Regioselective Synthesis of Functionalized Salicylates, Isotetronic Acids, and Alkylidene-Isobenzofurans based on One-Pot Cyclizations of Silyl Enol Ethers

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Die vorliegende Arbeit wurde in der Zeit vom Oktober 2003 bis September 2005 am Institut für Chemie und Biochemie der Ernst-Moritz-Arndt-Universität Greifswald und vom Oktober 2005 bis April 2008 am Institut für Chemie der Universität Rostock angefertigt.

Who of you by worrying can add a single hour to his life?

Matthew 6:27

Es gibt keinen Menschen auf der Welt, von dem man nicht etwas lernen könnte.

Albert Schweitzer

Table of Contents

1 Introduction

When in 1828 Friedrich Wöhler transformed ammonium cyanate into urea this was the first synthesis of an organic substance, i.e. a substance which was only known as part of living nature. Until that time it was assumed that there was a fundamental difference between substances originating from plants and animals and those that could be synthesized.

Millions of organic compounds have been synthesized since and many methods have been developed to access more and more complex chemical structures. The synthesis of penicillin by Sheehan and Henery-Logan[1] and of vancomycin by Nicolaou[2] and independently by Evans[3] can be considered milestones in synthetic organic chemistry.

Due to numerous challenges especially in the development of new and more efficient drugs for medical purposes not only the intelligent application but also the development of new synthetic methods remains a central task in organic chemistry. Domino reactions[4] and the reactions of dielectrophiles with dinucleophiles constitute interesting concepts for the formation of more than one bond in a single step. Thus more complex transformations become possible.

The development of cyclization reactions of dianions[5] and dianion equivalents leading to various biologically relevant ring systems is one of the focuses of research in the group of Prof. Langer. Although the idea of reacting dielectrophiles with dinucleophiles seems simple many side reactions can occur. For instance, 1,3-dicarbonyl dianions are only accessible by the use of strong bases. Therefore they constitute not only highly reactive nucleophiles but also strong bases themselves. In practice polymerization, decomposition,[6] formation of open-chain products,[7] elimination,[8] and SET-reactions[9] can occur. In order to overcome these problems optimization of reaction conditions and reactivity matching are necessary. In many cases the use of electroneutral and less reactive silyl enol ethers instead of mono- and dianions leads to higher yields.

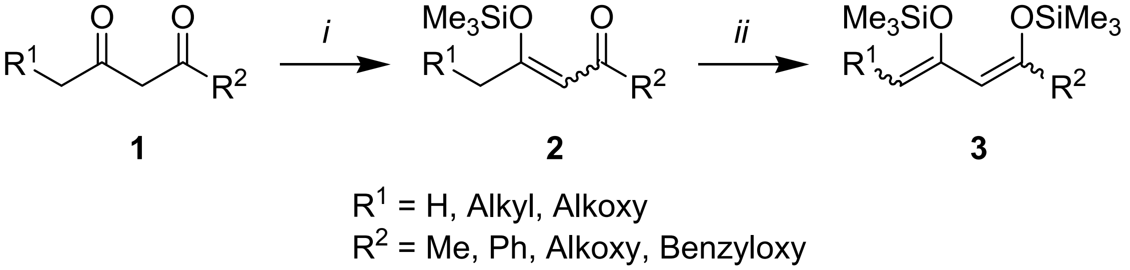
This work is a contribution to the chemistry of different types of silyl enol ethers which were applied to the regioselective synthesis of functionalized salicylates (Chapter 4), isotetronic acids (Chapter 5), and alkylidene-isobenzofurans (Chapter 6).

In addition, the competition between the recently developed domino "Staudinger / semi-aza-Wittig / fragmentation" reaction of γ-azido-β-hydroxyketones and the normal aza-Wittig reaction pathway was studied. The results are presented in Chapter 3.

2 Synthesis of Mono-Silyl Enol Ethers and 1,3-Bis-Silyl Enol Ethers

The synthesis of 1,3-bis(trimethylsilyloxy)-1,3-dienes – electroneutral 1,3-dicarbonyl dianion equivalents[10,11] – of type **3** was carried out according to a two step procedure described by Molander und Chan[10b] which was slightly varied. The first step yields – depending on R^2 – 3-trimethylsilyloxy-2-ene-carboxylates and 3-trimethylsilyloxy-2-ene-1-ones **2** which were also used as starting materials.

Scheme 1. Synthesis of silyl enol ethers of type **2** and **3**.



(*i*) Benzene, **1**, 1.4 eq. NEt_3, 30 min, then 1.4 eq. Me_3SiCl, 20 °C, 3 d; (*ii*) THF, 1.4 eq. LDA, –78 °C, **2**, 1 h, then 1.7 eq. Me_3SiCl, –78 → 20 °C in 12-18 h.

An alternative route to 1,3-diketone-derived silyl enol ethers, based on the use of trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) and triethylamine,[12] is possible and was implemented for 3-acceptor-substituted acetylacetones (for comparison, see Chapter 4).

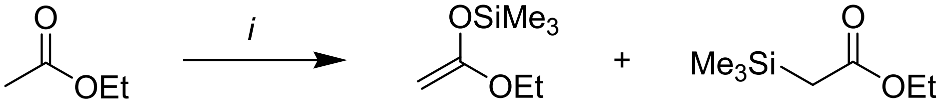
Some compounds of type **1** (with $R^1 \neq H$) are not commercially available and had, thus, to be synthesized.

Alkyl substituents R^1 were introduced by reaction of the unsubstituted dicarbonyl compound ($R^1 = H$) with two equivalents of LDA, generating the dianion, and subsequent addition of the appropriate alkyl bromide R^1Br.

Alkoxy substituents R^1 were introduced by sodium hydride mediated reaction of the chlorinated dicarbonyl compound ($R^1 = Cl$) with the appropriate alcoholate generated from R^1OH (Williamson ether synthesis).

The synthesis of 1-ethoxy-1-trimethylsilyloxy-ethene **5a** is described in the literature.[13] However, this method yielded a 1:3 mixture of **5a** and ethyl trimethylsilanyl acetate **5b**. A ratio of 1:1 was obtained when the procedure was slightly varied.

Scheme 2. Silylation of ethyl acetate **4b**.



4b **5a**[a] **5b**[a]

(*i*) THF, 1.3 eq. LDA, –78 °C, **4b**, 1 h, then 1.5 eq. Me_3SiCl, –78 → 20 °C in 16 h. [a] **5a**:**5b** = 1:1.

3 Reactions of γ-Azido-β-hydroxyketones

3.1 Introduction

Organic azides can be used for a large number of transformations in organic synthesis.[14] For example, the reaction of azides with triphenylphosphine (PPh_3) (Staudinger reaction)[15] has been applied to the synthesis of primary amines,[15,16] imines and a number of nitrogen heterocycles.[17] Pyrroles have been prepared by reaction of α-azidoketones with 1,3-dicarbonyl dianions,[18] of α-azidoketals with silyl enol ethers,[19] of 2-azido-1,1-dimethoxyethane with 1,3-bis-silyl enol ethers,[20] and of 2-azido-1,1-dimethoxyethane with 1,3-diketones.[21] Iminophosphoranes, generated by reaction of PPh_3 with organic azides, have also been reacted with other functional groups, such as epoxides,[22] alcohols,[23] phthalic anhydride,[24] and carboxylic acids.[25]

Langer *et al.* investigated the reaction of γ-azido-β-hydroxyketones with triphenylphosphine leading to 2-alkylidenepyrrolidines by an intramolecular domino[4] Staudinger-aza-Wittig reaction with subsequent migration of the double bond.[18] The products were reacted with trifluoroacetic acid (TFA) furnishing the corresponding pyrroles by elimination of water and migration of the exocyclic double bond.

In further studies a new PPh_3 mediated transformation of γ-azido-β-hydroxyketones was discovered.[26] The reaction of PPh_3 with 2-azido-1-hydroxy-1-(2,4-dioxoalkyl)cyclopentanes, obtained by addition of 1,3-dicarbonyl dianions to 2-azidocyclopentanones, yielded 1-(1,3-dioxoalkyl)amino-2-(alkylidene)cyclopentanes rather than the expected pyrrolidines or pyrroles. The formation of these unexpected products was explained by a domino “Staudinger / semi-aza-Wittig / fragmentation” reaction pathway.

The structural features of the γ-azido-β-hydroxyketones influenced the competition between the normal aza-Wittig and the domino “Staudinger / semi-aza-Wittig / fragmentation” reaction.[27,28] For example, the novel domino reaction was observed for 2-azido-1-hydroxy-1-(2,4-dioxoalkyl)cyclopentanes whereas for open-chained starting materials this reaction was observed only for 1,3-diketones, but not for β-ketoesters.

The aim of the present work was to investigate a possible extension of the new results to other substrates, especially those derived from 1-tosylpropan-2-one where a sulfonyl group is replacing a ketone or ester functionality.

3.2 Synthesis of Starting Materials

3.2.1 Synthesis of 1-Tosylpropan-2-one

β-Ketosulfones constitute a well known class of compounds and are readily available by reaction of sodium sulfinates with α-halogenated ketones.[29] 1-Tosylpropan-2-one **7** was obtained according to a procedure reported for the reaction of sodium tosylsulfinate with chloroacetone.[29a] This procedure was slightly varied.

3.2.2 Synthesis of Azidoketones

α-Azidoketones **6a-c** were prepared by treatment of the appropriate α-chloroketone with sodium azide either in methanol or in water in the presence of catalytic amounts of acetic acid.[30,31]

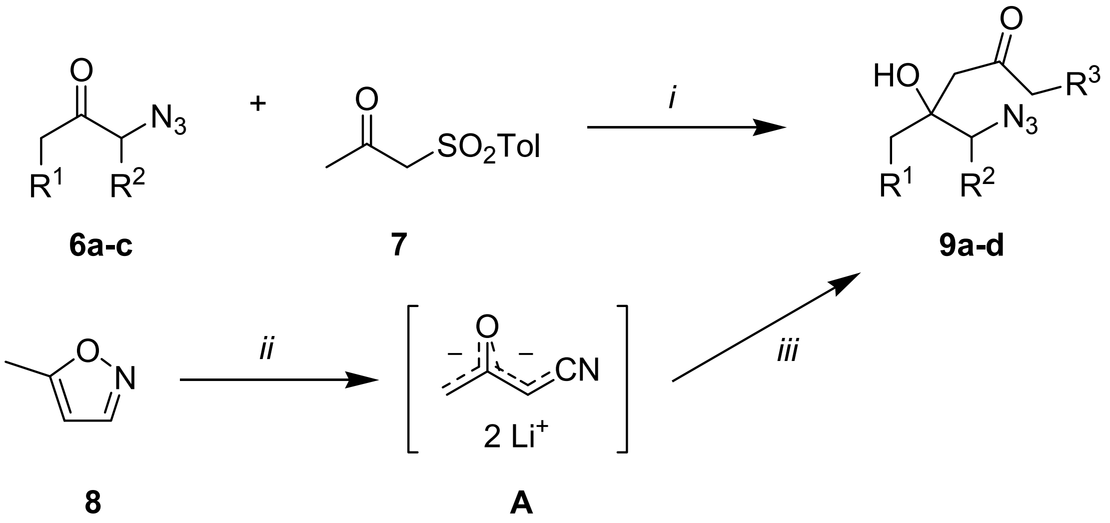
β-Azidoketone **13** was obtained from cyclohex-2-enone **12** and sodium azide in the presence of acetic acid.

3.2.3 Synthesis of γ- and δ-Azido-β-hydroxyketones

Synthesis of γ-azido-β-hydroxyketones **9a-c** was achieved by addition of the dianion[5a,32] of 1-tosylpropan-2-one **7** and α-azidoketones **6a-c**. The reactions were carried out under similar conditions as described previously for the additon of 1,3-dicarbonyl dianions and α-azidoketones.[26]

Compound **9d** was prepared by treatment of 5-methylisoxazole **8** with LDA[33] leading to the dianion **A** of α-cyanoacetone and subsequent addition of α-azidoketone **6c**.

Scheme 3. Synthesis of γ-azido-β-hydroxyketones **9**.



(*i*) THF, 2.4 eq LDA, 0 °C / –78 °C, **7**, 1 h, (then) –78 °C, **6a-c**, –78 → 20 °C; (*ii*) THF, 2.4 eq. LDA, –20 °C, 2 h; (*iii*) **6c**, –78 → 20 °C within 15 h, then 25 h 20 °C.

Table 1. Products and yields.

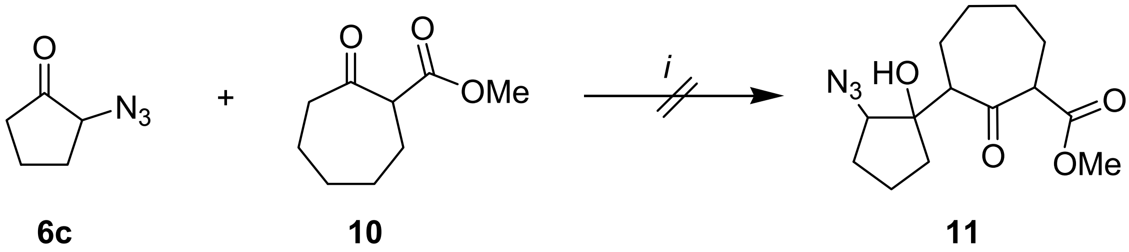
Educt	**Educt**	**9**	R^1	R^2	R^3	dr (**9**)[a]	% (**9**)[b]
6a	**7**	**a**	H	H	Tos	–	44
6b	**7**	**b**	H	Me	Tos	2 : 1	30
6c	**7**	**c**	$–(CH_2)_2–$		Tos	10 : 1	23
6c	**8**	**d**	$–(CH_2)_2–$		CN	≥ 5 : 1	7

[a] Diastereomeric ratio referring to the relative configurations of alcohol and azido group; [b] yields of isolated products.

γ-Azido-β-hydroxyketones **9** were obtained in moderate to low yields depending on the substituents R^1 – R^3. The yields decrease with increasing number of substituents, due to increasing steric hindrance and thus lower reaction rate (which favours side reactions, such as deprotonation of the azidoketone). At the same time, steric hindrance and conformational restriction result in a better diastereoselectivity when **9b** is compared to **9c** and **9d**. Compound **9d** was isolated in low yield only. This is partly due to the limits of column chromatography as impurities were difficult to be separated even after optimization of the eluent system. Therefore **9d** seems to be less readily accessible than its tosyl analogues under the conditions employed. The diastereoselectivity in the formation of **9d** was observed to be slightly lower than for **9c**, probably due to the smaller size of the cyano group compared to the tosyl group.

The attempt to synthesize compound **11** by addition of methyl 2-oxo-cycloheptanecarboxylate **10** and **6c** by the same methodology proved unsuccessful. Bringing together two cyclic compounds in this way probably fails due to steric reasons.

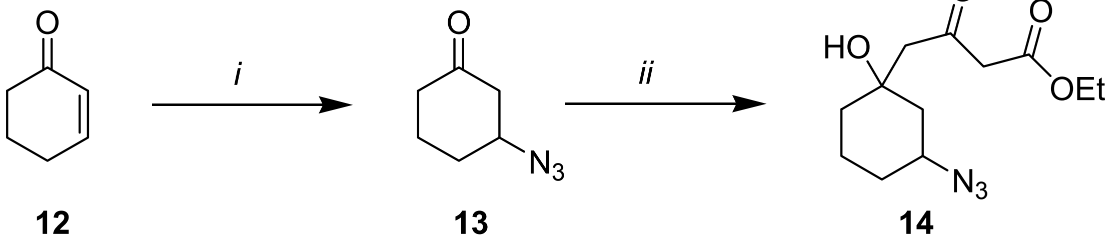
Scheme 4. Unsuccessful synthesis of a γ-azido-β-hydroxyketone containing two carbacycles.



(*i*) THF, 2.2 eq LDA, 0 °C, **10**, 1 h, then –78 °C, **6c**, –78 → 20 °C.

Similar to the γ-azido-β-hydroxyketones **6**, the cyclohexane derived δ-azido-β-hydroxyketone **14** was prepared by reaction of the dianion of ethyl acetoacetate with 3-azidocyclohexanone **13** in 75% yield. The diastereomeric ratio was 3:2.

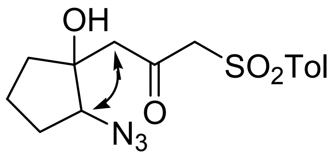
Scheme 5. Synthesis of δ-azido-β-hydroxyketone **14**.



(*i*) H_2O, NaN_3, CH_3COOH, 20 °C, 40 h; (*ii*) THF, 2.3 eq. LDA, CH_3COCH_2COOEt, 0°C, 1 h, then –78 °C, **13**, –78 → 20 °C in 14 h, then 4 h 20 °C.

The relative configurations of alcohol and azido group in compounds **9b-d** and **14** could not be unambiguously assigned. **9c** was studied by NMR techniques in order to determine the structures of the isomers. NOESY experiments showed NOE signals between the hydrogen atoms CHN_3 and at least one of the $C_{ring}CH_AH_B(C{=}O)$ hydrogens for both the main and the minor isomer. Therefore, an assignment was not possible by means of this experiment.

Scheme 6. Relevant NOE signals observed in **9c** for hydrogen atoms located at the carbons indicated.



9c

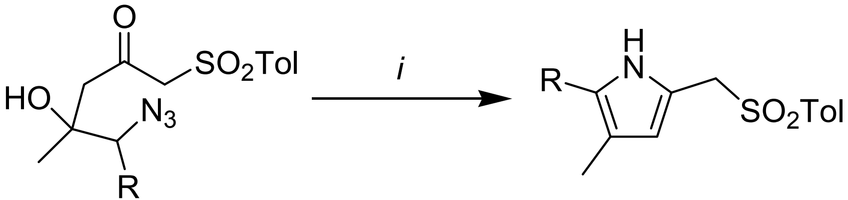
However, the signal of hydrogen atom CHN_3 is significantly shifted lowfield for the minor compared to the major diastereomer. A possible explanation for this lowfield shift is based on the assumption that the hydrogen atom CHN_3 of the minor isomer (presumably the *cis*-diastereomer) is located within the anisotropic cone of the carbonyl group. For steric reasons, this effect is not expected for the *trans*-diastereomer.

As no additions of nucleophiles to the carbonyl group of 2-azidocyclopentan-1-ones were found in the literature, it may be helpful to compare the results presented here with those of similar reactions. In fact, a number of reactions of enolates with 2-substituted cyclopentanones are published. In most of these reactions, the *cis*-configured diastereomers were predominantly formed,[34] i.e. the attack of the nucleophile mainly occurred from the sterically less hindered side. This does not necessarily mean that the attack is exclusively directed by steric effects as electronic effects may also be of great importance.

3.3 Reactions with PPh_3

On treatment with PPh_3, **9a** and **9b** were directly transformed into pyrroles **15a** and **15b** in moderate yield. This corresponds to an intramolecular domino Staudinger-aza-Wittig reaction followed by elimination of water. Thus, the pyrroles were formed in one reaction rather than in a sequence of two reactions as described by Langer *et al.* for a similar reaction. In that work hydroxypyrrolidines were isolated after initial reaction with PPh_3. The products were subsequently transformed into pyrroles by treatment with TFA.[18,28]

Scheme 7. Reactions of **9a,b** leading to pyrroles **15a,b**.



9a,b

a: R=H
b: R=Me

15a,b

(*i*) THF, PPh_3, 24 – 44 h, 45 °C.

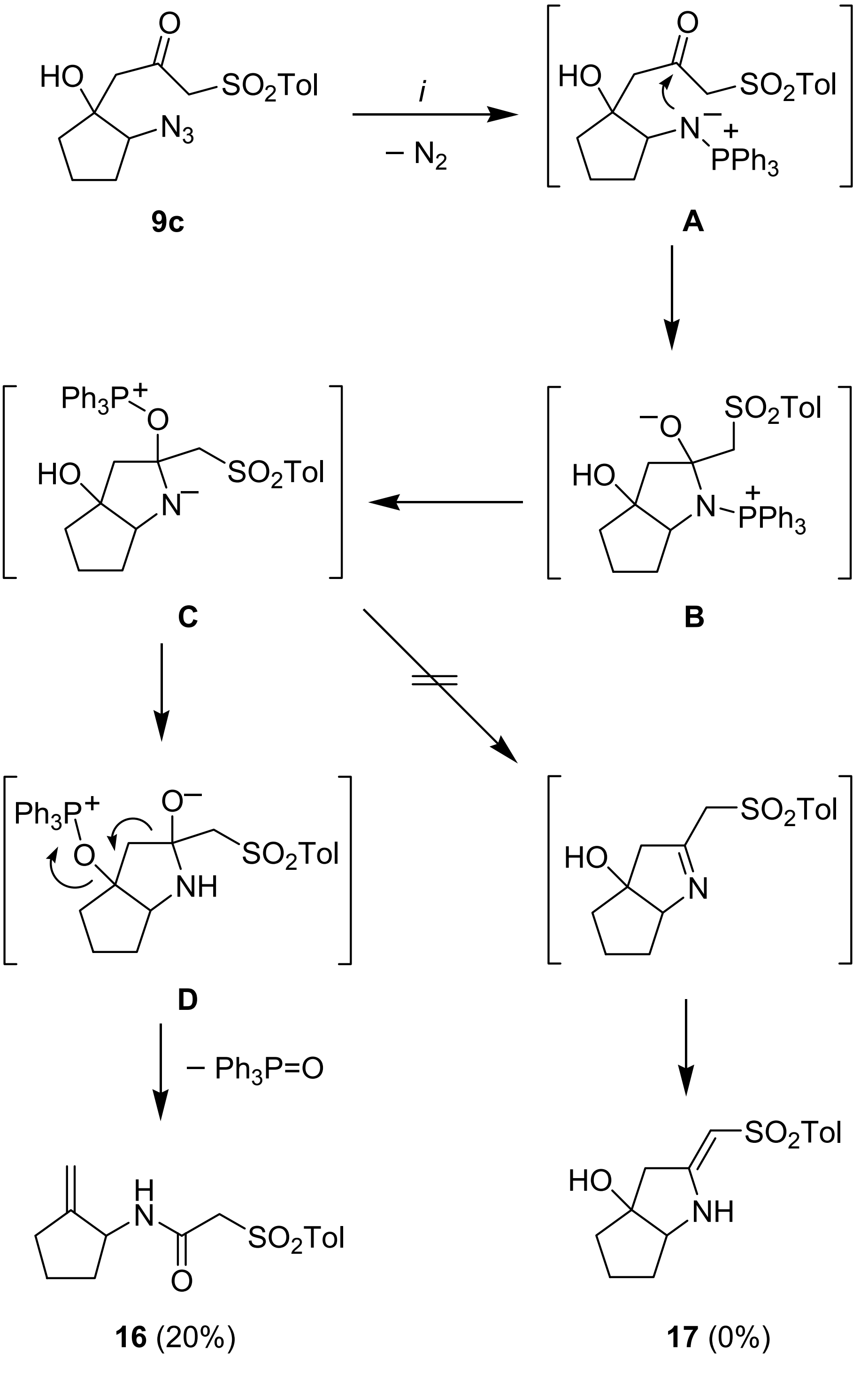
Table 2. Products and yields.

9	**15**	R	% (**15**)[a]
a	**a**	H	54
b	**b**	Me	27

[a] Yields of isolated products.

By contrast, the cyclic γ-azido-β-hydroxyketone **9c** showed a different behaviour. Treatment with PPh_3 led to the 1-amino-2-(methylidene)cyclopentane **16** in 20% yield (Scheme 8). This transformation can be explained by Staudinger reaction of the azide with PPh_3 to give the iminophosphorane **A** and attack of the nitrogen atom of **A** onto the carbonyl group (intermediate **B**), followed by a shift of the phosphonium moiety (intermediate **C**) and fragmentation (intermediate **D**) with extrusion of triphenylphosphine oxide. The overall process can be regarded as a domino[4] “Staudinger / semi-aza-Wittig / fragmentation” reaction. Despite the low yield, side-products such as **17**, which would be formed by a normal aza-Wittig reaction, could not be isolated.

Scheme 8. Possible mechanism for the formation of **16**.



(*i*) THF, PPh_3, 38 h, 45 °C.

Due to the low yield in the preparation of **9d** (*vide supra*) and a major loss of material after the ^{13}C-NMR-measurement, this compound was not further reacted with PPh_3.

Treatment of δ-azido-β-hydroxyketone **14** with triphenylphosphine resulted in a complex mixture. This may be explained by the fact that in this compound the azido group is located at the δ-position rather than at the γ-position as in all other structures under investigation (the γ-azido-analogue had already been found to lead to the corresponding bicyclic 2-alkylidene-pyrrolidine by Freifeld *et al.*[18,28]). After initial formation of the corresponding iminophosphorane an intramolecular attack onto the oxo group seems to be very unlikely, due to steric reasons and due to the conformational restriction of the six-membered ring. Instead, an intermolecular reaction potentially leading to oligomers or even polymers should be favoured.

3.4 Conclusion

The synthesis of tosyl-substituted γ-azido-β-hydroxyketones was carried out successfully. Regarding the competition between the domino “Staudinger / semi-aza-Wittig / fragmentation” reaction and the normal aza-Wittig reaction tosyl-substituted derivatives behave similar to their β-ketoester analogues (i.e. ethyl 4-(2-azido-1-hydroxyalkyl)-3-oxobutyrates).[18,26,27]

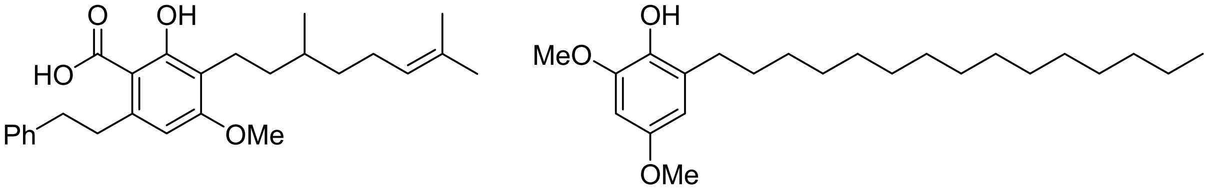
The open-chained examples followed the normal aza-Wittig pathway with subsequent elimination of water resulting in the formation of pyrroles. The cyclopentane derivative showed a different behaviour and followed the domino sequence. In conclusion, the results outlined herein contribute to the understanding of the chemical behaviour of γ-azido-β-hydroxyketones towards PPh_3.

4 Synthesis of Functionalized Acetophenones and Cyanobenzoates by [3+3] Cyclizations

4.1 Introduction

Functionalized acetophenones are present in a number of pharmacologically relevant natural products and natural product analogues[35] and are useful synthetic building blocks. Alkylated phenols and salicylates occur in natural products,[35] such as amorfrutin B,[36] hierridin B,[37] 5-chloroflexirubin[38] as well as belamcandol A.[39]

Figure 1. Amorfrutin B and hierridin B.



Amorfrutin B

Hierridin B

Chan and co-workers introduced an elegant synthesis of salicylates by cyclization of 1,3-bis-silyl enol ethers with 1,1,3,3-tetramethoxypropane or 3-silyloxyalk-2-en-1-ones.[10a,40] This methodology has been applied to the synthesis of various arenes[41] and can be considered as a powerful tool for the formation of six-membered carbacycles, especially when the substitution pattern is difficult to obtain by alternative methods.

In this work, the method of Chan was applied to the construction of functionalized acetophenones and 3-cyano-6-hydroxy-2,4-dimethylbenzoates.

4.2 Synthesis of Starting Materials

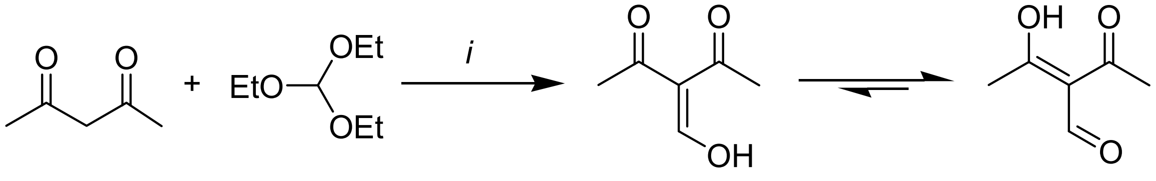
The synthesis of 1,3-bis-silyl enol ethers is described in Chapter 2 as their precursors – mono-silyl enol ethers derived from β-keto-esters and unsubstituted acetylacetone – are also relevant for Chapter 6.

4.2.1 Substituted Acetylacetones

4.2.1.1 3-Formylacetylacetone

The synthesis of 3-formylacetylacetone **19a** was carried out according to a procedure described by Sankar *et al.*[42] from acetylacetone, triethyl orthoformate and acetic acid anhydride.

Scheme 9. Synthesis of 3-formylacetylacetone **19a**.



1a **18** **19a**$_{\text{minor}}$ **19a**$_{\text{major}}$

(*i*) Ac_2O, reflux, 3 h, then H_2O, reflux, 10 min.

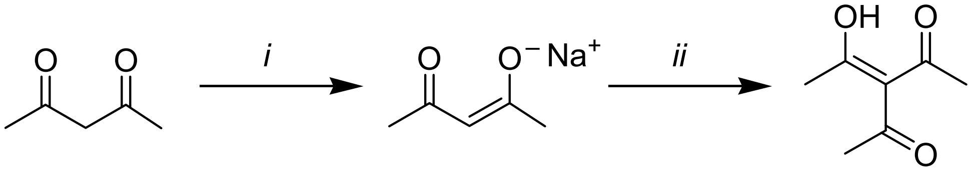
It was assumed for a long time that **19a** exists as 3-(hydroxymethylidene)acetylacetone **19a**$_{\text{minor}}$.[42,43] However, it was later shown that **19a** mainly resides as 3-formyl-4-hydroxypent-3-en-2-one **19a**$_{\text{major}}$.[44,45]

Both tautomers are observed in the ^1H NMR spectrum. The observed ratio ($CDCl_3$, 25 °C) **19a**$_{\text{major}}$: **19a**$_{\text{minor}}$ is approximately 4 : 1. The main isomer shows one singlet for both CH_3 groups at 2.54 ppm indicating a fast proton exchange between the hydroxy- and keto group in **19a**$_{\text{major}}$ on the NMR timescale resulting in the spectroscopic equivalence of both methyl groups for the main isomer **19a**$_{\text{major}}$. By contrast, the CH_3 groups of **19a**$_{\text{minor}}$ give two separate singlets at 2.34 and 2.57 ppm. The CHO signal of **19a**$_{\text{major}}$ is observed as a singlet at 10.03 ppm. The CH signal of **19a**$_{\text{minor}}$ is a doublet located at 8.98 ppm. The signals of the OH protons are strongly shifted lowfield and are detected at 18.36 and 17.20 ppm for the major and minor tautomers, respectively. The latter appears as a doublet (coupling with the CH group, $^3J = 7.0$ Hz).

4.2.1.2 Triacetylmethane

Triacetylmethane **19b** was prepared from acetylacetone, sodium hydride and acetylchloride according to a literature procedure.[46]

Scheme 10. Synthesis of triacetylmethane **19b**.



1a **20** **19b**

(*i*) Et_2O, 0 °C, NaH; (*ii*) CH_3COCl, then 0 → 20 °C in 3 h, then 12 h 20 °C.

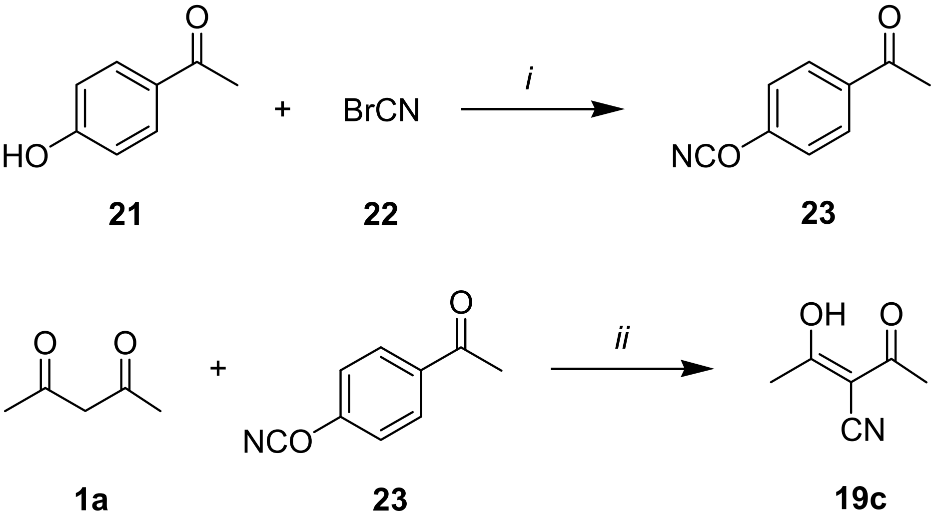
19b resides in the enolic form. The ^1H NMR spectrum shows a singlet at 2.24 representing two methyl groups, a singlet at 2.44 for one methyl group and a singlet at 17.23 ppm for the OH group. This indicates that only two carbonyl groups are involved in the tautomeric exchange of the proton at a time while the third one remains temporarily unaffected.

4.2.1.3 3-Cyanoacetylacetone

3-Cyanoacetylacetone **19c** (residing as the tautomeric 2-acetyl-3-hydroxy-but-2-enenitrile) was prepared according to a literature procedure[47] from acetylacetone and 1-(4-cyanatophenyl)-ethanone[48] **23**.

Compound **19c** is present in the enolic form ($CDCl_3$, 25 °C). In the ^1H NMR spectrum one singlet at 2.39 represents both methyl groups and the OH is located at 16.82 ppm. Again, the proton exchange between the hydroxy- and keto group is fast on the NMR time-scale.

Scheme 11. Synthesis of 3-cyanoacetylacetone **19c**.



(*i*) Acetone, NEt_3, –10 °C; (*ii*) Et_2O, EtOH, NaOEt, then **1a** in Et_2O, 0 °C, then **23** in THF, 0 °C, 1 h, then 20 °C, 20 h.

4.2.2 Silylation of Substituted Acetylacetones

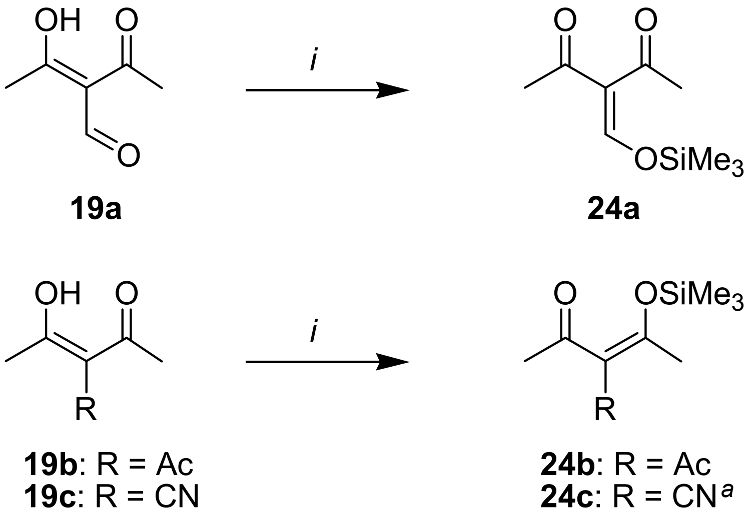
Only few reactions of **19a** have been published in the literature.[42,45] The first attempt to perform the silylation of **19a** by reaction with Me_3SiCl/NEt_3 resulted in the formation of a complex mixture. The reaction was successful and **24a** was obtained when Me_3SiOTf/NEt_3[12] was applied. Compounds **19b** and **19c** were transformed in the same way into their silyl enol ether derivatives **24b**[49] and **24c**. Silylations were performed in good yields (Table 3). The reaction of **19a** proceeded regioselectively by silylation of the formyl rather than an acetyl group.

Table 3. Products and yields.

Entry	% (**19**)[a]	% (**24**)[b]
a	55	88
b	53	84
c	37	88

[a] Yields of isolated products; [b] used without further purification.

Scheme 12. Silylation of **19a,b,c**.



(*i*) Et_2O, NEt_3, Me_3SiOTf, 0 °C, 4.5 – 6 h. [a] For **24c** (R = CN) *E*- and *Z*-isomers were observed.

4.3 [3+3] Cyclizations

4.3.1 Synthesis of Functionalized Acetophenones

4.3.1.1 Products and Reaction Pathway

The mono-silyl enol ethers **24a** and **24b** were reacted with 1,3-bis-silyl enol ethers **3a-k** under similar conditions as described by Chan and co-workers[40] to give the functionalized acetophenones **25a-p** by a [3+3] cyclization (Scheme 13, Table 4).

The regioselective formation of products **25a-k** can be explained based on general observations reported by Chan:[11,40] An initial conjugate addition of the carbon atom C4 of the 1,3-bis-silyl enol ether **3a-k** onto **24a** gave intermediate **A**, cyclization afforded intermediate **B**, and – presumably upon work-up – aromatization gave the final product. The regioselective conjugate addition in the first step can be explained by coordination of the 1,3-diketo moiety of **24a** with $TiCl_4$ enhancing the electrophilicity of the carbon atom attached to the silyloxy group.[40] Transmetallation and formation of a titanium enolate are possible as well.

For **24b** the position of the initial attack has no influence on the final constitution of the products (**25l-p**) as a methyl group is located at both postitons *ortho* to the acetyl group in any case.

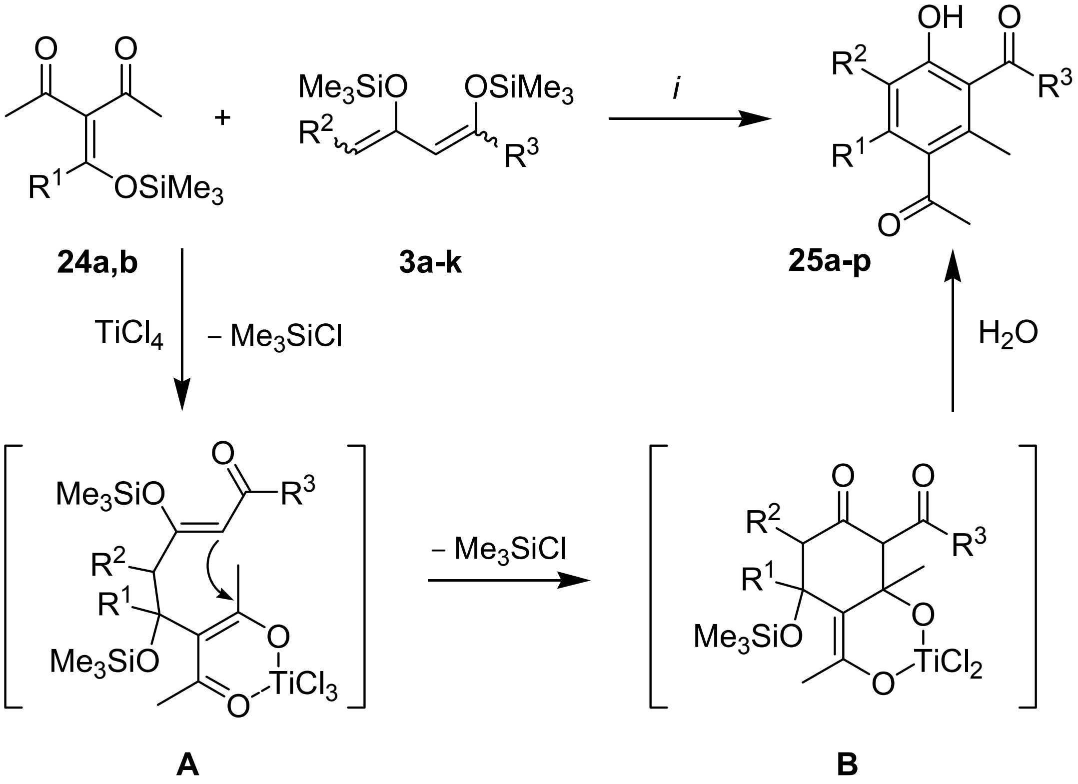
For the cyclization of **24a** and **24b** the best results were obtained when 1.4 equivalents of the bis-silyl enol ether and 1–1.15 equivalents of $TiCl_4$ were used. Changes in yield by a factor of up to 5 were observed when 1.0 or 2.1 equivalents of the bis-silyl enol ether were employed. Apparently, an excess of the bis-silyl enol ether enhances the yield. This may be explained by partial decomposition under the conditions employed, whereas the presence of an excess of bis-silyl enol ether may cause an over-addition (formation of 2:1 open-chain products). Such interference may be explained by the fact that, after the initial attack of the bis-silyl enol ether (Scheme 13, intermediate **A**), different reaction paths are possible. One possibility is an intramolecular attack (cyclization) resulting in the formation of the desired products. Other pathways may involve the competitive (intermolecular) attack of another bis-silyl enol ether (which is a stronger nucleophile) than cyclization by attack of the mono-silyl enol ether moiety. Thus, the presence of a large excess of **3a-k** will decrease the yields.

The preparative scope was studied by systematic variation of the substituents of the 1,3-bis-silyl enol ether (Scheme 13, Table 4). Substituent R^1 is introduced by the mono-silyl enol ether and can be hydrogen or methyl for **24a** and **24b**, respectively. Substituents R^2 and R^3 are introduced by the respective bis-silyl enol ether. For R^2, alkyl, allyl, and alkoxy were chosen. Substituent R^3 covers methyl, alkoxy, and benzyloxy substituents.

For acetophenones derived from **24a** (**25a-k**), alkyl and allyl substituents located at position R^2 significantly enhance the yields whereas alkoxy substituents lead to lower yields compared to their R^2 = H analogues. This may be explained by electronic effects, since the inductive effect of alkyl substituents will enhance the nucleophilicity (and thus the reactivity towards the electrophile) of carbon C4. Alkoxy substituents at the same position are expected to have a contrary effect, since the lone pairs of the oxygen will stabilize the neighbouring double bond and reduce the reactivity of the nucleophilic centre.

Acetophenones derived from **24b** (**25l-p**) generally were obtained in lower yields than their analogues synthesized from **24a** which have no extra methyl substituent (R^1). The presence of alkyl substituents (R^2) further reduce the yields. These effects can be explained by steric reasons. Due to the presence of the methyl group (R^1), the initial conjugate addition of carbon atom C4 of the 1,3-bis-silyl enol ether (see the mechanism proposed in Scheme 13) is expected to be more difficult. The presence of a substituent R^2 (other than hydrogen) will also hinder the nucleophilic attack. The results reported herein indicate that, in the cases under investigation, the positive effect of enhanced nucleophilicity of the 1,3-bis-silyl enol ether is outweighed by steric effects.

Scheme 13. Reactions of **24a,b** and possible mechanism.



(*i*) CH_2Cl_2, molecular sieves (4 Å), $TiCl_4$, –78 → 20 °C in 20 h, then 20 °C (various reaction times).

Table 4. Products and yields.

24	**3**	**25**	R^1	R^2	R^3	% (**25**) ^{a}
a	**a**	**a**	H	H	Me	35
a	**b**	**b**	H	H	OMe	55
a	**c**	**c**	H	H	OEt	39
a	**d**	**d**	H	H	OBn	33
a	**e**	**e**	H	H	OCH_2CH_2OMe	14
a	**f**	**f**	H	Me	OMe	72
a	**g**	**g**	H	Et	OEt	59
a	**h**	**h**	H	*n*Bu	OMe	77
a	**i**	**i**	H	Allyl	OEt	74
a	**j**	**j**	H	OMe	OMe	35
a	**k**	**k**	H	OEt	OEt	29
b	**a**	**l**	Me	H	Me	29
b	**b**	**m**	Me	H	OMe	41
b	**c**	**n**	Me	H	OEt	33
b	**f**	**o**	Me	Me	OMe	24
b	**h**	**p**	Me	*n*Bu	OMe	21

^{a} Yields of isolated products.

4.3.1.2 Proof of Structure

Depending on the site of initial attack of **3a-k** on **24a** (R^1 = H), the formation of two regioisomers is possible. In these isomers R^1 can be located *ortho* or *para* to R^2. In all reactions, the products containing R^1 *ortho* to R^2 were regioselectively formed.

For R^1 = R^2 = H (**25a-e**) the structures were elucidated by means of one-dimensional ^{1}H NMR spectroscopy where aromatic coupling constants $^3J = 8.7 – 8.8$ Hz were found. These values are typical for an *ortho* coupling constant and can be well distinguished from *para* coupling constants.

For **25f-k**, the one-dimensional ^{1}H NMR spectra are consistent with both possible regioisomers as there is only one aromatic proton left. NOESY experiments were carried out to overcome this problem for **25f-i** and **25k**.

For **25j**, the NOESY experiment would have been very difficult to interpret correctly. The methyl groups have similar chemical shifts (δ = 2.47 and 2.54 ppm). The same is true for the methoxy moieties (δ = 3.91 and 3.98 ppm). Moreover, NOESY correlations are possible between the aromatic proton and the protons of one methoxy moiety in *both* regioisomers. Additional correlations might be observed between the aromatic methyl substituent and the other methoxy group – again in *both* isomers. In order to avoid ambiguous results and additional experiments for the correct assignment of the methoxy groups the structure of **25j** was confirmed by single-crystal X-ray diffraction (Scheme 14).

For **25l-p**, no regioisomers are expected (*vide supra*). Thus the structures were confirmed by standard methods (^{1}H and ^{13}C NMR, MS etc.).

Scheme 14. X-ray structure of **25j**; thermal ellipsoids represent 50% probability.

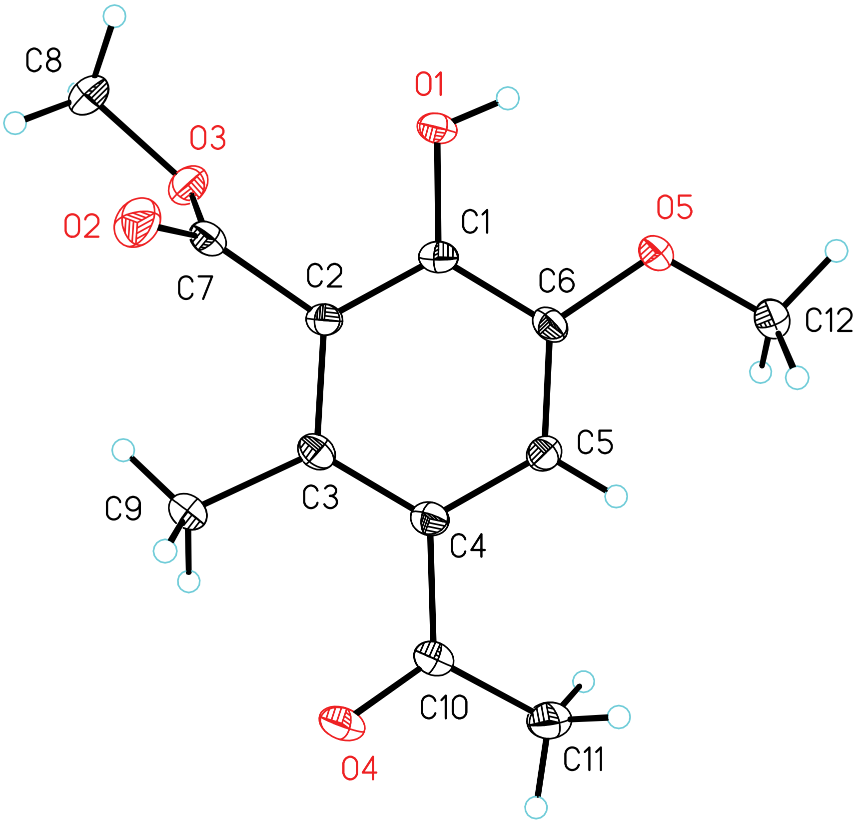
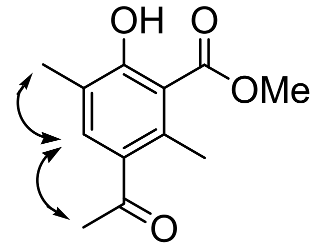
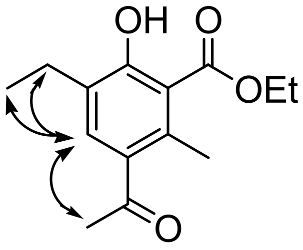
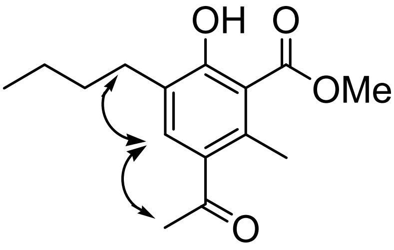
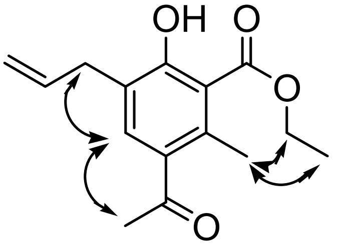
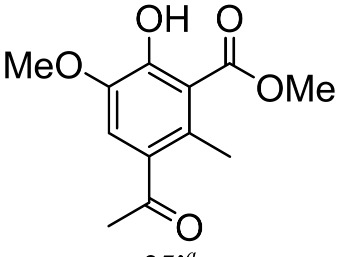
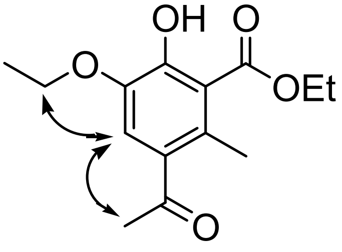


Table 5. Results of NOESY experiments for **25f-i** and **25k**. Arrows show relevant correlations between hydrogen atoms attached to the carbon atoms indicated.

 **25f**	 **25g**	 **25h**
 **25i**	 **25j**[a]	 **25k**

[a] X-ray structure measured instead of NOESY, compare Scheme 14.

In **25f** the aromatic hydrogen atom at δ = 7.47 correlates with the aromatic methyl group at 2.25 and the acetyl group at 2.53.

In **25g** the aromatic hydrogen atom at δ = 7.46 correlates with the aromatic ethyl group represented by a triplet at 1.22 and a quartet at 2.67 as well as with the acetyl group at 2.53.

In **25h** the aromatic hydrogen atom at δ = 7.45 correlates with the acetyl group at 2.53 and the aromatic methylene group giving rise to a triplet at 2.64.

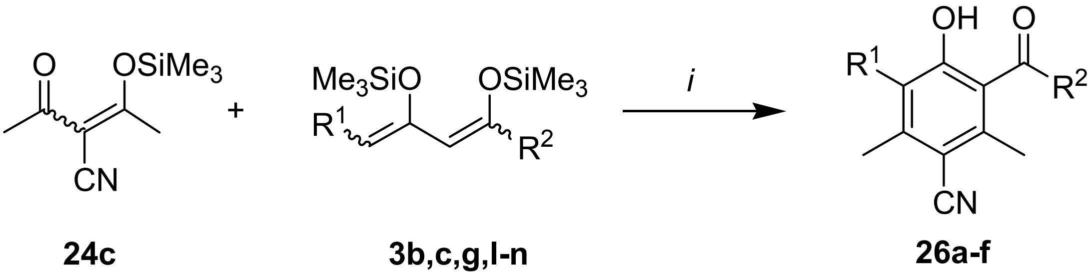
In **25i** the aromatic hydrogen atom at δ = 7.47 correlates with the acetyl group at 2.54 and the aromatic methylene group represented by a doublet at 3.42. In addition, the aromatic methyl group at 2.60 was found to correlate with the ethoxy group represented by a triplet at 1.44 and a quartet at 4.47.

In **25k** the aromatic hydrogen atom at δ = 7.15 correlates with the acetyl group at 2.53 and a quartet at 4.13 belonging to the methylene substructure of the aromatic ethoxy substituent. This assignment can be considered to be unambigious since the quartet at 4.13 is well separated from the quartet at 4.45 which belongs to the ester moiety which in turn is not expected to be strongly affected by a change in substitution of the aromatic ring. The methylene groups of the analogous ethyl esters **25g** and **25i** are found as quartets at 4.45 and 4.47 ppm in the corresponding ^{1}H NMR spectra, respectively.

4.3.2 Synthesis of Cyanobenzoates

The reaction of **24c** with 1,3-bis-silyl enol ethers **3b,c,g,l-n**, carried out under similar conditions as described in Chapter 4.3.1 and by Chan,[40] yielded salicylates **26a-f** by [3+3] cyclization (Scheme 15, Table 6).

Scheme 15. Reactions of **24c**.



(*i*) CH_2Cl_2, molecular sieves (4 Å), $TiCl_4$, –78 → 20 °C in 20 h, then 4 h 20 °C.

Table 6. Products and yields.

3	26	R^1	R^2	% (**26**)[a]
b	**a**	H	OMe	34
c	**b**	H	OEt	41
l	**c**	H	O*i*Bu	39
m	**d**	H	O*t*Bu	8
n	**e**	Et	OMe	44
g	**f**	Et	OEt	58

[a] Yields of isolated products.

The presence of an ethyl substituent R^1 (**26e,f**) led to increased yields compared to the presence of a hydrogen substituent R^1. This is probably due to the increased nucleophilicity of the bis-silyl enol ether because of the inductive effect of the alkyl group (compare Chapter 4.3.1).

Different alkoxy substituents R^2 proved to be applicable. The use of methyl and phenyl groups in this position resulted in complex mixtures and the desired products could not be isolated. The low yield for R^2 = *tert*-butoxy (8%, **26d**) can be explained by partial cleavage of the *tert*-butyl ester caused by traces of HCl formed during the reaction.

4.4 Conclusion

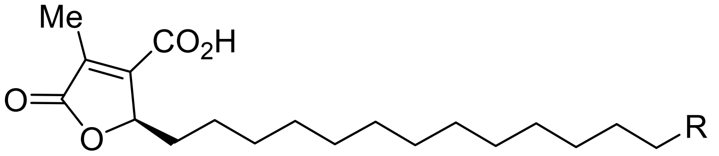
In summary, the cyclization of various 1,3-bis-silyl enol ethers with 2-acetyl-3-silyloxyalk-2-en-1-ones, derived from 3-formylacetylacetone and triacetylmethane, and with 2-acetyl-3-trimethylsilyloxy-but-2-enenitrile, derived from 3-cyanoacetylacetone, afforded various functionalized acetophenones and different 3-cyano-6-hydroxy-2,4-dimethylbenzoates in good to moderate yields. Where possible, products were regioselectively formed.

5 Synthesis of 4-Alkoxycarbonyl-butenolides

5.1 Introduction

4-Carboxy-, 4-alkoxycarbonyl-, and 4-acyl-butenolides are of considerable pharmacological relevance and occur in a variety of natural products.[50,51] This includes, for example, (+)- and (−)-lichesterolic acid,[52] neuropogolic acid,[53] isomuronic acid (Figure 2),[53a] (+)-praesorediosic acid,[54] dihydroconstiputic acid,[55] paniculid C,[56] medium-sized bicycles, such as 8,14-dioxo-7,11-dehydro-11,13-dihydroacanthospermolide,[57] cyclospinosolide,[58] pachycla-vulariolide P,[59] and phlogacanthoside B.[60] 4-Alkoxycarbonyl-butenolides are also important synthetic building blocks. For example, (+)-nephrosteranic acid and related γ-lactones were prepared by diastereoselective hydrogenation of 5-alkyl-3-mesyloxy-4-ethoxycarbonyl-butenolides.[61] Isotetronic acid derivatives, containing a hydroxy group at carbon atom C-3 of the butenolide moiety, are also occurring in many natural products. This includes (+)-leptosphaerin[62] and compound WF-3681,[63] distomadine B,[64] various ascorbic acid derivatives,[65] and many other pharmacolocically relevant natural products.[66] Isotetronic acids have been used also as synthetic building blocks during the synthesis of (–)-tetrodotoxin,[67] 6-thiosialic and neuraminic acids,[68] nactins,[69] and erythronolide A.[70]

Figure 2. Naturally occurring 4-carboxy-butenolides.



R = H: (+)-Lichesterolic acid
R = CH(OH)Me: Neuropogolic acid
R = COMe: Isomuronic acid

3-Hydroxy-4-alkoxycarbonyl-butenolides and related structures have been previously prepared mainly by base-mediated cyclization reactions. This includes the reaction of pyruvates with aldehydes,[69,71] of benzaldehyde with dimethyl methoxyfumarate,[72] of acetophenones with formaldehyde and diethyl oxalate,[73] and by DABCO mediated dimerization of methyl 2,4-dioxopentanoate.[74] A different approach relies on the PPh_3 mediated reaction of ketones with methyl acetoxypropynoate.[75] Nair *et al.* reported the synthesis of spirocycles based on PPh_3 mediated reactions of 1,2-quinones.[76] Saalfrank and coworkers reported the synthesis of 5-alkylidene-3-hydroxy-4-alkoxycarbonyl-butenolides by cyclization of 1,3-dicarbonyl compounds with oxalyl chloride.[77] Sonoda and co-workers reported the synthesis of 2,3-dioxo-2,3-dihydrofurans by cyclization of acetophenone derived silyl enol ethers with oxalyl chloride.[78]

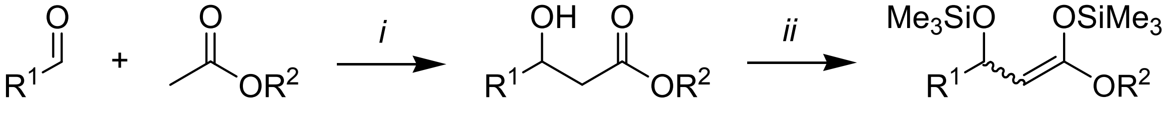
Some time ago, Langer *et al.* developed an efficient approach to 3-hydroxy-5-alkylidene-butenolides by cyclization of 1,3-bis(silyloxy)buta-1,3-dienes[11] with oxalyl chloride.[51]

In the present studies[79,80] a new and convenient one-pot synthesis of 3-hydroxy-4-alkoxycarbonyl-butenolides was developed. This method relies on the cyclization of oxalyl chloride with 1-alkoxy-1,3-bis(silyloxy)alk-1-enes[81] which can be regarded as bis-silylated 3-hydroxyesters. This includes the synthesis of an enantiomerically pure butenolide. The products could be further functionalized by Suzuki reactions.

5.2 Synthesis of Starting Materials

The 3-hydroxyesters **28** are readily available by aldol reaction of alkyl acetates **4** with the corresponding aldehyde **27**.[82,83] The 1-alkoxy-1,3-bis(silyloxy)alk-1-enes **29** are obtained by twofold deprotonation and subsequent reaction with chlorotrimethylsilane (Scheme 16, Table 7).

Scheme 16. Synthesis of 3-hydroxyesters **28** and silyl enol ethers **29**.



27a-o **4a-c** **28a-p** **29a-i,k-n,p**

(*i*) THF, 1 eq. LDA, –78 °C, **4**, 1 h, **27**, 3–5 min, then HCl (2 M); (*ii*) THF, 2.2 eq. LDA, –78 °C, **28**, 1 h, then Me_3SiCl, –78 → 20 °C in 14 – 24 h.

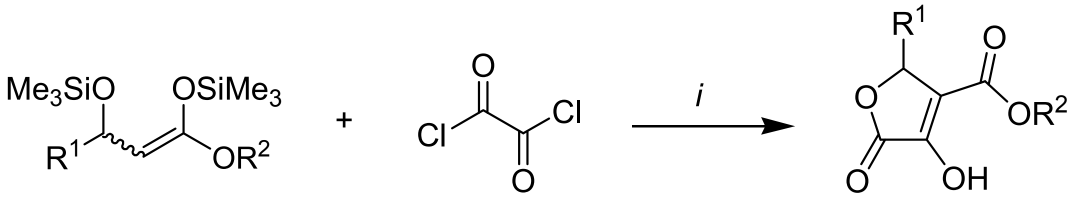
5.3 Cyclizations with Oxalyl Chloride

5.3.1 Products

The cyclization of **29** with oxalyl chloride **30** afforded the 3-hydroxy-4-alkoxycarbonyl-butenolides **31**. The best yields were obtained when the reactions were carried out *without* the presence of a Lewis acid.

Likewise, the reaction of 1,3-bis(silyl enol ethers) with simple acid chlorides[84] and the condensation of silyl ketene acetals with oxalyl chloride[85] were reported to be best carried out in the absence of Lewis acid. In contrast, the cyclization reactions of 1,3-bis(silyl enol ethers)[51] and 1,1-bis(silyloxy)ketene acetals[86] with oxalyl chloride were reported to require the use of catalytic amounts of Me_3SiOTf.

Scheme 17. Synthesis of 4-alkoxycarbonyl-butenolides.



29a-i,k-n,p **30** **31a-i,k-n**

(*i*) CH_2Cl_2, –78 → 20 °C in 15–24 h.

Most butenolides **31** were isolated in moderate to good yields. The relatively low yields of **31e** and **31g** can be explained by steric hindrance of the *tert*-butyl group and cleavage of the *tert*-butyl ester (by traces of HCl formed during the cyclization), respectively.

The synthesis of **31j** failed as the precursor **29j** could not be synthesized in pure form, probably due to the CH-acidic nature of the propenyl moiety in **28j** which may be a problem during the reaction with LDA. The synthesis of the vinyl analogue was reported to be successful,[79,80,87] albeit, in relatively low yield because of the labile vinyl group.

By contrast, **31i** carrying a decenyl group containing a terminal double bond was synthesized in 83% yield which marks the best yield observed for compounds **31**.

Products **31o** and **31p** were not formed. The 3-hydroxyester **28o** was observed to rapidly eliminate water upon standing in solution (about 50% in less than one day at 20 °C in chloroform). Due to this instability, the synthesis of silyl enol ether **29o** proved problematic.

Presumably, **28o** decomposes under the reaction conditions; alternatively, the product **29o** may be unstable itself and prone to decomposition. As a result, **29o** could not be synthesized in pure form and, after reaction with oxalyl chloride, the desired butenolide **31o** could not be isolated.

The disturbing influence of the pyridyl moiety probably is the reason why **31p** is not formed, although the precursor **29p** was obtained in acceptable purity.

Table 7. Products and yields.

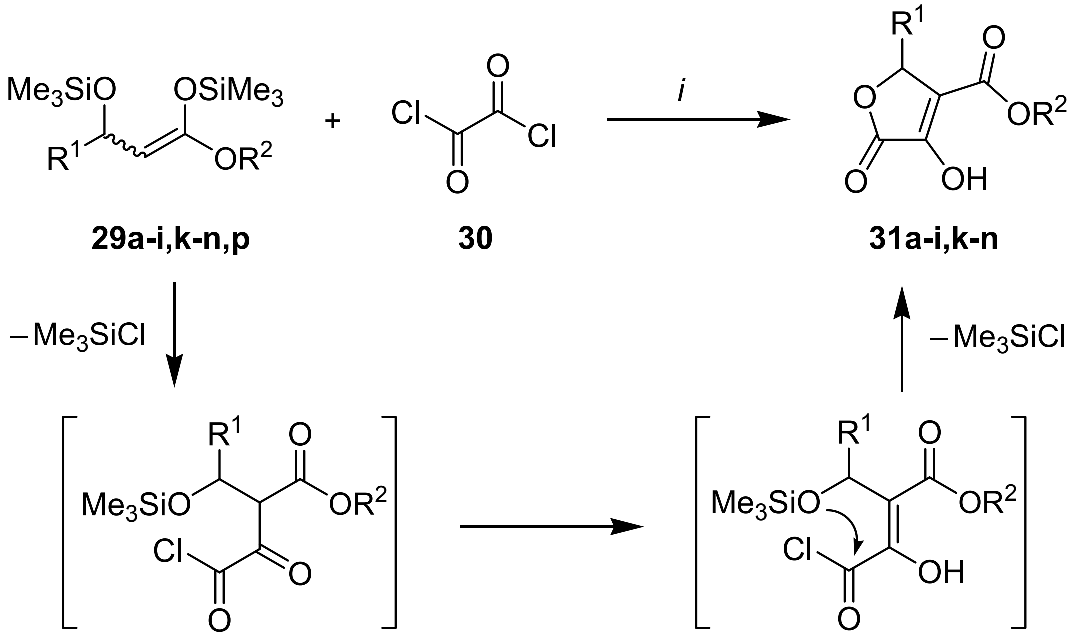
27	**4**	**Entry**	R^1	R^2	% (**28**)[a]	% (**29**)[b]	% (**31**)[a]
a	**a**	**a**	Me	Me	54	73	52
b	**b**	**b**	Et	Et	83	99	77
c	**b**	**c**	*i*Pr	Et	78[c]	86[c]	54
d	**b**	**d**	*n*Bu	Et	83	100	75
d	**c**	**e**	*n*Bu	*t*Bu	92	76	21
e	**b**	**f**	*i*Bu	Et	62[c]	75[c]	63
f	**a**	**g**	*t*Bu	Me	60	73	35
g	**a**	**h**	*n*Hex	Me	65	91	61
h	**b**	**i**	$CH_2=CH(CH_2)_8$	Et	65	93	83
i	**b**	**j**	(*E*)-$CH_3CH=CH$	Et	88	≤ 80[d]	0
j	**b**	**k**	Ph	Et	78	92	62
k	**b**	**l**	*p*-MeC_6H_4	Et	73	95	67
l	**b**	**m**	*p*-ClC_6H_4	Et	76	95	43
m	**b**	**n**	*o*-$MeOC_6H_4$	Et	37[e]	88	60
n	**b**	**o**	2,4-$(MeO)_2C_6H_3$	Et	16[f]	≤ 79[d]	0
o	**b**	**p**	Pyridin-3-yl	Et	46	80	0

[a] Yields of isolated products; [b] used without further purification; [c] synthesis by Lars Michaelis;[79,80,87] [d] structure not proved due to unclean product; [e] only 55% of the raw product were used for column chromatography; [f] additional 69% were collected but partly decomposed in solution.

5.3.2 Mechanism

The cyclization reaction can be rationalized by nucleophilic attack of the bis-silyl enol ether **29** onto oxalyl chloride and formation of one equivalent of Me_3SiCl in the first step. After tautomerization, the cyclization occurred by nucleophilic attack onto the second acid chloride group with extrusion of one more equivalent of Me_3SiCl. A different order of the bond formation cannot be excluded.

Scheme 18. Proposed reaction pathway.

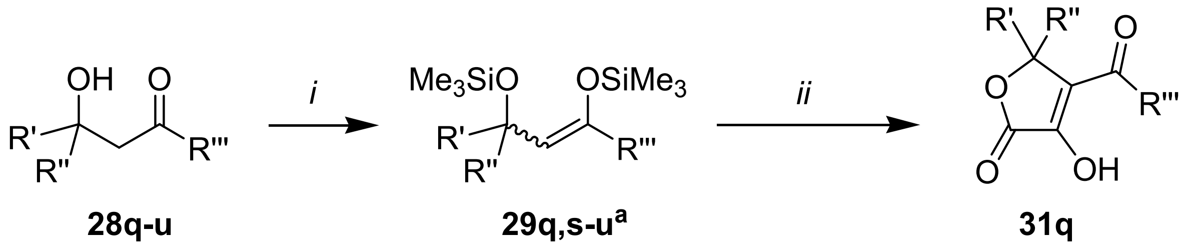


(*i*) CH_2Cl_2, –78 → 20 °C in 15–24 h.

5.3.3 Further Experiments

Table 8 shows the results of attempts to introduce a second alkyl substituent into the ring and to replace the ester by a keto moiety (i.e. to use 3-hydroxyketones rather than 3-hydroxyesters).

Scheme 19. Further syntheses.



(*i*) THF, 2.2 eq. LDA, –78 °C, **28**, 1 h, then Me_3SiCl, –78 → 20 °C in 14 – 24 h; (*ii*) CH_2Cl_2, **30**, –78 → 20 °C in 15–24 h. [a] for **29s** the isomer with a terminal double bond (derived from the kinetic enolate) was formed.

For this purpose the same methodology as described above was applied. The 3-hydroxyketones and 3-hydroxyesters were synthesized by simple aldol reactions.

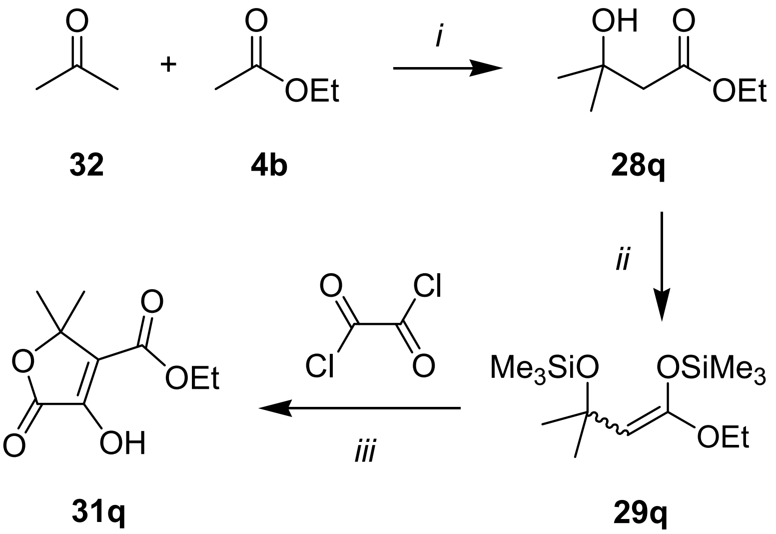
Table 8. Products and yields.

Entry	R'	R"	R'''	% (**28**)[a]	% (**29**)[b]	% (**31**)[a]
q	Me	Me	OEt	77	35	21
r	–$(CH_2)_5$–		OEt	94	0[c]	–
s	H	Et	Me	37	82[d]	–
t	H	Me	Ph	60	96	0
u	H	Et	*o*-$MeOC_6H_4$	65	86	0

[a] Yields of isolated products; [b] used without further purification; [c] only one trimethylsilyl group was incorporated into the molecule rather than two, probably due to steric reasons; [d] the isomer with a terminal double bond (derived from the kinetic enolate) was formed.

The cyclization of oxalyl chloride with 1,3-bis(silyloxy)alk-1-ene **29q**, prepared from acetone and ethyl acetate, gave the 5,5-dimethyl-butenolide **31q** in low yield, presumably due to the increased steric impact (R' ≠ H).

Scheme 20. Synthesis of **31q**.



(*i*) THF, 1 eq. LDA, –78 °C, **4b**, 1 h, then –60 °C, **32**, 10 min, then HCl (2 M); (*ii*) THF, 2.2 eq. LDA, –78 °C, **28q**, 1 h, then Me_3SiCl, –78 → 20 °C in 14 h; (*iii*) CH_2Cl_2, –78 → 20 °C in 22 h.

The conversion of **28r**, containing a cyclohexane moiety, failed, probably for steric reasons. Only one trimethylsilyl group was incorporated into the molecule.

Hydroxyketone **28s** yielded its bis-silyl derivative **29s**. However, it turned out that the isomer containing a terminal double bond (derived from the kinetic enolate) was formed which was not suitable for further reactions.

Arylketones were successfully reacted with aldehydes to yield compounds **28t** and **28u**. Their bis-silyl derivatives **29t** and **29u** could be formed as well. Their reaction with oxalyl chloride did not yield any of the desired products (both in the presence or absence of Me_3SiOTf).

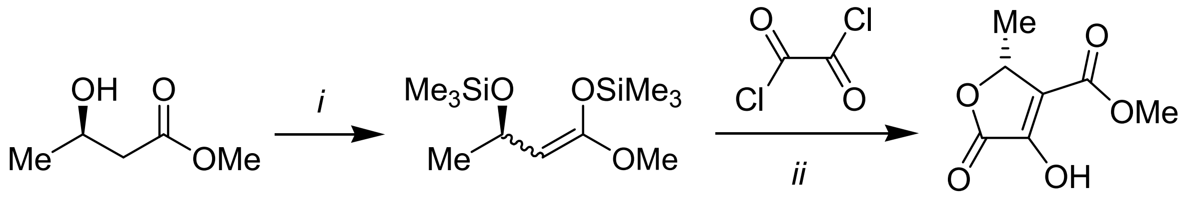
Thus, the introduction of a keto instead of an ester group could not be accomplished. It was shown that two alkyl substituents can be introduced into the molecule, albeit, in rather low yield.

5.4 Synthesis of an Enantiomerically Pure Isotetronic Acid

As 3-hydroxyesters **28** are derived from achiral starting materials by simple aldol addition they are present in racemic form only. Consequently, silyl enol ethers **29** and butenolides **31** are prepared as racemates as well.

Starting with commercially available (*R*)-**28a**, the optically pure butenolide (*R*)-**31a** could be successfully prepared (Scheme 21) with high enantiomeric excess (ee ≥ 98%). This experiment shows that no racemization took place during the formation of 1,3-bis(trimethylsilyloxy)alk-1-ene (*R*)-**29a** and during the subsequent cyclization.
This result was expected, since, according to the proposed mechanism (Scheme 18), 1,3-bis(trimethylsilyloxy)alk-1-enes **29** do not undergo racemization when reacted with oxalyl chloride. Likewise, no racemization was expected during the silylation of 3-hydroxyesters **28**.

Scheme 21. Synthesis of (*R*)-**31a**.

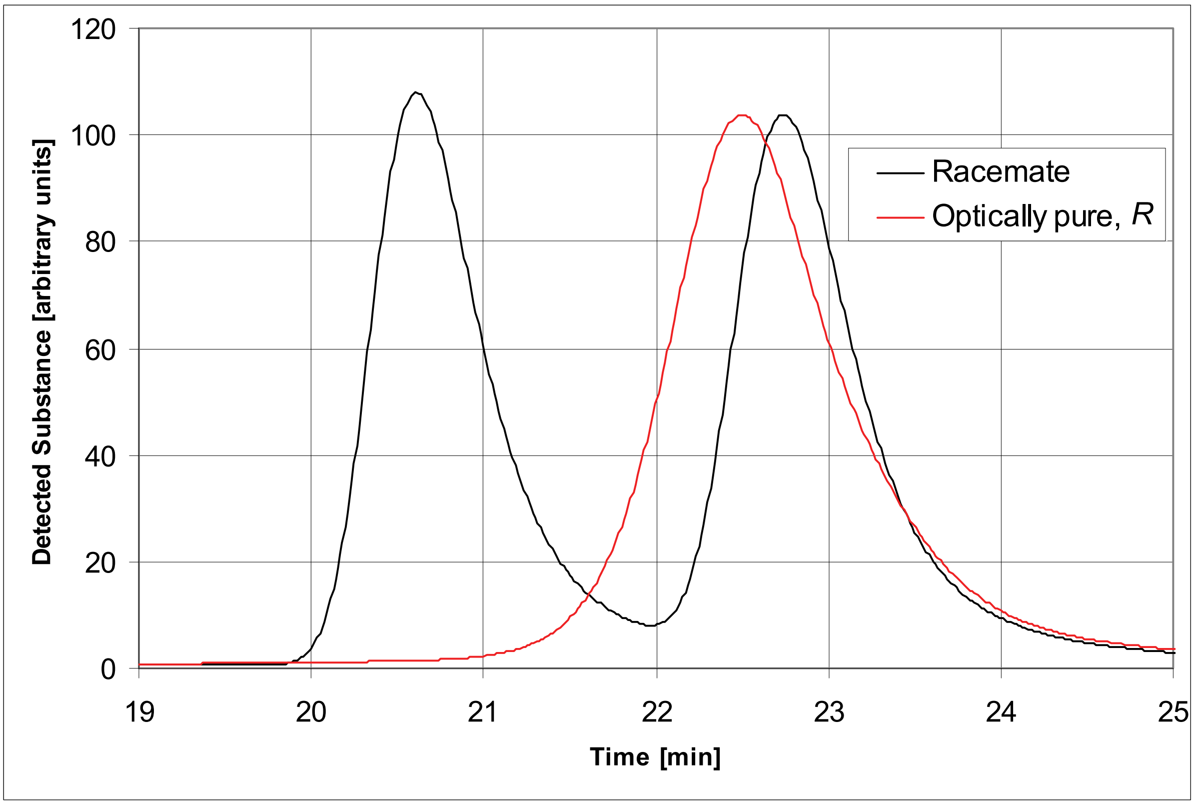


(*R*)-**28a** (*R*)-**29a** (*R*)-**31a**

(*i*) THF, 2.2 eq. LDA, –78 °C, (*R*)-**28a**, 1 h, then Me_3SiCl, –78 → 20 °C in 14 h; (*ii*) CH_2Cl_2, –78 → 20 °C in 22 h.

The enantiomeric excess of (*R*)-**31a** was determined by chiral HPLC on a CHIRALCEL OD-H column.

Figure 3. Resolution of enantiomers by chiral HPLC.



Chiral HPLC on a CHIRALCEL OD-H column. Substance detected by UV absorption at λ = 251 nm; λ_{max} = 254 nm. Baseline correction was carried out and maxima have been equalized for the plot. Conditions: hexane/ethanol = 95:5 + 0.1 % CF_3COOH (0.5 mL/min). Maxima after 20.61/22.50/22.74 min. Enantiomeric excess of the optically pure sample: ee ≥ 98%.

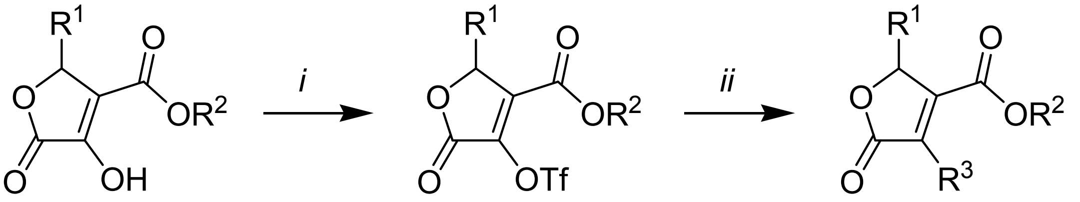
Figure 3 shows good separation of *R*- and *S*-enantiomers and equally well detection since areas for the enantiomers were determined equal. The slightly broader distribution for the pure *R*-enantiomer is due to higher concentration of that enantiomer in the investigated sample compared to the racemic sample.

The enantiomeric excess of (*R*)-**31a** in the optically active sample was determined as
ee ≥ 98%.

5.5 Functionalization by Suzuki Coupling

The hydroxy groups of different isotetronic acids were successfully functionalized by transition metal catalysed cross-coupling reactions (Scheme 22, Table 9) with various arylboronic acids. The products were isolated in moderate to good yields, except for **34c** prepared from 2-(methoxyphenyl)boronic acid.

Scheme 22. Suzuki coupling reactions.



31d,f-h,k **33a-e** **34a-j**

(*i*) CH_2Cl_2, 2.5 eq. pyridine, 15 min, then –78 °C, 1.3 eq. Tf_2O, then –78 → 0 °C in 90–120 min; (*ii*) 1,4-dioxane, 1.5 eq. K_3PO_4, 1.3 eq. $R^3B(OH)_2$, 3 mol % $Pd(PPh_3)_4$, 90 – 95 °C, 4–8 h.

Table 9. Synthesis of triflates **33a-e** and coupling products **34a-j**.

31	**33**	**34**	R^1	R^2	R^3	% (**33**)[a]	% (**34**)[a]
d	**a**	**a**	*n*Bu	OEt	Ph	84	76
d	**a**	**b**	*n*Bu	OEt	*p*-MeC_6H_4	84	45
d	**a**	**c**	*n*Bu	OEt	*o*-$(MeO)C_6H_4$	84	24
d	**a**	**d**	*n*Bu	OEt	3,4-$(MeO)_2C_6H_3$	84	56
d	**a**	**e**	*n*Bu	OEt	3,4,5-$(MeO)_3C_6H_2$	84	64
d	**a**	**f**	*n*Bu	OEt	Thien-2-yl	84	66
f	**b**	**g**	*i*Bu	OEt	*p*-$(MeO)C_6H_4$	86	57
g	**c**	**h**	*t*Bu	OMe	Ph	51	86
h	**d**	**i**	*n*Hex	OMe	Ph	77	61
k	**e**	**j**	Ph	OEt	Ph	53	45

[a] Yields of isolated products.

5.6 Conclusion

In conclusion, a variety of 3-hydroxy-4-alkoxycarbonyl-butenolides were prepared by one-pot cyclizations of 1,3-bis(silyloxy)alk-1-enes with oxalyl chloride. The method is applicable to the synthesis of enantiomerically pure butenolides. This is useful, since many methods for the enantioselective synthesis of 3-hydroxyesters exist. The oxalyl derived hydroxy group can be functionalized by Suzuki cross-coupling reactions of the enol triflate.

6 Synthesis of Alkylidene-Isobenzofurans

6.1 Introduction

γ-Alkylidenebutenolides are present in a number of natural products.[50a,b,d,f,g] This important class of heterocyclic compounds is accessible by lactonization of 2-en-4-ynoic acids[50e,88] or by stereospecific β-eliminations[89] and other methods. Highly unsaturated derivatives, such as the natural products lissoclinolide or dihydroxerulin, are available by Wittig reaction of γ-(3-phosphaprop-2-enylidene)butenolides with aldehydes or, by reaction of γ-(3-oxaprop-2-enylidene)butenolides with phosphoranes.[90] Simple γ-alkylidenebutenolides, containing only one exocyclic double bond, can be synthesized by Wittig reaction of maleic anhydrides with stabilized phosphorus ylides.[91]

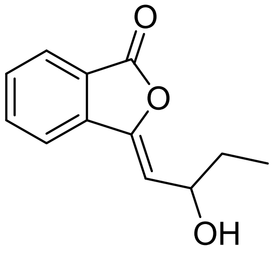
Some years ago, Langer *et al.* reported the synthesis of γ-alkylidenebutenolides by cyclization of 1,3-bis-silyl enol ethers, which can be regarded as masked 1,3-dicarbonyl dianions,[11] with oxalyl chloride.[51,92]

Later, the preparation of γ-(2,4-dioxobut-1-ylidene)butenolides by Wittig reaction of (2,4-dioxobutylidene)triphenylphosphoranes with maleic anhydrides was described together with a new synthesis of 3-(2,4-dioxobut-1-ylidene)-3*H*-isobenzofuran-1-ones based on the reaction of 1,3-bis-silyl enol ethers with phthaloyl dichloride.[93]

3-Alkylidene-3*H*-isobenzofuran-1-ones can be regarded as benzo-annulated γ-alkylidene-butenolides. Naturally occurring derivatives include senkyunolide C and E,[94] thunberginol F,[95] and dactylicapnosine.[96] They have been mainly synthesized by means of the condensation of 1,3-dicarbonyl compounds with phthaloyl dichloride,[97] Wittig reactions of phthalic anhydride[98] and palladium catalyzed cyclizations.[99]

The syntheses of 3-alkylidene-3*H*-isobenzofuran-1-ones reported by Albrecht, Nguyen, and Langer[93,100] are focussed on the reaction of 1,3-bis-silyl enol ethers with phthaloyl dichloride. In these reactions, β-ketoester derived 1,3-bis-silyl enol ethers reacted – as expected – at carbon atom C4. In contrast, the bis-silyl enol ether derived from acetylacetone surprisingly reacted at the central rather than at the terminal carbon atom. Noteworthy, the corresponding mono-silyl enol ether led to the same product, albeit, in lower yield. All efforts directed towards the reaction of mono-silyl enol ethers derived from β-ketoesters were unsuccessful.

Figure 4. A naturally occurring 3-alkylidene-3*H*-isobenzofuran-1-one.



Senkyunolide E

The aim of the present work was to extend this methodology to ester-derived mono-silyl enol ethers which proved to be unsuccessful in earlier investigations.

6.2 Synthesis of Starting Materials

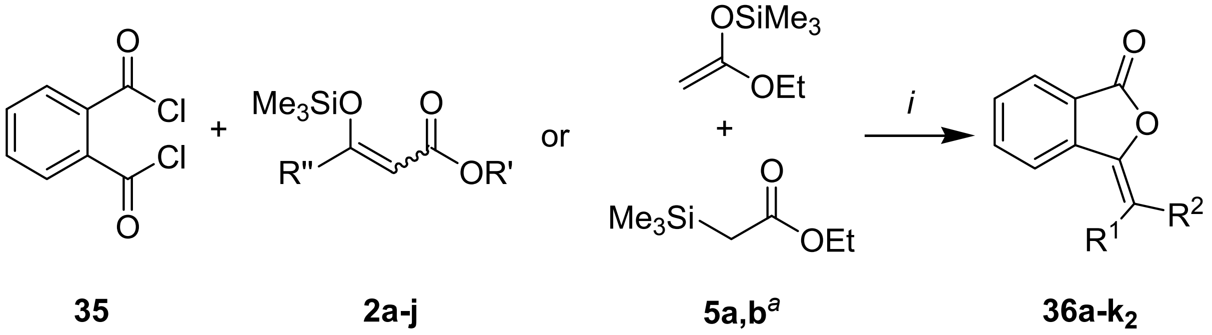
The syntheses of silyl enol ethers **2** and **5** used for the following reactions are described in Chapter 2 as they are also relevant in the context of [3+3] cyclizations (Chapter 4).

6.3 Reactions of Silyl Enol Ethers with Phthaloyl Chloride

6.3.1 Products and Reaction Pathway

The reactions presented in this chapter deal with the formation of alkylidene-3-oxo-3*H*-isobenzofurans and are shown in a general way in Scheme 23.

Scheme 23. Synthesis of **36a-k$_2$**.



(*i*) CH_2Cl_2, –78 → 20 °C, various conditions; [a] **5a** (top) and **5b** (bottom) were obtained as an unseparable 1:1 mixture.

The first step was to find out under which conditions the desired reactions can be accomplished. The reaction of mono-silyl enol ether **2a** with phtaloyl chloride in the absence of any Lewis acid resulted in the formation of a complex mixture. The same result was obtained when 0.3 equivalents of Me_3SiOTf were added.

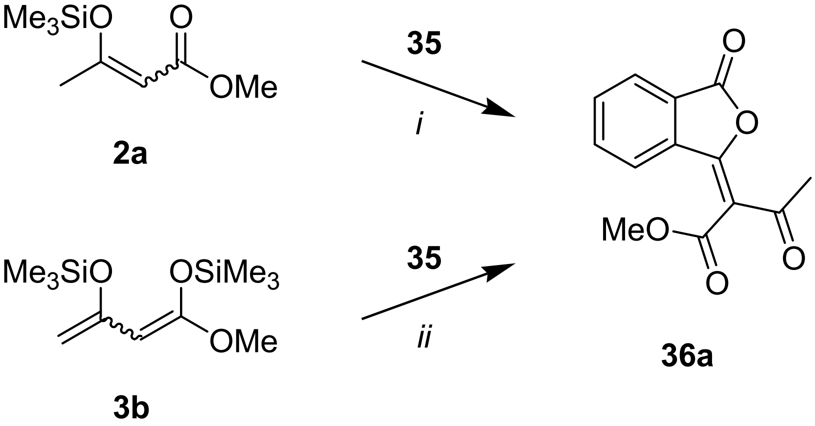
The desired 3-alkylidene-3*H*-isobenzofuran-1-one **36a** was formed in 48% yield when 1.0 equivalent of $TiCl_4$ and molecular sieves were present. Interestingly, the same product was formed in 14% yield when phthaloyl chloride was reacted with **3b** and 2.3 equivalents of $TiCl_4$ in the presence of molecular sieves (Table 10, Scheme 24). The original purpose of that reaction was to induce a [4+3] cyclization with formation of a benzo[*d*]tropone. A similar type of product has been previously prepared by reaction of **3b** and phthaldialdehyde.[100,101,102,103]

Table 10. Reactions of **2a** and **3b** with phthaloyl chloride.

Entry	**Educt**	Lewis acid	*E* : *Z* [a]	% (**36a**)[b]
1	**2a**	–	–	0
2	**2a**	0.3 eq. Me_3SiOTf	–	0
3	**2a**	1.0 eq. $TiCl_4$	≥ 98 : 2	48
4	**3b**	2.3 eq. $TiCl_4$	≥ 95 : 5	14

[a] Ratio referring to isolated product; [b] yields of isolated products.

Scheme 24. Syntheses of **36a**.

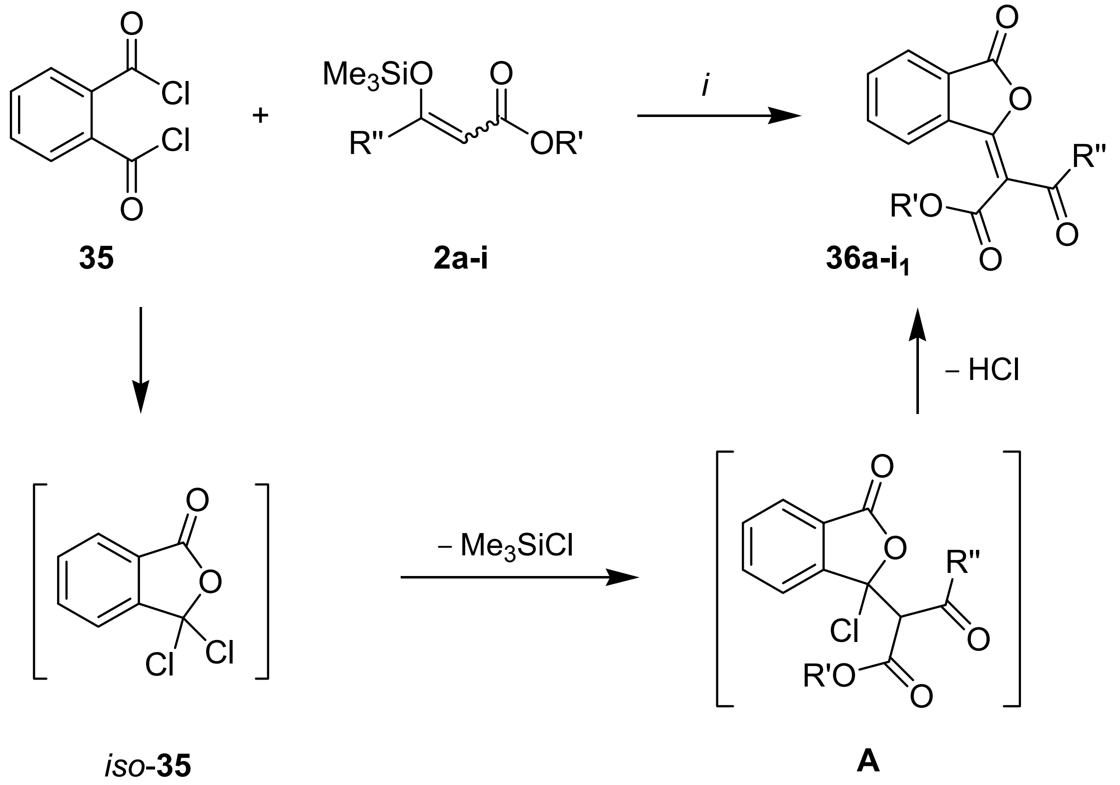


(i), (ii) CH_2Cl_2, molecular sieves (4 Å), $TiCl_4$, –78 → 20 °C in 20 h (i) / 16 h (ii).

It was surprising that product **36a** was also formed when bis-silyl enol ether **3b** was used as the latter usually reacts at its terminal carbon rather than at its central carbon atom.[11] Nevertheless, exceptions have been previously observed for the 1,3-bis-silyl enol ether **3a** derived from acetylacetone.[93,100] Partial decomposition of **3b** is another possible explanation for this result, but it seems more likely that, under the conditions employed, **3b** shows a similar behaviour as was found for its acetylacetone derived analogue **3a**.

The formation of 3-alkylidene-3*H*-isobenzofuran-1-ones can be rationalized by the proposed reaction pathway presented in Scheme 25. Phthaloyl chloride **35** is in equilibrium with *iso*-phtaloylchloride *iso*-**35**. Attack of the silyl enol ether onto the latter leads to intermediate **A** with extrusion of Me_3SiCl. Elimination of HCl then leads to the final product.

Scheme 25. Proposed reaction pathway for the formation of 3-alkylidene-3*H*-isobenzofuran-1-ones (neglecting fragmentation which was observed in some cases).



(*i*) CH_2Cl_2, molecular sieves (4 Å), $TiCl_4$, –78 → 20 °C in 20 h.

To further explore this method, the mono-silyl enol ether was systematically varied.

Reactions of mono-silyl enol ethers **2a-h** led to products **36a-h** in reasonable yields (Table 11). The products were formed with good to excellent *E*-selectivity. The values given in Table 11 refer to isolated products, i.e. stereoisomers where obtained as mixtures of *E*- and *Z*-isomers when both isomers where formed. In all cases, the minor isomer constitutes not more than 10% of the product, except for **36f** where the *Z*-isomer constitutes about 17%.

When **2i** was employed, the expected product **36i$_1$** was isolated as the pure *E*-isomer. In addition, a second product was isolated. It was identified as (*Z*)-methyl (3-oxo-3*H*-isobenzofuran-1-ylidene)-acetate **36i$_2$** where the *tert*-butylcarbonyl group was eliminated and the configuration of the exocyclic double bond is reversed with respect to the non-fragmented product **36i$_1$**.

The reaction of **2j** led to (*Z*)-3-(2-oxo-propylidene)-3*H*-isobenzofuran-1-one **36j**. This result can be explained by cleavage of the *tert*-butyl ester in the presence of HCl and subsequent decarboxylation. Product **36j** was isolated as the pure *Z*-isomer. The low yield is probably due to the instability of **2j** which may decompose before addition to *iso*-phtaloylchloride *iso*-**35** under the reaction conditions employed.

Table 11. Products and yields.

Educt	R'	R''	**36**	$R^{1\,a}$	$R^{2\,a}$	$E:Z^{b}$	$\%^{c}$
2a	Me	Me	**a**	CO_2Me	COMe	≥ 98 : 2	48
2b	Et	Me	**b**	CO_2Et	COMe	≥ 95 : 5	68
2c	*i*Pr	Me	**c**	CO_2*i*Pr	COMe	91 : 9	45
2d	*i*Bu	Me	**d**	CO_2*i*Bu	COMe	91 : 9	48
2e	Allyl	Me	**e**	CO_2Allyl	COMe	91 : 9	59
2f	$CH_2CH_2OCH_3$	Me	**f**	$CO_2CH_2CH_2OCH_3$	COMe	83 : 17	37
2g	Me	*n*Pr	**g**	CO_2Me	CO*n*Pr	≥ 98 : 2	46
2h	Et	*n*Pr	**h**	CO_2Et	CO*n*Pr	91 : 9	41
2i	Me	*t*Bu	$\mathbf{i_1}$	CO_2Me	CO*t*Bu	≥ 98 : 2	25
2i	Me	*t*Bu	$\mathbf{i_2}$	H	CO_2Me	9 : 91	17
2j	*t*Bu	Me	**j**	H	COMe	≤ 2 : 98	8
5a,b [d]	–	–	$\mathbf{k_1}$	H	CO_2Et	≤ 2 : 98	12
5a,b [d]	–	–	$\mathbf{k_2}$	CO_2Et	H	≥ 98 : 2	4

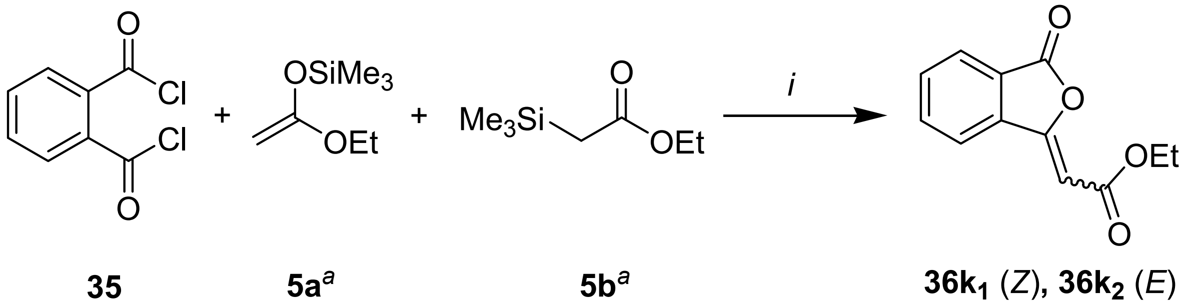
[a] R^1 and R^2: compare Scheme 23 (for drawings see also Table 13); [b] ratio referring to isolated products; [c] yields of isolated products; [d] **5a** and **5b** where obtained and used as a 1:1 mixture.

When ethyl acetate was employed to form the corresponding silyl enol ether **5a**, a non-separable 1:1 mixture of **5a** and **5b** was obtained (compare Chapter 2). For this reason and due to the fact that **5a** structurally differs from compounds **2**, the reaction conditions were varied with respect to stoichiometry and Lewis acid (Table 12).

The best results were obtained when the reaction was carried out using 2.0 equivalents of the **5a,b** mixture (i.e. 1.0 equivalent of **5a** and 1.0 equivalent of **5b**) in the absence of Lewis acid. This reaction led to the formation of product $\mathbf{36k_1}$ and its isomer $\mathbf{36k_2}$ which could be successfully separated. However, the yields were still low (12% and 4% for **36k$_1$** and **36k$_2$**, respectively).

The use of $TiCl_4$ and molecular sieves (4Å) led to the formation of complex mixtures. The use of Me_3SiOTf resulted in the formation of only a small amount of **36k$_1$** which was hard to purify.

Scheme 26. Synthesis of **36k$_1$** and **36k$_2$**.



(*i*) CH_2Cl_2, –78 → 20 °C in 20 h; [a] **5a** and **5b** where obtained and used as a 1:1 mixture.

Table 12. Different conditions for the conversion of **5a,b** into **36k$_1$** and **36k$_2$**.

Entry	Equivalents [a] of **5a,b**	Lewis acid	**36**	*E* : *Z* [b]	% [c]
1	**2.0**	–	**k$_1$**	≤ 2 : 98	12
1	**2.0**	–	**k$_2$**	≥ 98 : 2	4
2	**1.0**	–	**k$_1$**	≤ 2 : 98	4
3	**2.0**	1.0 eq. $TiCl_4$	–	–	0
4	**1.1**	1.2 eq. $TiCl_4$	–	–	0
5	**2.0**	0.3 eq. Me_3SiOTf	**k$_1$**	≤ 10 : 90 [d]	≤ 6 [d]

[a] 2 eq. of the 1:1 mixture of **5a** and **5b** nets 1 eq. of isomer **5a** and 1 eq. of isomer **5b**; [b] ratio refers to isolated products; [c] yields of isolated product; [d] sample contains some impurities which could not be removed.

6.3.2 Proof of Structures

For **36a-k$_2$**, the one-dimensional ^{1}H NMR spectra are consistent with both the *E*- and *Z*-isomers. NOESY experiments were carried out and X-ray structures were measured to overcome this problem (Table 13, Scheme 27).

In **36a** the aromatic hydrogen atom at δ = 8.14 – 8.19 correlates with the methoxy group at 3.94.

In **36b** the aromatic hydrogen atom at δ = 8.15 correlates with a triplet at 1.36 and a quartet at 4.40 both belonging to the ethoxy group.

In **36c** the aromatic hydrogen atom at δ = 8.15 correlates with a doublet at 1.34 and a septet at 5.27 both belonging to the isopropyloxy group.

In **36d** the aromatic hydrogen atom at δ = 8.16 correlates with a doublet at 4.08 representing the methylene group in the isobutyloxy moiety.

In **36e** the aromatic hydrogen atom at δ = 8.14 – 8.18 correlates with a doublet of triplets at 4.83 representing the oxygen-connected methylene group in the allyloxy moiety.

In **36f** the aromatic hydrogen atom at δ = 8.14 – 8.19 correlates with a multiplet at 4.51 representing the methylene group directly connected to the CO_2 moiety. The structure has also been confirmed by an X-ray measurement (Scheme 27).

In **36g** the aromatic hydrogen atom at δ = 8.27 correlates with the methoxy group at 3.87.

In **36h** the aromatic hydrogen atom at δ = 8.30 correlates with a quartet at 4.35 belonging to the methylene group in the ethoxy moiety.

For **36i$_1$** no clear NOESY correlations were found. Therefore, it was necessary to determine the structure by a single-crystal X-ray diffraction experiment (Scheme 27).

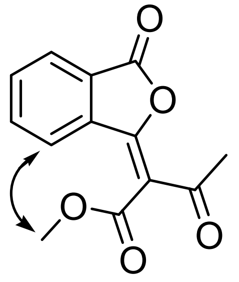
The structure of **36i$_2$** was obtained by means of X-ray diffraction (Scheme 27).

In **36j** the aromatic hydrogen atom at ca. δ = 7.8 (the correlating hydrogen is part of a multiplet representing more than one aromatic hydrogen atom; therefore its chemical shift was derived from the two-dimensional spectrum) correlates with the hydrogen atom of the exocyclic double bond located at 6.02.

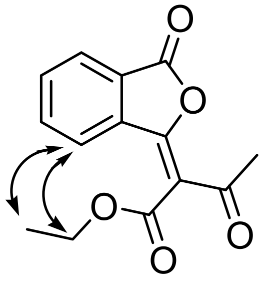
In **36k$_1$** the aromatic hydrogen atom at ca. δ = 7.8 (the correlating hydrogen is part of a multiplet representing more than one aromatic hydrogen atom; therefore its chemical shift was derived from the two-dimensional spectrum) correlates with the hydrogen atom of the exocyclic double bond located at 5.88.

For **36k$_2$** no relevant NOESY correlations were found. This structure was determined by comparison with isomeric **36k$_1$** the exocyclic double bond of which was found to be *Z*-configured. According to these findings **36k$_2$** possesses an *E*-configured double bond.

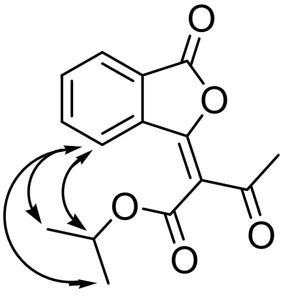
Table 13. Results of NOESY experiments for **36a-h** and **36j-k$_1$**. Arrows show relevant correlations between hydrogen atoms attached to the carbon atoms indicated.



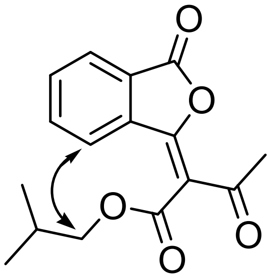
36a



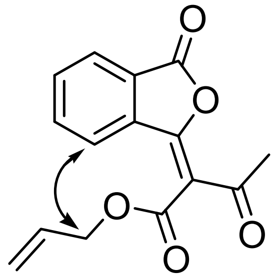
36b



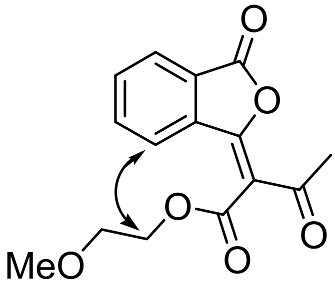
36c



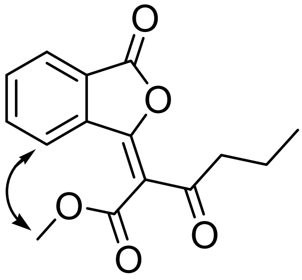
36d



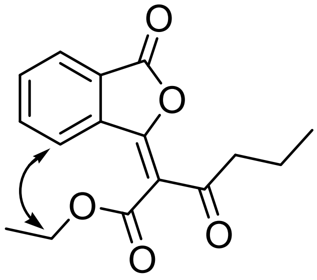
36e



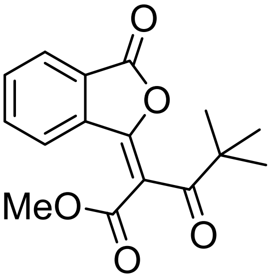
36f[a]



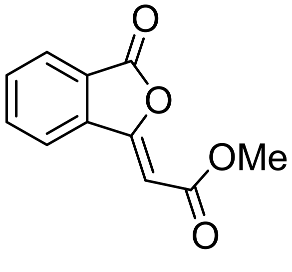
36g



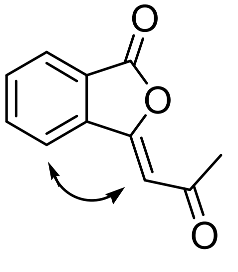
36h



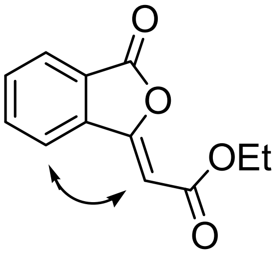
36i$_1$[b]



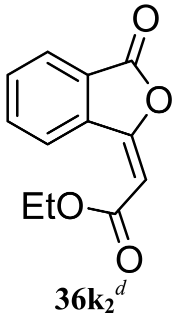
36i$_2$[c]



36j



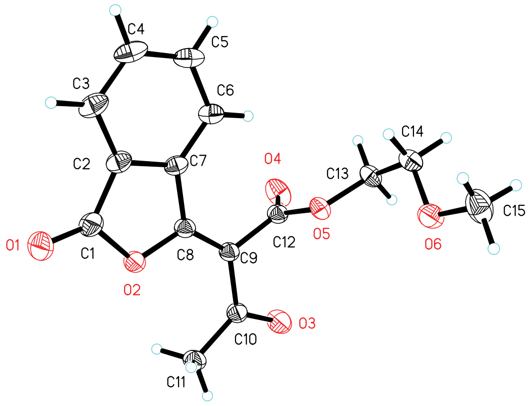
36k$_1$



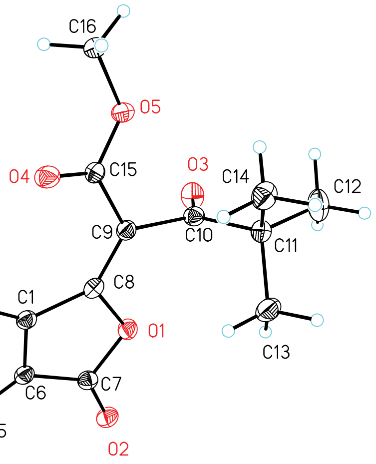
36k$_2$[d]

[a] X-ray structure also measured*; [b] X-ray structure measured as NOESY experiments led to no clear result*; [c] X-ray structure measured instead of NOESY*; [d] relevant NOESY correlations were not found, *E*-configuration concluded form the isomeric **36k$_1$**; * for X-ray structures, see Scheme 27.

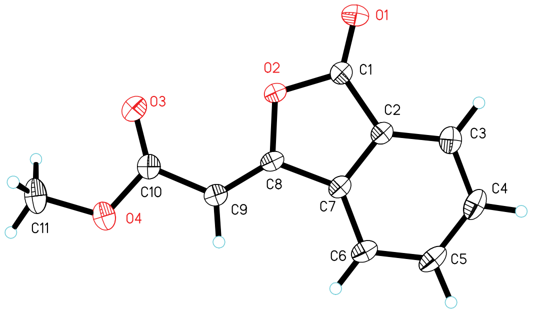
Scheme 27. ORTEP plots of **36f**, **$36i_1$**, and **$36i_2$**; thermal ellipsoids represent 50% probability.



36f



$36i_1$



$36i_2$

6.4 Conclusion

In summary, a convenient synthesis of 3-alkylidene-3*H*-isobenzofuran-1-ones by reaction of ester-derived mono-silyl enol ethers with phthaloyl chloride was developed.

7 Summary

In this work, cyclization reactions of silyl enol ethers providing access to functionalized salicylates (Chapter 4), isotetronic acids (Chapter 5), and alkylidene-isobenzofurans (Chapter 6) were presented.

Salicylates were obtained by $TiCl_4$ mediated [3+3] cyclization reactions of mono-silyl enol ethers with 1,3-bis-silyl enol ethers. Where regio-isomers could potentially occur only one cyclization product was regioselectively formed. The methodology employed provides access to substitution patterns which are not readily available by alternative methods.

Isotetronic acids were synthesized by cyclization of 1,3-bis(silyloxy)alk-1-enes with oxalyl chloride. It was shown that this method is applicable to the synthesis of enantiomerically pure butenolides which is particularly interesting because many methods for the enantioselective synthesis of the starting materials exist. In addition, isotetronic acids were successfully transformed into aryl-substituted 4-alkoxycarbonyl-butenolides by Suzuki cross-coupling reactions of the enol triflate.

A convenient synthesis of 3-alkylidene-3*H*-isobenzofuran-1-ones by reaction of ester-derived mono-silyl enol ethers with phthaloyl chloride was developed. The reaction is mediated by $TiCl_4$. In most cases the *E*-isomer is predominantly formed.

The results of Chapter 3 contribute to the understanding of the recently developed domino "Staudinger / semi-aza-Wittig / fragmentation" reaction of γ-azido-β-hydroxyketones and the competitive normal aza-Wittig reaction pathway when the substrates are reacted with PPh_3.

8 Experimental Section

8.1 Material and Methods

8.1.1 General Remarks

Reactions were carried out under inert atmosphere (Argon 4.6) in order to simultaneously exclude oxygen and water when appropriate. Schlenck techniques were applied. Solvents for reactions were dried and destilled by standard methods or purchased from Merck, Aldrich, Acros Organics, and others whenever exclusion of water was desired. Solvents for liquid chromatography and extraction were always destilled prior to use and partly reused after fractionating destillation (*n*-heptane, ethyl acetate).

8.1.2 Methods for Compound Characterization and Analysis

NMR Spectroscopy

Bruker AC 250, Bruker ARX 300, Bruker ARX 500, Bruker Avance 600. For NMR characterization the one-dimensional ^{1}H NMR, proton-decoupled ^{13}C NMR, and DEPT 135 spectra were collected. If necessary, other techniques (APT, NOESY, COSY, HMBC) were applied as well. All NMR spectra presented in this work were collected in $CDCl_3$ solution. All chemical shifts are given in ppm.

References (^{1}H NMR): TMS ($\delta = 0.00$) or residual $CHCl_3$ ($\delta = 7.26$) were taken as internal standard. When these reference peaks were superimposed by signals belonging to the compound under investigation a small amount of CH_2Cl_2 ($\delta = 5.30$) was added and taken as reference instead.

References (^{13}C NMR): TMS ($\delta = 0.0$) or residual $CHCl_3$ ($\delta = 77.0$) were taken as internal standard.

Multiplicities are given as follows: s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, m = multiplet, br = broad signal. More complex coupling patterns are represented by combinations of the respective symbols. For example, td indicates a triplet of doublets with the larger coupling constant associated with the first symbol (here: triplet).

Infrared Spectroscopy (IR)

Nicolet 205 FT-IR, Nicolet Protége 460 FT-IR. Peaks are given the following assignments: w = weak, m = medium, s = strong, br = broad.

Mass Spektrometry (MS)

AMD MS40, Varian MAT CH 7, MAT 731 (EI, 70 eV), Intecta AMD 402 (EI, 70 eV and CI), Finnigan MAT 95 (CI, 200 eV).

High Resolution Mass Spectrometry (HRMS)

Varian MAT 311, Intecta AMD 402.

Elemental Analysis

LECO CHNS-932, Thermoquest Flash EA 1112.

Melting Points

Micro heating table HMK 67/1825 Kuestner (Büchi Apparatus), Leitz Labolux 12 Pol with heating table Mettler FP 90. Melting points are uncorrected.

Rotation Angles

LµP (IBZ Meßtechnik, Na^D = 589 nm).

X-ray Structures

Bruker X8Apex diffractometer with CCD camera (Mo K_α radiation and graphite monochromator, $\lambda = 0.71073$ Å). The space group is determined by the XPREP program and the structures were solved via the SHELX-97 program package. Refinements were carried out according to the minimum square error method.

8.1.3 Chromatographic Methods

Thin Layer Chromatography (TLC)

Merck Kieselgel 60 F254 on aluminium foil from Macherey-Nagel. Detection was carried out under UV light at 254 nm and 365 nm. As colourizing reagent the following mixtures were used: 1-2/100 p-Anisaldehyde or vanillin, 10/100 glacial acetic acid, 5/100 sulphuric acid, 83-84/100 methanol.

Column Chromatography

Column chromatography was performed with Merck Silica Gel 60 or Macherey-Nagel Silica Gel 60 (0.063-0.200 mm, 70-230 mesh). The finer Merck Silica Gel 60 (0.040-0.063 mm, 230-400 mesh) was chosen when appropriate.

High Performance Liquid Chromatography (HPLC)

For separation of enantiomers an analytical column type CHIRALCEL OD-H was used. Purification of diastereomers was carried out on a Knauer LiChrosorb RP 18 column.

8.2 General Procedures (GP)

General Procedure for the Preparation of Salicylates 25 (GP 1)

To a CH_2Cl_2 solution of **24a** or **24b** was added $TiCl_4$ at −78 °C in the presence of molecular sieves (4 Å). The appropriate bis-silyl enol ether **3** was subsequently added. The reaction mixture was allowed to warm to 20 °C in about 20 h and was stirred for another 4 h (**24a**) or 2–7 d (**24b**). CH_2Cl_2 was added, the molecular sieves were removed, and a saturated aqueous solution of $NaHCO_3$ was added. The organic layer was separated and the aquaeous layer was repeatedly extracted with CH_2Cl_2 or CH_2Cl_2 and ether. When still colourful, the aqueous layer was acidified by hydrochloric acid (10%) and again extracted. All organic extracts were combined, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel) to give salicylates **25**.

General Procedure for the Preparation of Salicylates 26 (GP 2)

To a CH_2Cl_2 solution of **24c** was added $TiCl_4$ at −78 °C in the presence of molecular sieves (4 Å). The appropriate bis-silyl enol ether **3** was subsequently added. The reaction mixture was allowed to warm to 20 °C in about 20 h and was stirred for another 4 h. CH_2Cl_2 was added, the molecular sieves were removed, and a saturated aqueous solution of $NaHCO_3$ was added. The organic layer was separated and the aquaeous layer was repeatedly extracted with CH_2Cl_2. All organic extracts were combined, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel) to give salicylates **26**.

General Procedure for the Preparation of 3-Hydroxycarbonyl Compounds 28 (GP 3)

An LDA solution was prepared by addition of *n*BuLi to a THF solution of diisopropylamine at 0 °C. After stirring for 1 h, the solution was cooled to –78 °C and the respective ester or ketone was dropwise added. After stirring for 1 h at –78 °C, the appropriate electrophile (aldehyde or ketone) was added within 30 seconds. After stirring for 3–5 minutes, hydrochloric acid (2 M) was added. The organic and the aqueous layer were separated and the solvents were removed under reduced pressure. The aqueous layer was extracted with ethyl acetate (2 x 150 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (2 x 50 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo*. The residue was destilled under reduced pressure or purified by column chromatography (silica gel) to give 3-hydroxyesters and 3-hydroxyketones **28**.

General Procedure for the Preparation of 1,3-Bis(trimethylsilyloxy)alk-1-enes 29 (GP 4)

An LDA solution was prepared by addition of *n*BuLi to a THF solution of diisopropylamine at 0 °C. After stirring for 1 h, the solution was cooled to –78 °C and the respective 3-hydroxyester or 3-hydroxyketone **28** was added. After stirring for 1 h at –78 °C, Me_3SiCl was added and the solution was allowed to warm to 20 °C within 14 – 24 h. The solvent and volatile compounds were removed *in vacuo*. The residue was dissolved in *n*-hexane and the suspension was filtered under inert atmosphere. The filtrate was concentrated *in vacuo* to give 1,3-bis(trimethylsilyloxy)alk-1-enes **29** which were used without further purification.

General Procedure for the Preparation of Isotetronic Acids 31 (GP 5)

To a CH_2Cl_2 solution of the appropriate 1,3-bis(trimethylsilyloxy)alk-1-ene **29** was added a CH_2Cl_2 solution of oxalyl chloride at −78 °C. The reaction mixture was allowed to warm to 20 °C within 15–24 h. Ether (60 mL) and brine (20 mL) were added, the organic and the aqueous layer were separated and the latter was extracted with ether (3 x 30 mL). The combined organic layers were washed with water (10 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel) or recrystallized (CH_2Cl_2/*n*-hexane) to give isotetronic acids **31**.

General Procedure for the Preparation of Triflates 33 (GP 6)

To a CH_2Cl_2 solution of the appropriate isotetronic acid **31** was added pyridine. After stirring for 15 minutes the solution was cooled to –78 °C and Tf_2O was added. The reaction mixture was allowed to warm to 0 °C within 90–120 minutes and the reaction mixture was directly purified (without aqueous work-up) by column chromatography (silica gel) to give triflates **33**.

General Procedure for the Preparation of Aryl-substituted Isotetronic Acids 34 by Suzuki Coupling (GP 7)

A mixture of the respective triflate **33**, K_3PO_4, appropriate arylboronic acid, $Pd(PPh_3)_4$, and 1,4-dioxane was heated at 90–95 °C for 4–8 hours. To the solution was added ether, the mixture was filtered and the filtrate was concentrated *in vacuo*. The coupling product **34** was isolated by column chromatography (silica gel).

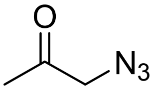
General Procedure for the Preparation of Alkylidene-Isobenzofurans 36 (GP 8)

To a CH_2Cl_2 solution of phthaloyl chloride was added $TiCl_4$ at –78 °C in the presence of molecular sieves (4 Å). The appropriate mono-silyl enol ether **2** or **5** was subsequently added and the reaction mixture was allowed to warm to 20 °C in 16–23 h. CH_2Cl_2 was added, the molecular sieves were removed, and a saturated aqueous solution of $NaHCO_3$ was added. The aqueous layer was repeatedly extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel) to yield alkylidene-isobenzofurans **36**.

8.3 Explicit Procedures and Compound Characterization

8.3.1 Azido-β-hydroxyketones and Precursors

1-Azidopropan-2-one (6a):

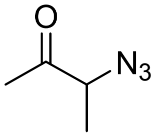


To an emulsion of chloroacetone (14.1 g, 153 mmol) and water (50 mL), was added NaN_3 (9.92 g, 153 mmol). After stirring for 30 min glacial acetic acid (1 mL) was added. After 42 h the reaction mixture was extracted with ether (3 x 30 mL), and the extracts were concentrated *in vacuo*. In order to complete the reaction water (20 mL) and NaN_3 (3.00 g, 46 mmol) were added and after stirring for 30 min glacial acetic acid (0.5 mL) was added. After 44 h the reaction mixture was extracted with ether (4 x 30 mL), dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* and destillation yielded **6a** as a clear, colourless liquid (9.41 g; 62%); bp. < 50 °C (0.1 mbar).

^1H NMR (300 MHz, $CDCl_3$): $\delta = 2.21$ (s, 3H, CH_3), 3.96 (s, 2H, CH_2).

The spectroscopic data are in accordance with those presented in the literature.[30a]

3-Azidobutan-2-one (**6b**):

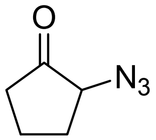


To a solution of NaN_3 (19.4 g, 298 mmol) in water (100 mL) was added 3-chlorobutan-2-one (16.0 g, 150 mmol). After stirring for 30 min glacial acetic acid (2 mL) was added. After stirring for 40 h the organic layer was isolated and the aqueous layer was extracted with ether (4 x 30 mL). The organic layer and extracts were combined, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* and destillation yielded **6b** as a clear, colourless liquid (13.0 g, 77%); bp. 48 – 49 °C (0.1 mbar).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.44$ (d, $^3J = 7.1$ Hz, 3H, $CHCH_3$), 2.24 (s, 3H, CCH_3), 3.94 (q, $^3J = 7.1$ Hz, 1H, CH).

The spectroscopic data are in accordance with those presented in the literature.[30b]

2-Azidocyclopentanone (**6c**):

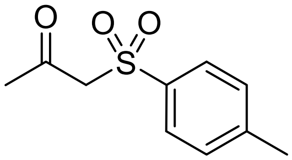


To a mixture of NaN_3 (21.0 g, 322 mmol) methanol (15 mL) was added 2-chlorocyclopentanone (7.59 g, 64 mmol) at 0 °C. The reaction mixture was allowed to warm to 20 °C and was kept stirring for 3 d. The reaction mixture was filtered, washed with ether, and the filtrate was concentrated *in vacuo*. Ether was added and the mixture was filtered again. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; *n*-hexane/EtOAc = 10:1) yielding **6c** as a colourless liquid (3.91 g, 48%); R_f 0.29 (*n*-hexane/EtOAc = 10:1).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.68 - 1.94$ (m, 2H, CH_2), 2.03 – 2.14 (m, 1H, CH_2), 2.19 – 2.38 (m, 3H, CH_2), 3.82 (t, $^3J = 9.1$ Hz, 1H, CHN_3).

The spectroscopic data are in accordance with those presented in the literature.[30c]

1-Tosylpropan-2-one (**7**):

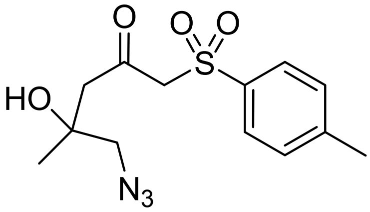


Sodiumtosylate dihydrate (19.1 g, 89.2 mmol) and chloroacetone (8.78 g, 94.9 mmol) were refluxed in ethanol (90 mL) for 6 h. Then the reaction mixture was left stirring for 16 h at 20 °C. Water (200 mL) and ether (300 mL) were added and the organic layer was separated. The aqueous layer was extracted with ether (2 x 100 mL). The organic layers were combined, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; *n*-hexane/EtOAc = 3:1) to give **7** a slightly yellow solid (13.2 g, 70%); R_f 0.17 (*n*-hexane/EtOAc = 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.41$ (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 4.14 (s, 2H, CH_2), 7.37 (m, 2H, Ar), 7.77 (m, 2H, Ar).

The spectroscopic data are in accordance with those presented in the literature.[104]

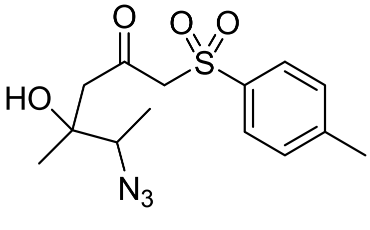
5-Azido-4-hydroxy-4-methyl-1-tosylpentan-2-one (**9a**):



To a THF solution (35 mL) of diisopropylamine (810 mg, 8.0 mmol) was added a 1.6 M solution of *n*BuLi in hexane (5.0 mL, 8.0 mmol) at 0 °C. After stirring for 30 minutes, the solution was cooled to –78 °C and 1-tosylpropan-2-one **7** (743 mg, 3.5 mmol), dissolved in THF (7 mL), was added and the solution was stirred for 1 h. 1-Azidopropanone **6a** (361 mg, 3.6 mmol), dissolved in THF (7 mL), was added at –78 °C and the reaction mixture was warmed to ambient temperature within 15 h and left stirring for 33 h more. Ether (20 mL), CH_2Cl_2 (20 mL), and a saturated solution of NH_4Cl (50 mL) were added and the organic layer was separated. The aqueous layer was extracted with ether (2 x 50 mL) and CH_2Cl_2 (2 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; petroleum ether/EtOAc = 5:1 → 3:1) to give **9a** as a slightly yellow oil (481 mg, 44%); R_f 0.14 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (s, 3H, CH_2CCH_3), 2.47 (s, 3H, $ArCH_3$), 2.88 (d, ^2J = 17.3 Hz, 1H, CH_AH_B), 3.05 (d, ^2J = 17.3 Hz, 1H, CH_AH_B), 3.18 (s, 1H, OH), 3.23 (d, ^2J = 12.3 Hz, 1H, CH_AH_B), 3.32 (d, ^2J = 12.3 Hz, 1H, CH_AH_B), 4.17 (d, ^2J = 13.1 Hz, 1H, $CH_AH_BSO_2$), 4.24 (d, ^2J = 13.1 Hz, 1H, $CH_AH_BSO_2$), 7.39 (d, ^3J = 8.0 Hz, 2H, Ar), 7.77 (m, 2H, Ar). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.8, 25.3 (CH_3), 51.4 ($COHCH_2CO$), 60.0 (CH_2N_3), 68.2 (CH_2SO_2), 72.4 (COH), 128.4, 130.2 (CH_{Ar}), 135.7, 145.9 (C_{Ar}), 199.1 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3504 (br, s), 2979 (m), 2931 (m), 2106 (s), 1717 (s), 1597 (m), 1455 (m), 1398 (s), 1378 (s), 1320 (s), 1294 (s), 1151 (s), 1087 (s), 1048 (s), 918 (m), 816 (s), 516 (s). MS (CI, isobutane): *m/z* (%) = 312 ([M + 1]$^+$, 8), 284 (33), 255 (40), 213 (100). HRMS (EI, 70 eV): Calcd for $C_{13}H_{17}N_3NaO_4S$ ([M + Na]$^+$) 334.08320, found 334.08384. Anal. Calcd for $C_{13}H_{17}N_3O_4S$ (311.36): C, 50.15; H, 5.50; N, 13.50; S, 10.30. Found: C, 50.11; H, 5.38; N, 12.97; S, 9.58.

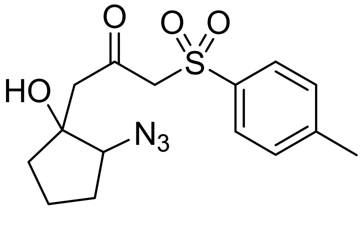
5-Azido-4-hydroxy-4-methyl-1-tosylhexan-2-one (**9b**):



To a THF solution (40 mL) of diisopropylamine (3.23 g, 32 mmol) was added a 1.6 M solution of *n*BuLi in hexane (20 mL, 32 mmol) at 0 °C. After stirring for 30 minutes, the solution was cooled to –78 °C and 1-tosylpropan-2-one **7** (2.87 g, 13.5 mmol), dissolved in THF (7 mL), was added and the solution was stirred for 1 h. 3-Azidobutan-2-one **6b** (1.61 g, 14.2 mmol), was added at –78 °C and the reaction mixture was warmed to ambient temperature within 14 h. A saturated solution of NH_4Cl (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 50 mL) and ether (50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; *n*-hexane/EtOAc = 7:1 → 5:1) to give **9b** as a brown oil (1.32 g, 30%, mixture of diastereomers: dr = 2:1); R_f 0.08 (*n*-hexane/EtOAc = 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (s, 3H, CH_3COH, major), 1.22 (s, 3H, CH_3COH, minor), 1.25 (d, ^3J = 6.8 Hz, 3H, CHCH_3, major), 1.29 (d, ^3J = 6.7 Hz, 3H, CHCH_3, minor), 2.47 (s, 3H, ArCH$_3$, both), 2.80 (d, ^2J = 17.0 Hz, 1H, COHCH_AH$_\mathrm{B}$, major), 2.84 (d, ^2J = 16.3 Hz, 1H, COHCH_AH$_\mathrm{B}$, minor), 3.01 (d, ^2J = 16.3 Hz, 1H, COHCH$_\mathrm{A}$$H_\mathrm{B}$, minor), 3.05 (s, 1H, OH, minor), 3.08 (d, ^2J = 17.0 Hz, 1H, COHCH$_\mathrm{A}$$H_\mathrm{B}$, major), 3.25 (s, 1H, OH, major), 3.43 (q, ^3J = 6.7 Hz, 1H, CHN$_3$, minor), 3.53 (q, ^3J = 6.8 Hz, 1H, CHN$_3$, major), 4.16 (d, ^2J = 13.2 Hz, 1H, CH_AH$_\mathrm{B}$SO$_2$, both), 4.30 (d, ^2J = 13.2 Hz, 1H, CH$_\mathrm{A}$$H_\mathrm{B}SO_2$, both), 7.38 (d, ^3J = 8.2 Hz, 2H, Ar, both), 7.77 (m, 2H, Ar, both). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.1, 13.4 (CHCH$_3$), 21.4, 21.4, 22.9, 23.1 (CCH$_3$), 49.9, 51.1 (COHCH$_2$), 63.9, 64.3 (CHN$_3$), 67.7, 67.8 (CH$_2$SO$_2$), 74.08, 74.13 (COH), 127.9. 128.0, 129.8, 129.8 (CH$_\mathrm{Ar}$), 135.45, 135.47, 145.31, 145.34 (C$_\mathrm{Ar}$), 198.6, 199.1 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3508 (br, s), 2983 (s), 2937 (m), 2097 (br, s), 1716 (s), 1597 (m), 1454 (m), 1379 (s), 1321 (s), 1293 (s), 1261 (s), 1151 (s), 1086 (s), 816 (m), 516 (s). MS (CI, isobutane): *m/z* (%) = 326 ([M + 1]$^+$, 4), 280 (44), 255 (48), 213 (100). HRMS (CI, isobutane): Calcd for $C_{14}H_{20}N_3O_4S$ ([M + 1]$^+$) 326.11690, found 326.11791.

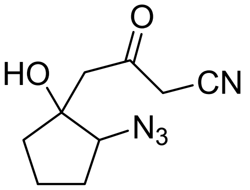
3-(2-Azido-1-hydroxycyclopentyl)-1-tosylpropan-2-one (**9c**):



To a THF solution (100 mL) of diisopropylamine (3.68 g, 36.4 mmol) was added a 1.6 M solution of *n*BuLi in hexane (22.8 mL, 36.5 mmol) at 0 °C. After stirring for 20 minutes, 1-tosylpropan-2-one **7** (2.89 g, 13.6 mmol) was added and the solution was stirred for 1 h at 0 °C. 2-Azidocyclopentanone **6c** (1.70 g, 13.6 mmol) was added at –78 °C and the reaction mixture was warmed to ambient temperature within 21 h. A saturated solution of NH_4Cl (100 mL) was added and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 x 50 mL) and CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; *n*-hexane/EtOAc = 3:1) to give **9c** as a brownish, slightly turbid oil (1.06 g, 23%, mixture of diastereomers: dr = 10:1); R_f 0.13 (*n*-hexane/EtOAc = 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 – 1.75 (m, 2H, CH_2), 1.75 – 2.10 (m, 4H, CH_2), 2.46 (s, 3H, CH_3), 2.83 (d, ^2J = 16.4 Hz, 1H, COHC$H_A$$H_B$CO), 2.91 (s, 1H, OH), 3.14 (d, ^2J = 16.4 Hz, 1H, COHC$H_A$$H_B$CO), 3.37 (dd, $^3J_1$ = $^3J_2$ = 8.4 Hz, 1H, CHN_3), 4.17 (d, ^2J = 13.1 Hz, 1H, C$H_A$$H_B$$SO_2$), 4.31 (d, ^2J = 13.1 Hz, 1H, C$H_A$$H_B$$SO_2$), 7.38 (d, ^3J = 8.2 Hz, 2H, Ar), 7.76 (d, ^3J = 8.2 Hz, 2H, Ar). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 19.2 (CH_2), 21.6 (CH_3), 27.0, 35.9 (CH_2), 51.4 (COHCH_2CO), 67.7 (CHN_3), 68.0 (CH_2SO_2), 79.8 (COH), 128.2, 130.0 (CH_{Ar}), 135.5, 145.6 (C_{Ar}), 198.5 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3498 (s), 2988 (m), 2936 (m), 2101 (s), 1694 (m), 1312 (s), 1254 (m), 1152 (s), 1128 (m), 535 (m), 518 (m). MS (CI, isobutane): *m/z* (%) = 338 ([M + 1]$^+$, 0.7), 310 (100). HRMS (CI neg., isobutane): Calcd for $C_{15}H_{18}N_3O_4S$ ([M – 1]$^-$) 336.38667, found 336.10125. Anal. Calcd for $C_{15}H_{19}N_3O_4S$ (337.39): C, 53.40; H, 5.68; N, 12.45; S, 9.50. Found: C, 53.64; H, 5.61; N, 11.83; S, 8.84.

4-(2-Azido-1-hydroxycyclopentyl)-3-oxobutyronitrile (**9d**):

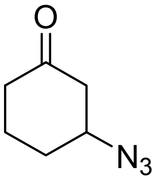


To a THF solution (35 mL) of diisopropylamine (965 mg, 9.5 mmol) was added a 1.6 M solution of *n*BuLi in hexane (6.0 mL, 9.6 mmol) at 0 °C. After stirring for 15 minutes, the solution was cooled to –20 °C and 5-methylisoxazole **8** (332 mg, 4.0 mmol), dissolved in THF (5 mL), was added and the solution was stirred for 2 h at –20 °C. 2-Azidocyclopentanone **6c** (455 mg, 3.6 mmol), dissolved in THF (5 mL), was added at –78 °C and the reaction mixture was warmed to ambient temperature within 15 h and left stirring for 25 h more. A saturated solution of NH_4Cl (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with Et_2O (2 x 70 mL) and CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; petroleum ether/EtOAc = 3:1) to give **9d** as a slightly brown oil (53 mg, 7%, mixture of diastereomers: dr ≥ 5:1); R_f 0.14 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 – 2.15 (m, 6H, CH_2), 2.63 (d, ^2J = 15.0 Hz, 1H, C$H_A$$H_B$CO), 2.78 (br, 1H, OH), 2.98 (d, ^2J = 15.0 Hz, 1H, C$H_A$$H_B$CO), 3.48 (t, ^3J = 7.9 Hz, 1H, CHN_3), 3.59 – 3.74 (m, 2H, CH_AH_BCO). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (CH_2, major), 20.5 (CH_2, minor), 27.0 (CH_2, major), 28.7 (CH_2, minor), 33.2 (CH_2, minor), 33.7 (CH_2, major), 35.8 (CH_2, major), 36.6 (CH_2, minor), 46.7 (COHCH_2CO, minor), 49.6

(COHCH_2CO, major), 67.9 (CHN_3, major), 69.2 (CHN_3, minor), 79.7 (COH, major), 81.8 (COH, minor), 113.3 (CN, minor), 113.7 (CN, major), 197.4 (CO, major), 199.5 (CO, minor).

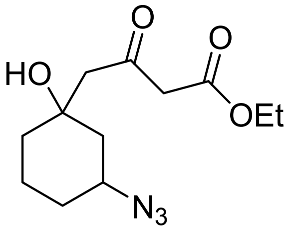
3-Azidocyclohexanone (**13**):



To a solution of NaN_3 (19.5 g, 300 mmol) and cyclohex-2-enone (15.1 g, 157 mmol) in water (100 mL) was added acetic acid (9.94 g, 166 mmol) and the reaction mixture was stirred for 40 h. After separation the aqueous layer was extracted with ether (4 x 40 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo*. Destillation yielded **13** as a clear, slightly yellow liquid (9.75 g, 45%); bp. 83 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.66 – 1.87 (m, 2H, CH_2), 2.01 – 2.14 (m, 2H, CH_2), 2.35 (m, 2H, CH_2), 2.43 (dd, ^2J = 14.3 Hz, ^3J = 8.6 Hz, 1H, $CHN_3C\mathit{H}_AH_BCO$), 2.66 (dd, ^2J = 14.3 Hz, ^3J = 4.6 Hz, 1H, $CHN_3CH_A\mathit{H}_BCO$), 3.89 (m, 1H, CHN_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 29.3, 40.3, 46.1 (CH_2), 59.2 (CH), 207.2 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2951 (s), 2874 (m), 2101 (s), 1717 (s), 1314 (m), 1251 (s), 1222 (s), 1101 (m), 515 (w). MS (GC-EI, 70 eV): *m/z* (%) = 139 (M^+, 30), 82 (19), 69 (27), 68 (30), 56 (54), 55 (80), 54 (33), 42 (86), 41 (100), 39 (39). Anal. Calcd for $C_6H_9N_3O$ (139.16): C, 51.79; H, 6.52; N, 30.20. Found: C, 52.17; H, 6.62; N, 29.93.

Ethyl 4-(3-azido-1-hydroxycyclohex-1-yl)-3-oxo-butyrate (**14**):

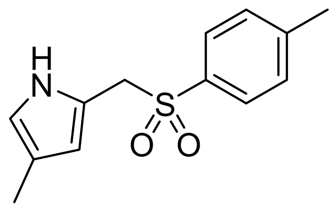


To a THF solution (50 mL) of diisopropylamine (1.35 g, 13.3 mmol) was added a 1.6 M solution of *n*BuLi in hexane (8.3 mL, 13.3 mmol) at 0 °C. After stirring for 20 minutes, ethyl acetoacetate (0.77 g, 5.9 mmol) was added and the solution was left stirring at 0 °C. After 1 h, the solution was cooled to –78 °C and 3-azidocyclohexanone **13** (0.93 g, 6.7 mmol) was added. The reaction mixture was warmed to ambient temperature within 14 h and was stirred for 4 h more. A saturated solution of NH_4Cl (50 mL) was added and the aqueous layer was extracted with THF (2 x 50 mL) and ether (2 x 50 mL). The THF extracts were concentrated *in vacuo* to remove the THF. The residue and ether extracts were combined, washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; *n*-hexane/EtOAc = 5:1) to give **14** as a brown solid (1.20 g, 75%, mixture of diastereomers: dr = 3:2); R_f 0.28 (*n*-hexane/EtOAc = 3:1). Spectroscopic data refer to main isomer.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.29 (t, ^3J = 7.1 Hz, 3H, CH$_3$), 1.35 – 1.97 (m, 8H, CH$_2$), 2.72 (s, 2H, COHC*H*$_2$CO), 3.52 (s, 2H, CH$_2$COOEt), 3.63 (m, 1H, CHN$_3$), 3.69 (s, 1H, OH), 4.20 (q, ^3J = 7.1 Hz, 2H, OCH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.9 (CH$_3$), 18.4, 29.8, 36.9, 40.9, 50.6, 51.2 (CH$_2$), 57.2 (CHN$_3$), 61.3 (OCH$_2$), 71.1 (COH), 166.9 (COOEt), 203.2 (CO).

8.3.2 Pyrroles

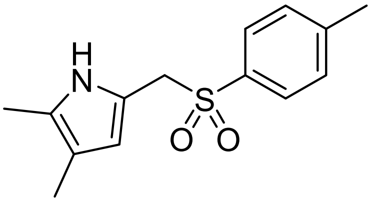
2-[(Toluene-4-sulfonyl)-methyl]-4-methyl-1*H*-pyrrole (**15a**):



Compound **9a** (200 mg, 0.64 mmol) was dissolved in dry THF (10 mL) and PPh$_3$ (205 mg, 0.78 mmol) was added. The reaction mixture was stirred at 45 °C for 24 h. Water (50 mL) and CH$_2$Cl$_2$ (50 mL) were added and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na$_2$SO$_4$), filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; petroleum ether/EtOAc = 4:1) to give **15a** as a slightly orange solid (86 mg, 54%). Mp 131 – 132 °C; R_f 0.41 (petroleum ether/EtOAc = 3:1).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.00 (s, 3H, CH$_3$), 2.42 (s, 3H, CH$_3$), 4.29 (s, 2H, CH$_2$), 5.68 (s, 1H, Hetar), 6.58 (s, 1H, Hetar), 7.26 (d, ^3J = 8.2 Hz, 2H, Ar), 7.51 (d, ^3J = 8.2 Hz, 2H, Ar), 8.42 (br, 1H, NH). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 11.6 (HetarCH$_3$), 21.6 (ArCH$_3$), 55.9 (CH$_2$), 112.7 (CH$_{\text{Hetar}}$), 117.4 (C$_{\text{Hetar}}$), 117.8 (CH$_{\text{Hetar}}$), 119.1 (C$_{\text{Hetar}}$), 128.3, 129.4 (CH$_{\text{Ar}}$), 134.8, 144.7 (C$_{\text{Ar}}$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3419 (m), 3380 (s), 1295 (s), 1149 (s), 1129 (m), 1085 (m), 811 (m), 759 (w), 677 (m), 548 (m), 512 (w). MS (EI, 70 eV): *m/z* (%) = 249 (M$^+$, 6), 94 (100), 66 (14). HRMS (EI, 70 eV): Calcd for C$_{13}$H$_{15}$NO$_2$S (M$^+$) 249.08180, found 249.08124.

2-[(Toluene-4-sulfonyl)-methyl]-4,5-dimethyl-1*H*-pyrrole (**15b**):

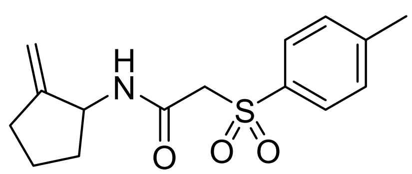


Compound **9b** (270 mg, 0.83 mmol) was dissolved in dry THF (10 mL) and PPh$_3$ (274 mg, 1.04 mmol) was added. The reaction mixture was stirred at 45 °C for 44 h. A saturated solution of NH$_4$Cl (30 mL) and CH$_2$Cl$_2$ (50 mL) were added and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; *n*-hexane/EtOAc = 5:1) to give **15b** as a red-violet solid (58 mg, 27%). Mp 128 – 129 °C; R_f 0.32 (*n*-hexane/EtOAc = 3:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.90 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 4.25 (s, 2H, CH_2), 5.61 (d, ^4J = 2.7 Hz, 1H, Hetar), 7.27 (d, ^3J = 8.2 Hz, 2H, Ar), 7.55 (m, 2H, Ar), 8.20 (br, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.6, 11.0 (HetarCH_3), 21.6 (ArCH_3), 56.0 (CH_2), 113.2 (CH_{Hetar}), 114.3, 114.7, 126.3 (C_{Hetar}), 128.3, 129.5 (CH_{Ar}), 135.0, 144.6 (C_{Ar}). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3377 (s), 2926 (w), 1284 (s), 1242 (m), 1164 (m), 1148 (m), 1086 (m), 806 (m), 546 (m), 514 (m). MS (EI, 70 eV): *m/z* (%) = 263 (M^+, 5), 107 (100), 91 (15), 66 (9), 39 (6). HRMS (EI, 70 eV): Calcd for $C_{14}H_{17}NO_2S$ (M^+) 263.09745, found 263.09689.

8.3.3 Rearrangement

***N*-(2-Methylidenecyclopentyl)-2-tosylacetamide (16)**:

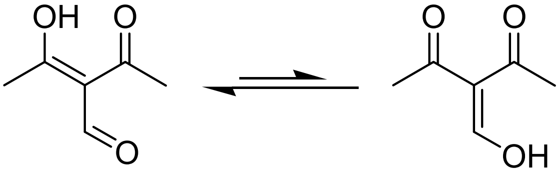


9c (260 mg, 0.77 mmol) was dissolved in dry THF (10 mL) and PPh_3 (244 mg, 0.93 mmol) was added. The reaction mixture was stirred at 45 °C for 38 h. Water (50 mL) and CH_2Cl_2 (50 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; *n*-hexane/EtOAc = 5:1 → 3:1) to give **16** as a slightly yellow solid (46 mg, 20%). Mp 157 – 158 °C; R_f 0.54 (*n*-hexane/EtOAc = 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 – 1.52 (m, 1H, CH_2), 1.52 – 1.71 (m, 1H, CH_2), 1.71 – 1.85 (m, 1H, CH_2), 2.07 – 2.20 (m, 1H, CH_2), 2.36 – 2.44 (m, 2H, CCH_2CH_2), 2.45 (s, 3H, CH_3), 4.02 (m, 2H, $CH_AH_BSO_2$), 4.58 (m, br, 1H, NHC*H*); 5.03 (m, 2H, C=CH_2), 6.67 (d, br, ^3J = 7.3 Hz, 1H, NH), 7.37 (d, ^3J = 8.2 Hz, 2H, Ar), 7.79 (d, ^3J = 8.2 Hz, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7 (CH_3), 22.4, 30.9, 33.6 (CH_2), 54.1 (CHNH), 62.0 (CH_2SO_2), 107.5 (C=*C*H_2), 128.1, 130.0 (CH_{Ar}), 135.2, 145.6 (C_{Ar}), 151.3 (*C*=CH_2), 160.3 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3331 (s), 2993 (m), 2964 (m), 2917 (m), 1650 (s), 1521 (s), 1324 (s), 1299 (m), 1159 (s), 1087 (m), 814 (m), 522 (m). MS (EI, 70 eV): *m/z* (%) = 293 (M^+, 20), 214 (4), 155 (6), 138 (100), 96 (30), 91 (36), 32 (23), 28 (90). HRMS (EI, 70 eV): Calcd for $C_{15}H_{19}NO_3S$ (M^+) 293.10802, found 293.10758.

8.3.4 Starting Materials for [3+3] Cyclizations

3-Formyl-4-hydroxypent-3-en-2-one (**19a**):

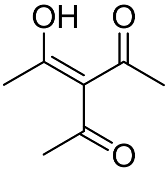


A mixture of acetylacetone (25.2 g, 252 mmol), triethyl orthoformate (37.8 g, 255 mmol), and acetic acid anhydride (43.2 g, 423 mmol) was refluxed for 3 h and then cooled to 0 °C. Water (10 mL) was added and the reaction mixture was refluxed for 10 minutes. Volatile compounds were removed *in vacuo* and the residue was destilled to yield **19a** as a colourless solid quickly developing an oily surface (17.8 g, 55%, ratio of tautomers = 4:1 in $CDCl_3$ at 25 °C); bp. 57 °C (0.1 mbar).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.34 (s, 3H, CH_3, minor), 2.54 (s, 6H, CH_3, major), 2.57 (s, 3H, CH_3, minor), 8.98 (d, ^3J = 7.0 Hz, 1H, CH, minor), 10.03 (s, 1H, CHO, major), 17.20 (d, ^3J = 7.0 Hz, 1H, OH, minor), 18.36 (s, 1H, OH, major). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 25.0 (CH_3, major), 28.4 (CH_3, minor), 114.8 (C, major), 117.2 (C, minor), 184.5 (CHOH, minor), 187.2 (CO, COH, major), 194.3 (CO, minor), 200.3 (CHO, major), 202.7 (CO, minor). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3443 (br, w), 1787 (m), 1771 (m), 1723 (m), 1674 (s), 1614 (s), 1568 (s), 1411 (s), 1363 (m), 1029 (m). MS (EI, 70 eV): *m/z* (%) = 128 (M^+, 20), 100 (41), 72 (35), 68 (32), 43 (100).

The spectroscopic data (IR) are in accordance with those presented in the literature.[105]

Triacetylmethane (**19b**):

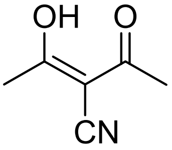


NaH (8.11 g, 338 mmol) was suspended in dry ether (300 mL) and the suspension was cooled to 0 °C. Acetylacetone (33.7 g, 337 mmol) was dropwise added. Freshly destilled acetylchloride (26.4 g, 336 mmol) was dropwise added at 0 °C. The reaction mixture was warmed to 20 °C within 3h. After stirring for 12 h more the reaction mixture was filtered and washed with ether. The precipitate was dissolved in water (100 mL) and extracted with ether (3 x 75 mL). The filtrate and organic extracts were combined, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo*. A small amount of sodium tritylate was added for stabilization and destillation yielded **19b** as a clear yellow liquid (25.6 g, 53%); bp. 60 °C (0.1 mbar).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 6H, CH_3), 2.44 (s, 3H, CH_3), 17.23 (s, 1H, OH).

The spectroscopic data are in accordance with those presented in the literature.[106]

2-Acetyl-3-hydroxy-but-2-enenitrile (**19c**):

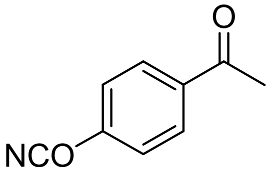


A solution of sodium ethanolate was prepared from ether (20 mL), ethanol (20 mL), and sodium (1.17 g, 51 mmol). Acetylacetone (5.01 g, 50 mmol), dissolved in ether (20 mL), was dropwise added at 0 °C. **23** (8.06 g, 50 mmol), dissolved in THF (50 mL), was subsequently added dropwise. Stirring continued for 1 h at 0 °C and 20 h at 20 °C. Solvents and volatile compounds were removed *in vacuo* and ether (150 mL) was added. The suspension was filtered and washed with ether. The precipitate was suspended in HCl (2 M, 100 mL) and ice (25 g). This mixture was filtered and the residing solid was washed with ice water, dissolved in ether, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* and the residue was recrystallized from *n*-heptane (20 mL) to yield **19c** as a colourless solid (2.32 g, 37%); mp 51 – 52 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 6H, CH_3), 16.82 (br, 1H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 24.5 (CH_3), 90.7, 116.5 (C), 197.0 (CO/COH). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2218 (s), 1609 (br, s), 1419 (s), 1292 (m), 1022 (m), 926 (m), 521 (m). Anal. Calcd for $C_6H_7NO_2$ (125.13): C, 57.59; H, 5.64; N, 11.19. Found: C, 57.85; H, 5.61; N, 11.03.

The spectroscopic data (^{1}H NMR, ^{13}C NMR, IR) are in accordance with those presented in the literature.[47]

1-(4-Cyanatophenyl)-ethanone (**23**):



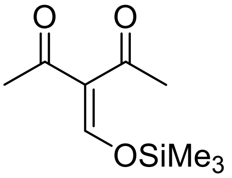
To a solution of 4-hydroxyacetophenone (13.60 g, 100 mmol) and BrCN (11.50 g, 109 mmol) in dry acetone (200 mL) was added in 30 min triethylamine (10.27 g, 101 mmol), dissolved in dry acetone (50 mL), at –10 °C. After stirring for 30 min the reaction mixture was filtered and the residue was washed with acetone (4 x 50 mL). The filtrate was concentrated *in vacuo*. Triethylamine (3.0 g, 30 mmol) and 4-hydroxyacetophenone (3.0 g, 22 mmol) were added to the condensate in order to remove excess BrCN prior to disposal. The residue, i.e. the concentrated filtrate (see above), was suspended in water (0 °C) in order to dissolve traces of NEt_3•HBr and filtered. The residue was dissolved in acetone, dried (Na_2SO_4), filtered, and recrystallized from ether/*n*-pentane. The obtained crystals were washed with *n*-pentane to yield **23** as a colourless solid (12.85 g, 80%); mp 64 – 65 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.62 (s, 3H, CH_3), 7.40 (m, 2H, Ar), 8.07 (m, 2H, Ar).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.6 (CH_3), 107.8 (C), 115.4, 131.0 (CH_{Ar}), 135.7, 155.5 (C), 195.8 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2288 (m), 2267 (m), 2241 (m), 1693 (s), 1593 (s), 1496 (m), 1414 (m), 1367 (m), 1268 (s), 1196 (s), 1168 (s), 830 (s), 801 (m). Anal. Calcd for $C_9H_7NO_2$ (161.16): C, 67.07; H, 4.38; N, 8.69. Found: C, 66.76; H, 4.43; N, 8.45.

This compound has been prepared before but no comparable spectroscopic data are given. Melting points of 59 °C and 62 – 63 °C are given in the literature.[48]

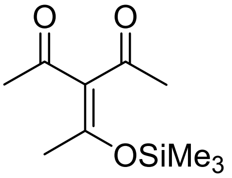
3-(Trimethylsilyloxy-methylidene)-pentane-2,4-dione (24a):



To an ether solution (50 mL) of **19a** (3.49 g, 27.2 mmol) was added NEt_3 (2.82 g, 27.9 mmol). The reaction mixture was cooled to 0 °C and Me_3SiOTf (5.93 g, 26.7 mmol) was added in 20 minutes under vigorous stirring. The reaction was stirred for 6 h at 0 °C. The ether phase was isolated and the residue was washed with ether (20 mL). The ether phases were combined and concentrated *in vacuo* to yield **24a** as a clear orange liquid (4.82 g, 88%).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.31 (s, 9H, $Si(CH_3)_3$), 2.28 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 7.71 (s, 1H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –0.9 ($Si(CH_3)_3$), 29.0, 31.8 (CH_3), 126.0 (*C*CH), 159.6 (CH), 197.2, 198.2 (CO).

3-(1-Trimethylsilyloxy-ethylidene)-pentane-2,4-dione (24b):

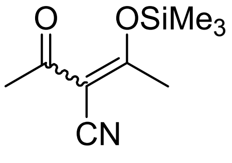


To an ether solution (50 mL) of triacetylmethane **19b** (3.58 g, 25.2 mmol) was added NEt_3 (2.61 g, 25.7 mmol). The reaction mixture was cooled to 0 °C and Me_3SiOTf (5.49 g, 24.7 mmol) was added in 15 minutes under vigorous stirring. The reaction was stirred for 4.5 h at 0 °C. The ether phase was isolated and the residue was washed with ether (20 mL). The ether phases were combined and concentrated *in vacuo* to yield **24b** as a clear yellow liquid (4.52 g, 84%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.26 (s, 9H, $Si(CH_3)_3$), 2.14 (s, 6H, CH_3), 2.32 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.6 ($Si(CH_3)_3$), 21.4, 30.5 (CH_3), 127.2, 165.4 (C), 199.1 (CO).

This compound has been prepared before but no comparable spectroscopic data are given.[49]

2-Acetyl-3-trimethylsilyloxy-but-2-enenitrile (24c):



To an ether solution (40 mL) of **19c** (2.22 g, 17.7 mmol) was added NEt_3 (1.85 g, 18.3 mmol). The reaction mixture was cooled to 0 °C and Me_3SiOTf (3.87 g, 17.4 mmol), dissolved in ether (10 mL), was added in 10 minutes under vigorous stirring. The reaction was stirred for 5 h at 0 °C. The ether phase was isolated and the residue was washed with ether (20 mL). The ether phases were combined and concetrated *in vacuo* to yield **24c** as a yellow-brown solid (3.10 g, 88%, ratio of isomers = 2:1).

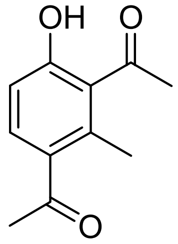
E/*Z*-isomerization was observed upon storage and/or standing in solution although the compound was stored at –20 °C and NMR spectra were quickly measured from freshly prepared samples. For the ratio of isomers A : B values of 2 : 1 (^{1}H NMR spectrum given below) and 1 : 4 were determined from ^{1}H NMR spectra. The ^{13}C spectrum shows only one isomer.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 9H, $Si(CH_3)_3$, major), 0.39 (s, 9H, $Si(CH_3)_3$, minor), 2.39 (s, 6H, CCH_3, major), 2.41 (s, 3H, CCH_3, minor), 2.47 (s, 3H, CCH_3, minor). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.8 ($Si(CH_3)_3$), 22.4, 30.4 (CH_3), 98.4, 117.4, 181.5, 193.2 (C).

8.3.5 [3+3] Cyclizations

8.3.5.1 Functionalized Acetophenones

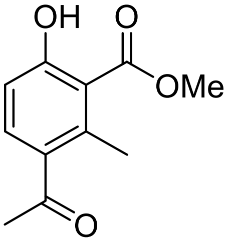
1-(3-Acetyl-4-hydroxy-2-methylphenyl)-ethanone (**25a**):



(GP 1) Starting with **24a** (212 mg, 1.06 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.13 mL, 1.2 mmol), and **3a** (385 mg, 1.57 mmol), **25a** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 10:1 → 3:1) as an orange solid (71 mg, 35%). Mp 152 – 153 °C; R_f 0.14 (*n*-hexane/EtOAc = 3:1). Reaction time: 25 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.56 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 2.64 (s, 3H, CH_3), 6.87 (dd, ^3J = 8.8 Hz, ^4J = 0.4 Hz, 1H, Ar), 7.71 (d, ^3J = 8.8 Hz, 1H, Ar), 10.75 (br, 1H, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.1 ($ArCH_3$), 30.1, 33.1 ($COCH_3$), 115.3 (CH_{Ar}), 126.3, 131.7 (C_{Ar}), 134.7 (CH_{Ar}), 140.4 (C_{Ar}), 161.2 ($C_{Ar}OH$), 200.9, 207.2 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3037 (br, m), 2926 (m), 1695 (s), 1643 (m), 1557 (s), 1441 (m), 1364 (m), 1267 (m), 1215 (m), 818 (w). MS (EI, 70 eV): *m/z* (%) = 192 (M^+, 65), 177 (100), 159 (20), 103 (11), 77 (20). Anal. Calcd for $C_{11}H_{12}O_3$ (192.21): C, 68.74; H, 6.29. Found: C, 68.56; H, 6.54.

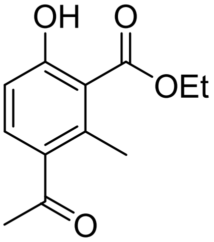
Methyl 3-acetyl-6-hydroxy-2-methylbenzoate (**25b**):



(GP 1) Starting with **24a** (863 mg, 4.31 mmol), CH_2Cl_2 (20 mL), molecular sieves (4 Å, 2.0 g), $TiCl_4$ (0.47 mL, 4.3 mmol), and **3b** (1.56 g, 5.98 mmol), **25b** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 3:1) as a yellow solid (495 mg, 55%). Mp 112 – 113 °C; R_f 0.30 (*n*-hexane/EtOAc = 3:1). Reaction time: 22 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.54 (s, 3H, CCH_3), 2.61 (s, 3H, CCH_3), 3.99 (s, 3H, OCH_3), 6.88 (d, ^3J = 8.8 Hz, 1H, Ar), 7.62 (d, ^3J = 8.8 Hz, 1H, Ar), 11.06 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.9 ($ArCH_3$), 30.2 ($COCH_3$), 52.4 ($COOCH_3$), 114.7 (CH_{Ar}), 114.9, 132.7 (C_{Ar}), 133.9 (CH_{Ar}), 141.2 (C_{Ar}), 162.9, 171.4 ($C_{Ar}OH$, $COOCH_3$), 201.6 ($COCH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3068 (br, s), 2932 (s), 2852 (m), 2787 (m), 2712 (m), 1729 (s), 1643 (s), 1563 (s), 1437 (s), 1292 (s), 1235 (s), 1102 (s), 822 (m). MS (EI, 70 eV): *m/z* (%) = 208 (M^+, 38), 193 (19), 176 (36), 161 (100), 77 (13). Anal. Calcd for $C_{11}H_{12}O_4$ (208.21): C, 63.45; H, 5.81. Found: C, 63.32; H, 5.87.

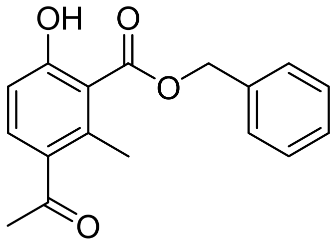
Ethyl 3-acetyl-6-hydroxy-2-methylbenzoate (**25c**):



(GP 1) Starting with **24a** (195 mg, 0.97 mmol), CH_2Cl_2 (5.0 mL), molecular sieves (4 Å, 0.6 g), $TiCl_4$ (0.11 mL, 1.0 mmol), and **3c** (386 mg, 1.41 mmol), **25c** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 5:1) as an orange solid (83 mg, 39%). Mp 130 – 132 °C; R_f 0.63 (*n*-hexane/EtOAc = 1:1). Reaction time: 23 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (t, ^3J = 7.2 Hz, 3H, CH_2CH_3), 2.54 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 4.47 (q, ^3J = 7.2 Hz, 2H, CH_2), 6.88 (dd, ^3J = 8.8 Hz, ^4J = 0.3 Hz, 1H, Ar), 7.61 (d, ^3J = 8.8 Hz, 1H, Ar), 11.13 (s, 1H, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.2 (CH_2CH_3), 20.3 ($ArCH_3$), 30.5 ($COCH_3$), 62.3 (CH_2), 115.1 (CH_{Ar}), 115.2, 133.1 (C_{Ar}), 134.1 (CH_{Ar}), 141.6 (C_{Ar}), 163.4, 171.3 ($C_{Ar}OH$, COOEt), 201.9 ($COCH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3173 (br, s), 2992 (s), 1731 (s), 1650 (s), 1568 (s), 1445 (m), 1359 (m), 1293 (s), 1232 (s), 1098 (s), 822 (m). MS (EI, 70 eV): *m/z* (%) = 222 (M^+, 33), 207 (12), 177 (18), 176 (46), 161 (100). Anal. Calcd for $C_{12}H_{14}O_4$ (222.24): C, 64.85; H, 6.35. Found: C, 64.91; H, 6.64.

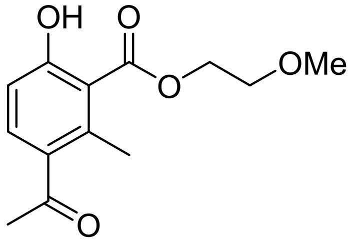
Benzyl 3-acetyl-6-hydroxy-2-methylbenzoate (**25d**):



(GP 1) Starting with **24a** (226 mg, 1.13 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.12 mL, 1.1 mmol), and **3d** (532 mg, 1.58 mmol), **25d** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 8:1) as a colourless solid (105 mg, 33%). Mp 99 – 100 °C; R_f 0.35 (*n*-hexane/EtOAc = 3:1). Reaction time: 23 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.45 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 5.36 (s, 2H, CH_2), 6.81 (dd, ^3J = 8.7 Hz, ^4J = 0.4 Hz, 1H, Ar), 7.28 – 7.40 (m, 5H, Ph), 7.53 (d, ^3J = 8.7 Hz, 1H, Ar), 10.96 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.4 ($ArCH_3$), 30.4 ($COCH_3$), 67.9 (CH_2), 114.7 (C_{Ar}), 115.1, 128.6, 128.7, 128.7 (CH_{Ar}), 133.1 (C_{Ar}), 134.1 (CH_{Ar}), 134.6, 141.5 (C_{Ar}), 163.4, 171.0 ($C_{Ar}OH$, $\mathit{C}OOCH_2$), 201.7 ($\mathit{C}OCH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3065 (s), 3036 (s), 2929 (s), 2707 (m), 1732 (s), 1641 (m), 1559 (s), 1450 (m), 1288 (s), 1229 (s), 1102 (m), 820 (m). MS (EI, 70 eV): *m/z* (%) = 284 (M^+, 9), 193 (19), 91 (100), 66 (7), 28 (6). Anal. Calcd for $C_{17}H_{16}O_4$ (284.31): C, 71.82; H, 5.67. Found: C, 71.64; H, 5.86.

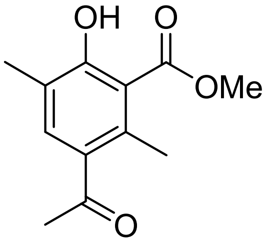
2-Methoxy-ethyl 3-acetyl-6-hydroxy-2-methylbenzoate (**25e**):



(GP 1) Starting with **24a** (205 mg, 1.02 mmol), CH_2Cl_2 (5.0 mL), molecular sieves (4 Å, 0.5 g), $TiCl_4$ (0.11 mL, 1.0 mmol), and **3e** (432 mg, 1.42 mmol), **25e** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 5:1) as a slightly yellow solid (36 mg, 14%). Mp 113 – 115 °C; R_f 0.20 (*n*-hexane/EtOAc = 3:1). Reaction time: 22 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.54 (s, 3H, CCH_3), 2.63 (s, 3H, CCH_3), 3.42 (s, 3H, OCH_3), 3.73 (m, 2H, $C\mathit{H_2}OCH_3$), 4.54 (m, 2H, $C\mathit{H_2}CH_2OCH_3$), 6.87 (dd, ^3J = 8.8 Hz, ^4J = 0.3 Hz, 1H, Ar), 7.62 (d, ^3J = 8.8 Hz, 1H, Ar), 10.57 (br, 1H, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 20.0 ($ArCH_3$), 30.6 ($CO\mathit{C}H_3$), 59.1 (OCH_3), 64.7, 70.0 (CH_2), 115.2 (CH_{Ar}), 115.7, 133.1 (C_{Ar}), 134.2 (CH_{Ar}), 141.7 (C_{Ar}), 162.8, 170.5 ($C_{Ar}OH$, $\mathit{C}OOCH_2$), 201.8 ($\mathit{C}OCH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3101 (br, s), 2934 (s), 1733 (s), 1645 (s), 1562 (s), 1356 (m), 1296 (s), 1243 (s), 1100 (m), 814 (m). MS (EI, 70 eV): *m/z* (%) = 252 (M^+, 42), 193 (12), 177 (31), 176 (70), 161 (100). Anal. Calcd for $C_{13}H_{16}O_5$ (252.26): C, 61.90; H, 6.39. Found: C, 61.86; H, 6.21.

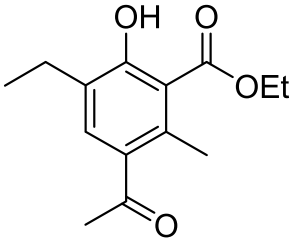
Methyl 3-acetyl-6-hydroxy-2,5-dimethylbenzoate (**25f**):



(GP 1) Starting with **24a** (206 mg, 1.03 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.13 mL, 1.2 mmol), and **3f** (418 mg, 1.52 mmol), **25f** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 10:1) as a colourless solid (164 mg, 72%). Mp 65 – 66 °C; R_f 0.56 (*n*-hexane/EtOAc = 3:1). Reaction time: 24 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.25 (s, 3H, $ArCH_3$), 2.53 (s, 3H, CCH_3), 2.57 (s, 3H, $ArCH_3$), 3.98 (s, 3H, OCH_3), 7.47 (s, 1H, Ar), 11.31 (s, 1H, OH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.7, 19.8 ($ArCH_3$), 30.4 ($COCH_3$), 52.4 (OCH_3), 113.9, 123.8, 132.3 (C_{Ar}), 134.6 (CH_{Ar}), 138.4 (C_{Ar}), 161.7, 172.1 ($C_{Ar}OH$, $COOCH_3$), 201.9 ($COCH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3222 (br, s), 2951 (m), 1733 (s), 1647 (s), 1561 (s), 1439 (m), 1362 (m), 1303 (s), 1211 (s), 1149 (s), 1065 (m). MS (EI, 70 eV): *m/z* (%) = 222 (M^+, 49), 191 (23), 190 (84), 175 (100), 162 (24), 91 (23). Anal. Calcd for $C_{12}H_{14}O_4$ (222.24): C, 64.85; H, 6.35. Found: C, 64.94; H, 6.28.

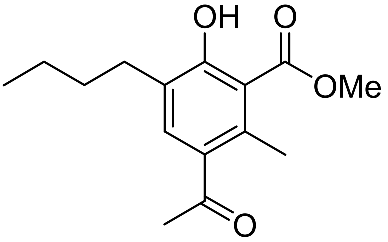
Ethyl 3-acetyl-5-ethyl-6-hydroxy-2-methylbenzoate (**25g**):



(GP 1) Starting with **24a** (113 mg, 0.56 mmol), CH_2Cl_2 (3.0 mL), molecular sieves (4 Å, 0.2 g), $TiCl_4$ (0.07 mL, 0.6 mmol), and **3g** (229 mg, 0.76 mmol), dissolved in CH_2Cl_2 (0.5 ml) **25g** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 10:1) as a colourless solid (83 mg, 59%). Mp 39 – 40 °C; R_f 0.40 (*n*-hexane/EtOAc = 10:1). Reaction time: 27 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, ^3J = 7.5 Hz, 3H, $ArCH_2CH_3$), 1.43 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 2.53 (s, 3H, $COCH_3$), 2.58 (s, 3H, $ArCH_3$), 2.67 (q, ^3J = 7.5 Hz, 2H, $ArCH_2CH_3$), 4.45 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 7.46 (s, 1H, Ar), 11.35 (s, 1H, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.8, 14.3 (CH_2CH_3), 20.2 ($ArCH_3$), 23.2 ($ArCH_2$), 30.7 ($COCH_3$), 62.2 (OCH_2), 114.3, 129.9, 132.8 (C_{Ar}), 133.2 (CH_{Ar}), 138.5 (C_{Ar}), 161.7, 172.0 ($C_{Ar}OH$, COOEt), 202.5 ($COCH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3168 (br, s), 2978 (s), 2937 (s), 1717 (s), 1652 (s), 1558 (s), 1458 (m), 1365 (m), 1298 (s), 1204 (s), 1066 (m), 1027 (m). MS (EI, 70 eV): *m/z* (%) = 250 (M^+, 53), 205 (23), 204 (100), 189 (43), 176 (99), 28 (71). Anal. Calcd for $C_{14}H_{18}O_4$ (250.29): C, 67.18; H, 7.25. Found: C, 67.18; H, 7.21.

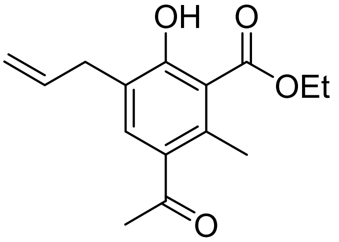
Methyl 3-acetyl-5-butyl-6-hydroxy-2-methylbenzoate (**25h**):



(GP 1) Starting with **24a** (198 mg, 0.99 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.12 mL, 1.1 mmol), and **3h** (469 mg, 1.48 mmol), **25h** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 10:1) as a colourless solid (200 mg, 77%). Mp 54 – 55 °C; R_f 0.42 (*n*-hexane/EtOAc = 5:1). Reaction time: 25 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, ^3J = 7.3 Hz, 3H, CH_2CH_3), 1.31 – 1.44 (m, 2H, CH_2), 1.53 – 1.64 (m, 2H, CH_2), 2.53 (s, 3H, CCH_3), 2.56 (s, 3H, $ArCH_3$), 2.64 (t, ^3J = 7.7 Hz, 2H, $ArCH_2$), 3.98 (s, 3H, OCH_3), 7.45 (s, 1H, Ar), 11.27 (s, 1H, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.2 (CH_2CH_3), 20.2 ($ArCH_3$), 22.8, 29.8 (CH_2), 30.8 ($COCH_3$), 31.7 (CH_2), 52.7 (OCH_3), 114.3, 128.7, 132.8 (C_{Ar}), 134.2 (CH_{Ar}), 138.6 (C_{Ar}), 161.8, 172.5 ($C_{Ar}OH$, $COOCH_3$), 202.5 ($COCH_3$). IR (nujol, cm^{-1}): $\tilde{\nu}$ = 3193 (br, s), 1721 (s), 1648 (s), 1563 (s), 1298 (s), 1254 (s), 1220 (s), 1145 (m), 1066 (m), 959 (m). MS (GC-EI, 70 eV): *m/z* (%) = 264 (M^+, 61), 217 (51), 204 (100), 190 (81), 189 (61), 175 (20), 162 (36). Anal. Calcd for $C_{15}H_{20}O_4$ (264.32): C, 68.16; H, 7.63. Found: C, 68.17; H, 7.72.

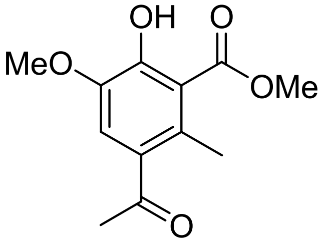
Ethyl 3-acetyl-5-allyl-6-hydroxy-2-methylbenzoate (**25i**):



(GP 1) Starting with **24a** (218 mg, 1.09 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.14 mL, 1.3 mmol), and **3i** (495 mg, 1.57 mmol), **25i** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 1:0 → 20:1) as a yellow oil (209 mg, 74%); R_f 0.38 (*n*-hexane/EtOAc = 10:1). Reaction time: 25 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 2.54 (s, 3H, $COCH_3$), 2.60 (s, 3H, $ArCH_3$), 3.42 (d, ^3J = 6.5 Hz, 2H, $ArCH_2$), 4.47 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 5.06 – 5.11 (m, 1H, $CHCH_AH_B$), 5.12 – 5.15 (m, 1H, $CHCH_AH_B$), 5.93 – 6.07 (m, 1H, $CHCH_AH_B$), 7.47 (s, 1H, Ar), 11.39 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 19.9 ($ArCH_3$), 30.3 ($COCH_3$), 33.6 ($ArCH_2$), 62.0 (CH_2CH_3), 114.2 (C_{Ar}), 116.1 ($CH_{2\ Allyl}$), 125.7, 132.5 (C_{Ar}), 133.7, 135.6 (CH), 138.8 (C_{Ar}), 161.2, 171.5 ($C_{Ar}OH$, COOEt), 201.8 ($COCH_3$). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3334 (br, w), 3079 (w), 2982 (m), 2939 (w), 1682 (s), 1658 (s), 1446 (m), 1323 (s), 1230 (s), 1199 (s), 1150 (m), 1018 (m). MS (GC-EI, 70 eV): *m/z* (%) = 262 (M^+, 70), 216 (49), 201 (67), 188 (89), 173 (100), 115 (30). HRMS (EI, 70 eV): Calcd for $C_{15}H_{18}O_4$ (M^+) 262.11996, found 262.12000.

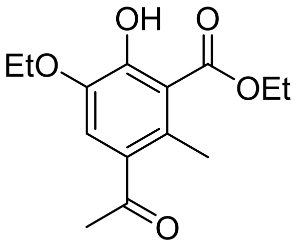
Methyl 3-acetyl-6-hydroxy-5-methoxy-2-methylbenzoate (**25j**):



(GP 1) Starting with **24a** (231 mg, 1.15 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.14 mL, 1.3 mmol), and **3j** (468 mg, 1.61 mmol), **25j** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 10:1 → 3:1) as a slightly yellow solid (96 mg, 35%). Mp 143 – 144 °C; R_f 0.12 (*n*-hexane/EtOAc = 3:1). Reaction time: 26 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 3H, CH_3), 2.54 (s, 3H, CH_3), 3.91 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 7.13 (s, 1H, Ar), 9.77 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.8 ($ArCH_3$), 30.4 ($COCH_3$), 52.5, 56.3 (OCH_3), 114.1 (CH_{Ar}), 117.3, 130.7, 131.9 (C_{Ar}), 145.4, 151.4 (C_{Ar}, $C_{Ar}OH$), 170.4 ($COOCH_3$), 201.5 ($COCH_3$). IR (nujol, cm^{-1}): $\tilde{\nu}$ = 3301 (br, m), 1732 (s), 1667 (s), 1573 (m), 1499 (m), 1291 (s), 1217 (s), 1196 (s), 1077 (s), 887 (w). MS (GC-EI, 70 eV): *m/z* (%) = 238 (M^+, 52), 207 (46), 206 (100), 191 (51), 178 (64), 177 (46), 163 (24). HRMS (EI, 70 eV): Calcd for $C_{12}H_{14}O_5$ (M^+) 238.08358, found 238.08392.

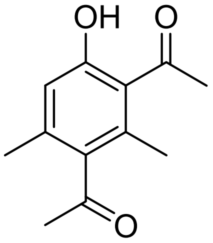
Ethyl 3-acetyl-5-ethoxy-6-hydroxy-2-methylbenzoate (**25k**):



(GP 1) Starting with **24a** (207 mg, 1.03 mmol), CH_2Cl_2 (5.0 mL), molecular sieves (4 Å, 0.5 g), $TiCl_4$ (0.11 mL, 1.0 mmol), and **3k** (454 mg, 1.43 mmol), **25k** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 5:1) as a yellow solid (80 mg, 29%). Mp 82 – 83 °C; R_f 0.19 (*n*-hexane/EtOAc = 3:1). Reaction time: 24 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, ^3J = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.47 (t, ^3J = 7.0 Hz, 3H, $ArOCH_2CH_3$), 2.49 (s, 3H, $ArCH_3$), 2.53 (s, 3H, $COCH_3$), 4.13 (q, ^3J = 7.0 Hz, 2H, $ArOCH_2CH_3$), 4.45 (q, ^3J = 7.1 Hz, 2H, $COOCH_2CH_3$), 7.15 (s, 1H, Ar), 9.53 (s, 1H, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.3, 14.9 (CH_2CH_3), 19.0 ($ArCH_3$), 30.6 ($COCH_3$), 62.2, 65.3 (CH_2), 115.6 (CH_{Ar}), 118.2, 131.0, 132.0 (C_{Ar}), 144.8, 151.5 (C_{Ar}, $C_{Ar}OH$), 170.1 (COOEt), 201.7 ($COCH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3223 (br, w), 2983 (w), 1726 (s), 1658 (m), 1574 (s), 1295 (s), 1201 (s), 1161 (m), 1077 (m). MS (EI, 70 eV): *m/z* (%) = 266 (M^+, 69), 221 (37), 220 (92), 205 (89), 192 (92), 177 (100), 148 (27). Anal. Calcd for $C_{14}H_{18}O_5$ (266.29): C, 63.15; H, 6.81. Found: C, 63.07; H, 7.04.

1-(3-Acetyl-4-hydroxy-2,6-dimethyl)-ethanone (**25l**):

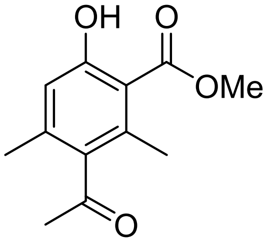


(GP 1) Starting with **24b** (203 mg, 0.95 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.12 mL, 1.1 mmol), and **3a** (323 mg, 1.32 mmol), **25l** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 3:1) as an orange-brown oil (56 mg, 29%); R_f 0.23 (*n*-hexane/EtOAc = 3:1). Reaction time: 3 d.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.18 (d, ^4J = 0.7 Hz, 3H, $ArCH_3$), 2.39 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 6.66 (s, 1H, Ar), 11.56 (br, 1H, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 19.8, 19.9 ($ArCH_3$), 32.9, 33.3 ($COCH_3$), 117.8 (CH_{Ar}), 121.5, 133.4, 136.3, 139.9 (C_{Ar}), 160.9 ($C_{Ar}OH$), 205.8, 207.9 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3293 (br, s), 2991 (m), 2927 (m), 1696 (s), 1597 (s), 1356 (s), 1307 (s), 1218 (s), 1188 (s), 1070 (m), 854 (m). MS (EI, 70 eV): *m/z* (%) = 206 (M$^+$, 39), 192 (11), 191 (100), 173 (22). HRMS (EI, 70 eV): Calcd for $C_{12}H_{14}O_3$ (M$^+$) 206.09375, found 206.09367.

This compound has been prepared before but no comparable spectroscopic data are given. In fact, it is clearly stated an *assumption* that this product has been prepared.[107]

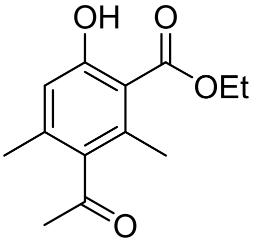
Methyl 3-acetyl-6-hydroxy-2,4-dimethylbenzoate (**25m**):



(GP 1) Starting with **24b** (208 mg, 0.97 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.12 mL, 1.1 mmol), and **3b** (411 mg, 1.58 mmol), **25m** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 10:1) as a slightly yellow solid (88 mg, 41%). Mp 103 – 105 °C; R_f 0.31 (*n*-hexane/EtOAc = 5:1). Reaction time: 1 week.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.19 (d, ^4J = 0.7 Hz, 3H, $ArCH_3$), 2.39 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 6.69 (s, 1H, Ar), 11.17 (s, 1H, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 19.8, 20.0 ($ArCH_3$), 33.0 ($COCH_3$), 52.4 (OCH_3), 110.7 (C_{Ar}), 117.4 (CH_{Ar}), 135.6, 136.4, 140.0 (C_{Ar}), 162.4, 171.8 ($C_{Ar}OH$, $COOCH_3$), 207.9 ($COCH_3$). IR (nujol, cm^{-1}): $\tilde{\nu}$ = 1703 (s), 1662 (s), 1602 (m), 1586 (m), 1320 (s), 1252 (s), 1233 (s), 1178 (m), 1105 (m), 811 (m). MS (GC-EI, 70 eV): *m/z* (%) = 222 (M$^+$, 20), 207 (18), 190 (21), 175 (100). Anal. Calcd for $C_{12}H_{14}O_4$ (222.24): C, 64.85; H, 6.35. Found: C, 64.72; H, 6.53.

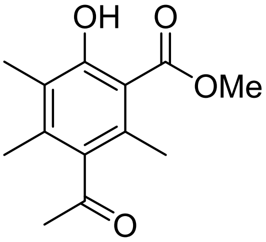
Ethyl 3-acetyl-6-hydroxy-2,4-dimethylbenzoate (**25n**):



(GP 1) Starting with **24b** (240 mg, 1.12 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.14 mL, 1.3 mmol), and **3c** (369 mg, 1.34 mmol), **25n** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 15:2) as a yellow solid (85 mg, 33%). Mp 108 – 109 °C; R_f 0.35 (*n*-hexane/EtOAc = 5:1). Reaction time: 3 d.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.43 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 2.20 (d, ^4J = 0.6 Hz, $ArCH_3$), 2.42 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 4.44 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 6.71 (s, 1H, Ar), 11.30 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_2CH_3), 19.5, 19.8 ($ArCH_3$), 32.7 ($COCH_3$), 61.7 (CH_2), 110.6 (C_{Ar}), 117.1 (CH_{Ar}), 135.4, 136.1, 139.6 (C_{Ar}), 162.2, 171.2 ($C_{Ar}OH$, COOEt), 207.7 ($COCH_3$). IR (nujol, cm^{-1}): $\tilde{\nu}$ = 1703 (s), 1655 (s), 1602 (m), 1586 (m), 1355 (s), 1318 (s), 1234 (s), 1186 (s), 809 (m). MS (GC-EI, 70 eV): *m/z* (%) = 236 (M^+, 20), 221 (16), 191 (13), 190 (28), 175 (100). Anal. Calcd for $C_{13}H_{16}O_4$ (236.26): C, 66.09; H, 6.83. Found: C, 65.94; H, 6.87.

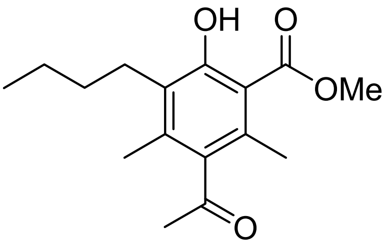
Methyl 3-acetyl-6-hydroxy-2,4,5-trimethylbenzoate (**25o**):



(GP 1) Starting with **24b** (234 mg, 1.09 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.14 mL, 1.3 mmol), and **3f** (406 mg, 1.48 mmol), **25o** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 20:1) as a colourless oil (63 mg, 24%); R_f 0.25 (*n*-hexane/EtOAc = 10:1). Reaction time: 5 d (T_{max} = 13 °C).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.15 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 3.96 (s, 3H, OCH_3), 11.57 (s, 1H, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 11.6, 17.3, 19.8 ($ArCH_3$), 33.4 ($COCH_3$), 52.4 (OCH_3), 110.2, 123.7, 131.8, 136.3, 137.8 (C_{Ar}), 160.5, 172.5 ($C_{Ar}OH$, $COOCH_3$), 208.8 $COCH_3$). IR (nujol, cm^{-1}): $\tilde{\nu}$ = 1700 (m), 1663 (s), 1595 (w), 1325 (m), 1263 (m), 1213 (s), 1149 (m), 1099 (w), 806 (w). MS (GC-EI, 70 eV): *m/z* (%) = 236 (M^+, 35), 221 (9), 204 (52), 189 (100), 176 (35), 161 (11). Anal. Calcd for $C_{13}H_{16}O_4$ (236.26): C, 66.09; H, 6.83. Found: C, 66.05; H, 6.95.

Methyl 3-acetyl-5-butyl-6-hydroxy-2,4-dimethylbenzoate (**25p**):

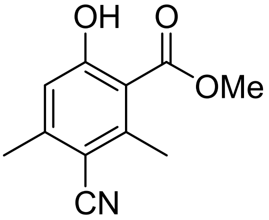


(GP 1) Starting with **24b** (174 mg, 0.81 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.10 mL, 0.9 mmol), and **3h** (360 mg, 1.14 mmol), **25p** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 10:1) as a slightly yellow oil (47 mg, 21%); R_f 0.25 (*n*-hexane/EtOAc = 10:1). Reaction time: 4 d.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 1.33 – 1.52 (m, 4H, $CH_2CH_2CH_3$), 2.17 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.66 (t, ^3J = 7.6 Hz, 2H, $ArCH_2$), 3.95 (s, 3H, OCH_3), 11.49 (s, 1H, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.0, 16.5 (CH_2CH_3, $ArCH_3$), 19.7 ($ArCH_3$), 23.1, 25.8, 31.0 (CH_2), 33.2 ($COCH_3$), 52.2 (OCH_3), 110.2, 128.4, 131.7, 136.3, 137.1 (C_{Ar}), 160.4, 172.4 ($C_{Ar}OH$, $COOCH_3$), 208.9 ($COCH_3$). IR (nujol, cm^{-1}): $\tilde{\nu}$ = 1705 (m), 1662 (s), 1598 (w), 1263 (w), 1215 (s), 1152 (m). MS (GC-EI, 70 eV): *m/z* (%) = 278 (M^+, 48), 263 (16), 231 (99), 218 (100), 204 (35), 203 (47), 176 (27). Anal. Calcd for $C_{16}H_{22}O_4$ (278.34): C, 69.04; H, 7.97. Found: C, 69.01; H, 8.05.

8.3.5.2 Cyanobenzoates

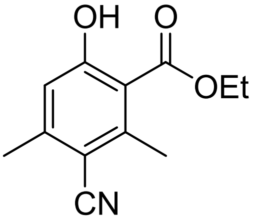
Methyl 3-cyano-6-hydroxy-2,4-dimethylbenzoate (**26a**):



(GP 2) Starting with **24c** (188 mg, 0.95 mmol), CH_2Cl_2 (3.0 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.11 mL, 1.0 mmol), and **3b** (356 mg, 1.37 mmol), **26a** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 10:1) as a colourless solid (67 mg, 34%). Mp 109 – 110 °C; R_f 0.21 (*n*-heptane/EtOAc = 10:1). Reaction time: 21 h.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.48 (d, ^4J = 0.9 Hz, 3H, $ArCH_3$), 2.75 (s. 3H, $ArCH_3$), 3.98 (s, 3H, OCH_3), 6.76 (s, 1H, CH_{Ar}), 11.72 (s. 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 21.8 ($ArCH_3$), 52.7 (OCH_3), 107.0, 111.0, 117.3 (2x C_{Ar}, CN), 117.4 (CH_{Ar}), 146.6, 148.4 (C_{Ar}), 165.1, 171.0 ($C_{Ar}OH$, CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3431 (br, m), 2957 (m), 2217 (s), 1668 (s), 1601 (s), 1581 (s), 1442 (s), 1368 (s), 1358 (s), 1319 (s), 1241 (s), 810 (s). MS (EI, 70 eV): *m/z* (%) = 205 (M^+, 83), 174 (76), 173 (100), 145 (66), 144 (37), 116 (20), 91 (14). Anal. Calcd for $C_{11}H_{11}NO_3$ (205.21): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.64; H, 5.52; N, 6.65.

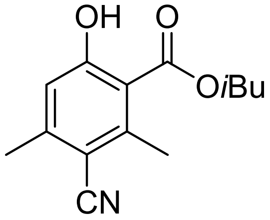
Ethyl 3-cyano-6-hydroxy-2,4-dimethylbenzoate (**26b**):



(GP 2) Starting with **24c** (196 mg, 0.99 mmol), CH_2Cl_2 (3.0 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.11 mL, 1.0 mmol), and **3c** (390 mg, 1.42 mmol), **26b** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 10:1 → 7:1) as a colourless solid (90 mg, 41%). Mp 114 – 115 °C; R_f 0.22 (*n*-heptane/EtOAc = 10:1). Reaction time: 25 h.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.45 (t, ^3J = 7.2 Hz, 3H, OCH_2CH_3), 2.49 (s, 3H, $ArCH_3$), 2.78 (s, 3H, $ArCH_3$), 4.46 (q, ^3J = 7.2 Hz, 3H, OCH_2CH_3), 6.77 (s, 1H, Ar), 11.83 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (OCH_2CH_3), 21.4, 21.9 ($ArCH_3$), 62.4 (OCH_2CH_3), 106.9, 111.2, 117.3 (2xC_{Ar}, CN), 117.4 (CH_{Ar}), 146.7, 148.3 (C_{Ar}), 165.2, 170.6 (C_{Ar}OH, CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3426 (br, w), 2995 (m), 2213 (s), 1662 (s), 1373 (s), 1315 (s), 1239 (s), 809 (m). MS (EI, 70 eV): *m/z* (%) = 219 (M^+, 64), 174 (63), 173 (100), 145 (42), 144 (17). Anal. Calcd for $C_{12}H_{13}NO_3$ (219.24): C, 65.74; H, 5.98; N, 6.39. Found: C, 65.92; H, 6.01; N, 6.17.

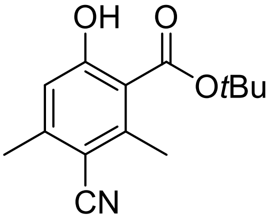
Isobutyl 3-cyano-6-hydroxy-2,4-dimethylbenzoate (**26c**):



(GP 2) Starting with **24c** (188 mg, 0.95 mmol), CH_2Cl_2 (3.0 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.11 mL, 1.0 mmol), and **3l** (394 mg, 1.30 mmol), **26c** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 10:1) as a colourless solid (91 mg, 39%). Mp 51 – 52 °C; R_f 0.29 (*n*-heptane/EtOAc = 10:1). Reaction time: 22 h.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.04 (d, ^3J = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.12 (m, 1H, OCH_2CH), 2.48 (s, 3H, $ArCH_3$), 2.79 (s, 3H, $ArCH_3$), 4.19 (d, ^3J = 6.4 Hz, 2H, OCH_2CH), 6.77 (s, 1H, Ar), 11.88 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.3 ($CH(CH_3)_2$), 21.4, 22.1 ($ArCH_3$), 27.6 (OCH_2CH), 72.7 (OCH_2CH), 106.9, 111.2, 117.3 (2xC_{Ar}, CN), 117.5 (CH_{Ar}), 146.5, 148.3 (C_{Ar}), 165.3, 170.8 (C_{Ar}OH, CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3427 (br, w), 2960 (s), 2930 (m), 2875 (m), 2216 (m), 1656 (s), 1318 (s), 1242 (s), 1080 (s), 814 (m). MS (EI, 70 eV): *m/z* (%) = 247 (M^+, 64), 191 (55), 174 (81), 173 (100), 145 (26), 91 (14), 57 (23). Anal. Calcd for $C_{14}H_{17}NO_3$ (247.29): C, 68.00; H, 6.93; N, 5.66. Found: C, 67.95; H, 7.04; N, 5.36.

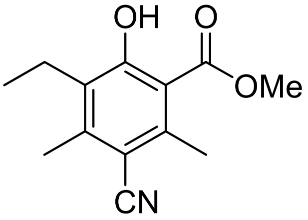
tert-Butyl 3-cyano-6-hydroxy-2,4-dimethylbenzoate (26d):



(GP 2) Starting with **24c** (300 mg, 1.52 mmol), CH_2Cl_2 (4.5 mL), molecular sieves (4 Å, 0.6 g), $TiCl_4$ (0.17 mL, 1.5 mmol), and **3m** (634 mg, 2.10 mmol), **26d** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 1:0 → 20:1) as a yellow solid (29 mg, 8%). Mp 92 – 94 °C; R_f 0.43 (*n*-heptane/EtOAc = 5:1). Reaction time: 26 h.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.63 (s, 9H, $C(CH_3)_3$), 2.48 (d, ^4J = 0.7 Hz, 3H, $ArCH_3$), 2.75 (s, 3H, $ArCH_3$), 6.75 (s, 1H, CH_{Ar}), 11.93 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.4, 22.1 ($ArCH_3$), 28.3 ($OC(\mathit{C}H_3)_3$), 85.0 ($O\mathit{C}(CH_3)_3$), 106.8, 112.5 (C), 117.4 (CH_{Ar}), 117.5 (C), 146.4, 147.9 (C_{Ar}), 165.2, 170.0 ($C_{Ar}OH$, CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2987 (m), 2928 (m), 2212 (m), 1661 (s), 1601 (m), 1575 (m), 1466 (m), 1377 (s), 1327 (s), 1245 (s), 1153 (s), 1080 (m), 839 (m), 813 (m). MS (GC-EI, 70 eV): *m/z* (%) = 247 (M^+, 4), 191 (34), 174 (40), 173 (100), 57 (29). HRMS (EI, 70 eV): Calcd for $C_{14}H_{17}NO_3$ (M^+) 247.12029, found 247.12041.

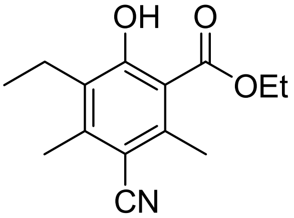
Methyl 3-cyano-5-ethyl-6-hydroxy-2,4-dimethylbenzoate (26e):



(GP 2) Starting with **24c** (186 mg, 0.94 mmol), CH_2Cl_2 (3.0 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.10 mL, 0.9 mmol), and **3n** (371 mg, 1.29 mmol), **26e** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 10:1) as a colourless solid (96 mg, 44%). Mp 95 – 96 °C; R_f 0.30 (*n*-heptane/EtOAc = 10:1). Reaction time: 21 h.

^1H NMR (250 MHz, $CDCl_3$): δ = 1.07 (t, ^3J = 7.5 Hz, 3H, $CH_2C\mathit{H}_3$), 2.49 (s, 3H, $ArCH_3$), 2.67 (q, ^3J = 7.5 Hz, 2H, $C\mathit{H}_2CH_3$), 2.70 (s, 3H, $ArCH_3$), 3.97 (s, 3H, OCH_3), 12.05 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8 ($CH_2\mathit{C}H_3$), 18.2 ($ArCH_3$), 19.5 (CH_2), 21.7 ($ArCH_3$), 52.6 (OCH_3), 107.0, 110.6, 118.0 (2xC_{Ar}, CN), 130.1, 143.4, 145.3 (C_{Ar}), 163.1, 171.6 ($C_{Ar}OH$, CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3432 (br, m), 2974 (s), 2962 (s), 2216 (s), 1660 (s), 1571 (s), 1366 (s), 1326 (s), 1209 (s), 947 (m). MS (EI, 70 eV): *m/z* (%) = 233 (M^+, 87), 202 (73), 201 (100), 186 (62), 174 (49), 173 (97), 158 (34), 130 (17). Anal. Calcd for $C_{13}H_{15}NO_3$ (233.26): C, 66.94; H, 6.48; N, 6.00. Found: C, 66.99; H, 6.64; N, 5.80.

Ethyl 3-cyano-5-ethyl-6-hydroxy-2,4-dimethylbenzoate (**26f**):



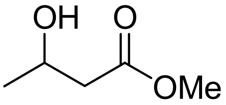
(GP 2) Starting with **24c** (189 mg, 0.96 mmol), CH_2Cl_2 (3.0 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.11 mL, 1.0 mmol), and **3g** (400 mg, 1.32 mmol), **26f** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 10:1) as a colourless solid (138 mg, 58%). Mp 48 – 49 °C; R_f 0.33 (*n*-heptane/EtOAc = 10:1). Reaction time: 26 h.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.07 (t, ^3J = 7.4 Hz, 3H, $ArCH_2CH_3$), 1.44 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 2.49 (s, 3H, $ArCH_3$), 2.68 (q, ^3J = 7.4 Hz, 2H, $ArCH_2CH_3$), 2.73 (s, 3H, $ArCH_3$), 4.45 (q, ^3J = 7.1 Hz, 2H, OCH_2CH_3), 12.14 (s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.8, 14.0 (CH_2CH_3), 18.2 ($ArCH_3$), 19.5 ($ArCH_2$), 21.8 ($ArCH_3$), 62.3 (OCH_2), 107.0, 110.7, 118.1 (2xC_{Ar}, CN), 130.1, 143.4, 145.2 (C_{Ar}), 163.2, 171.2 (C_{Ar}OH, CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3441 (br, m), 2978 (s), 2943 (m), 2879 (m), 2218 (s), 1654 (s), 1399 (s), 1377 (s), 1208 (s), 824 (m). MS (EI, 70 eV): *m/z* (%) = 247 (M^+, 40), 202 (29), 201 (100), 186 (14), 173 (99), 158 (10). Anal. Calcd for $C_{14}H_{17}NO_3$ (247.29): C, 68.00; H, 6.93; N, 5.66. Found: C, 68.34; H, 7.07; N, 5.49.

8.3.6 4-Alkoxycarbonyl-butenolides and Precursors

8.3.6.1 3-Hydroxycarbonyl Compounds

Methyl 3-hydroxybutyrate (**28a**):

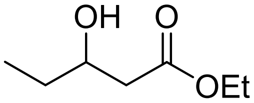


(GP 3) Starting with diisopropylamine (10.12 g, 100 mmol), THF (100 mL), *n*-BuLi (2.5 M in hexanes, 41 mL, 103 mmol), methyl acetate (7.41 g, 100 mmol), acetaldehyde (5.29 g, 120 mmol), and hydrochloric acid (2.0 M, 50 mL), **28a** was isolated by destillation as a clear colourless liquid (6.43 g, 54%); bp. 34 °C (0.1 mbar). Reaction time: 3.5 min.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.24 (d, ^3J = 6.3 Hz, 3H, $CHCH_3$), 2.43 (dd, ^2J = 16.5 Hz, ^3J = 7.4 Hz, 1H, CH_AH_B), 2.51 (dd, ^2J = 16.5 Hz, ^3J = 3.8 Hz, 1H, CH_AH_B), 2.8 (br, 1H, OH), 3.72 (s, 3H, OCH_3), 4.21 (m, 1H, CHOH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.3 ($CHCH_3$), 42.6 (CH_2), 51.4 (OCH_3), 64.0 (CH), 172.9 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3431 (br, s), 2974 (m), 2935 (w), 1737 (s), 1439 (m), 1377 (m), 1297 (m), 1196 (m), 1176 (m), 1126 (m), 1089 (m), 946 (w). MS (GC-EI, 70 eV): *m/z* (%) = 117 ($[M-1]^+$, 2), 103 (38), 100 (6), 87 (29), 74 (83), 71 (45), 59 (18), 45 (57), 43 (100).

The spectroscopic data (^{1}H NMR, ^{13}C NMR) are in accordance with those presented in the literature.[108]

Ethyl 3-hydroxyvalerate (28b):



(GP 3) Starting with diisopropylamine (10.12 g, 100 mmol), THF (100 mL), *n*-BuLi (2.5 M in hexanes, 41 mL, 103 mmol), ethyl acetate (8.81 g, 100 mmol), propionaldehyde (6.97 g, 120 mmol), and hydrochloric acid (2.0 M, 50 mL), **28b** was isolated by destillation as a clear colourless liquid (12.09 g, 83%); bp. 100 °C (5 mbar). Reaction time: 3.5 min.

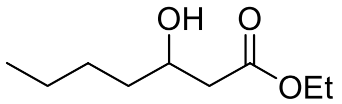
^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.97 (t, ^3J = 7.4 Hz, 3H, CH_3CH$_2$CH), 1.28 (t, ^3J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.52 (m, 2H, CH$_3$CH_2CH), 2.40 (dd, ^2J = 16.4 Hz, ^3J = 8.9 Hz, 1H, CH_AH$_B$CO), 2.51 (dd, ^2J = 16.4 Hz, ^3J = 3.3 Hz, 1H, CH$_A$$H_B$CO), 2.85 (br, 1H, OH), 3.94 (dddd, $^3J_1$ = 8.9 Hz, $^3J_2$ = 7.0 Hz, $^3J_3$ = 5.5 Hz, $^3J_4$ = 3.3 Hz, 1H, CHOH), 4.18 (q, ^3J = 7.1 Hz, 2H, OCH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 9.7 (CH$_3$CH$_2$CH), 14.0 (OCH$_2$$CH_3$), 29.3 (CH$_3$$CH_2$CH), 40.9 ($CH_2$CO), 60.5 (OCH$_2$), 69.2 (CHOH), 172.9 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3447 (br, m), 2968 (m), 2936 (m), 2880 (w), 1735 (s), 1465 (w), 1374 (m), 1282 (m), 1250 (m), 1179 (s), 1112 (m), 1034 (m), 983 (m). MS (GC-EI, 70 eV): *m/z* (%) = 145 ($[M-1]^+$, 1), 128 (3), 117 (100), 101 (29), 89 (48), 71 (93), 59 (40), 43 (49). HRMS (EI, 70 eV): Calcd for $C_7H_{13}O_3$ ($[M-1]^+$) 145.08592, found 145.08556.

The spectroscopic data (^{1}H NMR, IR) are in accordance with those presented in the literature.[109]

Ethyl 3-hydroxy-4-methylvalerate (28c):

This compound was prepared by Lars Michaelis.[80,87]

Ethyl 3-hydroxyheptanoate (28d):

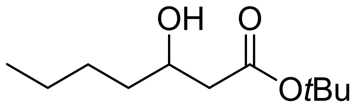


(GP 3) Starting with diisopropylamine (10.12 g, 100 mmol), THF (100 mL), *n*-BuLi (2.5 M in hexanes, 41 mL, 103 mmol), ethyl acetate (8.81 g, 100 mmol), valeraldehyde (10.34 g, 120 mmol), and hydrochloric acid (2.0 M, 50 mL), **28d** was isolated by destillation as a clear colourless liquid (14.52 g, 83%); bp. 70 °C (0.1 mbar). Reaction time: 3.5 min.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.91 (t, ^{3}J = 7.1 Hz, 3H, CH_3CH$_2$CH$_2$), 1.28 (t, ^{3}J = 7.1 Hz, 3H, OCH$_2$CH_3), 1.30 – 1.60 (m, 6H, (CH$_2$)$_3$), 2.40 (dd, ^{2}J = 16.4 Hz, ^{3}J = 8.8 Hz, 1H, CH_AH$_B$CO), 2.51 (dd, ^{2}J = 16.4 Hz, ^{3}J = 3.3 Hz, 1H, CH$_A$$H_B$CO), 2.89 (br, 1H, OH), 4.00 (m, 1H, CHOH), 4.17 (q, ^{3}J = 7.1 Hz, 2H, OCH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.9, 14.1 (CH$_3$), 22.5, 27.5, 36.2 ((CH$_2$)$_3$), 41.3 (CH$_2$CO), 60.5 (OCH$_2$), 67.9 (CHOH), 173.0 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3447 (br, m), 2959 (s), 2933 (s), 2873 (m), 2862 (m), 1735 (s), 1374 (m), 1300 (m), 1249 (m), 1176 (m), 1028 (m). MS (GC-EI, 70 eV): *m/z* (%) = 173 ([M – 1]$^+$, 0.5), 156 (2), 117 (100), 89 (33), 88 (31), 71 (59), 43 (30). HRMS (EI, 70 eV): Calcd for C$_9$H$_{17}$O$_3$ ([M – 1]$^+$) 173.11722, found 173.11724.

This compound has been prepared before but no comparable spectroscopic data are given.[110]

***tert*-Butyl 3-hydroxyheptanoate (28e)**:



(GP 3) Starting with diisopropylamine (10.12 g, 100 mmol), THF (100 mL), *n*-BuLi (2.5 M in hexanes, 41 mL, 103 mmol), *tert*-butyl acetate (11.62 g, 100 mmol), valeraldehyde (10.34 g, 120 mmol), and hydrochloric acid (2.0 M, 50 mL), **28e** was isolated by destillation as a clear colourless liquid (18.55 g, 92%); bp. 78 °C (0.1 mbar). Reaction time: 3.5 min.

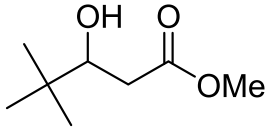
^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.91 (t, ^{3}J = 7.1 Hz, 3H, CH_3CH$_2$), 1.25 – 1.55 (m, 6H, (CH$_2$)$_3$), 1.47 (s, 9H, C(CH$_3$)$_3$), 2.31 (dd, ^{2}J = 16.3 Hz, ^{3}J = 8.8 Hz, 1H, CH_AH$_B$CO), 2.43 (dd, ^{2}J = 16.3 Hz, ^{3}J = 3.3 Hz, 1H, CH$_A$$H_B$CO), 2.94 (br, 1H, OH), 3.96 (m, 1H, CHOH). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.9 (CH$_3$CH$_2$), 22.6, 27.6 (CH$_2$), 28.1 (C(CH$_3$)$_3$), 36.1 (CH$_2$), 42.3 (CH$_2$CO), 68.1 (CHOH), 81.1 (C(CH$_3$)$_3$), 172.5 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3443 (br, m), 2959 (s), 2933 (s), 2873 (m), 2862 (m), 1730 (s), 1458 (m), 1393 (m), 1368 (s), 1298 (m), 1255 (m), 1156 (s), 1039 (w). MS (CI, isobutane): *m/z* (%) = 203 ([M + 1]$^+$, 1), 147 (100).

The spectroscopic data (^{1}H NMR) are in accordance with those presented in the literature.[111]

Ethyl 3-hydroxy-5-methylcaproate (28f):

This compound was prepared by Lars Michaelis.[80,87]

Methyl 3-hydroxy-4,4-dimethylvalerate (28g):

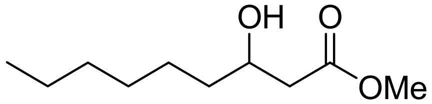


(GP 3) Starting with diisopropylamine (7.08 g, 70 mmol), THF (70 mL), *n*-BuLi (2.5 M in hexanes, 29 mL, 72 mmol), methyl acetate (5.19 g, 70 mmol), pivalaldehyde (7.24 g, 84 mmol), and hydrochloric acid (2.0 M, 35 mL), **28g** was isolated by destillation as a clear colourless liquid (6.76 g, 60%); bp. 69 °C (0.1 mbar). Reaction time: 4 min.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.92 (s, 9H, C(CH$_3$)$_3$), 2.36 (dd, ^2J = 16.1 Hz, ^3J = 10.5 Hz, 1H, CH_AH$_B$CO), 2.54 (dd, ^2J = 16.1 Hz, ^3J = 2.3 Hz, 1H, CH$_A$$H_B$CO), 2.85 (br, 1H, OH), 3.71 (dd, $^3J_1$ = 10.5 Hz, $^3J_2$ = 2.3 Hz, 1H, C*H*OH), 3.72 (s, 3H, OCH$_3$). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 25.5 (C(*C*H$_3$)$_3$), 34.3 (*C*CH), 36.4 (CH$_2$), 51.8 (OCH$_3$), 75.4 (CHOH), 174.2 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3515 (br, m), 2957 (s), 2909 (m), 2873 (m), 1731 (s), 1439 (m), 1366 (m), 1304 (m), 1166 (m), 1015 (m). MS (GC-EI, 70 eV): *m/z* (%) = 159 ([M – 1]$^+$, 0.1), 103 (100), 87 (14), 71 (65), 57 (35), 43 (41). HRMS (EI, 70 eV): Calcd for C$_8$H$_{15}$O$_3$ ([M – 1]$^+$) 159.10157, found 159.10226.

The spectroscopic data (^{1}H NMR, ^{13}C NMR, IR) are in accordance with those presented in the literature.[112]

Methyl 3-hydroxynonanoate (28h):

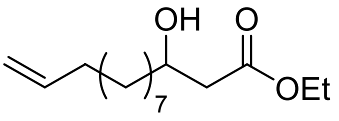


(GP 3) Starting with diisopropylamine (8.91 g, 88 mmol), THF (80 mL), *n*-BuLi (2.5 M in hexanes, 36 mL, 90 mmol), methyl acetate (5.93 g, 80 mmol), heptanal (9.14 g, 80 mmol), and hydrochloric acid (2.0 M, 44 mL), **28h** was isolated by destillation as a clear colourless liquid (9.83 g, 65%); bp. 77 °C (0.1 mbar). Reaction time: 4 min.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.88 (t, ^3J = 6.8 Hz, 3H, CH_3CH$_2$), 1.15 – 1.60 (m, 10H, (CH$_2$)$_5$), 2.41 (dd, ^2J = 16.4 Hz, ^3J = 8.8 Hz, 1H, CH_AH$_B$CO), 2.52 (dd, ^2J = 16.4 Hz, ^3J = 3.4 Hz, 1H, CH$_A$$H_B$CO), 2.94 (br, 1H, OH), 3.71 (s, 3H, OCH$_3$), 4.00 (m, 1H, C*H*OH). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.9 (*C*H$_3$CH$_2$), 22.5, 25.3, 29.1, 31.7, 36.5 ((CH$_2$)$_5$), 41.1 (*C*H$_2$CO), 51.6 (OCH$_3$), 67.9 (CHOH), 173.3 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3457 (br, m), 2955 (s), 2930 (s), 2858 (m), 1740 (s), 1438 (m), 1290 (m), 1197 (m), 1167 (m), 1056 (w). MS (GC-EI, 70 eV): *m/z* (%) = 187 ([M – 1]$^+$, 0.5), 170 (0.6), 103 (100), 74 (33), 71 (35), 55 (19), 43 (34). HRMS (EI, 70 eV): Calcd for C$_{10}$H$_{19}$O$_3$ ([M – 1]$^+$) 187.13287, found 187.13289.

The spectroscopic data (^{1}H NMR) are in accordance with those presented in the literature.[113]

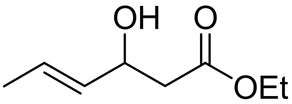
Ethyl 3-hydroxy-12-tredecenate (28i):



(GP 3) Starting with diisopropylamine (10.12 g, 100 mmol), THF (100 ml), *n*-BuLi (2.5 M in hexanes, 41 mL, 103 mmol), ethyl acetate (8.81 g, 100 mmol), 10-undecenal (13.46 g, 80 mmol), and hydrochloric acid (2.0 M, 50 mL), **28i** was isolated by column chromatography (silica gel; *n*-heptane/ethyl acetate = 7:1 → 5:1) as a clear slightly yellow oil (13.23 g, 65%); R_f 0.33 (*n*-heptane/ethyl acetate = 5:1). Reaction time: 4.5 min.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.23 – 1.55 (m, 17H, CHOH(CH_2)$_7$, CH$_3$), 2.03 (m, 2H, H$_2$C=CHCH_2), 2.38 (dd, ^2J = 16.4 Hz, ^3J = 8.7 Hz, 1H, CH_AH$_B$CO), 2.50 (dd, ^2J = 16.4 Hz, ^3J = 3.4 Hz, 1H, CH$_A$$H_B$CO), 2.66 (br, 1H, OH), 3.99 (m, 1H, C*H*OH), 4.16 (q, ^3J = 7.1 Hz, 2H, OCH$_2$), 4.88 – 5.03 (m, 2H, H_2C=CH), 5.80 (ddt, $^3J_1$ = 17.0 Hz, $^3J_2$ = 10.3 Hz, $^3J_3$ = 6.7 Hz, 1H, H$_2$C=C*H*). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.2 (CH$_3$), 25.5, 28.9, 29.1, 29.4, 29.5, 29.5, 33.8, 36.5, 41.3 ((CH$_2$)$_8$, *C*H$_2$CO), 60.7 (OCH$_2$), 68.0 (CHOH), 114.1 (H$_2$*C*=CH), 139.2 (H$_2$C=*C*H), 173.1 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3454 (br, w), 2979 (m), 2927 (s), 2855 (m), 1736 (s), 1641 (w), 1465 (m), 1373 (m), 1301 (m), 1182 (m), 1030 (m), 910 (m). MS (CI, isobutane): *m/z* (%) = 257 ([M + 1]$^+$, 100), 239 (20). Anal. Calcd for $C_{15}H_{28}O_3$ (256.38): C, 70.27; H, 11.01. Found: C, 70.10; H, 11.20.

(*E*)-Ethyl 3-hydroxyhex-4-enoate (28j):

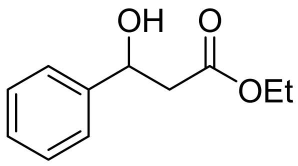


(GP 3) Starting with diisopropylamine (10.12 g, 100 mmol), THF (100 mL), *n*-BuLi (2.5 M in hexanes, 41 mL, 103 mmol), ethyl acetate (8.81 g, 100 mmol), crotonaldehyde (*E*:*Z* = 20:1, 8.41 g, 120 mmol), and hydrochloric acid (2.0 M, 50 mL), **28j** was isolated by destillation as a clear colourless liquid (13.87 g, 88%); bp. 78 °C (0.1 mbar). Reaction time: 3.5 min.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.27 (t, ^3J = 7.2 Hz, 3H, CH$_2$CH_3), 1.70 (ddd, ^3J = 6.4 Hz, ^4J = 1.6 Hz, ^5J = 0.8 Hz, 3H, CH_3CH), 2.51 (d, ^3J = 1.5 Hz, 1H, CH_AH$_B$CO), 2.53 (s, 1H, CH$_A$$H_B$CO), 2.79 (br, 1H, OH), 4.17 (q, ^3J = 7.2 Hz, 2H, OCH$_2$), 4.48 (m, 1H, C*H*OH), 5.51 (ddq, $^3J_1$ = 15.3 Hz, $^3J_2$ = 6.5 Hz, ^4J = 1.6 Hz, 1H, CH$_3$CHC*H*), 5.74 (dqd, $^3J_1$ = 15.3 Hz, $^3J_2$ = 6.4 Hz, ^4J = 1.1 Hz, 1H, CH$_3$C*H*). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.0 (CH$_2$*C*H$_3$), 17.5 (*C*H$_3$CH), 41.6 (*C*H$_2$CO), 60.5 (OCH$_2$), 68.8 (CHOH), 127.1, 131.9 (HC=CH), 172.2 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3441 (br, s), 2982 (m), 2939 (m), 2920 (m), 1735 (s), 1448 (m), 1372 (m), 1282 (m), 1247 (m), 1175 (s), 1029 (s), 967 (m). MS (GC-EI, 70 eV): *m/z* (%) = 158 (M$^+$, 6), 143 (25), 71 (100), 70 (44), 69 (40), 60 (26), 43 (28). HRMS (EI, 70 eV): Calcd for $C_8H_{14}O_3$ (M$^+$) 158.09375, found 158.09315.

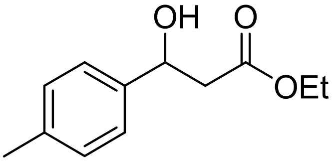
The spectroscopic data (^{1}H NMR, ^{13}C NMR, IR, MS) are in accordance with those presented in the literature.[114,115]

Ethyl 3-hydroxy-3-phenylpropionate (**28k**):



(GP 3) Starting with diisopropylamine (6.07 g, 60 mmol), THF (70 mL), *n*-BuLi (2.5 M in hexanes, 25 mL, 63 mmol), ethyl acetate (4.85 g, 55 mmol), benzaldehyde (5.31 g, 50 mmol), and hydrochloric acid (2.0 M, 28 mL), **28k** was isolated by destillation as a clear slightly yellow liquid (7.58 g, 78%); bp. 110 °C (0.1 mbar). Reaction time: 4 min.
^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.25 (t, ^3J = 7.1 Hz, 3H, CH$_3$), 2.68 (dd, ^2J = 16.3 Hz, ^3J = 4.4 Hz, 1H, CH_AH$_B$CO), 2.75 (dd, ^2J = 16.3 Hz, ^3J = 8.4 Hz, 1H, CH$_A$$H_B$CO), 3.34 (d, ^3J = 3.5 Hz, 1H, OH), 4.17 (q, ^3J = 7.1 Hz, 2H, OCH$_2$), 5.12 (m, 1H, C*H*OH), 7.24 – 7.39 (m, 5H, Ph). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.0 (CH$_3$), 43.3 (*C*H$_2$CO), 60.7 (OCH$_2$), 70.2 (CHOH), 125.6, 127.6, 128.4 (CH$_{Ar}$), 142.5 (C$_{Ar}$), 172.2 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3458 (br, m), 2982 (w), 1732 (s), 1454 (w), 1372 (m), 1298 (m), 1268 (m), 1196 (m), 1162 (m), 1038 (m), 701 (m). MS (EI, 70 eV): *m/z* (%) = 194 (M$^+$, 39), 147 (10), 120 (19), 107 (100), 106 (25), 105 (75), 88 (19), 79 (65), 77 (53). HRMS (EI, 70 eV): Calcd for C$_{11}$H$_{14}$O$_3$ (M$^+$) 194.09375, found 194.09339.
The spectroscopic data (^{1}H NMR, ^{13}C NMR) are in accordance with those presented in the literature.[116]

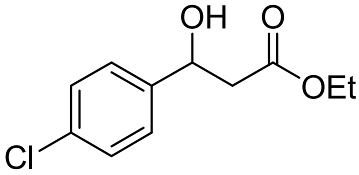
Ethyl 3-hydroxy-3-(4-methylphenyl)-propionate (**28l**):



(GP 3) Starting with diisopropylamine (10.12 g, 100 mmol), THF (100 ml), *n*-BuLi (2.5 M in hexanes, 42 mL, 105 mmol), ethyl acetate (8.81 g, 100 mmol), 4-methylbenzaldehyde (9.57 g, 80 mmol), and hydrochloric acid (2.0 M, 50 mL), **28l** was isolated by column chromatography (silica gel; *n*-heptane/ethyl acetate = 5:1) as a clear yellow oil (12.17 g, 73%); R_f 0.22 (*n*-heptane/ethyl acetate = 5:1). Reaction time: 5 min.
^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.26 (t, ^3J = 7.1 Hz, 3H, CH$_2$CH_3), 2.34 (s, 3H, ArCH$_3$), 2.67 (dd, ^2J = 16.1 Hz, ^3J = 4.3 Hz, 1H, CH_AH$_B$CO), 2.76 (dd, ^2J = 16.1 Hz, ^3J = 8.5 Hz, 1H, CH$_A$$H_B$CO), 3.21 (br, 1H, OH), 4.18 (q, ^3J = 7.1 Hz, 2H, OCH$_2$), 5.10 (dd, $^3J_1$ = 8.5 Hz, $^3J_2$ = 4.3 Hz, 1H, C*H*OH), 7.14 – 7.28 (m, 4H, Ar). ^{13}C NMR (62 MHz, CDCl$_3$): δ = 14.1 (CH$_2$*C*H$_3$), 21.1 (ArCH$_3$), 43.3 (*C*H$_2$CO), 60.8 (OCH$_2$), 70.1 (CHOH), 125.6, 129.2 (CH$_{Ar}$), 137.5, 139.5 (C$_{Ar}$), 172.4 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3459 (br, s), 2982 (m), 2925 (m),

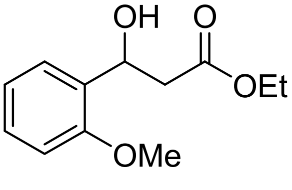
1734 (s), 1515 (m), 1372 (m), 1195 (m), 1160 (m), 1038 (m), 819 (m). MS (EI, 70 eV): *m/z* (%) = 208 (M^+, 12), 190 (13), 145 (29), 121 (67), 120 (64), 119 (100), 93 (21), 91 (90), 65 (20). Anal. Calcd for $C_{12}H_{16}O_3$ (208.25): C, 69.21; H, 7.74. Found: C, 69.09; H, 7.85.
The spectroscopic data (^{1}H NMR, ^{13}C NMR) are in accordance with those presented in the literature.[117]

Ethyl 3-(4-chlorophenyl)-3-hydroxypropionate (**28m**):



(GP 3) Starting with diisopropylamine (10.12 g, 100 mmol), THF (90 ml), *n*-BuLi (2.5 M in hexanes, 41 mL, 103 mmol), ethyl acetate (8.81 g, 100 mmol), 4-chlorobenzaldehyde (11.25 g, 80 mmol), dissolved in THF (10 ml), and hydrochloric acid (2.0 M, 50 mL), **28m** was isolated by column chromatography (silica gel; *n*-heptane/ethyl acetate = 3:1) as a clear slightly yellow oil (13.91 g, 76%); R_f 0.30 (*n*-heptane/ethyl acetate = 3:1). Reaction time: 4.5 min.
^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.26 (t, ^3J = 7.1 Hz, 3H, CH$_3$), 2.68 (s, 1H, CH_AH$_B$CO), 2.70 (d, ^3J = 2.1 Hz, 1H, CH$_A$$H_B$CO), 3.2 (br, 1H, OH), 4.18 (q, ^3J = 7.1 Hz, 2H, OCH$_2$), 5.10 (dd, $^3J_1$ = 7.3 Hz, $^3J_2$ = 5.5 Hz, 1H, C*H*OH), 7.31 (s, 4H, Ar). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.1 (CH$_3$), 43.2 (*C*H$_2$CO), 61.0 (OCH$_2$), 69.6 (CHOH), 127.1, 128.7 (CH$_{Ar}$), 133.5, 141.0 (C$_{Ar}$), 172.3 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3457 (br, s), 2983 (m), 1732 (s), 1493 (m), 1373 (m), 1194 (s), 1162 (m), 1091 (m), 1014 (s), 831 (m). MS (EI, 70 eV): *m/z* (%) = 230 (M^+, ^{37}Cl, 4), 228 (M^+, ^{35}Cl, 9), 165 (25), 141 (77), 140 (52), 139 (100), 111 (34), 88 (20), 77 (36). Anal. Calcd for $C_{11}H_{13}ClO_3$ (228.67): C, 57.78; H, 5.73. Found: C, 57.66; H, 5.78.
The spectroscopic data (^{1}H NMR, ^{13}C NMR) are in accordance with those presented in the literature.[117]

Ethyl 3-hydroxy-3-(2-methoxyphenyl)-propionate (**28n**):



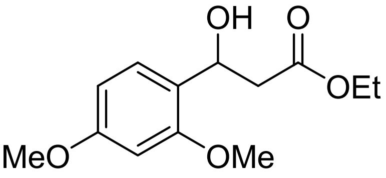
(GP 3) Starting with diisopropylamine (20.24 g, 200 mmol), THF (180 ml), *n*-BuLi (2.5 M in hexanes, 82 mL, 205 mmol), ethyl acetate (17.62 g, 200 mmol), 2-methoxybenzaldehyde (21.78 g, 160 mmol), dissolved in THF (20 ml), and hydrochloric acid (2.0 M, 100 mL), **28n** was isolated by column chromatography (silica gel; *n*-heptane/ethyl acetate = 3:1) as a clear slightly yellow oil (16.41 g, 37%*); R_f 0.27 (*n*-heptane/ethyl acetate = 3:1). Reaction time: 4.5 min.

* Only 55% of the raw product were used for column chromatography.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.26 (t, ^3J = 7.1 Hz, 3H, CH$_2$CH_3), 2.69 (dd, ^2J = 16.1 Hz, ^3J = 9.0 Hz, 1H, CH_AH$_B$CO), 2.83 (dd, ^2J = 16.1 Hz, ^3J = 4.0 Hz, 1H, CH$_A$$H_B$CO), 3.2 (br, 1H, OH), 3.85 (s, 3H, OCH$_3$), 4.17 (q, 7.1 Hz, 2H, OCH$_2$), 5.36 (dd, $^3J_1$ = 8.9 Hz, $^3J_2$ = 3.7 Hz, 1H, C*H*OH), 6.87 (dd, ^3J = 8.2 Hz, ^4J = 0.9 Hz, 1H, Ar), 6.97 (m, 1H, Ar), 7.26 (m, 1H, Ar), 7.43 (dd, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, Ar). ^{13}C NMR (62 MHz, CDCl$_3$): δ = 14.0 (CH$_2$*C*H$_3$), 41.6 (*C*H$_2$CO), 55.1 (OCH$_3$), 60.5 (OCH$_2$), 66.3 (CHOH), 110.1, 120.6, 126.4, 128.4 (CH$_{Ar}$), 130.5 (C_{Ar}CHOH), 155.9 (C_{Ar}OCH$_3$), 172.5 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3497 (br, s), 2981 (m), 2939 (m), 1733 (s), 1602 (m), 1492 (s), 1465 (s), 1286 (s), 1243 (s), 1190 (s), 1159 (s), 1029 (s), 756 (s). MS (EI, 70 eV): *m/z* (%) = 224 (M$^+$, 14), 206 (8), 175 (9), 161 (14), 150 (28), 137 (100), 135 (44), 107 (44), 77 (22). Anal. Calcd for $C_{12}H_{16}O_4$ (224.25): C, 64.27; H, 7.19. Found: C, 64.25; H, 7.26.

The spectroscopic data (^{1}H NMR) are in accordance with those presented in the literature.[118]

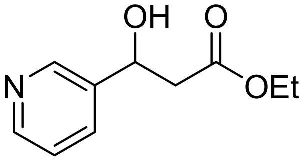
Ethyl 3-(2,4-dimethoxyphenyl)-3-hydroxypropionate (**28o**):



(GP 3) Starting with diisopropylamine (10.12 g, 100 mmol), THF (100 ml), *n*-BuLi (2.5 M in hexanes, 42 mL, 105 mmol), ethyl acetate (8.77 g, 100 mmol), 2,4-dimethoxybenzaldehyde (14.01 g, 84 mmol), dissolved in THF (30 ml), and hydrochloric acid (2.0 M, 50 mL), **28o** was isolated by column chromatography (silica gel; *n*-heptane/ethyl acetate = 2:1) as a yellow oil (3.38 g, 16%); R_f 0.30 (*n*-heptane/ethyl acetate = 2:1). A second fraction (14.87 g, 69%) was collected but it was found to be impure. It probably decomposed while standing or on removing the eluent at 40 °C. Reaction time: 5 min.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.25 (t, ^3J = 7.1 Hz, 3H, CH$_2$CH_3), 2.69 (dd, ^2J = 16.1 Hz, ^3J = 8.5 Hz, 1H, CH_AH$_B$CO), 2.78 (dd, ^2J = 16.1 Hz, ^3J = 4.4 Hz, 1H, CH$_A$$H_B$CO), 3.12 (br, 1H, OH), 3.79 (s, 3H, OCH$_3$), 3.80 (s, 3H, OCH$_3$), 4.16 (q, ^3J = 7.1 Hz, 2H, OCH$_2$), 5.27 (dd, $^3J_1$ = 8.5 Hz, $^3J_2$ = 4.3 Hz, 1H, C*H*OH), 6.43 – 6.49 (m, 2H, Ar), 7.30 (d, ^3J = 8.2 Hz, 1H, Ar). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.0 (CH$_2$*C*H$_3$), 41.8 (*C*H$_2$CO), 55.1, 55.2 (OCH$_3$), 60.5 (OCH$_2$), 66.2 (CHOH), 98.4, 104.0 (*C*H$_{Ar}$C$_{Ar}$OCH$_3$), 123.1 (C_{Ar}CHOH), 127.1 (*C*H$_{Ar}$C$_{Ar}$CHOH), 157.0, 160.1 (C_{Ar}OCH$_3$), 172.5 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3503 (br, m), 2979 (m), 2940 (m), 2838 (w), 1732 (s), 1614 (s), 1590 (m), 1507 (s), 1465 (m), 1292 (s), 1209 (s), 1157 (s), 1035 (s), 834 (m).

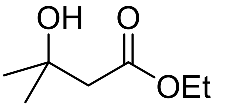
Ethyl 3-hydroxy-3-pyridin-3-yl-propionate (**28p**):



(GP 3) Starting with diisopropylamine (10.12 g, 100 mmol), THF (100 ml), *n*-BuLi (2.5 M in hexanes, 42 mL, 105 mmol), ethyl acetate (8.81 g, 100 mmol), pyridine-3-carbaldehyde (9.58 g, 89 mmol), and hydrochloric acid (2.0 M, 50 mL), **28p** was isolated by column chromatography (silica gel; *n*-heptane/ethyl acetate = 1:20) as a clear yellow oil (7.98 g, 46%); R_f 0.25 (*n*-heptane/ethyl acetate = 1:20). Reaction time: 4 min.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.26 (t, ^3J = 7.1 Hz, 3H, CH$_3$), 2.71 (dd, ^2J = 16.3 Hz, ^3J = 4.7 Hz, 1H, CH_AH$_\mathrm{B}$CO), 2.79 (dd, ^2J = 16.3 Hz, ^3J = 8.2 Hz, 1H, CH$_\mathrm{A}$$H_\mathrm{B}$CO), 3.9 (br, 1H, OH), 4.18 (q, ^3J = 7.1 Hz, 2H, OCH$_2$), 5.18 (dd, $^3J_1$ = 8.2 Hz, $^3J_2$ = 4.6 Hz, 1H, C*H*OH), 7.29 (ddd, $^3J_1$ = 8.0 Hz, $^3J_2$ = 4.7 Hz, ^5J = 1.0 Hz, 1H, Ar), 7.76 (dtd, ^3J = 8.0 Hz, $^4J_1 \approx {}^4J_2 \approx$ 1.9 Hz, $^4J_3$ = 0.6 Hz, 1H, Ar), 8.49 (dd, ^3J = 4.7 Hz, ^4J = 1.9 Hz, 1H, Ar), 8.57 (d, ^4J = 1.9 Hz, 1H, Ar). ^{13}C NMR (62 MHz, CDCl$_3$): δ = 14.0 (CH$_3$), 43.3 (*C*H$_2$CO), 60.8 (OCH$_2$), 67.9 (CHOH), 123.4, 133.7 (CH$_\mathrm{Ar}$), 138.6 (C$_\mathrm{Ar}$), 147.3, 148.6 (CH$_\mathrm{Ar}$), 171.5 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3185 (br, s), 2983 (s), 1733 (s), 1428 (m), 1372 (m), 1280 (s), 1161 (s), 1038 (s), 715 (m). MS (EI, 70 eV): *m/z* (%) = 195 (M$^+$, 34), 177 (6), 166 (16), 148 (36), 132 (28), 122 (28), 108 (100), 107 (67), 106 (88), 80 (55), 78 (61), 51 (30). Anal. Calcd for $C_{10}H_{13}NO_3$ (195.22): C, 61.53; H, 6.71; N, 7.18. Found: C, 61.51; H, 6.80; N, 6.91.

Ethyl 3-hydroxy-3-methylbutyrate (**28q**):

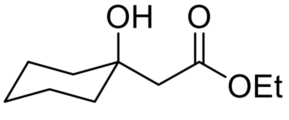


(GP 3) Starting with diisopropylamine (10.12 g, 100 mmol), THF (100 mL), *n*-BuLi (2.5 M in hexanes, 41 mL, 103 mmol), ethyl acetate (8.81 g, 100 mmol), acetone (6.97 g, 120 mmol), and hydrochloric acid (2.0 M, 50 mL), **28q** was isolated by destillation as a clear colourless liquid (11.33 g, 77%); bp. 48 °C (0.1 mbar). Reaction time: 10 min (–60 °C).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.25 (m, 9H, CH$_2$CH_3, C(CH$_3$)$_2$), 2.45 (s, 2H, CH$_2$CO), 3.59 (s, 1H, OH), 4.15 (q, ^3J = 7.1 Hz, 2H, OCH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.1 (CH$_2$*C*H$_3$), 29.1 (C(*C*H$_3$)$_2$), 46.3 (*C*H$_2$CO), 60.5 (OCH$_2$), 68.9 (COH), 172.9 (CO).

This compound has been prepared before but no comparable spectroscopic data are given.[119]

Ethyl (1-hydroxycyclohexyl)-acetate (**28r**):



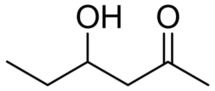
(GP 3) Starting with diisopropylamine (10.12 g, 100 mmol), THF (100 mL), *n*-BuLi (2.5 M in hexanes, 41 mL, 103 mmol), ethyl acetate (8.81 g, 100 mmol), cyclohexanone (8.00 g, 82 mmol), and hydrochloric acid (2.0 M, 50 mL), **28r** was isolated by destillation as a clear colourless liquid (14.33 g, 94%); bp. 81 °C (0.1 mbar). Reaction time: 15 min (–60 → –50 °C).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.25 (t, ^3J = 7.1 Hz, 3H, CH$_3$), 1.35 – 1.75 (m, 10H, (CH$_2$)$_5$), 2.44 (s, 2H, CH$_2$CO), 3.41 (s, 1H, OH), 4.15 (q, ^3J = 7.1 Hz, 2H, OCH$_2$).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.2 (CH$_3$), 22.0, 25.6 (CH$_2$(*C*H$_2$)$_3$CH$_2$), 37.4 ((*C*H$_2$)$_2$COH), 45.3 (*C*H$_2$CO), 60.5 (OCH$_2$), 69.9 (COH), 172.9 (CO).

The spectroscopic data (^{1}H NMR, ^{13}C NMR) are in accordance with those presented in the literature.[120]

4-Hydroxy-hexan-2-one (**28s**):

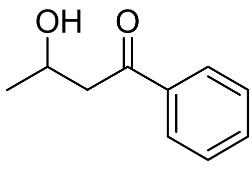


(GP 3) Starting with diisopropylamine (10.12 g, 100 mmol), THF (100 mL), *n*-BuLi (2.5 M in hexanes, 42 mL, 105 mmol), acetone (5.81 g, 100 mmol), propionaldehyde (6.46 g, 111 mmol), and hydrochloric acid (2.0 M, 50 mL), **28s** was isolated by destillation as a clear colourless liquid (4.31 g, 37%); bp. 53 °C (0.1 mbar). Reaction time: 5 min (–70 → –65 °C).

^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.94 (t, ^3J = 7.3 Hz, 3H, CH$_2$C*H*$_3$), 1.47 (m, 2H, C*H*$_2$CH$_3$), 2.17 (s, 3H, CH$_3$CO), 2.51 (dd, ^2J = 17.8 Hz, ^3J = 8.9 Hz, 1H, C*H*$_A$H$_B$CO), 2.63 (dd, ^2J = 17.8 Hz, ^3J = 2.9 Hz, 1H, CH$_A$*H*$_B$CO), 2.7 (br, 1H, OH), 3.95 (m, 1H, C*H*OH). ^{13}C NMR (62 MHz, CDCl$_3$): δ = 9.7 (CH$_2$*C*H$_3$), 29.2 (*C*H$_2$CH$_3$), 30.6 (*C*H$_3$CO), 49.5 (*C*H$_2$CO), 68.8 (CHOH), 209.9 (CO).

This compound has been prepared before but no comparable spectroscopic data are given.[121]

3-Hydroxy-1-phenyl-butan-1-one (**28t**):

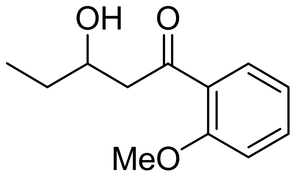


(GP 3) Starting with diisopropylamine (7.08 g, 70 mmol), THF (70 mL), *n*-BuLi (2.5 M in hexanes, 29 mL, 72 mmol), acetophenone (8.41 g, 70 mmol), acetaldehyde (3.70 g, 84 mmol), and hydrochloric acid (2.0 M, 35 mL), **28t** was isolated by destillation as a clear colourless liquid (6.91 g, 60%); bp. 96 °C (0.1 mbar). Reaction time: 3.5 min.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.31 (d, ^3J = 6.3 Hz, 3H, CH$_3$), 3.05 (dd, ^2J = 17.7 Hz, ^3J = 8.7 Hz, 1H, C*H*$_A$H$_B$), 3.18 (dd, ^2J = 17.7 Hz, ^3J = 3.0 Hz, 1H, CH$_A$*H*$_B$), 3.3 (br, 1H, OH), 4.41 (m, 1H, C*H*OH), 7.48 (m, 2H, Ph), 7.59 (m, 1H, Ph), 7.96 (m, 2H, Ph). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 22.4 (CH$_3$), 46.5 (CH$_2$), 63.9 (CHOH), 128.0, 128.5, 133.4 (CH$_{Ar}$), 136.6 (C$_{Ar}$), 200.6 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3421 (br, s), 2971 (m), 1681 (s), 1597 (m), 1449 (m), 1374 (m), 1284 (m), 1214 (m), 1003 (m), 755 (m), 691 (m).

The spectroscopic data (^{1}H NMR, ^{13}C NMR) are in accordance with those presented in the literature.[122]

3-Hydroxy-1-(2-methoxyphenyl)-pentan-1-one (**28u**):

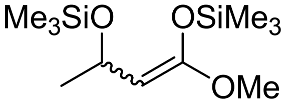


(GP 3) Starting with diisopropylamine (7.08 g, 70 mmol), THF (70 mL), *n*-BuLi (2.5 M in hexanes, 30 mL, 75 mmol), 2'-methoxyacetophenone (9.06 g, 60 mmol), propionaldehyde (4.36 g, 75 mmol), and hydrochloric acid (2.0 M, 35 mL), **28u** was isolated by destillation as a slightly turbid yellow liquid (8.20 g, 65%); bp. 134 °C (0.1 mbar). Reaction time: 4.5 min.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.99 (t, ^3J = 7.4 Hz, 3H, CH_3CH$_2$), 1.48 – 1.66 (m, 2H, CH$_3$CH_2), 3.00 (dd, ^2J = 17.9 Hz, ^3J = 9.2 Hz, 1H, CH_AH$_B$CO), 3.26 (dd, ^2J = 17.9 Hz, ^3J = 2.5 Hz, 1H, CH$_A$$H_B$CO), 3.3 (br, 1H, OH), 3.91 (s, 3H, OCH$_3$), 4.09 (m, 1H, CHOH), 7.00 (m, 2H, Ar), 7.48 (ddd, $^3J_1$ = 8.3 Hz, $^3J_2$ = 7.3 Hz, ^4J = 1.8 Hz, 1H, Ar), 7.73 (dd, ^3J = 7.7 Hz, ^4J = 1.8 Hz, 1H, Ar). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 9.8 (CH$_3$CH$_2$), 29.4 (CH$_3$$CH_2$), 49.9 ($CH_2$CO), 55.4 (OCH$_3$), 69.4 (CHOH), 111.6, 120.6 (CH$_{\text{Ar}}$), 127.8 (C_{Ar}CHOH), 130.2, 133.8 (CH$_{\text{Ar}}$), 158.7 (C_{Ar}OCH$_3$), 203.0 (CO). IR (nujol, cm^{-1}): $\tilde{\nu}$ = 3215 (br, s), 1667 (s), 1597 (s), 1295 (s), 1246 (s), 1182 (m), 1164 (m), 1115 (m), 1025 (s), 982 (m), 755 (s). MS (CI, isobutane): *m/z* (%) = 209 ([M + 1]$^+$, 100), 191 (24), 151 (37). Anal. Calcd for $C_{12}H_{16}O_3$ (208.25): C, 69.21; H, 7.74. Found: C, 69.50; H, 7.75.

8.3.6.2 Bis-Silyl Enol Ethers Derived from 3-Hydroxycarbonyl Compounds

1-Methoxy-1,3-bis(trimethylsilyloxy)but-1-ene (**29a**):

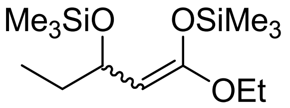


(GP 4) Starting with diisopropylamine (5.06 g, 50.0 mmol), THF (50 mL), *n*BuLi (2.5 M in hexanes, 20.5 mL, 51.2 mmol), **28a** (2.66 g, 22.5 mmol), and Me$_3$SiCl (6.11 g, 56.3 mmol), **29a** was obtained as a slightly yellow liquid (4.34 g, 73%). Reaction time: 18 h.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.08 (s, 9H, Si(CH$_3$)$_3$), 0.18 (s, 9H, Si(CH$_3$)$_3$), 1.20 (d, ^3J = 6.3 Hz, 3H, CHCH_3), 3.46 (s, 3H, OCH$_3$), 3.59 (d, ^3J = 8.8 Hz, 1H, CCH), 4.60 (dq, $^3J_1$ = 8.8 Hz, $^3J_2$ = 6.3 Hz, 1H, OCH). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 0.2, 0.3 (Si(CH$_3$)$_3$), 25.9 (CHCH$_3$), 54.3 (OCH$_3$), 64.6, 81.9 (CH), 156.5 (C).

The spectroscopic data (^{1}H NMR) are in accordance with those presented in the literature.[123]

1-Ethoxy-1,3-bis(trimethylsilyloxy)pent-1-ene (29b):



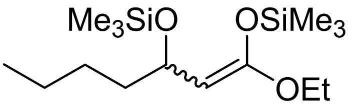
(GP 4) Starting with diisopropylamine (10.12 g, 100 mmol), THF (100 mL), *n*BuLi (2.5 M in hexanes, 41 mL, 103 mmol), **28b** (6.58 g, 45.0 mmol), and Me$_3$SiCl (12.22 g, 112 mmol), **29b** was obtained as a clear yellow liquid (12.92 g, 99%). Reaction time: 19 h.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.09 (s, 9H, Si(CH$_3$)$_3$), 0.21 (s, 9H, Si(CH$_3$)$_3$), 0.85 (t, ^3J = 7.4 Hz, 3H, CHCH$_A$H$_B$C*H*$_3$), 1.28 (t, ^3J = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.33 – 1.65 (m, 2H, CHC*H*$_A$*H*$_B$), 3.51 (d, ^3J = 8.9 Hz, 1H, CCH), 3.72 (q, ^3J = 7.1 Hz, 2H, OCH$_2$), 4.33 (dt, $^3J_1$ = 8.9 Hz, $^3J_2$ = 6.6 Hz, 1H, OCH). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 0.3, 0.4 (Si(CH$_3$)$_3$), 10.3, 14.3 (CH$_3$), 32.3 (CH*C*H$_2$), 62.8 (OCH$_2$), 70.0, 80.7 (CH), 156.1 (C). MS (EI, 70 eV): *m/z* (%) = 292 ([M + 2]$^+$, 2), 261 (16), 143 (29), 131 (33), 75 (50), 74 (100), 28 (75).

1-Ethoxy-4-methyl-1,3-bis(trimethylsilyloxy)pent-1-ene (29c):

This compound was prepared by Lars Michaelis.[80,87]

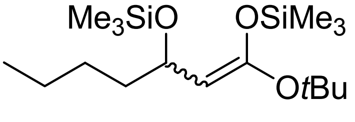
1-Ethoxy-1,3-bis(trimethylsilyloxy)hept-1-ene (29d):



(GP 4) Starting with diisopropylamine (5.06 g, 50.0 mmol), THF (50 mL), *n*BuLi (2.5 M in hexanes, 20.5 mL, 51.3 mmol), **28d** (3.92 g, 22.5 mmol), and Me$_3$SiCl (6.11 g, 56.3 mmol), **29d** was obtained as a clear yellow liquid (7.17 g, 100%). Reaction time: 24 h.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.10 (s, 9H, Si(CH$_3$)$_3$), 0.21 (s, 9H, Si(CH$_3$)$_3$), 0.86 – 0.94 (m, 3H, CH$_2$CH$_2$C*H*$_3$), 1.20 – 1.60 (m, 9H, (C*H*$_2$)$_3$, OCH$_2$C*H*$_3$), 3.51 (d, ^3J = 8.9 Hz, 1H, CCH), 3.72 (q, ^3J = 7.1 Hz, 2H, OCH$_2$), 4.41 (m, 1H, OCH). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 0.3, 0.5 (Si(CH$_3$)$_3$), 14.1, 14.3 (CH$_3$), 22.6, 28.1, 39.3 (CH$_2$), 62.8 (OCH$_2$), 68.6, 81.0 (CH), 156.0 (C). MS (EI, 70 eV): *m/z* (%) = 318 (M$^+$, 0.2), 261 (42), 231 (11), 189 (13), 159 (12), 146 (25), 143 (100), 110 (19), 28 (20).

1-(*tert*-Butoxy)-1,3-bis(trimethylsilyloxy)hept-1-ene (29e):



(GP 4) Starting with diisopropylamine (5.06 g, 50.0 mmol), THF (50 mL), *n*BuLi (2.5 M in hexanes, 20.5 mL, 51.3 mmol), **28e** (4.56 g, 22.5 mmol), and Me$_3$SiCl (6.11 g, 56.3 mmol), **29e** was obtained as a clear yellow liquid (5.95 g, 76%). Reaction time: 22 h.

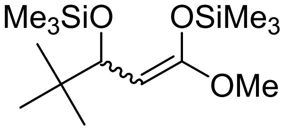
^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.08 (s, 9H, Si(CH$_3$)$_3$), 0.18 (s, 9H, Si(CH$_3$)$_3$), 0.86 (m, 3H, CH$_2$C*H*$_3$), 1.13 – 1.52 (m, 15H, (CH$_2$)$_3$), C(CH$_3$)$_3$), 3.90 (d, ^3J = 8.9 Hz, 1H, CCH), 4.33 (ddd,

${}^3J_1$ = 8.9 Hz, ${}^3J_2$ = 7.2 Hz, ${}^3J_3$ = 5.6 Hz, 1H, OCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.3, 0.5 ($Si(CH_3)_3$), 14.1 ($CH_2\mathit{C}H_3$), 22.5, 28.1 (CH_2), 28.4 ($C(\mathit{C}H_3)_3$), 38.9 (CH_2), 68.8 (CH), 78.6 ($O\mathit{C}(CH_3)_3$), 93.8 (CH), 151.4 (*C*CH).

1-Ethoxy-5-methyl-1,3-bis(trimethylsilyloxy)hex-1-ene (29f):

This compound was prepared by Lars Michaelis.[80,87]

1-Methoxy-4,4-dimethyl-1,3-bis(trimethylsilyloxy)pent-1-ene (29g):



(GP 4) Starting with diisopropylamine (5.06 g, 50.0 mmol), THF (50 mL), *n*BuLi (2.5 M in hexanes, 20.5 mL, 51.3 mmol), **28g** (3.58 g, 22.3 mmol), and Me_3SiCl (6.11 g, 56.3 mmol), **29g** was obtained as a clear yellow liquid (4.97 g, 73%). Reaction time: 19 h.

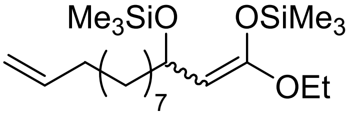
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.07 (s, 9H, $Si(CH_3)_3$), 0.20 (s, 9H, $Si(CH_3)_3$), 0.84 (s, 9H, $C(CH_3)_3$), 3.51 (s, 3H, OCH_3), 3.54 (d, ${}^3J$ = 9.3 Hz, 1H, OCHC*H*), 4.07 (d, ${}^3J$ = 9.3 Hz, 1H, OCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.3, 0.5 ($Si(CH_3)_3$), 25.8 ($C(\mathit{C}H_3)_3$), 35.9 ($\mathit{C}(CH_3)_3$), 54.4 (OCH_3), 75.9, 77.1 (CH), 157.2 (*C*=CH).

1-Methoxy-1,3-bis(trimethylsilyloxy)non-1-ene (29h):

(GP 4) Starting with diisopropylamine (5.06 g, 50.0 mmol), THF (50 mL), *n*BuLi (2.5 M in hexanes, 20.5 mL, 51.3 mmol), **28h** (4.23 g, 22.5 mmol), and Me_3SiCl (6.11 g, 56.3 mmol), **29h** was obtained as a clear yellow liquid (6.81 g, 91%). Reaction time: 17 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.09 (s, 9H, $Si(CH_3)_3$), 0.20 (s, 9H, $Si(CH_3)_3$), 0.88 (m, 3H, $CH_2C\mathit{H}_3$), 1.15 – 1.60 (m, 10H, $(CH_2)_5$), 3.49 (s, 3H, OCH_3), 3.54 (d, ${}^3J$ = 8.9 Hz, 1H, CCH), 4.40 (m, 1H, OCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.27, 0.34 ($Si(CH_3)_3$), 14.0 (CH_2CH_3), 22.6, 25.8, 29.1, 31.9, 39.5 (CH_2), 54.4 (OCH_3), 68.5, 80.7 (CH), 157.0 (C).

1-Ethoxy-1,3-bis(trimethylsilyloxy)tredeca-1,12-diene (29i):

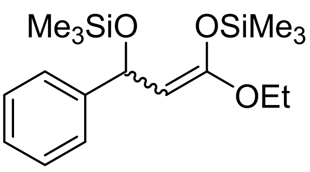


(GP 4) Starting with diisopropylamine (5.06 g, 50.0 mmol), THF (50 mL), *n*BuLi (2.5 M in hexanes, 20.5 mL, 51.3 mmol), **28i** (5.86 g, 22.9 mmol), dissolved in THF (6 mL), and Me_3SiCl

(6.23 g, 57.3 mmol), **29i** was obtained as a clear yellow liquid (8.51 g, 93%). Reaction time: 20 h.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.09 (s, 9H, Si(CH$_3$)$_3$), 0.20 (s, 9H, Si(CH$_3$)$_3$), 1.20 – 1.60 (m, 17H, OCH(C*H*$_2$)$_7$, CH$_3$), 2.03 (m, 2H, H$_2$C=CHC*H*$_2$), 3.49 (d, ^3J = 8.9 Hz, 1H, CCH), 3.71 (q, ^3J = 7.0 Hz, 2H, OCH$_2$), 4.40 (dt, $^3J_1$ = 8.9 Hz, $^3J_2$ = 6.4 Hz, 1H, OCH), 4.87 – 5.03 (m, 2H, *H*$_2$C=CH), 5.80 (ddt, $^3J_1$ = 17.0 Hz, $^3J_2$ = 10.3 Hz, $^3J_3$ = 6.7 Hz, 1H, H$_2$C=C*H*). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 0.3, 0.5 (Si(CH$_3$)$_3$), 14.3 (CH$_3$), 25.9, 28.9, 29.1, 29.5, 29.5, 29.6, 33.8, 39.5 ((CH$_2$)$_8$), 62.8 (OCH$_2$), 68.6, 81.0 (CH), 114.0 (*C*H$_2$CHCH$_2$CH$_2$), 139.1 (CH$_2$*C*HCH$_2$), 156.0 (C).

1-Ethoxy-3-phenyl-1,3-bis(trimethylsilyloxy)prop-1-ene (29k):

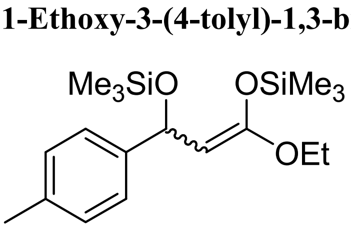


(GP 4) Starting with diisopropylamine (5.06 g, 50.0 mmol), THF (50 mL), *n*BuLi (1.6 M in hexanes, 32.0 mL, 51.2 mmol), **28k** (4.35 g, 22.4 mmol), and Me$_3$SiCl (6.11 g, 56.3 mmol), **29k** was obtained as a clear yellow-orange liquid (7.01 g, 92%, ratio of isomers = 2.6:1). Reaction time: 17 h.

Only ^{13}C NMR signals assigned to the main isomer are given below.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.25 (s, 9H, Si(CH$_3$)$_3$, major), 0.27 (s, 9H, Si(CH$_3$)$_3$, minor), 0.34 (s, 9H, Si(CH$_3$)$_3$, minor), 0.37 (s, 9H, Si(CH$_3$)$_3$, major), 1.37 (t, ^3J = 7.0 Hz, 3H, CH$_3$, major), 1.38 (t, ^3J = 7.0 Hz, 3H, CH$_3$, minor), 3.78 – 3.89 (m, 3H, OCH$_2$, OCHC*H*, major), 4.00 – 4.07 (m, 3H, OCH$_2$, OCHC*H*, minor), 5.72 (m, 1H, OCH, both), 7.30 (m, 1H, Ph, both), 7.39 (m, 2H, Ph, both), 7.49 (d, ^3J = 7.3 Hz, 2H, Ph, both). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 0.3, 0.6 (Si(CH$_3$)$_3$), 14.3 (CH$_3$), 62.9 (OCH$_2$), 70.1, 81.6 (CH), 125.6, 126.2, 127.9 (CH$_{Ar}$), 146.7, 156.5 (C).

1-Ethoxy-3-(4-tolyl)-1,3-bis(trimethylsilyloxy)prop-1-ene (29l):

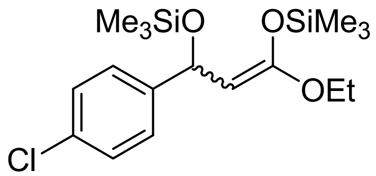


(GP 4) Starting with diisopropylamine (5.06 g, 50.0 mmol), THF (50 mL), *n*BuLi (2.5 M in hexanes, 20.5 mL, 51.3 mmol), **28l** (4.34 g, 20.8 mmol), dissolved in THF (8 mL), and Me$_3$SiCl (6.11 g, 56.3 mmol), **29l** was obtained as a clear orange liquid (6.97 g, 95%, ratio of isomers = 3.5:1). Reaction time: 19 h.

Only ^{13}C NMR signals assigned to the main isomer are given below.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 0.13 (s, 9H, Si(CH$_3$)$_3$, major), 0.16 (s, 9H, Si(CH$_3$)$_3$, minor), 0.24 (s, 9H, Si(CH$_3$)$_3$, minor), 0.26 (s, 9H, Si(CH$_3$)$_3$, major), 1.27 (t, ^3J = 7.0 Hz, 3H, CH$_3$, major), 1.28 (t, ^3J = 7.0 Hz, 3H, CH_3, minor), 2.33 (s, 3H, $ArCH_3$, both), 3.66 – 3.79 (m, 3H, OCH_2, OCHC*H*, major), 3.88 – 3.97 (m, 3H, OCH_2, OCHC*H*, minor), 5.58 (m, 1H, OCH, both), 7.06 – 7.13 (m, 2H, Ar, both), 7.23 – 7.30 (m, 2H, Ar, both). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.3, 0.5 ($Si(CH_3)_3$), 14.3 ($CH_2\mathit{C}H_3$), 21.0 ($ArCH_3$), 62.9 (CH_2), 70.0, 81.8 (CH), 125.5, 128.6 (CH_{Ar}), 135.7, 143.7, 156.4 (C).

3-(4-Chlorophenyl)-1-ethoxy-1,3-bis(trimethylsilyloxy)prop-1-ene (**29m**):

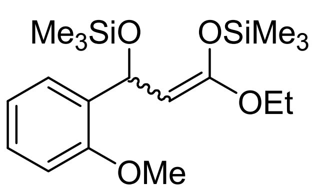


(GP 4) Starting with diisopropylamine (5.06 g, 50.0 mmol), THF (60 mL), *n*BuLi (2.5 M in hexanes, 20.5 mL, 51.3 mmol), **28m** (5.11 g, 22.3 mmol), and Me_3SiCl (6.19 g, 57.0 mmol), **29m** was obtained as a clear orange-red liquid (7.92 g, 95%, ratio of isomers = 2.3:1). Reaction time: 17 h.

Only ^{13}C NMR signals assigned to the main isomer are given below.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.14 (s, 9H, $Si(CH_3)_3$, major), 0.16 (s, 9H, $Si(CH_3)_3$, minor), 0.23 (s, 9H, $Si(CH_3)_3$, minor), 0.27 (s, 9H, $Si(CH_3)_3$, major), 1.28 (t, ^3J = 7.0 Hz, 3H, CH_3, both), 3.67 (d, ^3J = 8.9 Hz, 1H, OCHC*H*, major), 3.73 (m, 2H, OCH_2, major), 3.85 (d, ^3J = 8.9 Hz, 1H, OCHC*H*, minor), 3.93 (m, 2H, OCH_2, minor), 5.56 (d, ^3J = 8.9 Hz, 1H, OCH, major), 5.59 (d, ^3J = 8.9 Hz, 1H, OCH, minor), 7.23 – 7.34 (m, 4H, Ar, both). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.3, 0.6 ($Si(CH_3)_3$), 14.3 (CH_3), 63.0 (CH_2), 69.6, 81.2 (CH), 127.0, 128.0 (CH_{Ar}), 131.8, 145.3, 156.6 (C).

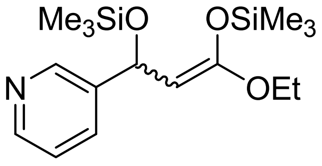
1-Ethoxy-3-(2-methoxyphenyl)-1,3-bis(trimethylsilyloxy)prop-1-ene (**29n**):



(GP 4) Starting with diisopropylamine (5.06 g, 50.0 mmol), THF (50 mL), *n*BuLi (2.5 M in hexanes, 20.5 mL, 51.3 mmol), **28n** (5.05 g, 22.5 mmol), dissolved in THF (10 mL), and Me_3SiCl (6.11 g, 56.3 mmol), **29n** was obtained as a clear yellow-orange liquid (7.28 g, 88%). Reaction time: 17 h.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.11 (s, 9H, $Si(CH_3)_3$), 0.28 (s, 9H, $Si(CH_3)_3$), 1.27 (t, ^3J = 7.0 Hz, 3H, $CH_2\mathit{CH_3}$), 3.73 (q, ^3J = 7.0 Hz, 2H, OCH_2), 3.80 (d, ^3J = 9.2 Hz, 1H, OCHC*H*), 3.84 (s, 3H, OCH_3), 5.95 (d, ^3J = 9.2 Hz, 1H, OCH), 6.82 – 7.03 (m, 2H, Ar), 7.17 – 7.29 (m, 1H, Ar), 7.50 – 7.57 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.2, 0.4 ($Si(CH_3)_3$), 14.3 ($CH_2\mathit{C}H_3$), 55.3 (OCH_3), 62.8 (CH_2), 64.7, 80.9 (CH), 110.5, 120.5, 126.9, 127.3 (CH_{Ar}), 135.0, 155.6, 156.4 (C).

1-Ethoxy-3-pyridin-3-yl-1,3-bis(trimethylsilyloxy)prop-1-ene (**29p**):

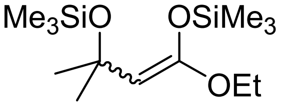


(GP 4) Starting with diisopropylamine (5.06 g, 50.0 mmol), THF (50 mL), *n*BuLi (2.5 M in hexanes, 20.5 mL, 51.3 mmol), **28p** (4.10 g, 21.0 mmol), dissolved in THF (8 mL), and Me_3SiCl (6.38 g, 58.7 mmol), **29p** was obtained as a clear red liquid (5.70 g, 80%, ratio of isomers = 1.5:1). Reaction time: 17 h.

Only ^{13}C NMR signals assigned to the main isomer are given below.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.14 (s, 9H, $Si(CH_3)_3$, major), 0.16 (s, 9H, $Si(CH_3)_3$, minor), 0.23 (s, 9H, $Si(CH_3)_3$, minor), 0.26 (s, 9H, $Si(CH_3)_3$, major), 1.27 (t, ^3J = 7.0 Hz, 3H, CH_3, minor), 1.28 (t, ^3J = 7.0 Hz, 3H, CH_3, major), 3.68 (d, ^3J = 9.0 Hz, 1H, OCHC*H*, major), 3.73 (m, 2H, OCH_2, major), 3.85 (d, ^3J = 9.0 Hz, 1H, OCHC*H*, minor), 3.93 (m, 2H, OCH_2, minor), 5.64 (m, 1H, OCH, both), 7.21 (m, 1H, Ar, both), 7.66 – 7.72 (m, 1H, Ar, both), 8.44 (m, 1H, Ar, both), 8.56 – 8.62 (m, 1H, Ar, both). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.2, 0.5 ($Si(CH_3)_3$), 14.2 (CH_3), 63.1 (CH_2), 68.3, 80.6 (CH), 122.9, 133.1 (CH_{Ar}), 141.8 (C_{Ar}), 147.6, 147.9 (CH_{Ar}), 156.8 (C).

1-Ethoxy-3-methyl-1,3-bis(trimethylsilyloxy)but-1-ene (**29q**):

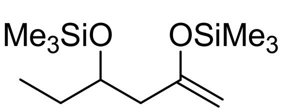


(GP 4) Starting with diisopropylamine (5.06 g, 50.0 mmol), THF (50 mL), *n*BuLi (2.5 M in hexanes, 20.5 mL, 51.3 mmol), **28q** (3.29 g, 22.5 mmol), and Me_3SiCl (6.11 g, 56.3 mmol), **29q** was obtained as a clear yellow liquid (2.32 g, 35%, ratio of isomers = 1.7:1). Reaction time: 14 h.

Only ^{13}C NMR signals assigned to the main isomer are given below.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.10 (s, 9H, $Si(CH_3)_3$, major), 0.11 (s, 9H, $Si(CH_3)_3$, minor), 0.15 (s, 9H, $Si(CH_3)_3$, major), 0.21 (s, 9H, $Si(CH_3)_3$, minor), 1.26 (t, ^3J = 7.2 Hz, 3H, CH_2CH_3, minor), 1.27 (t, ^3J = 7.0 Hz, 3H, CH_2CH_3, major), 1.37 (s, 6H, $C(CH_3)_2$, minor), 1.39 (s, 6H, $C(CH_3)_2$, major), 3.61 (s, 1H, CH, major), 3.67 (q, ^3J = 7.0 Hz, CH_2, major), 4.07 – 4.18 (m, 2H, CH_2 minor). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.5, 0.6 ($Si(CH_3)_3$), 14.4 (CH_2CH_3), 30.2 ($C(CH_3)_2$), 62.9 (CH_2), 72.7 (CH_3C), 85.5 (CH), 156.3 (C=CH).

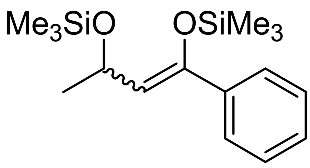
2,4-bis(Trimethylsilyloxy)hex-1-ene (**29s**):



(GP 4; varied) An LDA solution was prepared by addition of *n*BuLi (2.5 M in hexanes, 20.5 mL, 51.3 mmol) to a THF solution (50 mL) of diisopropylamine (5.06 g, 50.0 mmol) at 0 °C. After stirring for 1 h, the solution was cooled to –78 °C and **28s** (4.10 g, 21.0 mmol), dissolved in THF (6 ml), was added. After stirring for 1 h at –78 °C, the solution was warmed to 0 °C. After stirring for 1 h at 0 °C, the solution was cooled again to –78 °C. Me_3SiCl (6.56 g, 60.4 mmol) was added and the solution was allowed to warm to 20 °C within 24 h. The solvent and volatile compounds were removed *in vacuo*. The residue was dissolved in *n*-hexane and the suspension was filtered under inert atmosphere. The filtrate was concentrated *in vacuo* to give **29s** as a clear yellow liquid (5.13 g, 82%).

^1H NMR (250 MHz, $CDCl_3$): $\delta = 0.11$ (s, 9H, $Si(CH_3)_3$), 0.20 (s, 9H, $Si(CH_3)_3$), 0.89 (d, $^3J = 7.3$ Hz, 3H, CH_3), 1.30 – 1.63 (m, 2H, CH_3CH_2), 2.14 (m, 2H, CCH_2CH), 3.79 (m, 1H, OCH), 4.05 (m, 2H, $C{=}CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 0.04$, 0.3 ($Si(CH_3)_3$), 10.0 (CH_3), 29.7 (CH_3CH_2), 45.3 (CH_2), 71.3 (CH), 91.9 (CH_2), 156.5 (C).

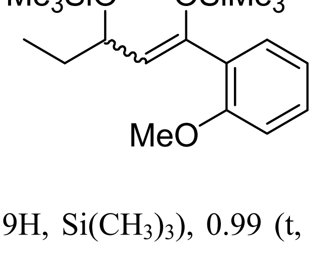
1-Phenyl-1,3-bis(trimethylsilyloxy)but-1-ene (**29t**):



(GP 4) Starting with diisopropylamine (5.06 g, 50.0 mmol), THF (50 mL), *n*BuLi (2.5 M in hexanes, 20.5 mL, 51.3 mmol), **28t** (3.70 g, 22.5 mmol), and Me_3SiCl (6.11 g, 56.3 mmol), **29t** was obtained as a slightly yellow liquid (6.64 g, 96%). Reaction time: 17 h.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.20$ (s, 9H, $Si(CH_3)_3$), 0.21 (s, 9H, $Si(CH_3)_3$), 1.39 (d, $^3J = 6.3$ Hz, 3H, CH_3), 4.90 (dq, $^3J_1 = 8.7$ Hz, $^3J_2 = 6.3$ Hz, 1H, OCH), 5.34 (d, $^3J = 8.7$ Hz, 1H, CCH), 7.34 (m, 3H, Ph), 7.53 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 0.3$, 0.6 ($Si(CH_3)_3$), 24.6 (CH_3), 64.1 (OCH), 116.1, 125.8, 127.9, 128.0 (CH), 138.8, 148.3 (C).

1-(2-Methoxyphenyl)-1,3-bis(trimethylsilyloxy)pent-1-ene (**29u**):

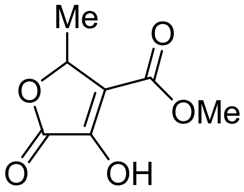


(GP 4) Starting with diisopropylamine (5.06 g, 50.0 mmol), THF (50 mL), *n*BuLi (2.5 M in hexanes, 20.5 mL, 51.3 mmol), **28u** (4.69 g, 22.5 mmol), and Me_3SiCl (6.11 g, 56.3 mmol), **29u** was obtained as a slightly yellow liquid (6.84 g, 86%). Reaction time: 15 h.

^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.04$ (s, 9H, $Si(CH_3)_3$), 0.20 (s, 9H, $Si(CH_3)_3$), 0.99 (t, $^3J = 7.4$ Hz, 3H, CH_2CH_3), 1.50 – 1.72 (m, 2H, CH_2), 3.82 (s, 3H, OCH_3), 4.62 (ddd, $^3J_1 = 8.7$ Hz, $^3J_2 = 7.1$ Hz, $^3J_3 = 6.0$ Hz, 1H, OCH), 4.98 (d, $^3J_1 = 8.7$ Hz, 1H, OCHC*H*), 6.84 – 6.94 (m, 2H, Ar), 7.23 – 7.32 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 0.3$, 0.5 ($Si(CH_3)_3$), 10.1 (CH_2CH_3), 31.3 (CH_2), 55.0 (OCH_3), 69.1 (OCH), 110.7, 117.0, 119.9 (CH), 128.3 (C), 129.1, 130.1 (CH), 146.1, 157.0 (C).

8.3.6.3 Isotetronic Acids

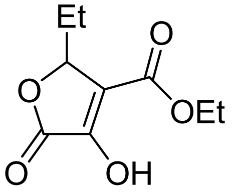
Methyl 4-hydroxy-2-methyl-5-oxo-2,5-dihydro-furan-3-carboxylate (**31a**):



(GP 5) Starting with **29a** (261 mg, 0.99 mmol), CH_2Cl_2 (10 mL), and oxalyl chloride (2.0 M in CH_2Cl_2, 0.50 mL, 1.00 mmol), **31a** was isolated by column chromatography (*n*-hexane/Et_2O = 1:1) as a slightly yellow solid (89 mg, 52%). Mp 48 – 49 °C; R_f 0.25 (tailing; Et_2O). Reaction time: 17 h. Data for (*R*)-**31a**: Mp 96 – 97 °C; $[\alpha]_D^{23}$ 24.5 (*c* 0.96, $CHCl_3$).

^1H NMR (250 MHz, $CDCl_3$): δ = 1.55 (d, ^3J = 6.4 Hz, 3H, $CHCH_3$), 3.91 (s, 3H, OCH_3), 5.16 (q, ^3J = 6.4 Hz, 1H, $CHCH_3$), 8.4 (br, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.4 ($CHCH_3$), 52.5 (OCH_3), 74.8 (OCH), 119.8 (*C*CH), 151.6 (COH), 164.6, 165.7 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3395 (br, s), 3344 (s), 2958 (w), 1781 (s), 1717 (s), 1456 (m), 1336 (m), 1229 (s), 1139 (s), 1053 (m), 772 (m). MS (EI, 70 eV): *m/z* (%) = 172 (M^+, 15), 127 (27), 112 (18), 100 (37), 85 (56), 70 (100), 53 (20), 39 (40), 29 (21). Anal. Calcd for $C_7H_8O_5$ (172.14): C, 48.84; H, 4.68. Found: C, 49.01; H, 4.81.

Ethyl 2-ethyl-4-hydroxy-5-oxo-2,5-dihydro-furan-3-carboxylate (**31b**):



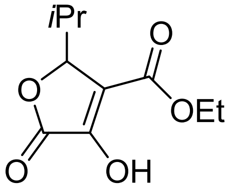
Method 1: (GP 5) Starting with **29b** (322 mg, 1.11 mmol), CH_2Cl_2 (10 mL), and oxalyl chloride (2.0 M in CH_2Cl_2, 0.55 mL, 1.10 mmol), **31b** was isolated by column chromatography (*n*-hexane/Et_2O = 1:1) as a slightly brown oil (170 mg, 77%); R_f 0.50 (tailing; Et_2O). Reaction time: 17 h.

Method 2: (GP 5; varied) Starting with **29b** (304 mg, 1.04 mmol), CH_2Cl_2 (10 mL), and oxalyl chloride (2.0 M in CH_2Cl_2, 0.52 mL, 1.04 mmol), TMSOTf (69 mg, 0.31 mmol) was additionally added at −78 °C. **31b** was isolated by column chromatography (*n*-hexane/Et_2O = 1:1) as a slightly brown oil (140 mg, 67%). Reaction time: 17 h.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.97 (t, ^3J = 7.3 Hz, 3H, $CHCH_2CH_3$), 1.38 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 1.62 – 1.76 (m, 1H, $CHCH_AH_B$), 2.10 – 2.23 (m, 1H, $CHCH_AH_B$), 4.39 (m, 2H, OCH_2), 5.09 (dd, $^3J_1$ = 7.3 Hz, $^3J_2$ = 3.2 Hz, 1H, CH), 8.78 (br, 1H, OH). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 8.2, 14.0 (CH_3), 26.0 ($CHCH_2$), 61.9 (OCH_2), 79.1 (CH), 118.4 (*C*CH), 152.1 (COH), 164.4, 165.9 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3326 (br, s), 2980 (s), 2939 (m), 1781 (s), 1703 (s), 1447 (s), 1379 (m), 1303 (s), 1224 (s), 1184 (s), 1137 (s), 1083 (m), 771 (m).

MS (EI, 70 eV): *m/z* (%) = 200 (M^+, 33), 155 (47), 143 (72), 114 (100), 70 (85), 29 (99). HRMS (EI, 70 eV): Calcd for $C_9H_{12}O_5$ (M^+) 200.06792, found 200.06746.

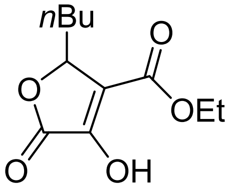
Ethyl 4-hydroxy-2-isopropyl-5-oxo-2,5-dihydro-furan-3-carboxylate (**31c**):



(GP 5) Starting with **29c** (287 mg, 0.94 mmol), CH_2Cl_2 (10 mL), and oxalyl chloride (2.0 M in CH_2Cl_2, 0.47 mL, 0.94 mmol), **31c** was isolated by column chromatography (*n*-hexane/Et_2O = 1:1) as a slightly yellow solid (109 mg, 54%). Mp 52 – 54 °C; R_f 0.38 (tailing; Et_2O). Reaction time: 16 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.72 (d, ^3J = 6.9 Hz, 3H, CHCH_3), 1.18 (d, ^3J = 7.0 Hz, 3H, CHCH_3), 1.38 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 2.39 (m, 1H, CH(CH_3)$_2$), 4.38 (m, 2H, OCH_2), 5.06 (d, ^3J = 2.5 Hz, 1H, OCH), 8.2 (br, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 14.0 (OCH_2CH_3, CHCH_3), 19.4 (CHCH_3), 30.0 (CH(CH_3)$_2$), 61.9 (OCH_2), 82.2 (OCH), 117.8 (CCH), 152.4 (COH), 164.6, 166.1 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3332 (m), 2976 (m), 1786 (s), 1693 (s), 1440 (m), 1377 (m), 1303 (m), 1222 (s), 1185 (m), 1123 (m), 1000 (m). MS (EI, 70 eV): *m/z* (%) = 214 (M^+, 18), 172 (100), 144 (36), 126 (49), 114 (28), 70 (32), 43 (38). Anal. Calcd for $C_{10}H_{14}O_5$ (214.22): C, 56.07; H, 6.59. Found: C, 56.25; H, 6.75.

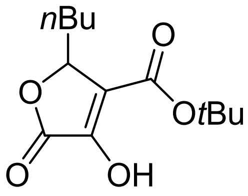
Ethyl 2-butyl-4-hydroxy-5-oxo-2,5-dihydro-furan-3-carboxylate (**31d**):



(GP 5) Starting with **29d** (322 mg, 1.01 mmol), CH_2Cl_2 (10 mL), and oxalyl chloride (2.0 M in CH_2Cl_2, 0.50 mL, 1.00 mmol), **31d** was isolated by column chromatography (*n*-hexane/Et_2O = 1:1) as a slightly orange solid (173 mg, 75%). Mp < 40 °C; R_f 0.45 (tailing; Et_2O). Reaction time: 17 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, ^3J = 7.1 Hz, 3H, $CH_2CH_2CH_3$), 1.25 – 1.45 (m, 7H, OCH_2CH_3, $CH_2CH_2CH_3$), 1.50 – 1.70 (m, 1H, CHCH_AH$_B$), 2.00 – 2.20 (m, 1H, CHCH$_A$$H_B$), 4.39 (m, 2H, OCH_2), 5.11 (dd, $^3J_1$ = 7.9 Hz, $^3J_2$ = 2.9 Hz, 1H, CH), 8.1 (br, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 14.1 (CH_3), 22.2, 26.3, 32.7 (CH_2), 61.9 (OCH_2), 78.3 (CH), 118.7 (CCH), 152.1 (COH), 164.5, 165.9 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3330 (br, w), 2960 (m), 2935 (m), 2870 (w), 1780 (s), 1708 (s), 1662 (m), 1443 (m), 1378 (w), 1336 (m), 1301 (m), 1226 (m), 1183 (m), 1138 (m) 1103 (m), 1018 (w), 770 (w). MS (EI, 70 eV): *m/z* (%) = 228 (M^+, 3), 183 (43), 172 (25), 143 (100), 126 (33), 114 (92), 113 (89), 97 (46), 86 (52), 70 (71), 41 (60), 29.0 (90), 28 (47), 27 (47). Anal. Calcd for $C_{11}H_{16}O_5$ (228.24): C, 57.88; H, 7.07. Found: C, 57.52; H, 7.12.

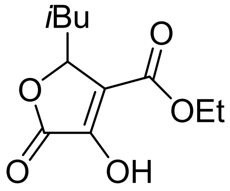
***tert*-Butyl 2-butyl-4-hydroxy-5-oxo-2,5-dihydro-furan-3-carboxylate (31e)**:



(GP 5) Starting with **29e** (674 mg, 1.94 mmol), CH_2Cl_2 (20 mL), and oxalyl chloride (2.0 M in CH_2Cl_2, 0.97 mL, 1.94 mmol), **31e** was isolated by column chromatography (*n*-hexane/Et_2O = 4:1) as a slightly brown oil (104 mg, 21%); R_f 0.59 – 0.77 (tailing; Et_2O). Reaction time: 22 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (m, 3H, CH_2CH_3), 1.25 – 1.50 (m, 4H, $CH_2CH_2CH_3$), 1.57 (s, 9H, $C(CH_3)_3$), 1.59 – 1.70 (m, 1H, $CHCH_AH_B$), 2.03 – 2.15 (m, 1H, $CHCH_AH_B$), 5.06 (dd, $^3J_1$ = 7.7 Hz, $^3J_2$ = 2.9 Hz, 1H, CH), 8.7 (br, 1H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 13.7 (CH_2CH_3), 22.1, 26.1 (CH_2), 28.0 ($C(CH_3)_3$), 32.4 (CH_2), 78.3 (OCH), 84.1 ($C(CH_3)_3$), 120.1 (*C*CH), 151.9 (COH), 164.1, 165.9 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3327 (br, s), 2960 (s), 2933 (s), 2874 (s), 1786 (s), 1685 (s), 1458 (m), 1371 (s), 1237 (s), 1151 (s), 771 (m). MS (CI, isobutane): *m/z* (%) = 257 ($[M + 1]^+$, 19), 202 (21), 201 (100), 157 (11).

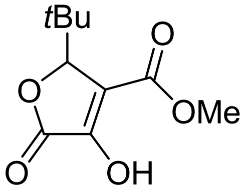
Ethyl 4-hydroxy-2-isobutyl-5-oxo-2,5-dihydro-furan-3-carboxylate (31f):



(GP 5) Starting with **29f** (306 mg, 0.96 mmol), CH_2Cl_2 (10 mL), and oxalyl chloride (2.0 M in CH_2Cl_2, 0.48 mL, 0.96 mmol), **31f** was isolated by column chromatography (*n*-hexane/Et_2O = 1:1) as a colourless solid (138 mg, 63%). Mp 99 – 100 °C; R_f 0.38 (tailing; Et_2O). Reaction time: 16 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, ^3J = 6.4 Hz, 3H, $CHCH_3$), 1.01 (d, ^3J = 6.2 Hz, 3H, $CHCH_3$), 1.38 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 1.46 (m, 1H, CH_AH_BCH), 1.85 – 2.00 (m, 2H, $CH_AH_BCH(CH_3)_2$), 4.39 (m, 2H, OCH_2CH_3), 5.13 (dd, $^3J_1$ = 9.9 Hz, $^3J_2$ = 2.0 Hz, 1H, CH), 8.7 (br, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.0 (OCH_2CH_3), 21.6, 23.4, 24.8 ($CH(CH_3)_2$), 42.5 ($CHCH_2$), 61.8 (OCH_2), 77.0 (OCH), 119.3 (*C*CH), 151.8 (COH), 164.5, 165.8 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3276 (br, w), 2958 (m), 1747 (s), 1710 (s), 1676 (w), 1464 (w), 1344 (w), 1299 (m), 1218 (m), 1190 (m), 1144 (w). MS (EI, 70 eV): *m/z* (%) = 228 (M^+, 2), 184 (40), 172 (72), 143 (100), 126 (50), 114 (93), 86 (42), 70 (68), 41 (81), 29 (77). Anal. Calcd for $C_{11}H_{16}O_5$ (228.24): C, 57.88; H, 7.07. Found: C, 58.16; H, 7.43.

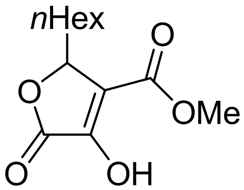
Methyl 2-*tert*-butyl-4-hydroxy-5-oxo-2,5-dihydro-furan-3-carboxylate (31g):



(GP 5) Starting with **29g** (4.07 g, 13.4 mmol), CH_2Cl_2 (100 mL), and oxalyl chloride (2.0 M in CH_2Cl_2, 6.68 mL, 13.4 mmol), **31g** was isolated by column chromatography (*n*-hexane/Et_2O = 2:1 → 1:1) as an orange oil (1.01 g, 35%); R_f 0.18 – 0.37 (tailing; Et_2O). Reaction time: 15 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99 (s, 9H, $C(CH_3)_3$), 3.90 (s, 3H, OCH_3), 4.93 (s, 1H, CH), 7.3 (br, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.8 ($C(\mathit{C}H_3)_3$), 36.5 ($\mathit{C}(CH_3)_3$), 52.4 (OCH_3), 85.5 (OCH), 117.6 (*C*=COH), 153.2 (COH), 165.5, 165.6 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3348 (br, w), 2966 (m), 1776 (s), 1724 (s), 1654 (m), 1456 (m), 1324 (m), 1231 (s), 1180 (m), 1128 (m), 1019 (w), 979 (w), 773 (w). MS (EI, 70 eV): *m/z* (%) = 214 (M^+, 0.53), 158 (100), 126 (22), 70 (33), 57 (98), 29 (27).

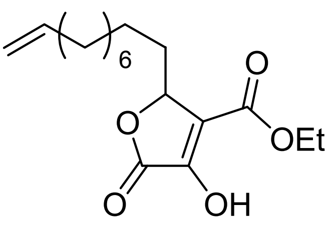
Methyl 2-hexyl-4-hydroxy-5-oxo-2,5-dihydro-furan-3-carboxylate (31h):



(GP 5) Starting with **29h** (377 mg, 1.13 mmol), CH_2Cl_2 (10 mL), and oxalyl chloride (2.0 M in CH_2Cl_2, 0.57 mL, 1.14 mmol), **31h** was isolated by column chromatography (*n*-hexane/Et_2O = 1:1) as a slightly yellow solid (168 mg, 61%). Mp 73 – 74 °C; R_f 0.42 (tailing; Et_2O). Reaction time: 15 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, ^3J = 6.6 Hz, 3H, $CH_2C\mathit{H}_3$), 1.18 – 1.49 (m, 8H, $(C\mathit{H}_2)_4CH_3$), 1.52 – 1.67 (m, 1H, $CHC\mathit{H}_AH_B$), 2.05 – 2.18 (m, 1H, $CHCH_A\mathit{H}_B$), 3.92 (s, 3H, OCH_3), 5.11 (dd, $^3J_1$ = 8.1 Hz, $^3J_2$ = 2.8 Hz, 1H, CH), 8.38 (br, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 ($CH_2\mathit{C}H_3$), 22.3, 24.2, 28.7, 31.4, 33.0 (CH_2), 52.4 (OCH_3), 78.4 (OCH), 118.3 (*C*CH), 151.6 (COH), 164.6, 166.1 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3321 (s), 2925 (s), 2857 (m), 1788 (s), 1699 (s), 1456 (m), 1343 (m), 1309 (m), 1220 (s), 1115 (m), 994 (w), 772 (w). MS (EI, 70 eV): *m/z* (%) = 242 (M^+, 2), 186 (37), 158 (82), 129 (100), 100 (72), 70 (28). Anal. Calcd for $C_{12}H_{18}O_5$ (242.27): C, 59.49; H, 7.49. Found: C, 59.68; H, 7.66.

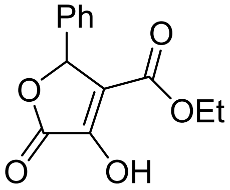
Ethyl 2-(9-decenyl)-4-hydroxy-5-oxo-2,5-dihydro-furan-3-carboxylate (**31i**):



(GP 5) Starting with **29i** (374 mg, 0.93 mmol), CH_2Cl_2 (10 mL), and oxalyl chloride (2.0 M in CH_2Cl_2, 0.42 mL, 0.84 mmol), repeated crystallization from *n*-hexane (2 – 5 mL) at −24 °C yielded **31i** as a slightly turbid brown oil (216 mg, 83%). Reaction time: 24 h.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.23 – 1.45 (m, 15H, $OCHCH_2(CH_2)_6$, CH_3), 1.52 – 1.67 (m, 1H, $OCHCH_AH_B$), 1.97 – 2.16 (m, 3H, $H_2C{=}CHCH_2$, $OCHCH_AH_B$), 4.37 (m, 2H, OCH_2), 4.89 – 5.02 (m, 2H, $H_2C{=}CH$), 5.09 (dd, $^3J_1$ = 7.8 Hz, $^3J_2$ = 2.9 Hz, 1H, OCH), 5.80 (ddt, $^3J_1$ = 17.0 Hz, $^3J_2$ = 10.3 Hz, $^3J_3$ = 6.7 Hz, 1H, $H_2C{=}CH$), 8.7 (br, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 24.3, 28.8, 29.0, 29.1, 29.2, 29.3, 33.0, 33.7 ($OCH(CH_2)_8$), 61.9 (OCH_2), 78.3 (OCH), 114.1 ($H_2C{=}CH$), 118.9 (CCH), 139.1 ($H_2C{=}CH$), 152.2 (COH), 164.6, 165.7 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3393 (br, s), 2980 (m), 2924 (s), 2854 (s), 1784 (s), 1748 (s), 1710 (s), 1669 (m), 1467 (m), 1300 (m), 1218 (s), 1190 (s), 776 (m). MS (CI, isobutane): *m/z* (%) = 311 ($[M + 1]^+$, 100), 265 (49). Anal. Calcd for $C_{17}H_{26}O_5$ (310.39): C, 65.78; H, 8.44. Found: C, 65.82; H, 8.65.

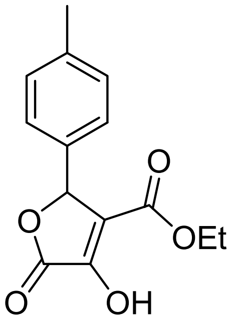
Ethyl 4-hydroxy-5-oxo-2-phenyl-2,5-dihydro-furan-3-carboxylate (**31k**):



(GP 5) Starting with **29k** (314 mg, 0.93 mmol), CH_2Cl_2 (10 mL), and oxalyl chloride (2.0 M in CH_2Cl_2, 0.46 mL, 0.92 mmol), **31k** was isolated by column chromatography (*n*-hexane/Et_2O = 1:1) as a slightly yellow solid (143 mg, 62%). Mp 105 °C; R_f 0.25 (tailing; Et_2O). Reaction time: 17 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, ^3J = 7.1 Hz, 3H, CH_3), 4.21 (q, ^3J = 7.1 Hz, 2H, OCH_2), 6.00 (s, 1H, OCH), 7.26 – 7.31 (m, 2H, Ph), 7.35 – 7.40 (m, 3H, Ph), 8.87 (br, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_3), 61.8 (OCH_2), 79.4 (OCH), 118.9 (C=COH), 127.2, 128.7, 129.6 (CH_{Ar}), 134.2 (C_{Ar}), 152.0 (COH), 164.3, 165.7 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3300 (br, m), 2992 (w), 1749 (s), 1715 (s), 1674 (m), 1456 (w), 1319 (m), 1207 (s), 1179 (s), 1127 (m), 998 (m). MS (EI, 70 eV): *m/z* (%) = 248 (M^+, 33), 203 (21), 175 (16), 158 (41), 130 (59), 105 (39), 77 (47), 28 (100). Anal. Calcd for $C_{13}H_{12}O_5$ (248.23): C, 62.90; H, 4.87. Found: C, 62.82; H, 4.93.

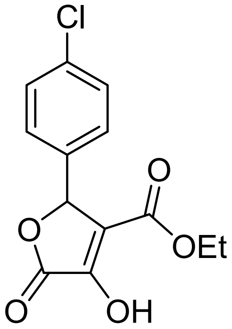
Ethyl 4-hydroxy-2-(4-methylphenyl)-5-oxo-2,5-dihydro-furan-3-carboxylate (31l):



(GP 5) Starting with **29l** (337 mg, 0.96 mmol), CH_2Cl_2 (10 mL), and oxalyl chloride (2.0 M in CH_2Cl_2, 0.45 mL, 0.90 mmol), recrystallization from a mixture of CH_2Cl_2 (3 mL) and *n*-hexane (25 mL) at −24 °C yielded **31l** as a slightly brown solid (159 mg, 67%); mp 113 – 114 °C. Reaction time: 24 h.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.18 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 2.36 (s, 3H, $ArCH_3$), 4.21 (m, 2H, OCH_2), 5.98 (s, 1H, OCH), 7.17 (s, 4H, Ar), 8.8 (br, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 21.2 ($ArCH_3$), 61.9 (OCH_2), 79.3 (OCH), 118.9 (*C*=COH), 127.2, 129.4 (CH_{Ar}), 131.2, 139.6 (C_{Ar}), 152.0 (COH), 164.4, 165.8 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3316 (br, m), 2997 (m), 1753 (s), 1744 (s), 1716 (s), 1671 (s), 1460 (m), 1318 (s), 1201 (s), 1174 (s), 992 (s), 775 (m). MS (EI, 70 eV): *m/z* (%) = 262 (M^+, 49), 217 (28), 189 (25), 145 (58), 144 (100), 121 (56), 119 (80), 117 (54), 116 (36), 115 (71), 91 (66), 44 (70). Anal. Calcd for $C_{14}H_{14}O_5$ (262.26): C, 64.12; H, 5.38. Found: C, 63.97; H, 5.22.

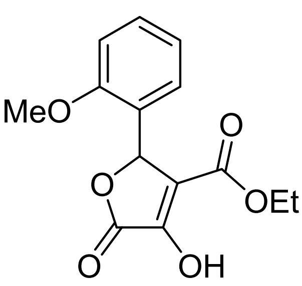
Ethyl 2-(4-chlorophenyl)-4-hydroxy-5-oxo-2,5-dihydro-furan-3-carboxylate (31m):



(GP 5) Starting with **29m** (336 mg, 0.90 mmol), CH_2Cl_2 (10 mL), and oxalyl chloride (2.0 M in CH_2Cl_2, 0.41 mL, 0.82 mmol), recrystallization from a mixture of CH_2Cl_2 (5 mL) and *n*-hexane (20 mL) at −24 °C yielded **31m** as a slightly brown solid (99 mg, 43%); mp 115 – 116 °C. Reaction time: 24 h.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.19 (t, ^3J = 7.1 Hz, 3H, CH_3), 4.22 (q, ^3J = 7.1 Hz, 2H, OCH_2), 5.97 (s, 1H, OCH), 7.18 – 7.27 (m, 2H, Ar), 7.32 – 7.39 (m, 2H, Ar), 8.9 (br, 1H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 13.8 (CH_3), 61.9 (OCH_2), 78.6 (OCH), 118.4 (*C*=COH), 128.6, 128.9 (CH_{Ar}), 132.9, 135.5 (C_{Ar}), 152.0 (COH), 164.0, 165.8 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3363 (br, s), 2999 (m), 1749 (s), 1713 (s), 1672 (s), 1496 (m), 1318 (s), 1202 (s), 1178 (s), 997 (s), 835 (m).

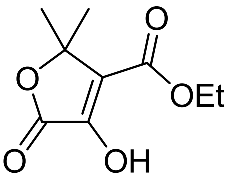
Ethyl 4-hydroxy-2-(2-methoxyphenyl)-5-oxo-2,5-dihydro-furan-3-carboxylate (**31n**):



(GP 5) Starting with **29n** (317 mg, 0.86 mmol), CH_2Cl_2 (10 mL), and oxalyl chloride (2.0 M in CH_2Cl_2, 0.41 mL, 0.82 mmol), recrystallization from a mixture of CH_2Cl_2 (2.5 mL) and *n*-hexane (25 mL) at −24 °C yielded **31n** as a slightly brown solid (137 mg, 60%); mp 111 – 112 °C. Reaction time: 24 h.

^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.13$ (t, $^3J = 7.1$ Hz, 3H, CH_2CH_3), 3.83 (s, 3H, OCH_3), 4.19 (q, $^3J = 7.1$ Hz, 2H, OCH_2), 6.36 (s, 1H, OCH), 6.89 – 6.96 (m, 2H, Ar), 7.06 – 7.10 (m, 1H, Ar), 7.31 – 7.38 (m, 1H, Ar), 8.9 (br, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 13.8$ (CH_2CH_3), 55.7 (OCH_3), 61.6 (OCH_2), 75.3 (OCH), 111.3 (CH_{Ar}), 118.2 (C), 120.5 (CH_{Ar}), 122.0 (C), 128.7, 131.0 (CH_{Ar}), 152.6, 158.1, 164.7, 166.1 (C). IR (KBr, cm^{-1}): $\tilde{\nu} = 3272$ (s), 2979 (m), 2939 (w), 1787 (s), 1749 (s), 1704 (s), 1690 (s), 1602 (m), 1496 (m), 1234 (s), 1186 (s), 761 (m). MS (EI, 70 eV): *m/z* (%) = 278 (M^+, 100), 233 (68), 188 (37), 161 (59), 135 (63), 131 (85), 44 (66). Anal. Calcd for $C_{14}H_{14}O_6$ (278.26): C, 60.43; H, 5.07. Found: C, 60.73; 5.29.

Ethyl 4-hydroxy-2,2-dimethyl-5-oxo-2,5-dihydro-furan-3-carboxylate (**31q**):

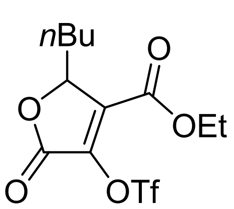


(GP 5) Starting with **29q** (291 mg, 1.00 mmol), CH_2Cl_2 (10 mL), and oxalyl chloride (2.0 M in CH_2Cl_2, 0.50 mL, 1.00 mmol), **31q** was isolated by column chromatography (*n*-heptane/Et_2O = 1:1) as a slightly yellow solid (43 mg, 21%). Mp 61 – 62 °C; R_f 0.22 (tailing; Et_2O). Reaction time: 22 h.

^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 1.38$ (t, $^3J = 7.1$ Hz, 3H, CH_2CH_3), 1.59 (s, 6H, $C(CH_3)_2$), 4.38 (q, $^3J = 7.1$ Hz, 2H, CH_2), 7.0 (br, 1H, OH). ^{13}C NMR (62 MHz, $CDCl_3$): $\delta = 14.1$ (CH_2CH_3), 25.9 ($C(CH_3)_2$), 61.9 (OCH_2), 83.4 ($OC(CH_3)_2$), 123.3 (*C*=COH), 151.7 (COH), 164.6, 165.0 (CO). IR (KBr, cm^{-1}): $\tilde{\nu} = 3314$ (br, s), 2981 (m), 1747 (s), 1707 (s), 1664 (s), 1448 (m), 1368 (m), 1315 (s), 1249 (s), 1182 (s), 1128 (s), 1065 (s), 986 (m), 772 (m). MS (EI, 70 eV): *m/z* (%) = 200 (M^+, 24), 185 (20), 157 (31), 155 (42), 129 (28), 100 (33), 86 (60), 84 (100), 69 (30), 49 (62). HRMS (EI, 70 eV): Calcd for $C_9H_{12}O_5$ (M^+) 200.06792, found 200.06864.

8.3.6.4 Triflates Prepared from Isotetronic Acids

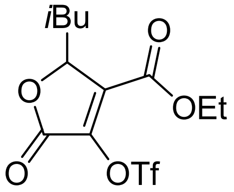
Ethyl 2-butyl-5-oxo-4-trifluoromethanesulfo-2,5-dihydro-furan-3-carboxylate (33a):



(GP 6) Starting with **31d** (1.16 g, 5.10 mmol), CH_2Cl_2 (100 mL), pyridine (1.03 g, 13.0 mmol), and Tf_2O (1.93 g, 6.84 mmol), **33a** was isolated as a yellow liquid (1.54 g, 84%); R_f 0.78 (CH_2Cl_2). After stirring for 120 minutes, the reaction mixture (temperature: –5 °C) was purified by column chromatography (CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (m, 3H, $CH_2CH_2CH_3$), 1.25 – 1.50 (m, 7H, OCH_2CH_3, $CH_2CH_2CH_3$), 1.70 – 1.85 (m, 1H, $CHCH_AH_B$), 2.15 – 2.28 (m, 1H, $CHCH_AH_B$), 4.42 (m, 2H, OCH_2), 5.30 (dd, $^3J_1$ = 7.6 Hz, $^3J_2$ = 3.2 Hz, 1H, OCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6, 13.7 (CH_3), 22.1, 26.0, 32.0 ($(CH_2)_3$), 63.2 (OCH_2), 79.3 (OCH), 118.3 (q, $^1J_{CF}$ = 321 Hz, CF_3), 137.7, 141.8 (C=C), 158.6, 163.2 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2964 (m), 2936 (m), 2877 (w), 1796 (s), 1735 (s), 1438 (s), 1254 (s), 1220 (s), 1135 (s), 608 (m). MS (EI, 70 eV): *m/z* (%) = 361 ($[M + 1]^+$, 0.4), 304 (5), 143 (100). HRMS (EI, 70 eV): Calcd for $C_{12}H_{16}F_3O_7S$ ($[M + 1]^+$) 361.05633, found 361.05555. Anal. Calcd for $C_{12}H_{15}F_3O_7S$ (360.30): C, 40.00; H, 4.20. Found: C, 40.34; H 4.09.

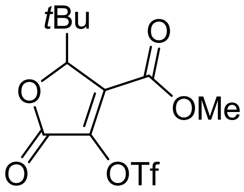
Ethyl 2-isobutyl-5-oxo-4-trifluoromethanesulfo-2,5-dihydro-furan-3-carboxylate (33b):



(GP 6) Starting with **31f** (106 mg, 0.46 mmol), CH_2Cl_2 (10 mL), pyridine (95 mg, 1.2 mmol), and Tf_2O (205 mg, 0.73 mmol), **33b** was isolated as a yellow oil (144 mg, 86%); R_f 0.79 (CH_2Cl_2). After stirring for 90 minutes, the reaction mixture (temperature: 12 °C) was purified by column chromatography (CH_2Cl_2).

^1H NMR (300 MHz, $CDCl_3$): δ = 0.99 (d, ^3J = 6.4 Hz, 3H, $CHCH_3$), 1.03 (d, ^3J = 6.3 Hz, 3H, $CHCH_3$), 1.41 (t, ^3J = 7.2 Hz, 3H, OCH_2CH_3), 1.55 (m, 1H, $CHCH_AH_B$), 1.88 – 2.04 (m, 2H, $CH_AH_BCH(CH_3)_2$), 4.42 (m, 2H, OCH_2), 5.31 (dd, $^3J_1$ = 9.9 Hz, $^3J_2$ = 2.2 Hz, 1H, OCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8 (OCH_2CH_3), 21.4, 23.3, 24.9 ($CH(CH_3)_2$), 41.7 ($CHCH_2$), 63.2 (OCH_2), 78.2 (OCH), 118.3 (q, $^1J_{CF}$ = 321 Hz, CF_3), 137.6, 142.4 (C=C), 158.7, 163.2 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2964 (m), 2876 (w), 1796 (s), 1735 (s), 1438 (s), 1254 (s), 1221 (s), 1134 (s), 1100 (m), 819 (m), 608 (m). MS (CI, isobutane): *m/z* (%) = 361 ($[M + 1]^+$, 35). Anal. Calcd for $C_{12}H_{15}F_3O_7S$ (360.30): C, 40.00; H, 4.20. Found: C, 40.58; H, 4.19.

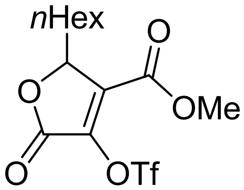
Methyl 2-*tert*-butyl-5-oxo-4-trifluoromethanesulfo-2,5-dihydro-furan-3-carboxylate (33c):



(GP 6) Starting with **31g** (900 mg, 4.20 mmol), CH_2Cl_2 (100 mL), pyridine (831 mg, 10.5 mmol), and Tf_2O (1.42 g, 5.04 mmol), **33c** was isolated as an orange oil (736 mg, 51%); R_f 0.76 (CH_2Cl_2). After stirring for 100 minutes, the reaction mixture (temperature: 0 °C) was purified by column chromatography (CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (s, 9H, $C(CH_3)_3$), 3.95 (s, 3H, OCH_3), 5.12 (s, 1H, OCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.6 ($C(\mathit{C}H_3)_3$), 36.7 ($\mathit{C}(CH_3)_3$), 53.4 (OCH_3), 86.0 (OCH), 118.3 (q, $^1J_{CF}$ = 321 Hz, CF_3), 137.3, 142.4 (C=C), 159.9, 162.8 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2971 (m), 2878 (w), 1798 (s), 1744 (s), 1438 (s), 1255 (s), 1225 (s), 1134 (s), 1107 (s), 609 (m). MS (EI, 70 eV): *m/z* (%) = 347 ($[M + 1]^+$, 0.2). HRMS (EI, 70 eV): Calcd for $C_{11}H_{14}F_3O_7S$ ($[M + 1]^+$) 347.04068, found 347.04000. Anal. Calcd for $C_{11}H_{13}F_3O_7S$ (346.28): C, 38.15; H, 3.78. Found: C, 38.39; H, 3.78.

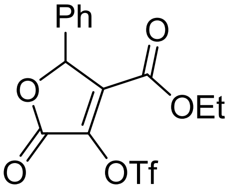
Methyl 2-hexyl-5-oxo-4-trifluoromethanesulfo-2,5-dihydro-furan-3-carboxylate (33d):



(GP 6) Starting with **31h** (1.52 g, 6.27 mmol), CH_2Cl_2 (100 mL), pyridine (1.24 g, 15.7 mmol), and Tf_2O (2.12 g, 7.52 mmol), **33d** was isolated as an orange liquid (1.81 g, 77%); R_f 0.80 (CH_2Cl_2). After stirring for 100 minutes, the reaction mixture (temperature: 0 °C) was purified by column chromatography (CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, ^3J = 6.8 Hz, 3H, $CH_2C\mathit{H}_3$), 1.20 – 1.48 (m, 8H, $(C\mathit{H}_2)_4CH_3$), 1.77 (m, 1H, $CHC\mathit{H}_AH_B$), 2.12 – 2.27 (m, 1H, $CHCH_A\mathit{H}_B$), 3.96 (s, 3H, OCH_3), 5.31 (dd, $^3J_1$ = 7.7 Hz, $^3J_2$ = 3.2 Hz, 1H, OCH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 ($CH_2\mathit{C}H_3$), 22.4, 23.9, 28.6, 31.4, 32.3 (CH_2), 53.2 (OCH_3), 79.2 (OCH), 118.3 (q, $^1J_{CF}$ = 321 Hz, CF_3), 138.1, 141.2 (C=C), 159.0, 163.1 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2960 (m), 2932 (m), 2861 (m), 1797 (s), 1740 (s), 1440 (s), 1255 (s), 1221 (s), 1134 (s), 608 (m). MS (EI, 70 eV): *m/z* (%) = 375 ($[M + 1]^+$, 0.2). HRMS (EI, 70 eV): Calcd for $C_{13}H_{18}F_3O_7S$ ($[M + 1]^+$) 375.07198, found 375.07116. Anal. Calcd for $C_{13}H_{17}F_3O_7S$ (374.33): C, 41.71; H, 4.58. Found: C, 42.15; H, 4.68.

Ethyl 5-oxo-2-phenyl-4-trifluoromethanesulfo-2,5-dihydro-furan-3-carboxylate (33e):

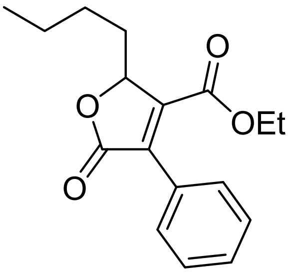


(GP 6) Starting with **31k** (62 mg, 0.25 mmol), CH_2Cl_2 (5 mL), pyridine (50 mg, 0.63 mmol), and Tf_2O (92 mg, 0.33 mmol), **33e** was isolated as an orange solid (50 mg, 53%); R_f 0.74 (CH_2Cl_2). After stirring for 110 minutes, the reaction mixture (temperature: 5 °C) was purified by column chromatography (CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, ^3J = 7.2 Hz, 3H, CH_3), 4.28 (m, 2H, OCH_2), 6.20 (s, 1H, OCH), 7.28 – 7.34 (m, 2H, Ph), 7.39 – 7.47 (m, 3H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6 (CH_3), 63.2 (OCH_2), 80.3 (OCH), 118.4 (q, $^1J_{CF}$ = 321 Hz, CF_3), 127.4, 129.2, 130.4 (CH_{Ar}), 131.6, 137.7, 141.2 (C), 158.2, 163.3 (CO). IR (nujol, cm^{-1}): $\tilde{\nu}$ = 1785 (s), 1726 (s), 1258 (s), 1224 (s), 1153 (s), 1117 (s), 1005 (m), 813 (m), 761 (m), 608 (m). MS (EI, 70 eV): *m/z* (%) = 380 (M^+, 11), 105 (100), 77 (34), 69 (27). HRMS (EI, 70 eV): Calcd for $C_{14}H_{11}F_3O_7S$ (M^+) 380.01721, found 380.01671. Anal. Calcd for $C_{14}H_{11}F_3O_7S$ (380.29): C, 44.22; H, 2.92. Found: C, 44.53; H, 2.83.

8.3.6.5 Suzuki Coupling Products

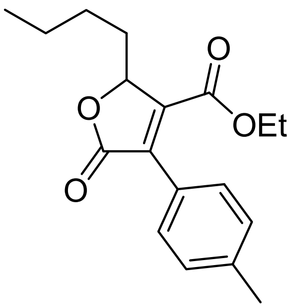
Ethyl 2-butyl-5-oxo-4-phenyl-2,5-dihydro-furan-3-carboxylate (34a):



(GP 7) Starting with **33a** (215 mg, 0.60 mmol), K_3PO_4 (190 mg, 0.90 mmol), phenylboronic acid (100 mg, 0.82 mmol), $Pd(PPh_3)_4$ (21 mg, 0.018 mmol), and 1,4-dioxane (3.0 mL), **34a** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 20:1) as a slightly yellow oil (130 mg, 76%); R_f 0.20 (*n*-hexane/EtOAc = 10:1). Reaction time: 4 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, ^3J = 7.1 Hz, 3H, $CH_2CH_2CH_3$), 1.22 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 1.32 – 1.53 (m, 4H, $CH_2CH_2CH_3$), 1.65 – 1.78 (m, 1H, $CHCH_AH_B$), 2.05 – 2.17 (m, 1H, $CHCH_AH_B$), 4.26 (m, 2H, OCH_2CH_3), 5.27 (dd, $^3J_1$ = 7.8 Hz, $^3J_2$ = 3.3 Hz, 1H, OCH), 7.38 – 7.44 (m, 3H, Ph), 7.52 – 7.59 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7 (2xCH_3), 22.2, 26.6, 32.3 ($(CH_2)_3$), 61.7 (OCH_2), 80.8 (OCH), 127.8 (CH_{Ar}), 128.4 (C), 129.4, 129.7 (CH_{Ar}), 135.4, 148.9 (C), 162.2, 171.1 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2959 (m), 2932 (m), 2873 (w), 1766 (s), 1721 (s), 1377 (w), 1224 (m), 1177 (m), 1015 (m), 696 (m). MS (EI, 70 eV): *m/z* (%) = 288 (M^+, 32), 243 (16), 204 (99), 203 (100), 175 (97), 147 (39), 129 (31), 77 (8), 57 (17). HRMS (EI, 70 eV): Calcd for $C_{17}H_{20}O_4$ (M^+) 288.13561, found 288.13484.

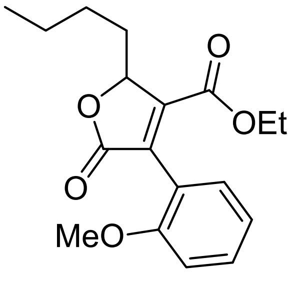
Ethyl 2-butyl-5-oxo-4-(4-tolyl)-2,5-dihydro-furan-3-carboxylate (**34b**):



(GP 7) Starting with **33a** (220 mg, 0.61 mmol), K_3PO_4 (194 mg, 0.91 mmol), 4-tolylboronic acid (108 mg, 0.79 mmol), $Pd(PPh_3)_4$ (21 mg, 0.018 mmol), and 1,4-dioxane (3.0 mL), **34b** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 100:1 → 20:1) as a colourless oil (84 mg, 45%); R_f 0.24 (*n*-hexane/EtOAc = 10:1). Reaction time: 6 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, ^3J = 7.2 Hz, 3H, $CH_2CH_2CH_3$), 1.25 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 1.29 – 1.52 (m, 4H, $CH_2CH_2CH_3$), 1.64 – 1.76 (m, 1H, $CHCH_AH_B$), 2.04 – 2.17 (m, 1H, $CHCH_AH_B$), 2.38 (s, 3H, $ArCH_3$), 4.27 (m, 2H, OCH_2CH_3), 5.25 (dd, $^3J_1$ = 7.8 Hz, $^3J_2$ = 3.3 Hz, 1H, OCH), 7.22 (d, ^3J = 8.2 Hz , 2H, Ar), 7.48 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.8, 13.9 (CH_2CH_3), 21.5 ($ArCH_3$), 22.3, 26.7, 32.5 ($(CH_2)_3$), 61.8 (OCH_2CH_3), 80.9 (OCH), 125.5 (C), 128.7, 129.5 (CH_{Ar}), 135.5, 140.2, 148.1 (C), 162.5, 171.4 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2959 (m), 2932 (m), 2873 (w), 1765 (s), 1729 (s), 1718 (s), 1376 (w), 1225 (m), 1177 (m), 1015 (m). MS (EI, 70 eV): *m/z* (%) = 302 (M^+, 69), 257 (23), 229 (25), 218 (99), 217 (99), 189 (100), 161 (76), 143 (37), 115 (30), 91 (11), 57 (21). Anal. Calcd for $C_{18}H_{22}O_4$ (302.36): C, 71.50; H, 7.33. Found: C, 71.34; H, 7.41.

Ethyl 2-butyl-4-(2-methoxyphenyl)-5-oxo-2,5-dihydro-furan-3-carboxylate (**34c**):

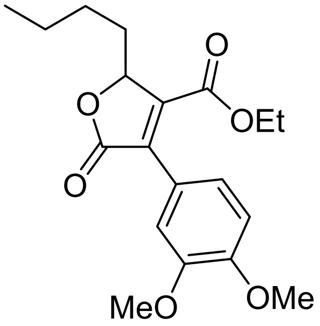


(GP 7) Starting with **33a** (211 mg, 0.59 mmol), K_3PO_4 (186 mg, 0.88 mmol), 2-methoxyphenylboronic acid (116 mg, 0.76 mmol), $Pd(PPh_3)_4$ (20 mg, 0.017 mmol), and 1,4-dioxane (3.0 mL), **34c** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 1:0 → 15:1) as a slightly yellow solid (44 mg, 24%). Mp 71 – 72 °C; R_f 0.13 (*n*-hexane/EtOAc = 10:1). Reaction time: 6 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, ^3J = 7.1 Hz, 3H, $CH_2CH_2CH_3$), 1.14 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 1.30 – 1.50 (m, 4H, $CH_2CH_2CH_3$), 1.63 – 1.80 (m, 1H, $CHCH_AH_B$), 2.03 – 2.17 (m, 1H, $CHCH_AH_B$), 3.76 (m, 3H, OCH_3), 4.19 (m, 2H, OCH_2), 5.30 (dd, $^3J_1$ = 7.7 Hz, $^3J_2$ = 3.3 Hz, 1H, OCH), 6.89 (d, ^3J = 8.0 Hz, 1H, Ar), 7.03 (dt, ^3J = 7.5 Hz, ^4J = 1.0 Hz, 1H, Ar), 7.35 – 7.44 (m, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.75, 13.83 (CH_2CH_3), 22.3, 26.6, 32.3 ($(CH_2)_3$), 55.3 (OCH_3), 61.3 (OCH_2), 81.0 (OCH), 110.6 (CH_{Ar}), 118.2 (C), 120.3, 130.4, 130.9 (CH_{Ar}), 132.1, 151.0, 156.9 (C), 162.5, 171.5 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2958 (m), 2936 (m), 2873 (w), 1762 (s), 1723 (s), 1494 (m), 1467 (m), 1381 (m), 1253 (m), 1240 (m), 1172 (m), 1016 (m), 763 (m). MS (EI, 70 eV): *m/z* (%) = 318 (M^+, 81), 272 (53), 257

(22), 234 (64), 233 (100), 205 (92), 177 (13), 159 (33), 57 (15). HRMS (EI, 70 eV): Calcd for $C_{18}H_{22}O_5$ (M^+) 318.14618, found 318.14636.

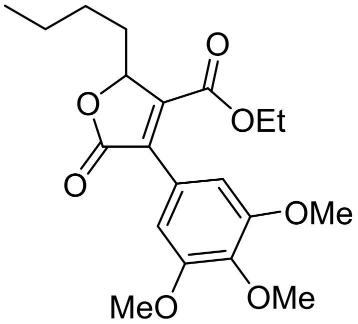
Ethyl 2-butyl-4-(3,4-dimethoxyphenyl)-5-oxo-2,5-dihydro-furan-3-carboxylate (**34d**):



(GP 7) Starting with **33a** (195 mg, 0.54 mmol), K_3PO_4 (172 mg, 0.81 mmol), 3,4-dimethoxyphenylboronic acid (128 mg, 0.70 mmol), $Pd(PPh_3)_4$ (19 mg, 0.016 mmol), and 1,4-dioxane (3.0 mL), **34d** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 5:1) as a slightly turbid yellow oil (105 mg, 56%); R_f 0.31 (*n*-hexane/EtOAc = 3:1). Reaction time: 6 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, ^3J = 7.1 Hz, 3H, $CH_2CH_2CH_3$), 1.29 (t, ^3J = 7.2 Hz, 3H, OCH_2CH_3), 1.32 – 1.53 (m, 4H, $CH_2CH_2CH_3$), 1.62 – 1.76 (m, 1H, $CHCH_AH_B$), 2.03 – 2.14 (m, 1H, $CHCH_AH_B$), 3.91 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.30 (m, 2H, OCH_2), 5.25 (dd, $^3J_1$ = 7.9 Hz, $^3J_2$ = 3.3 Hz, 1H, OCH), 6.91 (d, ^3J = 8.2 Hz, 1H, Ar), 7.23 (d, ^4J = 2.0 Hz, 1H, Ar), 7.25 (dd, ^3J = 8.2 Hz, ^4J = 2.0 Hz, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 13.9 (CH_2CH_3), 22.2, 26.6, 32.4 ($(CH_2)_3$), 55.76, 55.80 (OCH_3), 61.7 (OCH_2), 80.7 (OCH), 110.3, 112.6 (CH_{Ar}), 120.8 (C), 123.0 (CH_{Ar}), 134.6, 147.2, 148.2, 150.4 (C), 162.5, 171.3 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3007 (m), 2957 (s), 2935 (m), 2869 (m), 1763 (s), 1728 (s), 1603 (m), 1515 (s), 1466 (m), 1327 (m), 1262 (s), 1208 (s), 1143 (s), 1024 (s), 760 (m). MS (EI, 70 eV): *m/z* (%) = 348 (M^+, 100), 302 (28), 275 (32), 264 (49), 263 (94), 236 (33), 235 (90), 207 (72), 189 (17), 57 (13). Anal. Calcd for $C_{19}H_{24}O_6$ (348.39): C, 65.50; H, 6.94. Found: C, 65.73; H, 7.08.

Ethyl 2-butyl-5-oxo-4-(3,4,5-trimethoxyphenyl)-2,5-dihydro-furan-3-carboxylate (**34e**):

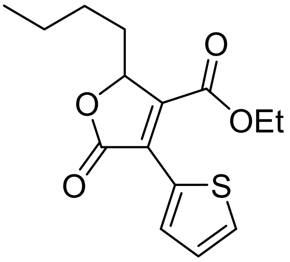


(GP 7) Starting with **33a** (154 mg, 0.43 mmol), K_3PO_4 (136 mg, 0.64 mmol), 3,4,5-trimethoxyphenylboronic acid (118 mg, 0.56 mmol), $Pd(PPh_3)_4$ (15 mg, 0.013 mmol), and 1,4-dioxane (2.5 mL), **34e** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 10:1 → 5:1) as a yellow oil (104 mg, 64%); R_f 0.25 (*n*-hexane/EtOAc = 3:1). Reaction time: 6 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.93 (t, ^3J = 7.2 Hz, 3H, $CH_2CH_2CH_3$), 1.28 (t, ^3J = 7.1 Hz, 3H, OCH_2CH_3), 1.32 – 1.54 (m, 4H, $CH_2CH_2CH_3$), 1.64 – 1.80 (m, 1H, $CHCH_AH_B$), 2.03 – 2.14 (m, 1H, $CHCH_AH_B$), 3.88 (s, 6H, OCH_3), 3.89 (s, 3H, OCH_3), 4.30 (m, 2H, OCH_2), 5.26 (dd, $^3J_1$ = 7.9 Hz, $^3J_2$ = 3.3 Hz, 1H, OCH), 6.89 (s, 2H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ =

13.7, 13.9 (CH_2CH_3), 22.2, 26.6, 32.4 ($(CH_2)_3$), 56.1, 60.7 (OCH_3), 61.8 (OCH_2), 80.7 (OCH), 106.9 (CH_{Ar}), 123.5, 134.5, 139.4, 148.6, 152.7 (C), 162.4, 171.0 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2959 (m), 2938 (m), 2873 (w), 1764 (s), 1726 (m), 1582 (m), 1507 (m), 1461 (m), 1418 (m), 1294 (m), 1246 (m), 1211 (m), 1129 (s), 1010 (m). MS (EI, 70 eV): *m/z* (%) = 378 (M^+, 100), 332 (19), 305 (26), 293 (84), 265 (77), 237 (39), 57 (16). Anal. Calcd for $C_{20}H_{26}O_7$ (378.42): C, 63.48; H, 6.93. Found: C, 63.46; H, 7.08.

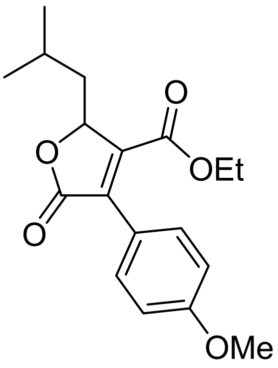
Ethyl 2-butyl-5-oxo-4-thien-2-yl-2,5-dihydro-furan-3-carboxylate (**34f**):



(GP 7) Starting with **33a** (188 mg, 0.52 mmol), K_3PO_4 (166 mg, 0.78 mmol), thiophene-2-boronic acid (87 mg, 0.68 mmol), $Pd(PPh_3)_4$ (18 mg, 0.016 mmol), and 1,4-dioxane (3.0 mL), **34f** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 20:1) as a yellow oil (101 mg, 66%); R_f 0.32 (*n*-hexane/EtOAc = 10:1). Reaction time: 4 h.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (t, ^3J = 7.1 Hz, 3H, $CH_2CH_2C\mathit{H}_3$), 1.25 – 1.50 (m, 7H, $OCH_2C\mathit{H}_3$, $C\mathit{H}_2C\mathit{H}_2CH_3$), 1.60 – 1.75 (m, 1H, $CHC\mathit{H}_AH_B$), 2.01 – 2.13 (m, 1H, $CHCH_A\mathit{H}_B$), 4.40 (m, 2H, OCH_2), 5.27 (dd, $^3J_1$ = 7.7 Hz, $^3J_2$ = 3.2 Hz, 1H, OCH), 7.14 (dd, $^3J_1$ = 5.1 Hz, $^3J_2$ = 3.9 Hz, 1H, Ar), 7.58 (dd, $^3J_1$ = 5.1 Hz, $^3J_2$ = 1.0 Hz, 1H, Ar), 8.31 (dd, $^3J_1$ = 3.9 Hz, $^3J_2$ = 1.0 Hz, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 14.0 (CH_3), 22.2, 26.6, 32.6 ($(CH_2)_3$), 61.9 (OCH_2), 80.9 (OCH), 127.1 (CH_{Ar}), 128.1, 129.5 (C), 131.1, 132.9 (CH_{Ar}), 142.5 (C), 162.3, 170.5 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2959 (m), 2932 (m), 2872 (w), 1764 (s), 1721 (s), 1306 (m), 1237 (s), 1204 (s), 1136 (m), 1016 (m). MS (EI, 70 eV): *m/z* (%) = 294 (M^+, 65), 237 (26), 210 (88), 209 (99), 181 (100), 153 (44), 135 (21), 57 (23). HRMS (EI, 70 eV): Calcd for $C_{15}H_{18}O_4S$ (M^+) 294.09203, found 294.09169.

Ethyl 2-isobutyl-4-(4-methoxyphenyl)-5-oxo-2,5-dihydro-furan-3-carboxylate (**34g**):

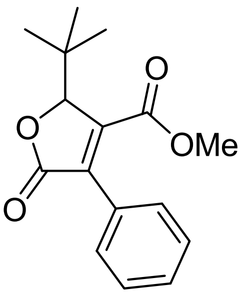


(GP 7) Starting with **33b** (40 mg, 0.11 mmol), K_3PO_4 (35 mg, 0.16 mmol), 4-methoxyphenylboronic acid (22 mg, 0.14 mmol), $Pd(PPh_3)_4$ (6 mg, 0.005 mmol), and 1,4-dioxane (1.5 mL), **34g** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 20:1) as a colourless solid (20 mg, 57%). Mp 56 – 58 °C; R_f 0.13 (*n*-heptane/EtOAc = 10:1). Reaction time: 8 h.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.99 (d, ^3J = 6.4 Hz, 3H, $CHC\mathit{H}_3$), 1.04 (d, ^3J = 6.4 Hz, 3H, $CHC\mathit{H}_3$), 1.27 (t, ^3J = 7.0 Hz, 3H, $OCH_2C\mathit{H}_3$), 1.52 (ddd, ^2J = 14.0

Hz, $^3J_1$ = 9.8 Hz, $^3J_2$ = 4.3 Hz, 1H, CHCH_AH$_B$), 1.84 (ddd, ^2J = 14.0 Hz, $^3J_1$ = 9.2 Hz, $^3J_2$ = 2.7 Hz, 1H, CHCH$_A$$H_B$), 1.92 – 2.05 (m, 1H, C$H$(CH$_3$)$_2$), 3.84 (s, 3H, OCH$_3$), 4.28 (m, 2H, OCH$_2$), 5.27 (dd, $^3J_1$ = 9.8 Hz, $^3J_2$ = 2.7 Hz, 1H, OCH), 6.94 (m, 2H, Ar), 7.58 (m, 2H, Ar). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 13.9 (OCH$_2$$CH_3$), 21.6, 23.5, 25.3 (CH(CH$_3$)$_2$), 42.3 (CHCH$_2$), 55.3 (OCH$_3$), 61.8 (OCH$_2$), 79.7 (OCH), 113.5 (CH$_{Ar}$), 120.8 (C), 131.4 (CH$_{Ar}$), 134.8, 147.5 (C), 161.0, 162.5 (C, CO), 171.6 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2950 (s), 2867 (m), 1747 (s), 1712 (s), 1607 (s), 1514 (s), 1300 (s), 1261 (s), 1247 (s), 1190 (s), 1184 (s), 1018 (s), 1001 (s), 769 (m). MS (EI, 70 eV): *m/z* (%) = 318 (M$^+$, 59), 272 (25), 234 (57), 233 (100), 205 (91), 177 (68), 57 (15). HRMS (EI, 70 eV): Calcd for $C_{18}H_{22}O_5$ (M$^+$) 318.14618, found 318.14633.

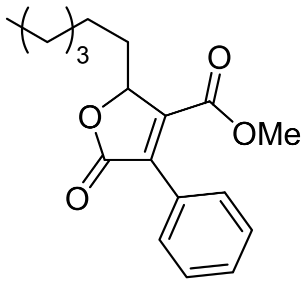
Methyl 2-*tert*-butyl-5-oxo-4-phenyl-2,5-dihydro-furan-3-carboxylate (**34h**):



(GP 7) Starting with **33c** (295 mg, 0.85 mmol), K_3PO_4 (271 mg, 1.28 mmol), phenylboronic acid (135 mg, 1.11 mmol), Pd(PPh$_3$)$_4$ (30 mg, 0.026 mmol), and 1,4-dioxane (4.0 mL), **34h** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 20:1 → 10:1) as a colourless oil (201 mg, 86%); R_f 0.17 (*n*-heptane/EtOAc = 10:1). Reaction time: 8 h.

^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.03 (s, 9H, C(CH$_3$)$_3$), 3.79 (s, 3H, OCH$_3$), 5.05 (s, 1H, OCH), 7.38 – 7.45 (m, 3H, Ph), 7.53 – 7.62 (m, 2H, Ph). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 25.5 (C(CH$_3$)$_3$), 36.3 (C(CH$_3$)$_3$), 52.7 (OCH$_3$), 88.0 (OCH), 128.29 (C), 128.34, 129.0, 129.9 (CH$_{Ar}$), 133.7, 149.3 (C), 164.7, 170.7 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2967 (m), 2911 (w), 2874 (w), 1767 (s), 1735 (s), 1437 (m), 1369 (m), 1319 (m), 1232 (s), 1166 (s), 1117 (m), 1043 (m), 977 (m), 696 (m). MS (EI, 70 eV): *m/z* (%) = 274 (M$^+$, 2), 218 (100), 186 (99), 129 (50), 57 (86). HRMS (EI, 70 eV): Calcd for $C_{16}H_{18}O_4$ (M$^+$) 274.11996, found 274.11928.

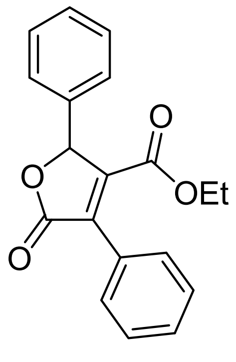
Methyl 2-hexyl-5-oxo-4-phenyl-2,5-dihydro-furan-3-carboxylate (**34i**):



(GP 7) Starting with **33d** (208 mg, 0.56 mmol), K_3PO_4 (177 mg, 0.83 mmol), phenylboronic acid (88 mg, 0.72 mmol), $Pd(PPh_3)_4$ (19 mg, 0.016 mmol), and 1,4-dioxane (3.0 mL), **34i** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 1:0 → 50:1) as a slightly yellow oil (103 mg, 61%); R_f 0.30 (*n*-hexane/EtOAc = 10:1). Reaction time: 4 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, ^3J = 6.8 Hz, 3H, CH_2CH_3), 1.20 – 1.42 (m, 6H, CH_2), 1.48 (m, 2H, CH_2), 1.63 – 1.76 (m, 1H, $CHCH_AH_B$), 2.03 – 2.15 (m, 1H, $CHCH_AH_B$), 3.78 (s, 3H, OCH_3), 5.26 (dd, $^3J_1$ = 7.9 Hz, $^3J_2$ = 3.3 Hz, 1H, OCH), 7.38 – 7.46 (m, 3H, Ph), 7.51 – 7.58 (m, 2H, Ph). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 22.4, 24.5, 28.8, 31.4, 32.7 (CH_2), 52.4 (OCH_3), 80.8 (OCH), 128.0 (CH_{Ar}), 128.3 (C), 129.4, 129.8 (CH_{Ar}), 135.6, 148.4 (C), 162.7, 171.0 (CO). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2955 (s), 2929 (s), 2858 (m), 1766 (s), 1733 (s), 1437 (m), 1225 (s), 1170 (s), 982 (m), 695 (m). MS (EI, 70 eV): *m/z* (%) = 302 (M^+, 36), 273 (26), 190 (99), 189 (100), 186 (34), 172 (12), 161 (66), 129 (49), 113 (67), 85 (16), 57 (8). Anal. Calcd for $C_{18}H_{22}O_4$ (302.36): C, 71.50; H, 7.33. Found: C, 71.48; H, 7.45.

Ethyl 5-oxo-2,4-diphenyl-2,5-dihydro-furan-3-carboxylate (**34j**):

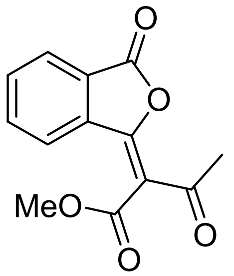


(GP 7) Starting with **33e** (190 mg, 0.50 mmol), K_3PO_4 (159 mg, 0.75 mmol), phenylboronic acid (79 mg, 0.65 mmol), $Pd(PPh_3)_4$ (17 mg, 0.015 mmol), and 1,4-dioxane (2.5 mL), **34j** was isolated by column chromatography (silica gel; *n*-hexane/EtOAc = 1:0 → 20:1) as a slightly yellow oil (70 mg, 45%). Mp 110 – 112 °C; R_f 0.13 (*n*-hexane/EtOAc = 10:1). Reaction time: 4 h.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, ^3J = 7.1 Hz, 3H, CH_3), 4.11 (m, 2H, OCH_2), 6.20 (s, 1H, OCH), 7.30 – 7.42 (m, 5H, Ph), 7.42 – 7.48 (m, 3H, Ph), 7.63 – 7.71 (m, 2H, Ph). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.6 (CH_3), 61.8 (OCH_2), 82.2 (OCH), 127.3, 128.05 (CH_{Ar}), 128.12 (C), 128.9, 129.6, 129.7, 130.1 (CH_{Ar}), 133.8, 134.8, 148.4 (C), 161.8, 171.2 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2981 (m), 1758 (s), 1729 (m), 1651 (m), 1494 (m), 1446 (m), 1369 (m), 1288 (m), 1220 (s), 1117 (m), 1014 (s), 792 (m), 692 (m). MS (EI, 70 eV): *m/z* (%) = 308 (M^+, 23), 279 (22), 235 (34), 203 (22), 175 (21), 105 (100), 77 (18). HRMS (EI, 70 eV): Calcd for $C_{19}H_{16}O_4$ (M^+) 308.10431, found 308.10351.

8.3.7 Alkylidene-Isobenzofurans

(*E*)-Methyl 3-oxo-2-(3-oxo-3*H*-isobenzofuran-1-ylidene)-butyrate (**36a**):

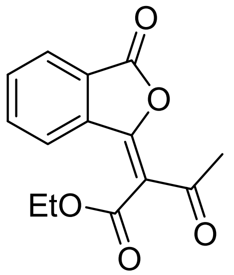


Method 1: (GP 8) Starting with phthaloyl chloride (385 mg, 1.90 mmol), CH_2Cl_2 (6 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.21 mL, 1.9 mmol), and **2a** (392 mg, 2.08 mmol), **36a** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 3:1) as a colourless solid (223 mg, 48%). Mp 119 – 121 °C; R_f 0.20 (*n*-heptane/EtOAc = 3:1).
Reaction time: 20 h.

Method 2: To a CH_2Cl_2 solution (150 mL) of phthaloyl chloride (641 mg, 3.16 mmol) was added 1,3-bis-silyl enol ether **3b** (941 mg, 3.61 mmol) at –78 °C in the presence of molecular sieves (4 Å, 4.0 g). $TiCl_4$ (0.80 mL, 7.3 mmol) was subsequently added and the reaction mixture was allowed to warm to 20 °C in 16 h. Water (50 mL) and hydrochloric acid (10%, 150 mL) were added. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic extracts were washed with brine (100 ml), dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography (silica gel; *n*-hexane/EtOAc = 10:1) to yield **36a** as a yellow solid (110 mg, 14%). Reaction time: 16 h.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.65 (s, 3H, CCH_3), 3.94 (s, 3H, OCH_3), 7.74 (td, ^3J = 7.3 Hz, ^4J = 1.2 Hz, 1H, Ar), 7.81 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, Ar), 8.00 – 8.05 (m, 1H, Ar), 8.14 – 8.19 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.8 ($\mathit{C}H_3CO$), 53.0 (OCH_3), 116.0, 125.3 (C), 126.0, 126.1, 133.0, 135.5 (CH_{Ar}), 136.2, 153.0, 164.1, 164.6 (C), 195.5 ($CH_3\mathit{C}O$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2952 (w), 1790 (s), 1726 (s), 1706 (s), 1641 (s), 1356 (m), 1286 (m), 1235 (s), 1063 (s), 1014 (s), 973 (m), 763 (s), 695 (s). MS (GC-EI, 70 eV): *m/z* (%) = 246 (M^+, 25), 231 (100), 204 (74), 187 (53), 174 (70), 173 (75), 172 (65), 163 (85), 104 (74), 76 (57), 43 (65). Anal. Calcd for $C_{13}H_{10}O_5$ (246.22): C, 63.42; H, 4.09. Found: C, 63.18; H, 4.05.

(*E*)-Ethyl 3-oxo-2-(3-oxo-3*H*-isobenzofuran-1-ylidene)-butyrate (**36b**):

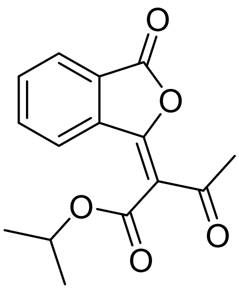


(GP 8) Starting with phthaloyl chloride (417 mg, 2.05 mmol), CH_2Cl_2 (6 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.23 mL, 2.1 mmol), and **2b** (419 mg, 2.07 mmol), **36b** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 3:1) as a slightly yellow solid (361 mg, 68%). Mp 117 – 119 °C; R_f 0.22 (*n*-heptane/EtOAc = 3:1). Reaction time: 23 h.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.36 (t, ^3J = 7.1 Hz, 3H, CH_2CH_3), 2.62 (s, 3H, $COCH_3$), 4.40 (q, ^3J = 7.1 Hz, 2H, OCH_2), 7.72 (td, ^3J = 7.3 Hz, ^4J = 1.2 Hz, 1H, Ar), 7.79 (td, ^3J = 7.6 Hz, ^4J = 1.5 Hz, 1H, Ar), 7.99 (ddd, ^3J = 7.3 Hz, ^4J = 1.5 Hz, ^5J = 0.7 Hz, 1H, Ar), 8.15 (ddd, ^3J = 7.6 Hz, ^4J = 1.2 Hz, ^5J = 0.7 Hz, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9 (CH_2CH_3), 31.8 ($COCH_3$), 62.2 (OCH_2), 116.3, 125.3 (C), 125.9, 126.1, 132.9, 135.4 (CH_{Ar}), 136.3, 152.7, 164.1, 164.2 (C), 195.5 ($COCH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2997 (w), 1804 (s), 1742 (s), 1635 (s), 1473 (m), 1370 (s), 1313 (s), 1290 (s), 1235 (s), 1053 (s), 1004 (s), 900 (m). MS (GC-EI, 70 eV): *m/z* (%) = 260 (M^+, 9), 245 (34), 218 (14), 174 (66), 173 (100), 172 (24), 104 (22), 89 (18), 76 (19), 43 (30). Anal. Calcd for $C_{14}H_{12}O_5$ (260.24): C, 64.61; H, 4.65. Found: C, 64.34; H, 4.63.

This compound (or its isomer) has been prepared before but no comparable spectroscopic data are given. For the configuration of the exocyclic double bond no assignment was made in the literature.[124]

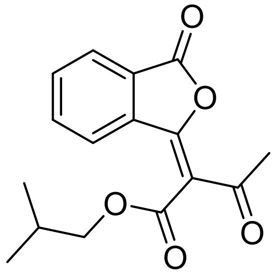
(*E*)-Isopropyl 3-oxo-2-(3-oxo-3*H*-isobenzofuran-1-ylidene)-butyrate (36c):



(GP 8) Starting with phthaloyl chloride (399 mg, 1.97 mmol), CH_2Cl_2 (6 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.22 mL, 2.0 mmol), and **2c** (435 mg, 2.01 mmol), **36c** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 4:1) as a colourless solid (244 mg, 45%, mixture of isomers: *E*:*Z* = 10:1). Mp 79 – 80 °C; R_f 0.26 (*n*-heptane/EtOAc = 3:1). Reaction time: 20 h.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.34 (d, ^3J = 6.3 Hz, 6H, $CH(CH_3)_2$), 2.61 (s, 3H, $COCH_3$), 5.27 (sep, ^3J = 6.3 Hz, 1H, OCH), 7.71 (td, ^3J = 7.4 Hz, ^4J = 1.2 Hz, 1H, Ar), 7.78 (td, ^3J = 7.4 Hz, ^4J = 1.5 Hz, 1H, Ar), 7.99 (ddd, ^3J = 7.4 Hz, ^4J = 1.5 Hz, ^5J = 0.7 Hz, 1H, Ar), 8.15 (ddd, ^3J = 7.4 Hz, ^4J = 1.2 Hz, ^5J = 0.7 Hz, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 ($CH(CH_3)_2$), 31.8 ($COCH_3$), 70.2 (OCH), 116.7, 125.3 (C), 125.9, 126.1, 132.8, 135.3 (CH_{Ar}), 136.4, 152.4, 163.8, 164.2 (C), 195.4 ($COCH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2991 (m), 2974 (m), 1816 (s), 1726 (s), 1665 (s), 1635 (s), 1475 (m), 1372 (s), 1309 (s), 1287 (s), 1248 (s), 1052 (s), 998 (s). MS (GC-EI, 70 eV): *m/z* (%) = 274 (M^+, 7), 259 (20), 190 (44), 174 (21), 173 (100), 172 (52), 43 (59). HRMS (EI, 70 eV): Calcd for $C_{15}H_{14}O_5$ (M^+) 274.08358, found 274.08319.

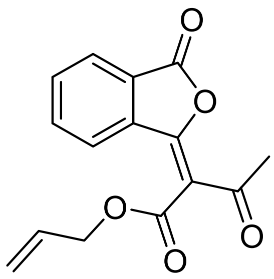
(*E*)-Isobutyl 3-oxo-2-(3-oxo-3*H*-isobenzofuran-1-ylidene)-butyrate (36d):



(GP 8) Starting with phthaloyl chloride (384 mg, 1.89 mmol), CH_2Cl_2 (6 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.21 mL, 1.9 mmol), and **2d** (452 mg, 1.96 mmol), **36d** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 5:1) as a colourless solid (262 mg, 48%, mixture of isomers: *E*:*Z* = 10:1). Mp 63 – 65 °C; R_f 0.36 (*n*-heptane/EtOAc = 3:1). Reaction time: 21 h.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.92 (d, ^3J = 6.7 Hz, 6H, $CH(CH_3)_2$), 1.99 (m, ^3J = 6.7 Hz, 1H, $CH(CH_3)_2$), 2.59 (s, 3H, CH_3CO), 4.08 (d, ^3J = 6.4 Hz, 2H, OCH_2), 7.69 (td, ^3J = 7.3 Hz, ^4J = 1.1 Hz, 1H, Ar), 7.76 (td, ^3J = 7.6, ^4J = 1.5 Hz, 1H, Ar), 7.95 (m, 1H, Ar), 8.16 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9 ($CH(CH_3)_2$), 27.5 ($CH(CH_3)_2$), 31.6 ($COCH_3$), 72.1 (OCH_2), 116.3, 125.2 (C), 125.9, 126.0, 132.8, 135.3 (CH_{Ar}), 136.2, 152.7, 164.03, 164.05 (C), 195.4 ($COCH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2969 (m), 1790 (s), 1706 (s), 1640 (s), 1473 (m), 1280 (m), 1242 (s), 1063 (s), 1011 (s), 969 (m). MS (EI, 70 eV): *m/z* (%) = 288 (M^+, 2), 273 (15), 190 (21), 174 (25), 173 (100), 172 (34), 57 (16), 43 (28). Anal. Calcd for $C_{16}H_{16}O_5$ (288.30): C, 66.66; H, 5.59. Found: C, 66.28; H, 5.61.

(*E*)-Allyl 3-oxo-2-(3-oxo-3*H*-isobenzofuran-1-ylidene)-butyrate (36e):

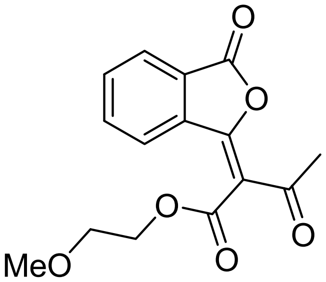


(GP 8) Starting with phthaloyl chloride (397 mg, 1.96 mmol), CH_2Cl_2 (6 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.22 mL, 2.0 mmol), and **2e** (445 mg, 2.08 mmol), **36e** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 3:1) as a colourless solid (314 mg, 59%, mixture of isomers: *E*:*Z* = 10:1). Mp 94 – 95 °C; R_f 0.23 (*n*-heptane/EtOAc = 3:1). Reaction time: 23 h.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.63 (s, 3H, CH_3), 4.83 (dt, ^3J = 5.8 Hz, $^4J_1 \approx {}^4J_2 \approx$ 1.3 Hz, 2H, OCH_2), 5.30 (dq, ^3J = 10.4 Hz, $^4J \approx {}^2J \approx$ 1.3 Hz, 1H, CH_AH_B=CH), 5.40 (dq, ^3J = 17.3 Hz, $^4J \approx {}^2J \approx$ 1.3 Hz, 1H, CH_AH_B=CH), 5.97 (ddt, $^3J_1$ = 17.3 Hz, $^3J_2$ = 10.4 Hz, $^3J_3$ = 5.8 Hz, 1H, CH_2=CH), 7.72 (td, ^3J = 7.3 Hz, ^4J = 1.3 Hz, 1H, Ar), 7.79 (td, ^3J = 7.3 Hz, ^4J = 1.5 Hz, 1H, Ar), 7.97 – 8.02 (m, 1H, Ar), 8.14 – 8.18 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.8 (CH_3), 66.6 (OCH_2), 116.0 (C), 119.5 (CH_2=CH), 125.2 (C), 126.1 (2 CH), 130.9, 133.0, 135.4 (CH), 136.2, 153.0, 163.8, 164.0 (C), 195.4 ($COCH_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 1804 (s), 1735 (s), 1665 (m), 1635 (s), 1373 (m), 1310 (m), 1288 (s), 1234 (s), 1052 (s), 993 (s), 894 (m). MS (GC-EI, 70 eV): *m/z* (%) = 272 (M^+, 1), 212 (23), 174 (30), 173 (100), 168 (40), 146

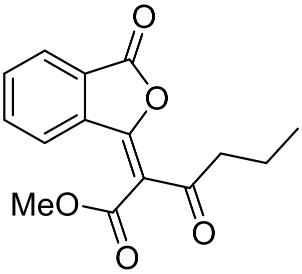
(30), 104 (25), 89 (21), 76 (31), 43 (53), 41 (63). Anal. Calcd for $C_{15}H_{12}O_5$ (272.25): C, 66.17; H, 4.44. Found: C, 65.88; H, 4.43.

(*E*)-2-Methoxy-ethyl 3-oxo-2-(3-oxo-3*H*-isobenzofuran-1-ylidene)-butyrate (**36f**):



(GP 8) Starting with phthaloyl chloride (365 mg, 1.80 mmol), CH_2Cl_2 (6 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.20 mL, 1.8 mmol), and **2f** (448 mg, 1.93 mmol), **36f** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 2:1) as a yellow solid (194 mg, 37%, mixture of isomers: *E*:*Z* = 5:1). Mp 81 – 82 °C; R_f 0.08 (*n*-heptane/EtOAc = 3:1). Reaction time: 16 h. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.64 (s, 3H, CCH_3), 3.38 (s, 3H, OCH_3), 3.68 (m, 2H, $CH_3OC\mathit{H}_2$), 4.51 (m, 2H, $COOCH_2$), 7.69 – 7.82 (m, 2H, Ar), 7.98 – 8.02 (m, 1H, Ar), 8.14 – 8.19 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.8 ($\mathit{C}H_3CO$), 58.9 (OCH_3), 65.0, 70.0 (CH_2), 116.0, 125.2 (C), 126.07, 126.09, 133.0, 135.4 (CH_{Ar}), 136.4, 152.9, 164.1, 164.3 (C), 195.3 ($CH_3\mathit{C}O$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2931 (m), 2894 (m), 1801 (s), 1740 (s), 1636 (s), 1368 (s), 1290 (s), 1240 (s), 1128 (s), 1055 (s), 991 (s). MS (GC-EI, 70 eV): *m/z* (%) = 290 (M^+, 0.5), 275 (10), 247 (20), 216 (17), 173 (100), 104 (14), 76 (16), 59 (32), 58 (33), 43 (49). HRMS (EI, 70 eV): Calcd for $C_{15}H_{14}O_6$ (M^+) 290.07849, found 290.07787.

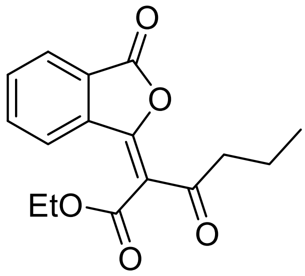
(*E*)-Methyl 3-oxo-2-(3-oxo-3*H*-isobenzofuran-1-ylidene)-caproate (**36g**):



(GP 8) Starting with phthaloyl chloride (397 mg, 1.96 mmol), CH_2Cl_2 (6 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.22 mL, 2.0 mmol), and **2g** (443 mg, 2.04 mmol), **36g** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 4:1) as a colourless solid (245 mg, 46%). Mp 79 – 80 °C; R_f 0.24 (*n*-heptane/EtOAc = 3:1). Reaction time: 20 h. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.95 (t, ^3J = 7.3 Hz, 3H, $CH_2C\mathit{H}_3$), 1.69 (sxt, ^3J = 7.3 Hz, 2H, $C\mathit{H}_2CH_3$), 2.85 (t, ^3J = 7.3 Hz, 2H, $COCH_2$), 3.87 (s, 3H, OCH_3), 7.68 (td, ^3J = 7.5 Hz, ^4J = 1.1 Hz, 1H, Ar), 7.76 (td, ^3J = 7.7 Hz, ^4J = 1.4 Hz, 1H, Ar), 7.94 (m, 1H, Ar), 8.27 (m, 1H, Ar). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 13.4 ($CH_2\mathit{C}H_3$), 16.9 ($\mathit{C}H_2CH_3$), 45.6 ($CO\mathit{C}H_2$), 52.7 (OCH_3), 116.0, 125.2 (C), 125.8, 126.4, 132.8, 135.4 (CH_{Ar}), 136.0, 152.8, 164.1, 164.4 (C), 198.3 ($\mathit{C}OCH_2$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2968 (w), 1819 (s), 1732 (s), 1659 (s), 1638 (s), 1376 (m), 1313 (m), 1279 (s), 1250 (s), 1088 (m), 1023 (s), 978 (s). MS (GC-EI, 70 eV): *m/z* (%) =

274 (M^+, 0.4), 231 (100), 187 (32), 173 (10), 163 (47), 104 (18), 76 (15), 59 (12). Anal. Calcd for $C_{15}H_{14}O_5$ (274.27): C, 65.69; H, 5.15. Found: C, 65.49; H, 5.14.

(*E*)-Ethyl 3-oxo-2-(3-oxo-3*H*-isobenzofuran-1-ylidene)-caproate (**36h**):



(GP 8) Starting with phthaloyl chloride (400 mg, 1.97 mmol), CH_2Cl_2 (6 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.22 mL, 2.0 mmol), and **2h** (480 mg, 2.08 mmol), **36h** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 5:1) as a colourless solid (232 mg, 41%, mixture of isomers: *E*:*Z* = 10:1). Mp 62 – 63 °C; R_f 0.31 (*n*-heptane/EtOAc = 3:1). Reaction time: 20 h.

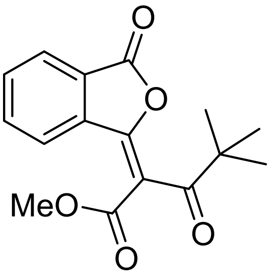
^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.96 (t, ^3J = 7.3 Hz, 3H, $CH_2CH_2CH_3$), 1.32 (t, ^3J = 7.2 Hz, 3H, OCH_2CH_3), 1.71 (sxt, ^3J = 7.3 Hz, 2H, $CH_2CH_2CH_3$), 2.86 (t, ^3J = 7.3 Hz, 2H, $CH_2CH_2CH_3$), 4.35 (q, ^3J = 7.2 Hz, 2H, OCH_2), 7.69 (td, ^3J = 7.3 Hz, ^4J = 1.2 Hz, 1H, Ar), 7.77 (td, ^3J = 7.6 Hz, ^4J = 1.4 Hz, 1H, Ar), 7.95 (ddd, ^3J = 7.3 Hz, ^4J = 1.4 Hz, ^5J = 0.8 Hz, 1H, Ar), 8.30 (m, 1H, Ar). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 13.5, 13.9 (CH_3), 16.9 ($CH_2CH_2CH_3$), 45.6 (CH_2CO), 62.0 (OCH_2), 116.4, 125.3 (C), 125.8, 126.4, 132.7, 135.3 (CH_{Ar}), 136.1, 152.5, 163.9, 164.2 (C), 198.3 (CH_2CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2966 (m), 2934 (w), 2875 (w), 1791 (s), 1710 (s), 1638 (s), 1472 (m), 1278 (m), 1231 (s), 1045 (s), 981 (s), 692 (m). MS (GC-EI, 70 eV): *m/z* (%) = 288 (M^+, 0.7), 246 (13), 245 (88), 174 (15), 173 (100), 104 (11), 89 (14), 76 (11). Anal. Calcd for $C_{16}H_{16}O_5$ (282.68): C, 66.66; H, 5.59. Found: C, 66.60; H, 5.68.

(*E*)-Methyl 4,4-dimethyl-3-oxo-2-(3-oxo-3*H*-isobenzofuran-1-ylidene)-valerate (**36i$_1$**) and **(*Z*)-Methyl (3-oxo-3*H*-isobenzofuran-1-ylidene)-acetate** (**36i$_2$**):

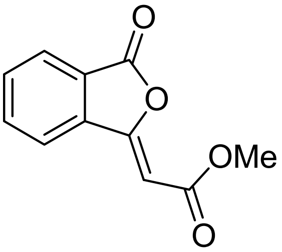
(GP 8) Starting with phthaloyl chloride (403 mg, 1.99 mmol), CH_2Cl_2 (6 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.22 mL, 2.0 mmol), and **2i** (536 mg, 2.33 mmol), **36i$_1$** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 5:1) as a colourless solid (141 mg, 25%). Mp 143 – 145 °C; R_f 0.33 (*n*-heptane/EtOAc = 3:1).

Compound **36i$_2$** was isolated from a second fraction as a colourless solid (69 mg, 17%, mixture of isomers: *E*:*Z* = 1:10). Mp 166 – 167 °C; R_f 0.16 (*n*-heptane/EtOAc = 3:1).

Reaction time: 16 h.



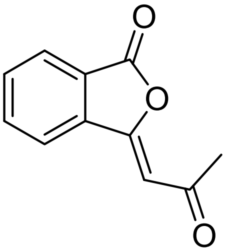
36i$_1$: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.28 (s, 9H, $C(CH_3)_3$), 3.87 (s, 3H, OCH_3), 7.71 (td, ^3J = 7.5 Hz, ^4J = 0.9 Hz, 1H, Ar), 7.82 (td, ^3J = 7.7 Hz, ^4J = 1.3 Hz, 1H, Ar), 7.97 (m, 1H, Ar), 8.84 (m, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.2 ($C(\mathit{C}H_3)_3$), 45.2 ($\mathit{C}(CH_3)_3$), 52.4 (OCH_3), 116.3 (C), 125.7 (CH_{Ar}), 126.0 (C), 128.0, 132.7, 135.4 (CH_{Ar}), 135.7, 153.0, 163.6, 164.4 (C), 206.5 ($\mathit{C}OC(CH_3)_3$). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2974 (m), 2962 (m), 1792 (s), 1719 (s), 1704 (s), 1631 (s), 1474 (m), 1244 (s), 1049 (s), 969 (s). MS (CI, isobutane): *m/z* (%) = 289 ([M + 1]$^+$, 100), 257 (57), 232 (32). Anal. Calcd for $C_{16}H_{16}O_5$ (288.30): C, 66.66; H, 5.59. Found: C, 66.55; H, 5.59.



36i$_2$: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.84 (s, 3H, OCH_3), 5.89 (s, 1H, CHCO), 7.66 – 7.83 (m, 3H, Ar), 7.97 (dt, ^3J = 7.5 Hz, ^4J = 1.1 Hz, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.0 (OCH_3), 95.6 (*C*HCO), 121.2 (CH_{Ar}), 124.7 (C), 126.0, 132.4, 135.1 (CH_{Ar}), 138.9, 154.2, 164.1, 165.5 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2951 (m), 1794 (s), 1719 (s), 1682 (s), 1328 (s), 1270 (s), 1198 (s), 1157 (s), 1025 (s), 978 (s), 782 (s). MS (GC-EI, 70 eV): *m/z* (%) = 204 (M$^+$, 22), 174 (11), 173 (100), 146 (10), 89 (29). Anal. Calcd for $C_{11}H_8O_4$ (204.18): C, 64.71; H, 3.95. Found: C, 64.68; H, 3.86.

The spectroscopic data (^{1}H NMR, IR) are in accordance with those presented in the literature.[98c,125]

(*Z*)-3-(2-Oxo-propylidene)-3*H*-isobenzofuran-1-one (**36j**):



(GP 8) Starting with phthaloyl chloride (406 mg, 2.00 mmol), CH_2Cl_2 (6 mL), molecular sieves (4 Å, 0.4 g), $TiCl_4$ (0.22 mL, 2.0 mmol), and **2j** (474 mg, 2.06 mmol), **36j** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 3:1) as a yellow-brown solid (29 mg, 8%). Mp 135 – 137 °C; R_f 0.26 (*n*-heptane/EtOAc = 2:1). Reaction time: 20 h.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.64 (s, 3H, CH_3), 6.02 (s, 1H, CHCO), 7.68 – 7.84 (m, 3H, Ar), 8.00 (dt, ^3J = 7.5 Hz, $^4J \approx {}^5J \approx$ 1.1 Hz, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.4 (CH_3), 105.4, 121.6 (CH), 124.4 (C), 126.1, 132.5, 135.2 (CH), 139.2, 153.0, 165.1 (C), 196.6 (CH*C*O). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3045 (m), 2917 (m), 1793 (s), 1782 (s), 1669 (s), 1637 (m), 1368 (m), 1261 (s), 984 (s), 976 (s), 695 (m). MS (EI, 70 eV): *m/z* (%) = 188 (M$^+$, 11), 174 (11), 173 (100), 89 (29), 49 (28). HRMS (EI, 70 eV): Calcd for $C_{11}H_8O_3$ (M$^+$) 188.04680, found 188.04625. Anal. Calcd for $C_{11}H_8O_3$ (188.18): C, 70.21; H, 4.29. Found: C, 70.18; H, 4.06.

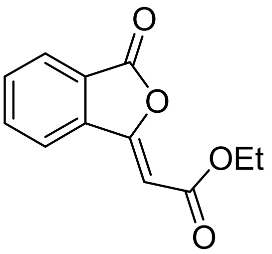
The spectroscopic data (^{1}H NMR) are in accordance with those presented in the literature.[91a]

(*Z*)-Ethyl (3-oxo-3*H*-isobenzofuran-1-ylidene)-acetate (**36k$_1$**) and
(*E*)-Ethyl (3-oxo-3*H*-isobenzofuran-1-ylidene)-acetate (**36k$_2$**):

(GP 8; varied) Starting with phthaloyl chloride (272 mg, 1.34 mmol), CH_2Cl_2 (4.5 mL), and **5a,b** (440 mg, 2.75 mmol), **36k$_1$** was isolated by column chromatography (silica gel; *n*-heptane/EtOAc = 20:1 → 3:1) as a colourless solid (36 mg, 12%). Mp 128 – 130 °C; R_f 0.19 (*n*-heptane/EtOAc = 3:1).

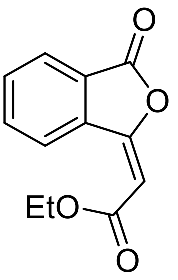
Compound **36k$_2$** was isolated from a preceding fraction (*n*-heptane/EtOAc = 20:1) as a colourless solid (12 mg, 4%). Mp 63 – 64 °C; R_f 0.45 (*n*-heptane/EtOAc = 3:1).

Reaction time: 20 h.



36k$_1$: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.34 (t, ^3J = 7.1 Hz, 3H, CH_3), 4.29 (q, ^3J = 7.1 Hz, 2H, OCH_2), 5.88 (s, 1H, CHCO), 7.65 – 7.82 (m, 3H, Ar), 7.96 (dt, ^3J = 7.4 Hz, ^4J = 1.1 Hz, 1H, Ar). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 14.2 (CH_3), 60.9 (OCH_2), 96.0 (*C*HCO), 121.2 (CH_{Ar}), 124.7 (C), 125.9, 132.3, 135.0 (CH_{Ar}), 138.9, 154.0, 163.6, 165.6 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2987 (w), 1791 (s), 1719 (s), 1676 (s), 1469 (m), 1323 (s), 1170 (s), 1157 (s), 989 (s), 781 (s). MS (GC-EI, 70 eV): *m/z* (%) = 218 (M^+, 10), 190 (17), 174 (15), 173 (100), 146 (49), 105 (10), 89 (34), 76 (11). Anal. Calcd for $C_{12}H_{10}O_4$ (218.21): C, 66.05; H, 4.62. Found: C, 65.92; H, 4.73.

The spectroscopic data (^{1}H NMR, IR) are in accordance with those presented in the literature.[91a,126]



36k$_2$: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.36 (t, ^3J = 7.1 Hz, 3H, CH_3), 4.30 (q, ^3J = 7.1 Hz, 2H, OCH_2), 6.15 (s, 1H, COCH), 7.70 (td, ^3J = 7.5 Hz, ^4J = 1.0 Hz, 1H, Ar), 7.82 (ddd, $^3J_1$ = 7.9 Hz, $^3J_2$ = 7.3 Hz, ^4J = 1.2 Hz, 1H, Ar), 7.97 (m, 1H, Ar), 9.06 (m, ^3J = 7.9 Hz, 1H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_3), 60.9 (OCH_2), 102.5 (*C*HCO), 125.3 (CH_{Ar}), 126.5 (C), 128.2, 132.5, 135.3 (CH_{Ar}), 136.1, 157.8, 165.5, 165.7 (C). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 2981 (w), 2934 (w), 1790 (s), 1714 (s), 1652 (s), 1471 (m), 1377 (m), 1243 (s), 1146 (m), 1040 (s), 783 (m). MS (CI, isobutane): *m/z* (%) = 219 ([M + 1]$^+$, 38). HRMS (CI neg., isobutane): Calcd for $C_{12}H_{10}O_4$ (M$^-$) 218.05846, found 218.05779.

The spectroscopic data (^{1}H NMR) are in accordance with those presented in the literature.[91a]

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10 Appendix

10.1 Crystallographic Data

10.1.1 Methyl 3-acetyl-6-hydroxy-5-methoxy-2-methylbenzoate

An ORTEP plot of this compound is shown in Scheme 14.

Crystal data and structure refinement for **25j**:

Empirical formula	$C_{12}H_{14}O_5$	
Formula weight	238.23	
Temperature	183(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 8.7850(7) Å	α = 90°.
	b = 7.3091(10) Å	β = 94.624(6)°.
	c = 18.1530(18) Å	γ = 90°.
Volume	1161.8(2) $Å^3$	
Z	4	
Density (calculated)	1.362 Mg/m^3	
Absorption coefficient	0.106 mm^{-1}	
F(000)	504	
Crystal size	0.05 x 0.05 x 0.04 mm^3	
Θ range for data collection	3.58 to 27.48°.	
Index ranges	$-11 \leq h \leq 11$, $-9 \leq k \leq 8$, $-22 \leq l \leq 23$	
Reflections collected	7822	
Independent reflections	2648 [R(int) = 0.1095]	
Completeness to Θ = 27.48°	99.5 %	
Absorption correction	NONE	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2648 / 0 / 210	
Goodness-of-fit on F^2	0.946	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0588, wR2 = 0.1096	
R indices (all data)	R1 = 0.1668, wR2 = 0.1466	
Largest diff. peak and hole	0.248 and -0.288 e.$Å^{-3}$	

10.1.2 (*E*)-2-Methoxy-ethyl 3-oxo-2-(3-oxo-3*H*-isobenzofuran-1-ylidene)-butyrate

An ORTEP plot of this compound is shown in Scheme 27.

Crystal data and structure refinement for **36f**:

Empirical formula	$C_{15}H_{14}O_6$	
Formula weight	290.26	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group (H.-M.)	$P\bar{1}$	
Space group (Hall)	-P 1	
Unit cell dimensions	a = 7.3780(15) Å	α = 83.68(3)°.
	b = 8.7710(18) Å	β = 86.04(3)°.
	c = 10.799(2) Å	γ = 81.78(3)°.
Volume	686.4(2) $Å^3$	
Z	2	
Density (calculated)	1.404 Mg/m^3	
Absorption coefficient	0.110 mm^{-1}	
F(000)	304	
Crystal size	0.64 x 0.52 x 0.17 mm^3	
Θ range for data collection	1.90 to 28.00°.	
Index ranges	$-9 \leq h \leq 9$, $-11 \leq k \leq 11$, $-14 \leq l \leq 14$	
Reflections collected	22327	
Independent reflections	3303 [R(int) = 0.0225]	
Completeness to Θ = 28.00°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9816 and 0.9332	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3303 / 0 / 190	
Goodness-of-fit on F^2	1.030	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0342, wR2 = 0.0927	
R indices (all data)	R1 = 0.0367, wR2 = 0.0967	
Largest diff. peak and hole	0.331 and -0.209 e.$Å^{-3}$	

10.1.3 (*E*)-Methyl 4,4-dimethyl-3-oxo-2-(3-oxo-3*H*-isobenzofuran-1-ylidene)-valerate

An ORTEP plot of this compound is shown in Scheme 27.

Crystal data and structure refinement for **36i₁**:

Empirical formula	$C_{16}H_{16}O_5$	
Formula weight	288.29	
Temperature	183(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 5.9481(3) Å	α = 90°.
	b = 31.3969(12) Å	β = 90.838(2)°.
	c = 7.5620(3) Å	γ = 90°.
Volume	1412.07(11) $Å^3$	
Z	4	
Density (calculated)	1.356 Mg/m^3	
Absorption coefficient	0.101 mm^{-1}	
F(000)	608	
Crystal size	0.05 x 0.05 x 0.04 mm^3	
Θ range for data collection	2.77 to 27.51°.	
Index ranges	$-7 \le h \le 7$, $-40 \le k \le 33$, $-9 \le l \le 7$	
Reflections collected	8018	
Independent reflections	3213 [R(int) = 0.0495]	
Completeness to Θ = 27.51°	98.9 %	
Absorption correction	NONE	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3213 / 0 / 254	
Goodness-of-fit on F^2	1.047	
Final R indices [$I>2\sigma(I)$]	R1 = 0.0548, wR2 = 0.1296	
R indices (all data)	R1 = 0.0794, wR2 = 0.1432	
Largest diff. peak and hole	0.301 and -0.245 $e.Å^{-3}$	

10.1.4 (*Z*)-Methyl (3-oxo-3*H*-isobenzofuran-1-ylidene)-acetate

An ORTEP plot of this compound is shown in Scheme 27.

Crystal data and structure refinement for **36i$_2$**:

Empirical formula	$C_{11}H_8O_4$	
Formula weight	204.17	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group (H.-M.)	Pnma	
Space group (Hall)	-P 2ac 2n	
Unit cell dimensions	a = 7.9740(16) Å	α = 90°.
	b = 6.3530(13) Å	β = 90°.
	c = 18.478(4) Å	γ = 90°.
Volume	936.1(3) Å^3	
Z	4	
Density (calculated)	1.449 Mg/m^3	
Absorption coefficient	0.112 mm^{-1}	
F(000)	424	
Crystal size	0.32 x 0.30 x 0.12 mm^3	
Θ range for data collection	2.78 to 28.00°.	
Index ranges	$-10 \le h \le 10$, $-8 \le k \le 8$, $-24 \le l \le 24$	
Reflections collected	7892	
Independent reflections	1181 [R(int) = 0.0225]	
Completeness to Θ = 28.00°	95.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9867 and 0.9651	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1181 / 0 / 93	
Goodness-of-fit on F^2	1.068	
Final R indices [I>2σ(I)]	R1 = 0.0332, wR2 = 0.0911	
R indices (all data)	R1 = 0.0388, wR2 = 0.0967	
Extinction coefficient	0.030(8)	
Largest diff. peak and hole	0.276 and -0.259 e.Å^{-3}	

10.2 Abbreviations

Ac	Acetyl
Anal.	Elemental Analysis
APT	Attached Proton Test
bp.	Boiling point
calcd	Calculated
CI	Chemical Ionization
COSY	Correlated Spectroscopy
DABCO	1,4-Diazabicyclo[2.2.2]octane
DEPT	Distortionless Enhancement by Polarization Transfer
dr	Diastereomeric ratio
ee	Enantiomeric excess
EI	Electron Impact
Et_2O	Diethyl ether
EtOH	Ethanol
GC	Gas Chromatography
GP	General Procedure
HMBC	Heteronuclear Multiple Bond Correlation
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
IR	Infrared Spectroscopy
LDA	Lithium diisopropylamide
Me_3SiCl	Chlorotrimethylsilane
Me_3SiOTf	Trimethylsilyl trifluoromethanesulfonate
MS	Mass Spectrometry
mp	Melting point
NaOEt	Sodium ethanolate
*n*BuLi	*n*-Butyllithium
NEt_3	Triethylamine
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser and Exchange Spectroscopy
ORTEP	Oak Ridge Thermal Ellipsoid Plot
OTf	Triflate
Ph	Phenyl
ppm	Parts per million
R_f	Retention factor
SET	Single electron transfer
Tf_2O	Trifluoromethanesulfonic anhydride (triflic anhydride)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Tetramethylsilane
Tol	Tolyl (p-MeC_6H_4)
Tos	Tosyl (p-$MeC_6H_4SO_2$)

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Erklärung

Ich versichere hiermit an Eides statt, daß ich die vorliegende Arbeit selbständig angefertigt und ohne fremde Hilfe verfasst habe, keine außer den von mir angegebenen Hilfsmitteln und Quellen dazu verwendet habe und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen als solche kenntlich gemacht habe.

Rostock, 4. April 2008

Zusammenfassung

Diese Arbeit ist ein Beitrag zur Chemie verschiedener Silyl-Enol-Ether, die zur regioselektiven Synthese von funktionalisierten Salicylaten, Isotetronsäuren und Alkyliden-Isobenzofuranen verwendet wurden.

Zusätzlich wurde die Konkurrenz zwischen der kürzlich entwickelten Domino „Staudinger / semi-aza-Wittig / Fragmentierungsreaktion" von γ-Azido-β-hydroxyketonen und der normalen Aza-Wittig-Reaktion untersucht.

Summary

This work is a contribution to the chemistry of different types of silyl enol ethers which were applied to the regioselective synthesis of functionalized salicylates, isotetronic acids, and alkylidene-isobenzofurans.

In addition, the competition between the recently developed domino "Staudinger / semi-aza-Wittig / fragmentation" reaction of γ-azido-β-hydroxyketones and the normal aza-Wittig reaction pathway was studied.

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