-H), 3.66 (s, 3 H, OMe).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 7.4 (q, C-5), 22.4, 22.6 (2 q, 2 × Me), 28.4 (t, C-4), 29.7 (s, C-5′), 38.2 (t, C-2), 51.7 (q, OMe), 70.4 (t, C-4′, C-6′), 98.9 (s, C-3), 170.0 (s, C-1).

A solution of the crude ketal (4.55 g, max 17.5 mmol) in $Et_2O$ (15 mL) was added dropwise to a suspension of $LiAlH_4$ (1.52 g, 40.2 mmol) in $Et_2O$ (35 mL) at 0 °C. The mixture was stirred for 2 h at this temperature, then EtOAc (30 mL) was added dropwise over 20 min, followed by the addition of aq 2 M NaOH (5 mL). The mixture was warmed to r.t., diluted with EtOAc (100 mL), and $MgSO_4$ was added. Filtration over silica gel (with EtOAc) and concentration of the filtrate in vacuo provided an oil, which was taken up in pentane (40 mL). After stirring for 20 min, the mixture was filtered (excess 2,2-dimethylpropanediol was thereby removed) and concentrated to dryness to provide the intermediate alcohol (3.60 g) as a colorless liquid.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 0.79 (s, 3 H, Me), 0.85 (t, *J* = 7.5 Hz, 3 H, 5-H), 1.12 (s, 3 H, Me), 1.82 (q, *J* = 7.5 Hz, 2 H, 4-H), 1.86 (t, *J* = 5.4 Hz, 2 H, 2-H), 3.10 (t, *J* = 5.4 Hz, 1 H, OH), 3.38, 3.60 (2 d, *J* = 11.6 Hz, 2 × 2 H, 4′-H, 6′-H), 3.83 (q, *J* = 5.4 Hz, 2 H, 1-H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 7.8 (q, C-5), 22.3, 23.0 (2 q, 2 × Me), 23.6 (t, C-4), 29.6 (s, C-5′), 37.7 (t, C-2), 58.6 (t, C-1), 69.9 (t, C-4′, C-6′), 101.9 (s, C-3).

A solution of DMSO (5.80 mL, 6.38 g, 81.7 mmol) in $CH_2Cl_2$ (10 mL) was added at –78 °C to a solution of oxalyl chloride (3.40 mL, 5.03 g, 39.6 mmol) in $CH_2Cl_2$ (60 mL). The mixture was warmed to –60 °C over 15 min, then a solution of the crude alcohol (3.60 g, max 17.5 mmol) in $CH_2Cl_2$ (15 mL) was added dropwise. The mixture was warmed to –40 °C over 30 min, *i*-$Pr_2NEt$ (30.0 mL, 23.5 g, 182 mmol) was added, before warming to 0 °C over 20 min. The mixture was poured onto aq $NaHCO_3$ (100 mL), the layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, concentrated in vacuo and chromatographed (silica gel, EtOAc–hexanes, 1:4) to provide aldehyde **21** (3.02 g, 93% over 3 steps) as a yellowish liquid.

IR (film): 2960–2870 (C–H), 2740, 2690 (=C–H), 1725 $cm^{-1}$ (C=O).

$^1$H NMR (500 MHz, $CDCl_3$): δ = 0.88 (s, 3 H, Me), 0.90 (t, *J* = 7.5 Hz, 3 H, 5-H), 1.01 (s, 3 H, Me), 1.83 (q, *J* = 7.5 Hz, 2 H, 4-H), 2.65 (d, *J* = 3.0 Hz, 2 H, 2-H), 3.44, 3.57 (2 d, *J* = 11.7 Hz, 2 × 2 H, 4′-H, 6′-H), 9.84 (d, *J* = 3.0 Hz, 1 H, 1-H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 7.5 (q, C-5), 22.4, 23.0 (2 q, Me), 26.2 (t, C-4), 29.6 (s, C-5′), 48.2 (t, C-2), 70.2 (t, C-4′, C-6′), 99.4 (s, C-3), 201.2 (d, C-1).

MS (ESI-TOF): *m*/*z* (%) = 209 ($[M + Na]^+$, 25), 143 ($[C_8H_{15}O_2]^+$, 44).

HRMS (ESI-TOF): *m*/*z* calcd $[M + Na]^+$ for $[C_{10}H_{18}O_3 + Na]^+$: 209.1154; found: 209.1162.

**2-Ethyl-2-[(3-methoxy-2,5-dihydrofuran-2-yl)methyl]-5,5-dimethyl-1,3-dioxane (23)**

In an experiment analogous to typical procedure 1, methoxyallene (**1a**, 2.00 mL, 1.68 g, 24.0 mmol, dissolved in 30 mL $Et_2O$), *n*-BuLi (8.00 mL, 2.50 M in hexanes, 20.0 mmol), and aldehyde **21** (1.46 g, 7.84 mmol, dissolved in 10 mL $Et_2O$) gave the intermediate allenyl alcohol (2.13 g, quant) as an orange oil.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 0.78 (s, 3 H, Me), 0.86 (t, *J* = 7.6 Hz, 3 H, 8-H), 1.14 (s, 3 H, Me), 1.77 (q, *J* = 7.6 Hz, 2 H, 7-H), 1.90 ($m_c$, 1 H, 5-H), 2.01 (dd, *J* = 10.0, 14.9 Hz, 1 H, 5-H), 3.39, 3.62 (2 d, *J* = 11.6 Hz, 2 × 2 H, 4′-H, 6′-H), 3.42 (s, 3 H, OMe), 4.71 ($m_c$, 1 H, 4-H), 5.52 (d, *J* = 1.8 Hz, 2 H, 1-H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 7.8 (q, C-8), 22.3, 23.0 (2 q, Me), 23.7 (t, C-7), 29.6 (s, C-5′), 40.3 (t, C-5), 56.3 (q, OMe), 67.2 (d, C-4), 69.96, 70.03 (2 t, C-4′, C-6′), 91.9 (t, C-1), 101.4 (s, C-6), 136.3 (s, C-3), 197.6 (s, C-2).

Cyclization of the crude product (2.13 g, max 7.84 mmol) with AuCl (91 mg, 0.39 mmol) and pyridine (100 μL, 97 mg, 1.23 mmol) in $CH_2Cl_2$ (120 mL), followed by column chromatography (silica gel, EtOAc–hexanes, 1:5), provided 2,5-dihydrofuran **23** (1.45 g, 72% over 2 steps, purity ~95% by $^{13}$C NMR) as a yellowish solid; mp 41–43 °C.

IR (KBr): 2955–2875 (=C–H, C–H), 1750, 1640 $cm^{-1}$ (C=C).

$^1$H NMR (500 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.4 Hz, 3 H, 9-H), 0.93 (br s, 6 H, 2 × Me), 1.79 (dd, *J* = 8.6, 15.1 Hz, 1 H, 6-H), 1.83 (q, *J* = 7.4 Hz, 2 H, 8-H), 2.17 (dd, *J* = 1.2, 15.1 Hz, 1 H, 6-H), 3.47, 3.53 (AB-system, $J_{AB}$ = 12.0 Hz, 2 × 2 H, 4′-H, 6′-H), 3.64 (s, 3 H, OMe), 4.54–4.63 (m, 3 H, 4-H, 5-H), 4.71–4.76 (m, 1 H, 2-H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 7.5 (q, C-9), 22.7, 22.8 (2 q, 2 × Me), 27.4 (t, C-8), 29.7 (s, C-5′), 36.9 (t, C-6), 57.5 (q, OMe), 69.9, 70.1 (2 t, C-4′, C-6′), 72.6 (t, C-5), 77.5 (d, C-2), 89.6 (d, C-4), 99.8 (s, C-7), 158.2 (s, C-3).

MS (pos. FAB): *m*/*z* (%) = 143 ($[C_8H_{15}O_2]^+$, 67), 69 (60), 57 ($[C_3H_5O]^+$, 100).

Anal. Calcd for $C_{14}H_{24}O_4$ (256.3): C, 65.60; H, 9.44. Found: C, 65.06; H, 9.23.

**(±)-Annularin H [4-Methoxy-5-(2-oxobutyl)furan-2(5*H*)-one, 24]**

In an experiment analogous to typical procedure 4, 2,5-dihydrofuran **23** (520 mg, 2.03 mmol), $Cs_2CO_3$ (335 mg, 1.03 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (27 mg, 0.10 mmol), TBHP (1.90 mL, 5.50 M in nonane, 10.5 mmol), and molecular sieves (4 Å, powder, 1.02 g) in MeCN (22 mL) gave a crude product, which was dissolved in acetone (8 mL) and $H_2O$ (0.50 mL) and treated with aq 37% HCl (0.20 mL) for 22 h. The mixture was poured onto pH 7 phosphate buffer (20 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 20) and the combined organic layers were dried ($MgSO_4$), filtered, evaporated, and chromatographed (silica gel, EtOAc) to afford (±)-annularin H **24** (192 mg, 51% over 2 steps) as a yellowish oil, which solidified upon storage at –20 °C; mp 55–57 °C (Lit.[46] oil).

$^1$H NMR (500 MHz, $CDCl_3$): δ = 1.02 (t, *J* = 7.3 Hz, 3 H, 4′-H), 2.46 (q, *J* = 7.3 Hz, 2 H, 3′-H), 2.67 (dd, *J* = 8.5, 16.9 Hz, 1 H, 1′-H), 2.85 (dd, *J* = 3.6, 16.9 Hz, 1 H, 1′-H), 3.86 (s, 3 H, OMe), 5.05 (d, *J* = 1.0 Hz, 1 H, 3-H), 5.21 (ddd, *J* = 1.0, 3.6, 8.5 Hz, 1 H, 5-H).

$^{13}$C NMR (126 MHz, $CDCl_3$): δ = 7.3 (q, C-4′), 36.7 (t, C-3′), 43.7 (t, C-1′), 59.5 (q, OMe), 74.4 (d, C-5), 88.7 (d, C-3), 171.8 (s, C-2), 181.8 (s, C-4), 206.1 (s, C-2′).

The NMR data match those previously reported.[46]

Anal. Calcd for $C_9H_{12}O_4$ (184.2): C, 58.69; H, 6.57. Found: C, 58.25; H, 6.56.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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