EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

# Accepted Article

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**To be cited as:** *Eur. J. Org. Chem.* 10.1002/ejoc.201801117

**Link to VoR:** http://dx.doi.org/10.1002/ejoc.201801117

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**Entry for the Table of Contents**

Full Paper

*David Peter, Reinhard Brückner**

***Page No. – Page No.***

**Synthesis of a Pair of Simplified Model Compounds of the Dihydroxy-Cyclopentenone Core of the Kodaistatins A–D**

*Cis*/*trans*-isomeric models of the dihydroxycyclopentenone core of the kodaistatins A–D were synthesized. NMR analogies show that kodaistatin A must be *trans*-configured. A key-step was a *syn*-selective aldol addition. An oxidation/reduction tandem furnished the β-epimeric *anti*-aldol. Each aldol was processed to a 5-brominated 1,4-diketone. The latter cyclized by an $SmI_2$-mediated aldol addition. Ensuing dehydrations delivered the cyclopentenone motive.

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FULL PAPER

# Syntheses of a Pair of Simplified Model Compounds of the Dihydroxycyclopentenone Core of the Kodaistatins A–D

David Peter[a] and Reinhard Brückner*[a]

***Abstract:*** *The kodaistatins A–D (**1**-**4**) are natural products from* Aspergillus terreus *with the potential of representing leads for a novel cure of type-2 diabetes. They possess an unusually and highly substituted dihydroxycyclopentenone core. Whether its OH groups are* cis- *or* trans-*configured remained unknown by spectroscopy. Previous syntheses of kodaistatin model compounds (*cis-***5***,* cis- *and* trans-***6****) allowed to make NMR comparisons with kodaistatin A (**1**). They led to the insight that the natural product **1** must be a* trans-*diol. These findings are corroborated by the synthesis and ensuing NMR study of another pair of* cis/trans-*isomeric kodaistatin models (*cis- *and* trans-***7****) described here. Its first key-step was a* syn-*selective aldol addition. An oxidation/reduction sequence allowed diverging to the corresponding* anti-*aldol. Each aldol furnished a kodaistatin model in eight additional steps. The most noteworthy transformation was an Sm(II)-induced intramolecular aldolization of a bromodiketone.*

## Introduction

The kodaistatins A–D (**1**–**4**, Figure 1a), isolated by a group from Hoechst Marion Roussel Deutschland GmbH from *Aspergillus terreus*, are strongly anti-diabetic.[1,2] This is because they inhibit the glucose-6-phosphate T1 translocase ($IC_{50}$ = 80–130 nM), an enzyme indispensable for hepatic gluconeogenesis and glycogenolysis.[2] Therefore, **1**–**4** might be novel leads for the chemotherapy of type-2 diabetes.[3]

The structures of the kodaistatins were inferred from mass and NMR spectra.[1,2] Each of these compounds comprises a trinuclear aromatic unit (Figure 1a, green), a dienone side chain (magenta) with a stereocenter (magenta asterix), and a pentasubstituted dihydroxycyclopentenone core with two stereocenters (blue asterixes). The absolute and relative configurations of all stereocenters remained unassigned.[1,2] Implicitly, kodaistatin A and B were considered as diastereomers as were kodaistatin C and D.[1,2] Kaczybura and Wüster from our group found that the configuration of the side-chain stereocenter is *S*.[4] In a 23-step endeavor they also synthesized the enantiomerically pure[5] 1st generation kodaistatin model compound *cis*-**5** (Figure 1b).[4] Comparing its $^{13}C$ NMR spectrum with that of kodaistatin A (**1**)[2] suggested that the cyclopentenone core of the latter is *trans*-dihydroxylated.[4] Of course, this was not a configurational proof – because we possessed only the *cis*- but not the *trans*-configured model **5**. The *trans*-configuration of kodaistatin A (**1**) was supported – if not ascertained – after devising the 2nd generation model compounds *cis*- and *trans*-**6** (Figure 1c) and synthesizing them isomerically pure (*cis*-**6** cost 11 steps and *trans*-**6** 12 steps, 2 of which were shared).[6] The pair of compounds allowed to deduce a *trans*-configuration of the cyclopentenone core of kodaistatin A (**1**) based on $^{13}C$-NMR shift comparisons.[6]

The present report concerns the synthesis and NMR spectra of another pair of kodaistatin models, namely the "simplified models" *cis*- and *trans*-**7** (Figure 1d). Devoid of a cyclopentenone side chain akin to those in the kodaistatins (**1**-**4**) or the previous model compounds **5**-**6** their carbon-2 might allow to introduce such a side chain at the very end[7] (current state of exploration: Scheme 8).

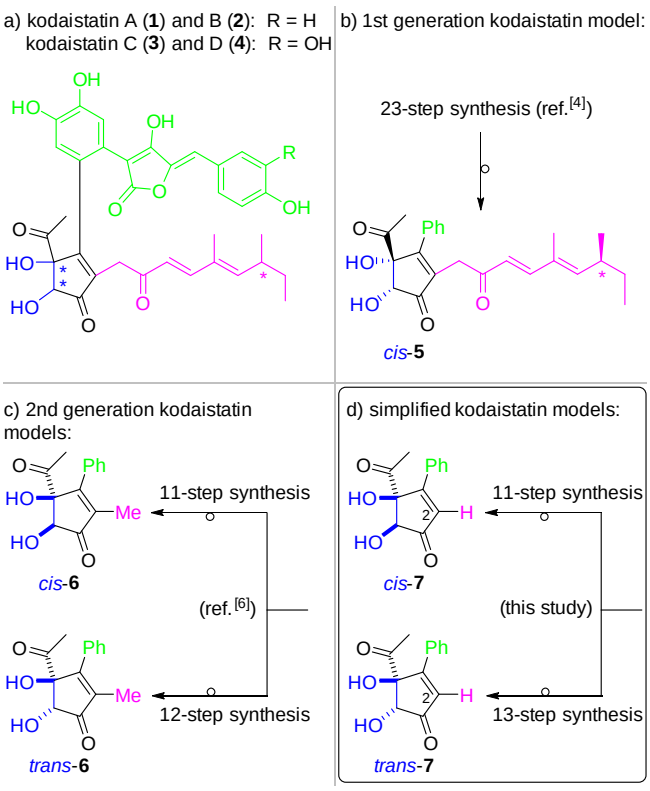


**Figure 1.** a) Structures[5] of the kodaistatins A–D (**1**–**4**).[1, 2] b) 1st generation kodaistatin model *cis*-**5**.[4] c) 2nd generation kodaistatin models *cis*- and *trans*-**6**[6] (step-count from methyl *trans*-crotonate and *cis*,*trans*-1-ethoxyprop-1-ene). d) The "simplified kodaistatin models" *cis*- and *trans*-**7** of the present work (step-count from methyl *trans*-crotonate and 2-chloroacrolein).

We set out to synthesize our simplified models *cis*- and *trans*-**7** by the same strategy as the 2nd generation kodaistatin models

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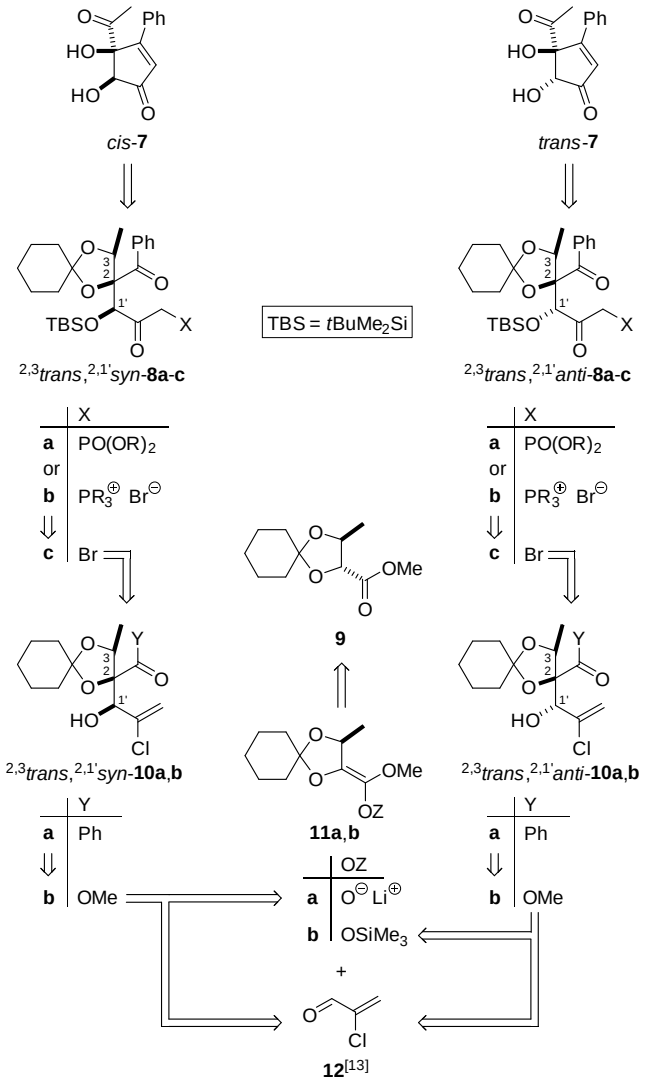
*cis*- and *trans*-**6**. Originally, we intended to establish the cyclopentenone backbone in **7** by a Horner-Wadsworth-Emmons cyclization of the β-ketophosphonate $^{2,3}$*trans*,$^{2,1'}$*syn*-**8a**[8] or by a Wittig cyclization of the ylide derived from the β-ketophosphonium salt $^{2,3}$*trans*,$^{2,1'}$*syn*-**8b**[8] (Scheme 1). The $^{2,1'}$*syn*-configurations of these reactants would translate into the *cis*-configured cyclopentenone **7** (Scheme 1 at left) whereas the phosphonate diastereomer $^{2,3}$*trans*,$^{2,1'}$*anti*-**8a**[8] or the phosphonium salt diastereomer $^{2,3}$*trans*,$^{2,1'}$*anti*-**8b**[8] would cyclize giving the cyclopentenone *trans*-**7** (Scheme 1 at right). The phosphonates **8a** and phosphonium salts **8b** should arise from $S_N$ reactions between the respective phosphite or phosphane and the appropriate α-bromoketone $^{2,3}$*trans*,$^{2,1'}$*syn*-**8c**[8] or $^{2,3}$*trans*,$^{2,1'}$*anti*-**8c**.[8]




**Scheme 1.** Retrosynthetic analysis of the simplified kodaistatin models *cis*-**7** (at left) and *trans*-**7** (at right).

The mentioned α-bromoketones, in turn, should stem from brominating hydrolyses[9] of the "chloroolefins" $^{2,3}$*trans*,$^{2,1'}$*syn*- and $^{2,3}$*trans*,$^{2,1'}$*anti*-**10a**,[8] respectively (Scheme 1). Such hydrolyses are known.[10] In the hands of Stoltz *et al.*[11] they served – like desired here – as an overture for proceeding via a phosphonium salt to an ylide and for engaging the latter into a cyclopentenone-forming Wittig cyclization. The "chloroolefins" $^{2,3}$*trans*,$^{2,1'}$*syn*- and $^{2,3}$*trans*,$^{2,1'}$*anti*-**10a**[8] are phenylketones as well. Because of that, they should be accessible by acylations of phenyllithium with the esters $^{2,3}$*trans*,$^{2,1'}$*syn*- and $^{2,3}$*trans*,$^{2,1'}$*anti*-**10b**,[8] respectively.

More specifically, the esters **10b** are β-hydroxyesters (Scheme 1). Accordingly, we envisaged synthesizing them by a pair of stereocomplementary aldol additions:[12] either by an aldol addition of the lithium enolate **11a** to 2-chloroacrolein (**12**[13]) or by a Mukaiyama aldol addition of the corresponding silyl ketene acetal **11b** to 2-chloroacrolein (**12**).[14] The nucleophiles **11a** and **b** would be generated from the known methyl dioxolane-4-carboxylate **9**.[15]

## Pertinent Retrospective Insights From our Preceding Study

Based on earlier precedents,[16,17] we had previously established[6] that lithium enolate and Mukaiyama aldol additions of the dioxolane-4-ester **9**[15] and its silyl ketene acetal **11b**,[6] respectively, to 2-chlorocrotonaldehyde exhibit excellent and complementary simple diastereoselectivities (Scheme 2). As a common start, the ester **9** was deprotonated with LDA in THF at −78 °C.[6] The resulting lithium enolate **11a** was combined either with 2-chlorocrotonaldehyde (**15**) giving the aldol $^{2,3}$*trans*,$^{2,1'}$*syn*-**18a** or with $Me_3SiCl$ yielding the silyl ketene acetal **11b** whose Mukaiyama aldol addition to 2-chlorocrotonaldehyde (**15**) gave the aldol $^{2,3}$*trans*,$^{2,1'}$*anti*-**18a**.[8] Analogous additions to 2-bromo- and 2-iodocrotonaldehyde rendered the aldols **18b** and **18c**, respectively, with similarly high $^{2,3}$*trans*,$^{2,1'}$*syn*- and $^{2,3}$*trans*,$^{2,1'}$*anti*-selectivities[8] (Scheme 2 and Table 1). The configurations of an aldol slightly differently protected than $^{2,3}$*trans,*$^{2,1'}$*syn*-**18a** and of the aldol $^{2,3}$*trans,*$^{2,1'}$*anti*-**18a** followed from X-ray crystal structure analyses of their 4-bromobenzoates.[6] The $^1$H-NMR shifts of the 1'-OH group in the aldols $^{2,3}$*trans,*$^{2,1'}$*syn*- and $^{2,3}$*trans,*$^{2,1'}$*anti*-**18b** and **c** reveal the relative configurations when compared to the respective shifts in the aldols $^{2,3}$*trans,*$^{2,1'}$*syn*- vs. $^{2,3}$*trans,*$^{2,1'}$*anti*-**18a**. (The homogeneity of these data allowed to assign the configurations of the aldols $^{2,3}$*trans,*$^{2,1'}$*syn*- and $^{2,3}$*trans,*$^{2,1'}$*anti*-**10b** of the present study (vide infra), none of which – nor any of their follow-up products – allowed an X-ray structural analysis.)

At the time we *assumed* that the silyl ketene acetal **11b** of our original Mukaiyama aldol addition (→ $^{2,3}$*trans*,$^{2,1'}$*anti*-**18a**) was *Z*-configured.[6] By now we *corroborated* this assignment by $^1$H-NMR shift similarities (Scheme 2, top right; details: SI) with the related silyl ketene acetal *Z*-**14b**[18] whose configuration we *proved* by a NOESY spectrum. Consequently, the preceding lithium enolate **11a** must have been *identically* configured; this amounts to its being *E*-configured according to the CIP nomenclature. We rationalize this stereoselectivity by a preferred deprotonation of the ester **9** via a type-**13** transition state. Therein, the dioxolane moiety and the ester group are tied up by $Li^{\oplus}$ to form a 5-membered ring. Irrespective of whether the deprotonation ensues "intramolecularly" – via transition state *cyclo*-**13** – or intermolecularly – via transition state *cyclo*-**13** – , the resulting enolate **11a** possesses the *E*-configuration.

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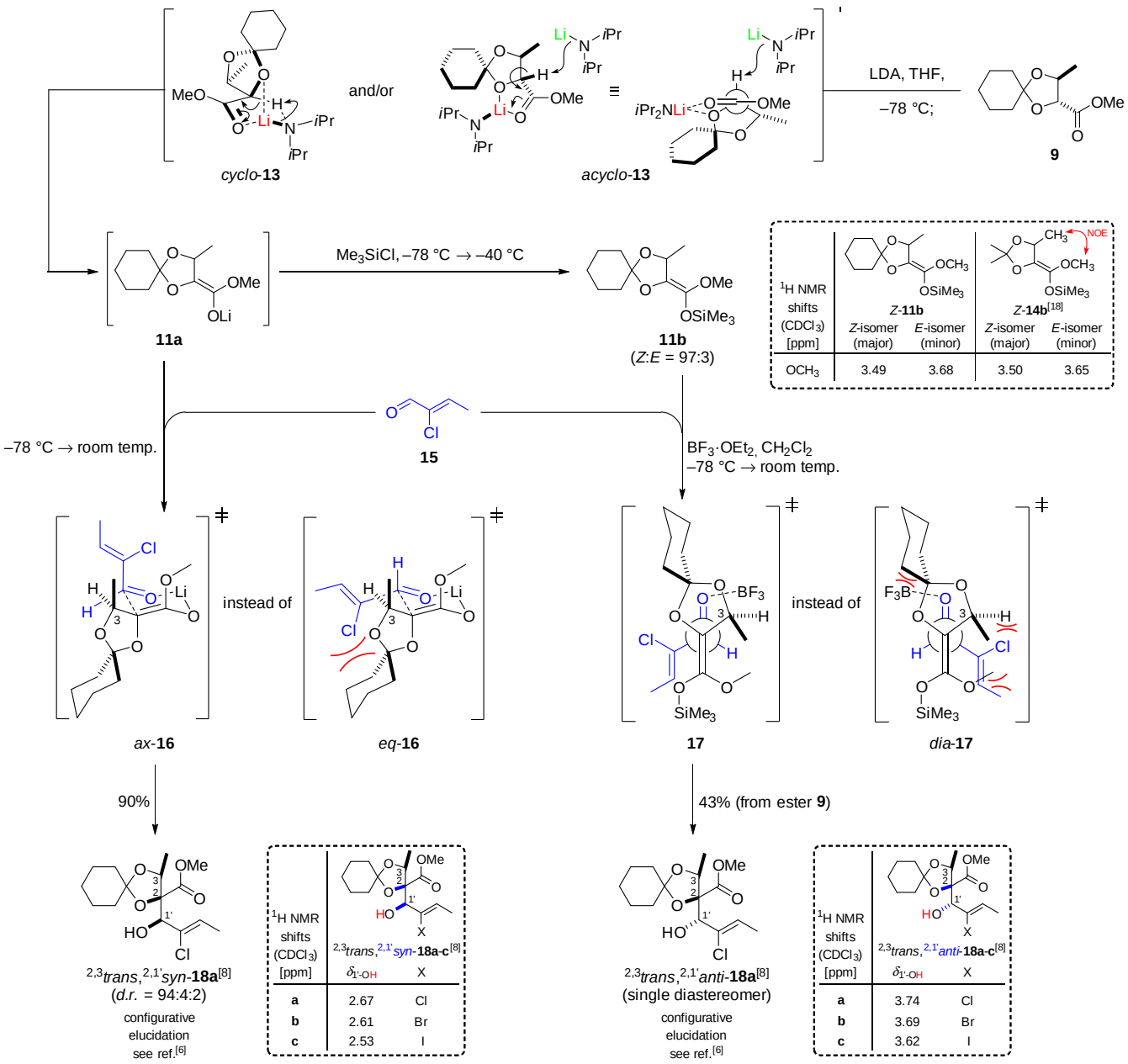
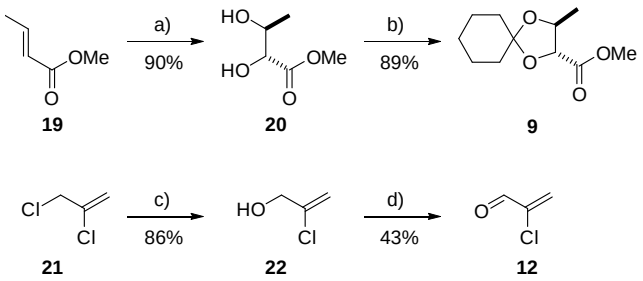



**Scheme 2.** An aldol addition of the litihium enolate **11a** of the ester **9** to 2-chlorocrotonaldehyde (**15**) and a Mukaiyama aldol addition of the silyl ketene acetal **11b** to 2-chlorocrotonaldehyde (**15**) that we published earlier.[6] The transition states **13** (deprotonation), *ax*-**16** (Li enolate aldol addition), and **17** (Mukaiyama aldol addition) correlate the known configurations of the ester **9**, the derived nucleophiles **11a** and **11b** (configurative elucidation unpublished), and the aldols *syn*-**18a** and *anti*-**18a** (configurative elucidation in ref.[6]).

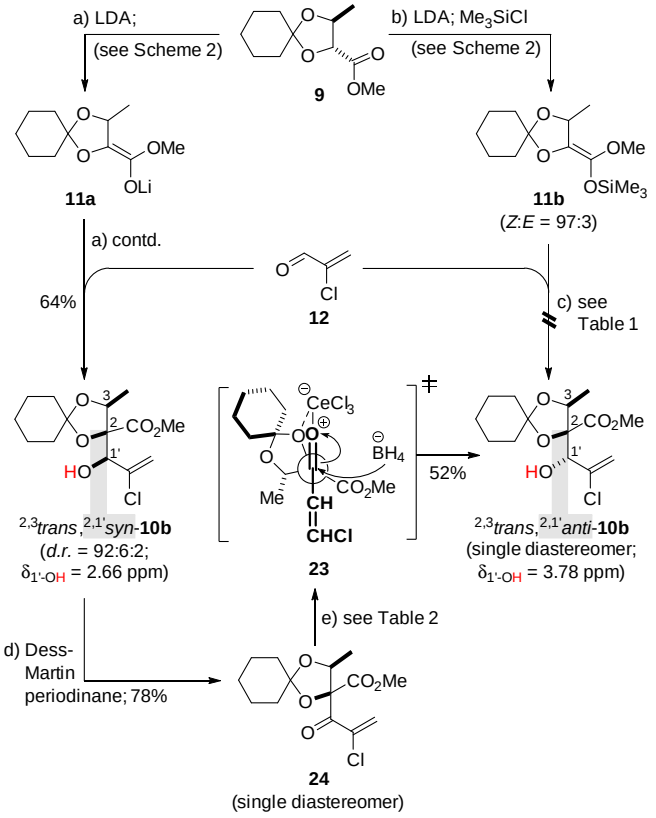
Based on these insights, the simple diastereoselectivities of the lithium enolate (**11a**) and silyl ketene acetal (**11b**) additions to 2-chlorocrotonaldehyde can be rationalized as shown in the penultimate row of Scheme 2: (1) In Zimmerman-Traxler transition states[19] **16** of the lithium enolate (**11a**) addition to the aldehyde **15** the $^{2,3}$*trans*-selectivity arises because the aldehyde approaches the enolate from the less hindered side, that is from opposite to the 3-Me group. The concomitant $^{2,1'}$*syn*-selectivity means that the chloropropenyl group binds axially (e. g. *ax*-**16**). This avoids the unfavorable interaction with the dioxolane ring – particularly its sterically encumbered spiro carbon – in the transition state *eq*-**16**. Apparently, the latter interaction, albeit remote, is more important than the 1,3-diaxial interaction of the chloropropenyl moiety and the methoxy group in *ax*-**16**.[20] (2) In acyclic transition states[21] (**17**, *dia*-**17**) of the silyl ketene acetal (**11b**) addition to the aldehyde **15** the $^{2,3}$*trans*-selectivity arises because the *trans*-configured Lewis acid / base complex[22] from $BF_3$ and the aldehyde approaches the acetal from the less hindered side, that is from opposite to the 3-Me group. The concomitant $^{2,1'}$*anti*-selectivity means that the favored transition state is akin to **17**, not *dia*-**17**. This may be due to repulsive interactions between $BF_3$ and the cyclohexane ring and between the chloropropenyl moiety and the highlighted $C_{sp^3}$–H bonds in *dia*-**17**. There always is some arbitrariness in advocating antiperiplanar rather than synclinal transition states for the addition of π-nucleophiles to π-acceptors, with the likely exception of especially designed intramolecular versions of such reactions.[23] One point favoring an antiperiplanar attack is that it establishes an *anti*- rather than *gauche*-conformation of the resulting C–C–C–X motif. A supporting factor may be that there is less repulsion between the C,O bond dipoles.[24]

## Results and Discussion




**Scheme 3.** Preparing the substrates for the aldol addition. *Reagents and conditions:* a) $K_2OsO_2(OH)_4$ (0.2 mol%), NMO (2.1 equiv.), citric acid (0.75 equiv.), *t*BuOH/$H_2O$ (1:1), room temp., 18 h; 90% (ref.[25]: 66%).– b) Cyclohexanone (1.2 equiv.), *p*TsOH (4 mol%), $CuSO_4$ (1.6 equiv.), $CH_2Cl_2$, room temp., 24 h; 89% (ref.[15]: 89%).– c) $K_2CO_3$ (1.1 equiv.), $H_2O$, 100 °C, 16 h; 86% (ref.[26]: 92%).– d) DMSO (1.1 equiv.) activated by $(COCl)_2$ (1.1 equiv.), $CH_2Cl_2$, −78 °C → −50 °C (in 90 min); $NEt_3$ (5 equiv.), −50 °C → room temp. (in 2 h); 43%.

The substrates required for the envisaged aldol additions were prepared based on literature procedures (Scheme 3). A citric acid-promoted dihydroxylation[25] of methyl *trans*-crotonate (**19**) and ketalization[15] of the resulting diol **20** furnished the *trans*-configured dioxolane-4-ester **9**. 2-Chloroacrolein (**12**) was prepared by hydrolyzing 2,3-dichloropropene (**21**) with base[26] and by subjecting the resulting alcohol **21** to a Swern oxidation. When we isolated 2-chloroacrolein (**12**) by distillation, its yield was only 43%. It was more advantageous preparing **12** as a THF solution and employing it as such for the aldol addition (see Experimental Section for details).[13b]




**Scheme 4.** Aldol additions to 2-chloroacrolein and epimerization of the allyl alcohol in *trans,syn*-**10b** by an oxidation-reduction sequence. *Reactions and conditions*: a) **9**, LDA (1.2 equiv.), THF, −78 °C, 1 h; **12** (1.1 equiv.), −78 °C, 4 h; 64%, *d.r.* = 92:6:2.– b) LDA (1.3 equiv.), THF, −78 °C, 25 min; $Me_3SiCl$ (1.6 equiv.), −78 °C → room temp (in 3 h): product not purified.– c) See Table 1.– d) Dess-Martin periodinane (1.2 equiv.), pyridine (5 equiv.), $CH_2Cl_2$, 0 °C, 15 min, room temp., 90 min; 78%.– e) $NaBH_4$ (2.0 equiv.), $CeCl_3{\cdot}7H_2O$ (1.8 equiv.), MeOH, −78 °C, 1 h; 52%.

We deprotonated the ester **9** at −78 °C with LDA in THF as described before[6] (Scheme 4). The resulting enolate **11a** added to 2-chloroacrolein (**12**) in 64% yield, delivering the desired aldol **10b** with high $^{2,3}$*trans*,$^{2,1'}$*syn*-selectivity (*d.r.* = 92:6:2, both minor diastereomers remaining unassigned). We attributed the $^{2,3}$*trans*-configuration of **10b** for analogy to related additions[6,16] and assigned the $^{2,1'}$*syn*-configuration for the similarity vs. dissimilarity of $\delta_{1'\text{-}OH}$ in $^{2,3}$*trans*,$^{2,1'}$*syn*-**10b** (Scheme 4) vs. the homologous aldols $^{2,3}$*trans*,$^{2,1'}$*syn*-**18a**[6] and $^{2,3}$*trans*,$^{2,1'}$*anti*-**18a**,[6] respectively (Scheme 2). The underlying diastereoselecitivity can be rationalized by a Zimmerman-Traxler transition state akin to *ax*-**16** (see Scheme 2).

**Table 1.** Mukaiyama aldol additions of the silyl ketene acetal **11b** to the enals **15**, **25**-**27**, and **12**.

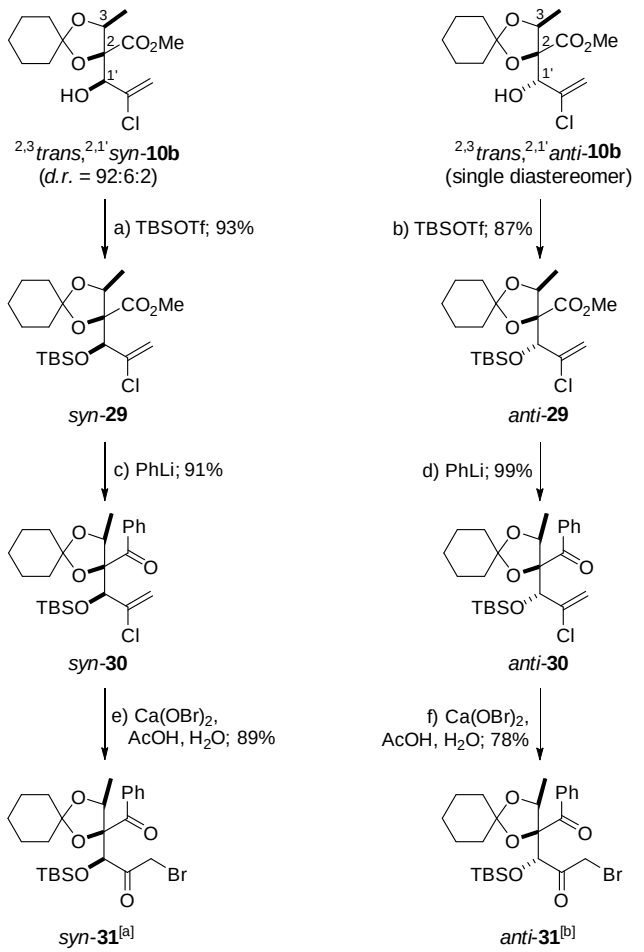
| # | Het | enal | promotor | *T*, *t* | aldol | yield |
|---|---|---|---|---|---|---|
| 1 | Cl | **15** (1.5 eq) | $MgBr_2 \cdot OEt_2$ (2.5 eq) | −78 °C → −40 °C (in 3 h) | **18a** | 29% |
| 2 | | **15** (1.1 eq) | $BF_3 \cdot OEt_2$ (1.1 eq) | −78 °C, 30 min, → −40 °C (in 1.5 h) | | 43% |
| 3 | Br | **25** (1.1 eq) | $BF_3 \cdot OEt_2$ (1.6 eq) | −78 °C, 45 min, → −25 °C (in 2 h) | **18b** | 32% |
| 4 | I | **26** (1.2 eq) | $MgBr_2 \cdot OEt_2$ (1.0 eq) | −78 °C, 4 h | **18c** | <5% (impure) |
| 5 | OEt | **27** (1.0 eq) | $MgBr_2 \cdot OEt_2$ (1.0 eq) | −78 °C, 2 h | **18d** | 17% |
| 6 | **12** (2.5 eq) | | $MgBr_2 \cdot OEt_2$ (1.5 eq) | −78 °C, 3 h, → −40 °C (in 3 h) | complex mixture | |
| 7 | | | $BF_3 \cdot OEt_2$ (1.5 eq) | | | |

As recalled in the context of Scheme 2 we had prepared the aldol $^{2,3}$*trans*,$^{2,1'}$*anti*-**18a** by a Mukaiyama aldol addition of the silyl ketene acetal **11b** to 2-chlorocrotonaldehyde (**15**). $BF_3 \cdot OEt_2$ promoted this reaction better than $MgBr_2 \cdot OEt_2$ (Table 1, entries 1-2).[6] The previously unpublished Br-, I-, and OEt-containing analogs **18b**-**d** were accessible by Mukaiyama aldol additions, too (entries 3-5). Their yields were lower even when we activated the unstable electrophiles 2-iodocrotonaldehyde (**26**) and 2-ethoxycrotonaldehyde (**27**) with the milder Lewis acid $MgBr_2 \cdot OEt_2$. However, neither $MgBr_2 \cdot OEt_2$ nor $BF_3 \cdot OEt_2$ engaged 2-chloroacrolein (**12**) and the trimethylsilyl ketene acetal **11b** in a chemoselective Mukaiyama aldol addition; nothing resulted but complex mixtures (entries 6-7).

**Table 2.** Luche and related reductions of chloroenone **24** (preparation: Scheme 4).

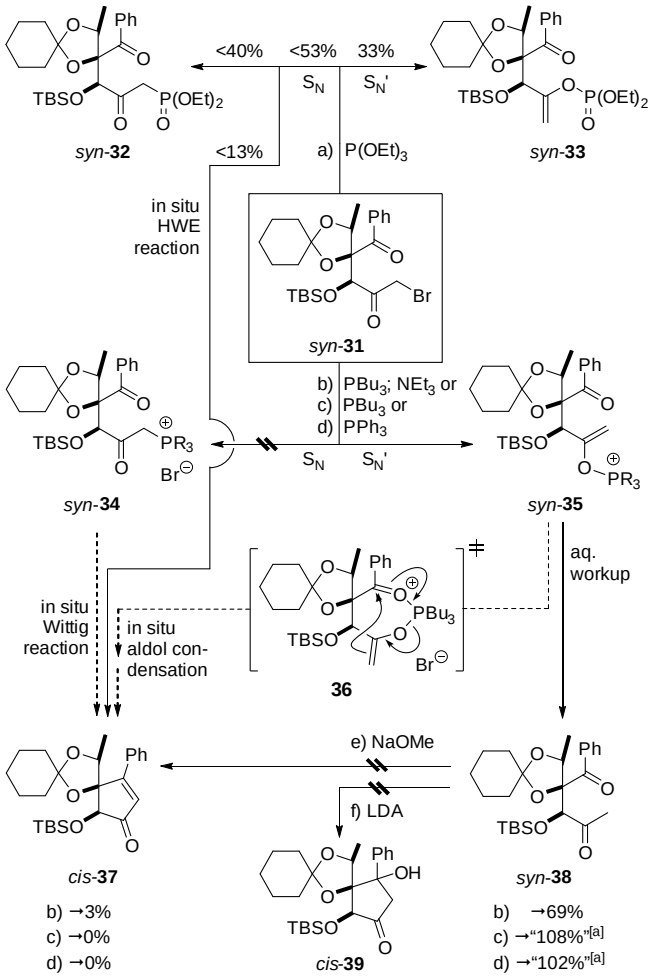
| # | reductant (eq) | $CeCl_3 \cdot 7H_2O$ | solvent | $t_1$ (→ *T*, $t_2$) | yield | |
|---|---|---|---|---|---|---|
| | | | | | *trans*,*anti*-**10b** | **28** |
| 1 | $Ca(BH_4)_2$ (1.2 eq) | – | THF | −78 °C, 1 h | – | 36% |
| 2 | $LiBH_4$ (2.0 eq) | 1.2 eq | THF | −78 °C, 1 h | – | 45% |
| 3 | $Na(CN)BH_3$ (2.0 eq) | 1.8 eq | MeOH | −78 °C, 2 h | – | 73% |
| 4 | $Ca(BH_4)_2$ (1.0 eq) | 1.2 eq | THF | −78 °C, 2 h | 25% | – |
| 5 | $NaBH_4$ (2.0 eq) | 1.2 eq | MeOH | −78 °C, 5 h, → −40 °C (in 2 h) | 41% | not isolated |
| 6 | $NaBH_4$ (2.0 eq) | 1.8 eq | MeOH | −78 °C, 1 h | 52% | not isolated |

We bypassed this obstacle by inverting the configuration of the C$^{1'}$–OH bond in the aldol $^{2,3}$*trans*,$^{2,1'}$*syn*-**10b** (Scheme 4) by a Dess-Martin oxidation[27] (→ enone **24**) and an ensuing Luche reduction.[28] This delivered the aldol $^{2,3}$*trans*,$^{2,1'}$*anti*-**10b** exclusively. In our proposed transition state **23** the carbonyl group, one of the dioxolane oxygen atoms, and Ce(III) form a five-membered chelate. Therein, the carbonyl group is reduced from the less hindered face, that is from opposite to the dioxolane ring. The optimization of this reduction of enone **24** is shown in Table 2. $Ca(BH_4)_2$, $LiBH_4$ or $Na(CN)BH_3/CeCl_3$ attacked the C=C bond, too, and thus gave the saturated chlorohydrin **28** as a diastereomeric mixture. Such an undesired over-reduction was prevented by using $NaBH_4/CeCl_3$ as a reductant in MeOH at −78 °C. The configuration of the newly formed stereocenter in the resulting chloroallylic alcohol *trans*,*anti*-**10b** followed from the chemical shift of the *O*-bound proton: It resembles the OH shifts in the homologous aldols $^{2,3}$*trans*,$^{2,1'}$*anti*-**18a**-**d** but differs from those in their epimers $^{2,3}$*trans*,$^{2,1'}$*syn*-**18a**-**d** (Scheme 2).




**Scheme 5.** Syntheses of the 5-bromo-1,4-diketones *syn*- and *anti*-**31** from the aldols *syn*- and *anti*-**10b**. *Reactions and conditions*: a) TBSOTf (1.5 equiv.), 2,6-lutidine (3.0 equiv.), $CH_2Cl_2$, 0 °C → room temp., 18 h; 93%.– b) Same as (a); 87%.– c) PhLi (1.2 equiv.), −78 °C, 1 h; 91%.– d) Same as (c) but 1.5 equiv.; 99%.– e) $Ca(OBr)_2$ (0.25 M in $H_2O$, 2.5 equiv.), AcOH (95 equiv.), MeCN, 0 °C, 1 h; 89%.– f) Same as (e) but 0 °C → room temp., 18 h; 78%.– [a]This compound was numbered $^{2,3}$*trans*,$^{2,1'}$*syn*-**8c** in Scheme 1; from her onwards the simplification *syn*-**31** is used. [b]This compound was numbered $^{2,3}$*trans*,$^{2,1'}$*anti*-**8c** in Scheme 1; from her onwards the simplification *anti*-**31** is used.

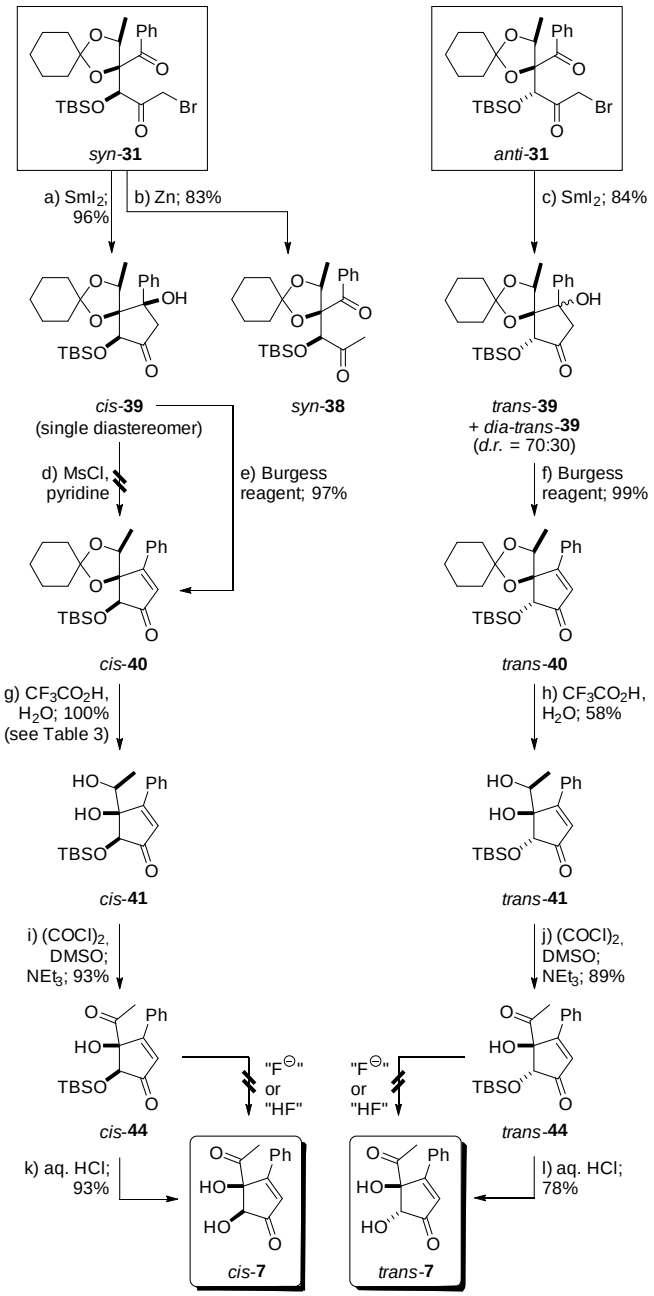
Scheme 5 displays 3-step conversions of the aldols $^{2,3}$*trans*,$^{2,1'}$*syn*- and $^{2,3}$*trans*,$^{2,1'}$*anti*-**10b** to the corresponding cyclization substrates, i. e., the bromodiketones *syn*- and *anti*-**31**. The aldol $^{2,3}$*trans*,$^{2,1'}$*syn*-**10b** was *O*-silylated with TBSOTf (→ 93% *syn*-**29**; Scheme 5 at left). PhLi reacted with the ester moiety giving the phenyl ketone *syn*-**30** (91% yield). Its chloroolefin moiety was subjected to the already-mentioned brominating hydrolysis[9] by exposure to freshly prepared $Ca(OBr)_2$ in a mixture of MeCN, AcOH, and $H_2O$.[10c] This furnished the bromodiketone *syn*-**31** in 89% yield. Its diastereomer *anti*-**31** resulted in 67% overall yield when we subjected the aldol $^{2,3}$*trans*,$^{2,1'}$*syn*-**10b** to the analogous transformations (Scheme 5 at right).




**Scheme 6.** Top: Unselective synthesis of the ketophosponate *syn*-**32**. Middle: Attempts at synthesing the β-ketophosphonium salt *syn*-**34** and realizing its cyclization (→ *cis*-**37**) by a Wittig reaction. Bottom: Cyclization attempts of the readily accessible methyl ketone *syn*-**38**. *Reactions and conditions*: a) $P(OEt)_3$ (60 equiv. = used as solvent), 150 °C, 2 h; 40% *syn*-**32** separated from 33% *syn*-**33** separated from <13% *cis*-**37**.– b) $PBu_3$ (2.0 equiv.), toluene, room temp., 2 h; $NEt_3$ (1.5 equiv.), 110 °C, 2 d; 3% *cis*-**37** separated from 69% *syn*-**38**.– c) $PBu_3$ (2.0 equiv.), MeCN, room temp., 3 h; "108%".– d) same as (c) but $PPh_3$; "102%".– e) NaOMe (1.5 equiv.), MeOH, room temp., 1 d; no conversion.– f) LDA (1.1 equiv.), THF, −78 °C → room temp. (in 4 h); "low conversion" + decomposition.– [a]This yield was calculated from the weight of product. It is reported as such, which, we believe, complies with the deliberations of M. Wernerova and T. Hudlicky "On the Practical Limits of Determining Isolated Product Yields and Ratios of Stereoisomers: Reflections, Analysis, and Redemption" (*Synlett* **2010**, 2701-2707).

In contrast to the retrosynthetic analysis of Scheme 1, we could not proceed from the bromodiketone *syn*-**31** to a ketophosphonate *syn*-**32** selectively or to a phosphonium salt *syn*-**34** at all (Scheme 6). Heating the bromoketone *syn*-**31** in $P(OEt)_3$ at 150 °C gave three products that were separated by flash chromatography: the ketophosphonate *syn*-**32** (<40%, containing an unidentified contaminant) from the desired Arbuzov reaction ($S_N$), the isomeric enol phosphate *syn*-**33** (33%) from an interfering Perkow reaction ($S_N$'), and the cyclopentenone *cis*-**37** (<13%, containing an unidentified contaminant) from a premature Horner-Wadsworth-Emmons cyclization of some of the mentioned ketophosphonate *syn*-**32**. Stoltz's protocol[11] – phosphonium salt formation with $PBu_3$ in toluene and $NEt_3$-induced Wittig cyclization – turned our bromodiketone *syn*-**31** into only 3% of the desired

cyclopentenone *cis*-**37** but into 69% of the debrominated diketone *syn*-**38**. The latter must have resulted from a protonolysis of the putative phosphonium enolate[29] *syn*-**35** which would have formed by an $S_N$' reaction akin to the Perkow reaction of *syn*-**31** with $P(OEt)_3$.




**Scheme 7**. Completing the syntheses of the kodaistatin models *cis*- and *trans*-7. *Reactions and conditions*: a) $SmI_2$ (2.2 equiv.), THF, −78 °C, 1 h, → room temp. (in 2 h); 96%.– b) Zn (2.0 equiv.), THF, room temp., 19 h, 50 °C, 7 h; 83%.– c) Same as (a) but 2.0 equiv.; 84%.– d) MsCl (1.2 equiv.), pyridine (5 equiv.), $CH_2Cl_2$, room temp., 24 h; no conversion.– e) Burgess reagent (3 equiv.), toluene, 100 °C, 12 h; 97%.– f) Same as (e) but 2 equiv., 15 h; 99%.– g) $CF_3CO_2H$ (13 equiv.), $H_2O$ (1 equiv.), $CH_2Cl_2$, room temp., 90 min; 100%.– h) $CF_3CO_2H$ (15 equiv.), $H_2O$ (14 equiv.), $CH_2Cl_2$, room temp., 14 h; 58%.– i) DMSO (2.9 equiv.) activated by $(COCl)_2$ (1.4 equiv.), $CH_2Cl_2$, −78 °C → −60 °C (in 90 min); $NEt_3$, −78 °C → room temp. (in 3 h); 93%.– j) Same as (i); 89%.– k) Aq. HCl (5 equiv.), MeOH, room temp., 17 h; 93%.– m) Same as (l) but 10 equiv, 3 d; 78%.

As a consequence, we cyclized the bromodiketones *syn*- and *anti*-**31** by an $SmI_2$-induced aldol addition (Scheme 7). It is akin to the one, which we had developed en route to the 2nd generation models *cis*- and *trans*-**6**.[6,30] Accordingly, the bromodiketone *syn*-**31** was reduced with $SmI_2$ using our previous procedure (ref.[6]). There were indications[6] that this gives an Sm(III) enolate which undergoes an intramolecular aldol addition. The β-hydroxyketone *cis*-**39** was obtained in 96% yield as a single diastereomer.[31] An attempted room temp. Reformatsky-type cyclization of the bromodiketone *syn*-**31** with Zn in THF gave the acyclic diketone *syn*-**38** in 83% yield; it must have originated from the protonolysis either of a zinc enolate or of an α-zincated ketone. The diastereomeric bromodiketone *anti*-**31** was cyclized with $SmI_2$ under the same conditions. This afforded a 70:30 mixture of the diastereomeric β-hydroxyketones *trans*-**39** and *dia-trans*-**39**. This lack of diastereoselectivity seemed inconsequential since the difference-making stereocenter would vanish in the subsequent dehydration.

At first we tried to dehydrate the β-hydroxyketone *cis*-**39** with MsCl and pyridine but observed no conversion (Scheme 7). Instead this dehydration was accomplished with the Burgess reagent.[32] This gave the cyclopentenone *cis*-**40** in 97% yield. The 70:30 mixture of the β-hydroxyketones *trans*-**39** and *dia-trans*-**39** dehydrated smoothly under the same conditions giving the cyclopentenone *trans*-**40** in 99% yield.

**Table 3.** Deprotection of type-**40** ketals in the presence of a TBSO group.

| # | substrate | acid | solvent | *t*, *T* | yield | | |
|---|---|---|---|---|---|---|---|
| | | | | | **41** | **42** | **43** |
| 1 | *cis*-**40** | fumaric acid (2.5 equiv.) | MeOH/ $HC(OMe)_3$ (20:1) | 0 °C, 30 min, RT, 18 h, 50 °C, 4 h | no conversion | | |
| 2 | | *p*TsOH (17 mol%) | MeOH | 0 °C, 1 h, RT, 30 h | 20% | – | – |
| 3 | | *p*TsOH (1.0 equiv.) | | RT, 3 d | 14% | 28% | – |
| 4 | | aq. HCl (5 mol%) | | 0 °C, 1 h, RT, 5 h | 52% | – | 4% |
| 5 | | aq HCl (5 equiv.) | MeOH/ $CH_2Cl_2$ (10:1) | RT, 3 d | 6% | 49% | – |
| 6 | | $CF_3CO_2H$ (10 mol%) | MeOH | 0 °C, 1 h, RT, 5 h | no conversion | | |
| 7 | | $CF_3CO_2H$ (13 equiv.), $H_2O$ (1.0 equiv.) | $CH_2Cl_2$ | RT, 2 h | 100% | – | – |
| 8 | *trans*-**40** | | | RT, 5 h | 33% | 4% | – |
| 9 | | $CF_3CO_2H$ (15 equiv.), $H_2O$ (14 equiv.) | | RT, 14 h | 58% | – | – |

Ketal removal from the cyclopentenones *cis*- and *trans*-**40** required extensive optimization (Table 3). Various acids in MeOH were inefficient or cleaved off not only the ketal (→ **41** and **42**) but

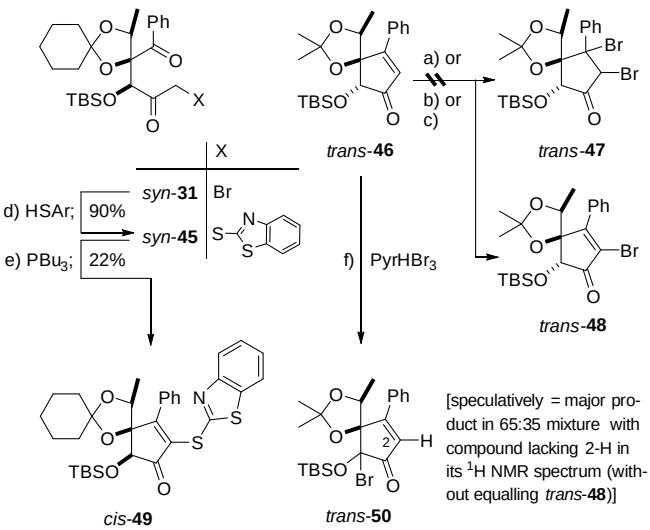
also the TBS-group (→ **42** and **43**). Quite differently, aqueous $CF_3CO_2H$ in $CH_2Cl_2$ rendered the desired diols *cis*-**41** in quantitative yield (entry 7) and *trans*-**41** in 58% yield (entry 9).

Swern oxidations[33] of the secondary OH group in the diols *cis*- as well as *trans*-**41** provided the hydroxyketones *cis*- and *trans*-**44** in yields of 93% and 89%, respectively (Scheme 7, bottom part). Several attempts to desilylate the last-mentioned compounds with $F^{\ominus}$ or HF failed. Instead, the TBS group was removed efficiently by aqueous HCl in MeOH. This afforded the simplified kodaistatin models *cis*-**7** – in 93% yield from *cis*-**44** – and *trans*-**7** in 78% yield from *trans*-**44**.

Having the simplified kodaistatin models *cis*- and *trans*-**7** in hand, we could compare pertinent $^{13}C$ NMR chemical shifts thereof and the corresponding shifts of our 2nd generation models *cis*- and *trans*-**6** as well as of kodaistatin A (**1**) itself (Table 4). The differential substitution patterns at C-2 – the latter binds to methyl in *cis*- and *trans*-**7**, to hydrogen in *cis*- and *trans*-**6**, and to a β-ketoalkyl chain in **1** – seem to affect no more than $\delta_{C\text{-}2}$ and $\delta_{C\text{-}3}$. The NMR shifts of the other five indicated $^{13}C$ nuclei are almost identical in the model compounds *cis*-**6** and *cis*-**7**. Importantly, the chemical shifts of the hydroxylated nuclei $^{13}C$-4 and $^{13}C$-5 in the two *trans*-isomers differ by at most 1.6 ppm from the analogous resonances of kodaistatin A (**1**). In contrast, the shifts of the corresponding nuclei in the respective *cis*-isomers deviate by as much as 4.6–9.0 ppm from their counterparts in kodaistatin A (**1**). The uniformness of these similarities vs. discrepancies underlines our claim[6] that the cyclopentenone core of kodaistatin A (**1**) is *trans*-dihydroxylated.

**Table 4.** $^{13}C$ NMR chemical shift comparisons (DMSO-$d_6$ solutions): kodaistatin A (**1**; 151 MHz),[2] *cis*-**6** (100.6 MHz),[6] *trans*-**6** (100.6 MHz),[6] *cis*-**7** (100.6 MHz, this study), and *trans*-**7** (100.6 MHz, this study). Shift differences $\Delta\delta$ ($\equiv \delta_{in\ model} - \delta_{in\ 1}$) discrediting a *cis*-configuration of the natural product (**1**) are printed on a reddish background, shift differences corroborating a *trans*-configuration of the natural product (**1**) on a greenish background, shift differences inapt for recognizing the configuration of the natural product (**1**) on a greyish background, and shift differences due to a constitutional rather than configurational effect on a bluish background.

| C | δ/ppm | δ/ppm | Δδ/ppm | δ/ppm | Δδ/ppm | δ/ppm | Δδ/ppm | δ/ppm | Δδ/ppm |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 200.0 | 205.0 | 5.0 | 202.0 | 2.0 | 204.1 | 4.1 | 201.3 | 1.3 |
| 2 | 137.2 | 136.4 | −0.8 | 137.0 | −0.2 | 127.5 | −9.7 | 127.8 | −9.4 |
| 3 | 161.6 | 162.7 | 1.1 | 160.5 | −1.1 | 170.0 | 8.4 | 166.4 | 4.8 |
| 4 | 89.7 | 85.1 | −4.6 | 88.6 | −1.1 | 84.7 | −5.0 | 88.6 | −1.1 |
| 5 | 84.5 | 75.5 | −9.0 | 82.9 | −1.6 | 75.9 | −8.6 | 83.6 | −0.9 |
| 1’ | 207.7 | 211.3 | 3.6 | 207.8 | 0.1 | 211.0 | 3.3 | 207.2 | −0.5 |
| 2’ | 27.7 | 27.1 | −0.6 | 26.9 | −0.8 | 26.6 | −1.1 | 26.8 | −0.9 |



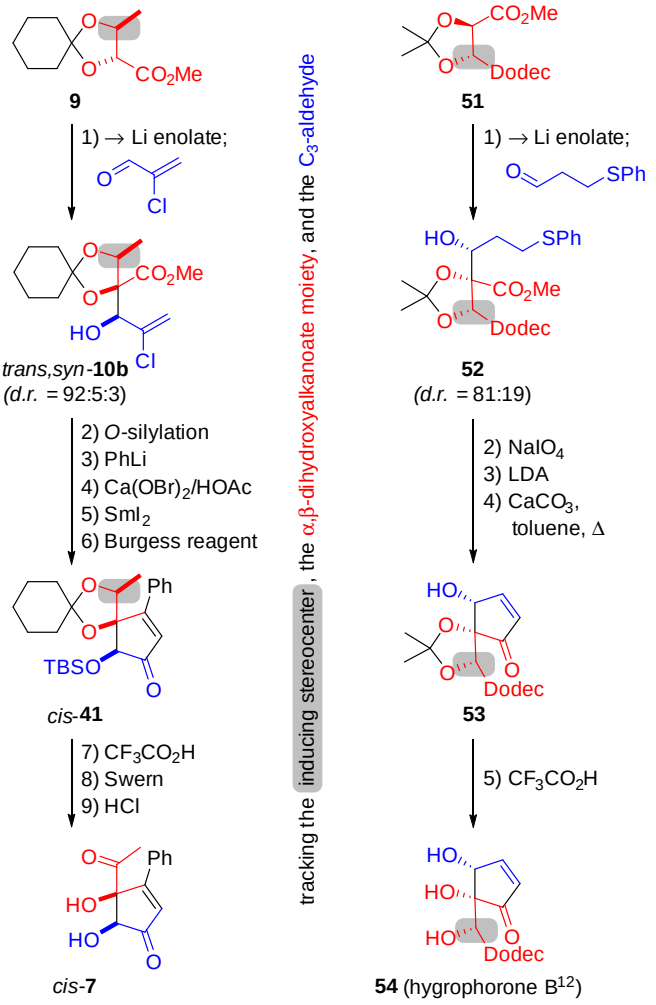

**Scheme 8.** Preparation of the sulfanylated ketone *syn*-**45** and its cyclization by an aldol condensation (→ *cis*-**49**; at left). Attempted 2-brominations of the cyclopentenone *trans*-**46** (at right). *Reagents and conditions*: a) $PyrHBr_3$ (2.0 equiv.), $K_2CO_3$ (5.0 equiv.), $CH_2Cl_2$, room temp., 5 h; no conversion.– b) $Br_2$ (1.0 equiv.), $NaHCO_3$ (5.0 equiv.), $CH_2Cl_2$, room temp., 23 h; decomposition.– c) NBS, $CH_2Cl_2$, 0 °C → room temp., 16 h; decomposition.– d) 2-Mercaptobenzo-1,3-thiazole (1.1 equiv.), $NEt_3$ (2.0 equiv.), MeCN, room temp., 4 h; 90%.– e) $PBu_3$ (2.0 equiv.), 90 °C, 17 h; 22%.– f) $PyrHBr_3$ (2.0 equiv.), $K_2CO_3$ (5.0 equiv.), $CH_2Cl_2$, 40 °C, 10 h; not purified (65:35 mixture of *trans*-**50** and an unidentified compound).

However, the two-step sequence depicted in Scheme 8 at left raises hopes that a 2-functionalized cyclopentenone might be accessible also in another way. We obtained the 2-(arylsulfanyl)cyclopentenone *cis*-**49** as the sole albeit undesired product in an attempt to cyclize the α-sulfanylated ketone *syn*-**45** to the 2-unsubstituted cyclopentenone *cis*-**37**. This attempt intended to convert this ketone and $PBu_3$ into the already mentioned phosphonium enolate **35** (formula: Scheme 6) in accordance with a pertinent report by Ueno *et al.*[34]. Instead, ketone *syn*-**45** conserved the arylsulfanyl group and cyclized in an aldol condensation. Whatever induced *this* reaction, the thioether moiety merely acted as a bystander! Future work shall therefore study the α-bromoketone analog *syn*-**31** of the α-sulfanylated

ketone *syn*-**45** as a conceivable substrate for a bromine-conserving cyclopentenone synthesis by a non-reductive aldol condensation.

## Conclusion

We synthesized a pair of simplified dihydroxycyclopentenones *cis*- and *trans*-**7** as model compounds of the kodaistatins A–D. Our synthetic route traced that to our 2nd generation models *cis*- and *trans*-**6** except for one step. This was because the aldol *anti*-**10b** was inaccessible by a Mukaiyama aldol addition. We circumvented this constraint by "epimerizing" the readily accessible aldol *syn*-**10b**, which resulted from a lithium enolate aldol addition, by a completely stereoselective oxidation/reduction sequence. Each of the diastereomeric aldols *syn*- and *anti*-**10b** was converted in eight steps into the respective kodaistatin model compound, providing *cis*-**7** in 61% yield and *trans*-**7** in 22% yield. $^{13}$C NMR analyses of the kodaistatin models *cis*- and *trans*-**7** confirmed our earlier conclusion that the natural product kodaistatin A (**1**) is a *trans*-diol. Other than our previous models *cis*- and *trans*-**6**[6] and the kodaistatins A-D, the newly prepared models *cis*- and *trans*-**7** are unsubstituted at C-2. It is conceivable that this difference can be turned into an advantage: It might allow introducing a variety of substituents *at C-2* of the otherwise already accomplished kodaistatin model *trans*-**7**. Functionalizations of such a potentially useful kind have been described in the literature.[7] Accordingly, this modus procedendi would represent a modular synthesis of a family of kodaistatin models.




**Scheme 9**. Contrasting roles of the dioxolane-based esters **9** (this work) vs. **51** (by Westermann, Wessjohann et al.[16d]) en route to the dihydroxycyclopentenone *cis*-**7** and the dihydroxycyclopentenone hygrophorone B$^{12}$.[5]

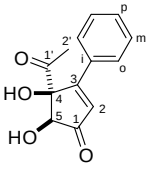
Finally, a comment concerning the strategic use of the ketal-protected α,β-dihydroxybutyrate-derived building block **9** in our syntheses is warranted. Its role is emphasized in the left half of Scheme 9 by our route to the model compound *cis*-**7**. The right half of Scheme 9 supplements a total synthesis of the somewhat related dihydroxycyclopentenone "hygrophorone B$^{12}$" (**54**)[16d] – although altogether, the substitution patterns of the two targets are distinct.[35] Remarkably, this synthesis, too, starts from a ketal-protected α,β-dihydroxyalkanoate-derived building block, namely from compound **51**. Three color codes serve for pointing out the differences between the two approaches, which, indeed, exhibit more differences than similarities. This is most obvious when comparing (1) where the (originally) inducing stereocenter ends up relative to the carbonyl group, namely at C$^{\gamma}$ (in *cis*-**7**) vs. C$^{\beta}$ (in **54**) or (2) which transformation the $CO_2Me$ group undergoes: It becomes part of the C=C double bond of target *cis*-**7** yet part of the C=O double bond of target **54**.

## Experimental Section

**Working technique**: All reactions, which did not require the presence of water, were carried out under an atmosphere of dry $N_2$ unless otherwise

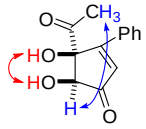
noted. Reaction flasks were pre-dried in an oven (110 °C) and, prior to use, dried with a heat gun under reduced pressure. Liquids were added with syringes and via cannula through a rubber septum. Solids were added in a countercurrent of inert gas. **Solvents**: Prior to use, tetrahydrofuran (THF) and toluene were freshly distilled over potassium, dichloromethane ($CH_2Cl_2$), diisopropylamine and triethylamine ($NEt_3$) over $CaH_2$ under an $N_2$ atmosphere. Other solvents were obtained commercially as "dry" or "extra dry" solvents and used without further purification. Solvents for reactions containing water were used as p. a. grade. Prior to use, Cyclo¬hexane, petroleum ether, ethyl acetate (EtOAc), and $CH_2Cl_2$ for workup and column chromatography were distilled using a rotary evaporator to remove high boiling fractions. Diethyl ether (p. a. grade, stabilized with BHT) was used without further purification. **Reagents**: Cyclohexanone and 2,6-lutidine were distilled prior to use and stored over molecular sieves (4 Å). Dess-Martin periodinane was synthesized from 2-iodobenzoic acid according to a literature procedure.[36] Other reagents were obtained commercially and used without further purification. Solutions of organolithium reagents were titrated using *N*-pivaloyl-*o*-toluidine prior to use.[37] **Chromatography**: Thin layer chromatography (TLC) on Merck silica plates with glass as supporting material (Merck TLC Silicagel 60 F254) was used to monitor reactions and assess purification procedures. If possible, thin layer chromatograms were marked in UV light at 254 nm and subsequently stained using one of the following stains: cerium sulfate/phosphomolybdic acid (10 g $Ce(SO_4)_2$, 25 g phospho¬molybdic acid, 1 L $H_2O$, 80 mL conc. $H_2SO_4$) or *p*-anisaldehyde (7.5 mL *p*-anisaldehyde, 3 mL AcOH, 10 mL conc. $H_2SO_4$, 270 mL EtOH). Macherey-Nagel silica gel 60 (230-400 mesh) was used for flash column chromatography. Chromatography conditions are documented at the respective experiment in the following manner: [d × h cm, V mL, solv1:solv2 = a:b (Fw–x) → c:d (Fy–z), Fm–n] which means: a column with the inner diameter d cm was packed with h cm silica gel; fractions of the size V mL were collected; the compounds were eluted with a mixture of the solvents solv1 and solv2 in the ratio a:b from fractions w to x; the ratio of the solvent mixture was changed to c:d and fractions y to z were collected; the desired product was isolated from fractions m to n. **Nuclear magnetic resonance spectroscopy**: NMR spectra were recorded by Dr. M. Keller, Mr. F. Reinbold or Ms. M. Schonhard on a Bruker Avance II 400 spectrometer [$^1$H (400 MHz), $^{13}$C (100 MHz), DQF-COSY, edHSQC, HMBC, and NOESY experiments) or a Bruker Avance III HD 500 spectrometer [$^1$H (500 MHz), $^{13}$C (126 MHz), DQF-COSY, edHSQC, HMBC, and NOESY experiments] at 303 K (unless otherwise noted). Self-service NMR measure¬ments were performed by D. Peter on a Bruker Avance II 300 spectrometer [$^1$H (300 MHz), $^{31}$P (121 MHz)] at 300 K. $^1$H NMR spectra were referenced internally to the solvent signal ($CHCl_3$: 7.26 ppm, $C_6HD_5$: 7.15 ppm, DMSO-$d_5$: 2.49 ppm), although tetramethylsilane (TMS) was added to most NMR samples as additional internal standard. $^{13}$C NMR spectra were referenced internally to the solvent signal ($CDCl_3$: 77.10 ppm, DMSO-$d_6$: 39.50 ppm). $^1$H NMR data are reported as follows: chemical shift (δ in ppm), multiplicity (s for singlet; d for doublet; t for triplet; q for quartet; m for multiplet; $m_c$ for symmetrical multiplet; br for broad signal), coupling constant(s) (*J* in Hz; $^3J$ couplings unless otherwise noted), integral, and specific assignment. $^{13}$C NMR data are reported in terms of chemical shift and assignment. For AB signals the high-field part was named A and the low-field part B. Signals were assigned unambiguously (unless otherwise noted) to the corresponding nuclei by means of 2D spectra (DQF-COSY, edHSQC, HMBC). In cases where an unambiguous assignment was not possible, a group of signals is listed in curly brackets and assigned to the corresponding group of nuclei. **High resolution mass spectra** were measured by Dr. J. Wörth and C. Warth on a Thermo Scientific Exactive mass spectrometer equipped with an orbitrap analyzer. Ionization method: Electron spray ionization (ESI; spray voltage: 4–5 kV) or atmospheric pressure chemical ionization (APCI; spray current: 5 µA). **Elemental analyses** were conducted by Ms. A. Siegel on an Elementar Vario EL CHNS analyzer. **Melting points** were determined on a Schorpp Gerätetechnik MPM-HV2 melting point meter using open glass capillaries. **IR** spectra (film on NaCl plate) were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer.

**(*rel*-4*S*,5*S*)-4-Acetyl-4,5-dihydroxy-3-phenylcyclopent-2-en-1-one (*cis*-7)**




*cis*-**7**

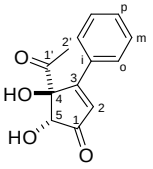
Aqueous HCl (3 M, 0.47 mL, 1.4 mmol, 5 equiv.) was added to a solution of *cis*-**42** (98 mg, 0.28 mmol) in MeOH (5 mL). The resulting solution was stirred at room temp. for 17 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ solution (6 mL). Brine (30 mL) was added and the mixture was extracted with $CH_2Cl_2$ (4 × 20 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography (1.0 × 18 cm, 7 mL, $CH_2Cl_2$/MeOH = 1:0 (F1–7) → 100:1 (F8–15) → 50:1 (F16–30), F21–29) afforded compound *cis*-**7** (60 mg, 0.26 mmol, 93%) as a white solid (mp 143–144 °C). $^1$H NMR (400.13 MHz, DMSO-$d_6$, sample contained 5 mol% *trans*-**7**) δ = 2.30 (s, 3H, 2'-$H_3$), 3.97 (s, 1H, 5-H), 6.02 (br. s, 1H, 4-OH), 6.25 (br. s, 1H, 5-OH), 6.84 (s, 1H, 2-H), 7.41–7.49 (m, 3H, Ar-H$^m$, Ar-H$^p$), 7.68–7.75 (m, 2H, Ar-H$^o$). $^{13}$C NMR (100.61 MHz, DMSO-$d_6$) δ = 26.64 (C-2'), 75.88 (C-5), 84.75 (C-4), 127.50 (C-2), 128.19 (Ar-C$^o$), 128.73 (Ar-C$^m$), 130.87 (Ar-C$^p$), 132.33 (Ar-C$^i$), 170.05 (C-3), 204.13 (C-1), 211.13 (C-1'). The configurations at C-4 and C-5 were confirmed by a NOESY experiment: NOESY (400.13 MHz/400.13 MHz, 600 ms, DMSO-$d_6$) [δ ($^1$H) ↔ δ ($^1$H)]: [2.30 (2'-$H_3$) ↔ 3.97 (5-H)], [6.02 (4-OH) ↔ 6.25 (5-OH)]. Graphical representation of crucial NOESY cross peaks:




*cis*-**7**

HRMS (pos. APCI) *m*/*z* = 250.10739 $[M+NH_4]^+$ corresponds to the formula $C_{13}H_{16}O_4N$ (*m*/*z* = 250.10738) with a deviation of 0.0 ppm. IR (film) $\tilde{\nu}\tilde{\nu}$ = 3420, 3070, 2930, 2850, 1715, 1600, 1570, 1495, 1450, 1360, 1275, 1205, 1130, 910, 770, 695 $cm^{-1}$. Elemental analysis $C_{13}H_{12}O_4$ (232.24): calcd. C 67.23, H 5.21; found C 67.18 H 5.22.

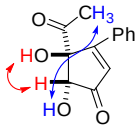
**(*rel*-4*S*,5*R*)-4-Acetyl-4,5-dihydroxy-3-phenylcyclopent-2-en-1-one (*trans*-7)**




*trans*-**7**

Aqueous HCl (3 M, 1.4 mL, 4.2 mmol, 10 equiv.) was added to a solution of *trans*-**42** (151 mg, 433 µmol) in MeOH (5 mL). The resulting solution was stirred at room temp. for 3 d. The reaction was quenched by addition of sat. aq. $NaHCO_3$ solution (5 mL). Brine (20 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated under reduced pressure.

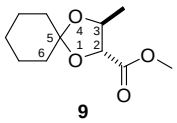
Purification by flash chromatography (1.5 × 15 cm, 7 mL, cyclohexane/EtOAc = 5:1 (F1–13) → 3:1 (F14–40), F20–39) afforded compound *trans*-**7** (78.4 mg, 336 µmol, 78%) as a white solid (mp 158–160 °C). $^1$H NMR (400.13 MHz, DMSO-d$_6$, sample contained 2 mol% *cis*-**7**) δ = 2.25 (s, 3H, 2'-H$_3$), 4.36 (d, $^3J_{5,5\text{-OH}}$ = 6.0 Hz, 1H, 5-H), 6.24 (d, $^3J_{5\text{-OH},5}$ = 5.9 Hz 1H, 5-OH), 6.55 (s, 1H, 4-OH), 6.91 (s, 1H, 2-H), 7.40–7.50 (m, 3H, Ar-H$^m$, Ar-H$^p$), 7.62–7.69 (m, 2H, Ar-H$^o$). $^{13}$C NMR (100.61 MHz, DMSO-d$_6$) = 26.76 (C-2'), 83.63 (C-5), 88.59 (C-4), 127.76 (C-2), 128.57 (Ar-C$^o$), 128.65 (Ar-C$^m$), 130.74 (Ar-C$^p$), 131.40 (Ar-C$^i$), 166.42 (C-3), 201.29 (C-1), 207.22 (C-1'). The configurations at C-4 and C-5 were confirmed by a NOESY experiment: NOESY (500.32 MHz/500.32 MHz, 600 ms, DMSO-d$_6$) [δ ($^1$H) ↔ δ ($^1$H)]: [2.25 (2'-H$_3$) ↔ 6.24 (5-OH)], [4.36 (5-H) ↔ 6.55 (4-OH)]. Graphical representation of crucial NOESY cross peaks:




*trans*-**7**

HRMS (neg. APCI) *m*/*z* = 267.04312 [M+Cl]$^-$ corresponds to the formula $C_{13}H_{12}O_4Cl$ (*m*/*z* = 267.04296) with a deviation of +0.6 ppm. IR (film) $\tilde{\nu}$ = 3455, 3430, 3015, 2920, 1700, 1590, 1570, 1445, 1360, 1270, 1205, 1165, 1140, 1105, 910, 770, 695 cm$^{-1}$. Elemental analysis $C_{13}H_{12}O_4$ (232.24): calcd. C 67.23, H 5.21; found C 67.11 H 5.29.

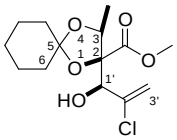
**Methyl (*rel*-2*R*,3*S*)-3-Methyl-1,4-dioxaspiro[4.5]decane-2-carboxylate (9)**



**9**

At room temp. cyclohexanone (1.5 mL, 1.4 g, 14 mmol, 1.2 equiv.), anhydrous CuSO$_4$ (3.0 g, 19 mmol, 1.6 equiv.) and *p*TsOH·H$_2$O (0.10 g, 0.50 mmol, 4 mol%) were added successively to a solution of methyl (*rel*-2*R*,3*S*)-dihydroxybutyrate (**20**, 1.61 g, 12.0 mmol) in CH$_2$Cl$_2$ (10 mL). The mixture was stirred at room temp. for 24 h. The reaction was quenched by addition of NEt$_3$ (0.10 mL, 73 mg, 9 mol%) and stirring for 5 min. The mixture was filtered through a pad of Celite® (8 × 2 cm) that was rinsed with CH$_2$Cl$_2$ (100 mL). The solvent was evaporated under reduced pressure. Purification by flash chromatography [2.5 × 17 cm, 20 mL, cyclohexane:EtOAc = 20:1 (F1–26) → 10:1 (F27–36), F15–27] afforded compound **9** [2.30 g, 10.7 mmol, 89% (ref.[15] 89%)] as a colorless oil. $^1$H NMR (400.13 MHz, CDCl$_3$) δ = {1.35–1.46 (m, 2H) and 1.51–1.76 (m, 8H)} (6-H$_2$, 7-H$_2$, 8-H$_2$, 9-H$_2$, 10-H$_2$), 1.43 (d, $J_{3\text{-CH}_3,3}$ = 6.0 Hz, 3H, 3-CH$_3$), 3.77 (s, 3H, CO$_2$CH$_3$), 4.06 (d, $J_{2,3}$ = 7.8 Hz, 1H, 2-H), 4.21 (dq, $J_{3,2}$ = 7.8 Hz, $J_{3,3\text{-CH}_3}$ = 6.0 Hz, 1H, 3-H). $^{13}$C NMR (100.61 MHz, CDCl$_3$) δ = 18.90 (3-CH$_3$), {23.76 and 23.95 and 25.15} (C-7, C-8, C-9), {35.12 and 36.93} (C-6, C-10), 52.32 (CO$_2$CH$_3$), 74.86 (C-3), 80.25 (C-2), 111.50 (C-5), 171.31 (CO$_2$CH$_3$).

**Methyl (*rel*-2*S*,3*S*)-2-((*S*)-2-Chloro-1-hydroxyprop-2-en-1-yl)-3-methyl-1,4-dioxaspiro[4.5]decane-2-carboxylate (*trans*,*syn*-10b)**



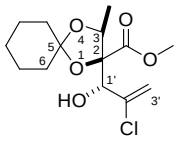

*trans*,*syn*-**10b**

Method A:[13b] At −78 °C DMSO (0.96 mL, 1.1 g, 14 mmol, 1.4 equiv.) was added dropwise within 5 min to a solution of oxalyl chloride (1.1 mL, 1.6 g, 13 mmol, 1.3 equiv.) in THF (25 mL). The solution was stirred at that temperature for 10 min, warmed to −35 °C within 45 min, and was again cooled to −78 °C. A solution of 2-chloroprop-2-en-1-ol (**17**, 1.11 g, 12.0 mmol, 1.20 equiv.) in THF (5 mL) was added within 5 min. The resulting solution was warmed to −35 °C within 1 h and then NEt$_3$ (8.3 mL, 6.1 g, 60 mmol, 6 equiv.) was added. The mixture was warmed to room temp. within 1 h. The solids were filtered under N$_2$ and the filtrate was cooled to −78 °C.

In a separate Schlenk flask a solution of diisopropylamine (1.7 mL, 1.2 g, 12 mmol, 1.2 equiv.) in THF (20 mL) was treated with *n*BuLi (2.4 M in hexanes, 5.0 mL, 12 mmol, 1.2 equiv.) at −78 °C. The mixture was warmed to 0 °C, stirred at that temperature for 30 min and cooled to −78 °C. A solution of the ester **9** (2.14 g, 10.0 mmol) in THF (4 mL) was added dropwise within 5 min and the resulting solution was stirred at −78 °C for 1 h. The cold filtrate of the Swern oxidation was added by means of a transfer cannula within 5 min. The resulting mixture was stirred at −78 °C for 4 h, was then poured on a mixture of sat. aq. NH$_4$Cl solution (80 mL), H$_2$O (20 mL), and Et$_2$O (30 mL), and stirred at room temp. for 10 min. The phases were separated and the aqueous phase was extracted with Et$_2$O (2 × 80 mL). The combined organic phases were washed with brine (50 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. Purification by flash chromatography [4.0 × 16 cm, 50 mL, petroleum ether (30–50 °C)/Et$_2$O = 15:1 (F1–27) → 10:1 (F28–61), F33–59] afforded compound *trans*,*syn*-**10b** (2.05 g, 6.73 mmol, 67%, d.r. 92:5:3) as a colorless oil.

Method B: At −78 °C a solution of diisopropylamine (3.0 mL, 2.1 g, 21 mmol, 1.4 equiv.) in THF (45 mL) was treated with *n*BuLi (2.4 M in hexanes, 8.0 mL, 20 mmol, 1.3 equiv.). The mixture was warmed to 0 °C, stirred at that temperature for 20 min and cooled to −78 °C. A solution of the ester **9** (3.21 g, 15.0 mmol) in THF (10 mL) was added dropwise within 6 min and the mixture was stirred at −78 °C for 1 h. A solution of 2-chloroacrolein (**12**, 1.5 g, 17 mmol, 1.1 equiv.) in THF (10 mL) was added dropwise within 3 min and the mixture was stirred at −78 °C for 4 h. The cold reaction mixture was poured on a mixture of sat. aq. NH$_4$Cl solution (120 mL), H$_2$O (10 mL) and Et$_2$O (50 mL) and stirred at room temp. for 10 min. The phases were separated and the aqueous phase was extracted with Et$_2$O (2 × 50 mL). The combined organic phases were washed with brine (100 mL), dried over MgSO$_4$ and concentrated under reduced pressure. Purification by flash chromatography [6.0 × 15 cm, 100 mL, cyclohexane/EtOAc = 30:1 (F1–10) → 10:1 (F11–45), F14–19] afforded compound *trans*,*syn*-**10b** (2.93 g, 9.61 mmol, 64%, d.r. 92:6:2) as a colorless oil. $^1$H NMR (400.13 MHz, CDCl$_3$) δ = 1.26 (d, $J_{3\text{-CH}_3,3}$ = 6.4 Hz, 3H, 3-CH$_3$), {1.37–1.45 (m, 2H) and 1.55–1.74 (m, 6H) and 1.79–1.94 (m, 2H)} (6-H$_2$, 7-H$_2$, 8-H$_2$, 9-H$_2$, 10-H$_2$), 2.66 (d, $J_{1'\text{-OH},1'}$ = 11.1 Hz, 1H, 1'-OH), 3.71 (s, 3H, 2-CO$_2$CH$_3$), 4.42 (d, $J_{1',1'\text{-OH}}$ = 11.1 Hz, 1H, 1'-H), 4.53 (q, $J_{3,3\text{-CH}_3}$ = 6.4 Hz, 1H, 3-H), 5.37 (d, $^2J_{A,B}$ = 1.8 Hz, 1H, 3'-H$^A$), 5.51 (dd, $^2J_{B,A}$ = 1.8 Hz, $^4J_{3',1'}$ = 0.4 Hz, 1H, 3'-H$^B$). $^{13}$C NMR (100.61 MHz, CDCl$_3$) δ = 15.17 (3-CH$_3$), {23.94 and 24.01 and 25.17} (C-7, C-8, C-9), {35.71 and 36.44} (C-6, C-10), 51.93 (2-CO$_2$CH$_3$), 72.88 (C-1'), 75.21 (C-3), 88.28 (C-2), 110.29 (C-5), 116.32 (C-3'), 140.62 (C-2'), 170.93 (4-CO$_2$CH$_3$). HRMS (pos. ESI) *m*/*z* = 327.0973 [M+Na]$^+$ corresponds to the formula $C_{14}H_{21}O_5ClNa^+$ (*m*/*z* = 327.0970) with a deviation of +1.0 ppm. IR (film) $\tilde{\nu}$ = 3500, 2940, 2860, 1760, 1730, 1635, 1450, 1370, 1255, 1145, 1115, 1065, 1005, 955, 910 cm$^{-1}$. Elemental analysis $C_{14}H_{21}ClO_5$ (304.77): calcd. C 55.17, H 6.95; found C 55.01, H 6.91.

**Methyl (*rel*-2*S*,3*S*)-2-((*R*)-2-Chloro-1-hydroxyprop-2-en-1-yl)-3-methyl-1,4-dioxaspiro[4.5]decane-2-carboxylate (*trans*,*anti*-10b)**



*trans,anti*-**10b**

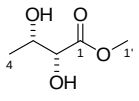
At −78 °C $NaBH_4$ (250 mg, 6.61 mmol, 2.0 equiv.) was added within 5 min to a solution of the enone **24** (1.00 g, 3.30 mmol) and $CeCl_3{\cdot}7H_2O$ (2.22 g, 5.95 mmol, 1.8 equiv.) in MeOH (30 mL). The resulting solution was stirred at −78 °C for 1 h and then poured on a mixture of sat. aq. $NH_4Cl$ solution (40 mL), aq. HCl (1 M, 5 mL) and $H_2O$ (30 mL). The mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$ solution (80 mL) and brine (80 mL) and dried over $Na_2SO_4$. The solvent was evaporated under reduced pressure. Purification of the residue by flash chromatography [2.5 × 15 cm, 20 mL, cyclohexane/EtOAc = 10:1 (F1–24) → 5:1 (F25–35), F15–20] afforded compound *trans*,*anti*-**10b** (525 mg, 1.72 mmol, 52%) as a colorless oil. $^1$H NMR (400.13 MHz, $CDCl_3$) δ = 1.32 (d, $J_{3\text{-}CH_3,3}$ = 6.3 Hz, 3H, 3-$CH_3$), {1.34–1.47 (m, 2H) and 1.52–1.73 (m, 6H) and 1.76–1.90 (m, 2H)} (6-$H_2$, 7-$H_2$, 8-$H_2$, 9-$H_2$, 10-$H_2$), 3.78 (d, $J_{1'\text{-}OH,1'}$ = 11.2 Hz, 1H, 1'-OH), 3.80 (s, 3H, 2-$CO_2CH_3$), 4.36 (d, $J_{1',1'\text{-}OH}$ = 11.2 Hz, 1H, 1'-H), 4.43 (q, $J_{3,3\text{-}CH_3}$ = 6.3 Hz, 1H, 3-H), 5.47–5.49 (m, 2H, 3'-$H_2$). $^{13}$C NMR (100.61 MHz, $CDCl_3$) δ = 16.85 (3-$CH_3$), {23.85 and 24.00 and 25.15} (C-7, C-8, C-9), {35.87 and 36.45} (C-6, C-10), 52.51 (2-$CO_2CH_3$), 78.36 (C-3), 78.93 (C-1'), 85.91 (C-2), 111.38 (C-5), 116.40 (C-3'), 139.97 (C-2'), 172.47 (4-$CO_2CH_3$). HRMS (pos. ESI) *m*/*z* = 327.0970 $[M+Na]^+$ corresponds to the formula $C_{14}H_{21}O_5ClNa^+$ (*m*/*z* = 327.0970) with a deviation of 0.0 ppm. IR (film) $\tilde{\nu}$ = 3475, 2940, 2860, 1755, 1730, 1630, 1450, 1370, 1255, 1145, 1110, 1060, 1000, 940, 905 $cm^{-1}$.

**2-Chloroacrolein (12)**

**12**

At −78 °C a solution of DMSO (8.0 mL, 8.8 g, 0.11 mol, 1.1 equiv.) in $CH_2Cl_2$ (10 mL) was added dropwise within 10 min to a solution of oxalyl chloride (9.3 mL, 14 g, 0.11 mol, 1.1 equiv.) in $CH_2Cl_2$ (170 mL). The solution was stirred at that temperature for 15 min, warmed to −60 °C, stirred for further 15 min and was then cooled to −78 °C. A solution of 2-chloroprop-2-en-1-ol (**22**, 9.09 g, 98.3 mmol) in $CH_2Cl_2$ (20 mL) was added within 10 min. The resulting solution was warmed to −50 °C within 1.5 h and then $NEt_3$ (68 mL, 50 g, 0.50 mol, 5.0 equiv.) was added. After stirring for 30 min at −50 °C the mixture was warmed to room temp. within 2 h. The mixture was poured on aqueous HCl (2.4 M, 250 mL), the phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic phases were washed with brine (200 mL) and dried over $MgSO_4$. The solvent was partially removed at 40 °C under reduced pressure (not below 300 mbar) and the residue was purified by vacuum distillation ($bp_{45\ mbar}$ = 32–33 °C).[38] Compound **12** (3.80 g, 42.0 mmol, 43%) was isolated as a colorless liquid and stored immediately at −80 °C. $^1$H NMR (300.13 MHz, $CDCl_3$) δ = 6.42 (d, $^2J_{A,B}$ = 2.0 Hz, 1H, 3-$H^A$), 6.59 (d, $^2J_{B,A}$ = 2.0 Hz, 1H, 3-$H^A$), 9.45 (s, 1H, 1-H).

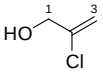
**Methyl (*rel*-2*R*,3*S*)-Dihydroxybutyrate (20)**



**20**

*N*-Methylmorpholine-*N*-oxide monohydrate (NMO·$H_2O$, 5.0 mL, 5.7 g, 42 mmol, 2.1 equiv.) was added to a solution of methyl crotonate (**19**, 2.00 g, 20.0 mmol), citric acid monohydrate (3.15 g, 15.0 mmol, 0.75 equiv.) and $K_2OsO_2(OH)_4$ (15 mg, 40 µmol, 0.2 mol%) in $H_2O$ (20 mL) and *t*BuOH (20 mL) at room temp. The solution was stirred vigorously for 18 h. The reaction was quenched by addition of sat. aq. $Na_2SO_3$ solution (10 mL) and the resulting mixture was stirred at room temp. for 30 min. The aqueous phase was saturated with solid NaCl and extracted with EtOAc (15 × 10 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography [3.5 × 16 cm, 50 mL, cyclohexane/EtOAc = 2:1 (F1–8) → 3:2 (F9–27) → 1:1 (F28–37), F16–28] afforded compound **20** [2.41 g, 18.0 mmol, 90% (ref.[25] 66%)] as a colorless oil. $^1$H NMR (500.32 MHz, $CDCl_3$, 333 K) δ = 1.28 (d, $J_{4,3}$ = 6.5 Hz, 3H, 4-$H_3$), {2.34 (br. s, 1H) and 3.18 (br. s, 1H)} (2-OH, 3-OH), 3.80 (s, 3H, 1'-$H_3$), 3.99 (d, $J_{2,3}$ = 3.0 Hz, 1H, 2-H), 4.05 (qd, $J_{3,4}$ = 6.4 Hz, $J_{3,2}$ = 3.0 Hz, 1H, 3-H). $^{13}$C NMR (125.81 MHz, $CDCl_3$) δ = 19.63 (C-4), 52.81 (C-1'), 68.75 (C-3), 74.54 (C-2), 173.87 (C-1). HRMS (pos. ESI) *m*/*z* = 157.0472 $[M+Na]^+$ corresponds to the formula $C_5H_{10}O_4Na^+$ (*m*/*z* = 157.0471) with a deviation of +0.7 ppm. IR (film) $\tilde{\nu}$ = 3395, 2980, 1740, 1645, 1445, 1380, 1295, 1220, 1150, 1075, 1015, 935, 900, 850, 780, 750, 680 $cm^{-1}$.

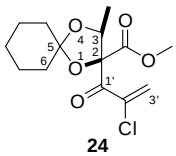
**2-Chloroprop-2-en-1-ol (22)**



**22**

2,3-Dichloropropene (**21**, 14.8 g, 133 mmol) was added to a solution of $K_2CO_3$ (20.2 g, 146 mmol, 1.1 equiv.) in $H_2O$ (130 mL). The biphasic mixture was heated to reflux and stirred for 16 h. After cooling to room temp. the mixture was extracted with $Et_2O$ (3 × 50 mL). The organic phase was washed with brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Purification by vacuum distillation [$bp_{50\ mbar}$ = 57–60 °C (ref.[39] $bp_{1\ atm}$ = 127–129 °C)] afforded compound **22** [10.6 g, 115 mmol, 86% (ref.[39] 92%)] as a colorless liquid. $^1$H NMR (300.13 MHz, $CDCl_3$) δ = 2.09 (br. s, 1H, OH), 4.18 (dd, $^4J_{1,3B}$ = 1.4 Hz, $^4J_{1,3A}$ = 0.9 Hz, 2H, 1-$H_2$), 5.34 (dt, $^2J_{A,B}$ = 1.7 Hz, $^4J_{3,1}$ = 0.9 Hz, 1H, 3-$H^A$), 5.48 (dt, $^2J_{B,A}$ = 1.5 Hz, $^4J_{3,1}$ = 1.5 Hz, 1H, 3-$H^B$).

**Methyl (*rel*-2*R*,3*S*)-2-(2-Chloroacryloyl)-3-methyl-1,4-dioxaspiro[4.5]-decane-2-carboxylate (24)**

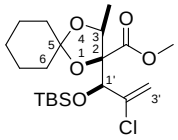


**24**

A solution of the alcohol *trans*,*syn*-**10b** (862 mg, 2.83 mmol) in $CH_2Cl_2$ (20 mL) was treated with pyridine (1.1 mL, 1.1 g, 14 mmol, 4.9 equiv.) and cooled to 0 °C. Dess-Martin periodinane (1.44 g, 3.40 mmol, 1.2 equiv.) was added and the resulting mixture was stirred at 0 °C for 15 min. The solution was warmed to room temp. and stirred for 1.5 h. Silica gel (4.3 g) was added and the solvent was evaporated under reduced pressure. Purification by flash chromatography [3.0 × 15 cm, 20 mL, cyclohexane/EtOAc = 100:1 (F1–19) → 50:1 (F20–45) → 20:1 (F45–58), F20–51] afforded compound **20** (670 mg, 2.21 mmol, 78%) as a colorless oil. $^1$H NMR (400.13 MHz, $CDCl_3$) δ = 1.31 (d, $J_{3\text{-}CH_3,3}$ = 6.4 Hz, 3H, 3-$CH_3$), {1.35–1.75 (m, 8H) and 1.80–1.98 (m, 2H)} (6-$H_2$, 7-$H_2$, 8-$H_2$, 9-$H_2$, 10-$H_2$), 3.78 (s, 3H, 2-$CO_2CH_3$), 4.86 (q, $J_{3,3\text{-}CH_3}$ = 6.3 Hz, 1H, 3-H), 6.30 (d, $^2J_{A,B}$ = 2.5 Hz, 1H, 3'-$H^A$), 6.65 (d, $^2J_{B,A}$ = 2.5 Hz, 1H, 3'-$H^B$). $^{13}$C NMR (100.61 MHz, $CDCl_3$) δ = 16.09 (3-$CH_3$), {23.81 and 24.04 and 25.10} (C-

7, C-8, C-9), {35.10 and 36.55} (C-6, C-10), 52.70 (2-$CO_2CH_3$), 75.84 (C-3), 87.76 (C-2), 112.71 (C-5), 128.46 (C-3'), 137.35 (C-2'), 169.01 (4-$CO_2CH_3$), 178.38 (C-1'). HRMS (pos. APCI) *m*/*z* = 320.1261 $[M+NH_4]^+$ corresponds to the formula $C_{14}H_{23}O_5ClN^+$ (*m*/*z* = 320.1259) with a deviation of +0.4 ppm. IR (film) $\tilde{\nu}$ = 2940, 2860, 1765, 1735, 1705, 1600, 1450, 1370, 1260, 1225, 1115, 1065, 925, 715 $cm^{-1}$.

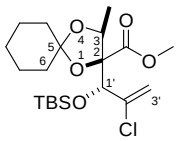
**Methyl (*rel*-2*R*,3*S*)-2-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-chloroprop-2-en-1-yl)-3-methyl-1,4-dioxaspiro[4.5]decane-2-carboxylate (*syn*-29)**




*syn*-**29**

At 0 °C *tert*-butyldimethylsilyl triflate (TBSOTf, 2.3 mL, 2.6 g, 9.9 mmol, 1.5 equiv.) was added dropwise to a solution of the alcohol *trans*,*syn*-**10b** (2.01 g, 6.60 mmol) and 2,6-lutidine (2.3 mL, 2.1 g, 20 mmol, 3.0 equiv.) in $CH_2Cl_2$ (13 mL). The solution was allowed to warm to room temp. with stirring for 20 h. Brine (20 mL) was added, the mixture was extracted with $CH_2Cl_2$ (3 × 20 mL), and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Purification by flash chromatography [5.0 × 15 cm, 100 mL, cyclohexane/EtOAc = 100:1 (F1–7) → 50:1 (F8–14) → 30:1 (F15–28), F14–22] afforded compound *syn*-**29** (2.58 g, 6.16 mmol, 93%) as a colorless oil. $^1$H NMR (400.13 MHz, $CDCl_3$) δ = 0.10 (s, 3H, $SiC^AH_3$), 0.11 (s, 3H, $SiC^BH_3$), 0.92 (s, 9H, $SiC(CH_3)_3$), 1.27 (d, $J_{3\text{-}CH_3,3}$ = 6.5 Hz, 3H, 3-$CH_3$), {1.29–1.48 (m, 2H) and 1.51–1.92 (m, 8H)} (6-$H_2$, 7-$H_2$, 8-$H_2$, 9-$H_2$, 10-$H_2$), 3.72 (s, 3H, 2-$CO_2CH_3$), 4.57 (q, $J_{3,3\text{-}CH_3}$ = 6.5 Hz, 1H, 3-H), 4.68 (d, $^4J_{1',3'B}$ = 0.7 Hz, 1H, 1'-H), 5.43 (d, $^2J_{A,B}$ = 1.2 Hz, 1H, 3'-$H^A$), 5.57 (dd, $^2J_{B,A}$ = 1.2 Hz, $^4J_{3',1'}$ = 0.8 Hz, 1H, 3'-$H^B$). $^{13}$C NMR (100.61 MHz, $CDCl_3$) δ = −5.13 ($SiC^BH_3$), −4.71 ($SiC^AH_3$), 15.99 (3-$CH_3$), 18.26 ($SiC(CH_3)_3$), {23.71 and 24.14 and 25.34} (C-7, C-8, C-9), 25.82 ($SiC(CH_3)_3$), {35.73 and 36.50} (C-6, C-10), 51.90 (2-$CO_2CH_3$), 74.22 (C-3), 74.84 (C-1'), 88.72 (C-2), 110.45 (C-5), 116.55 (C-3'), 140.44 (C-2'), 171.29 (2-$CO_2CH_3$). HRMS (pos. APCI) *m*/*z* = 419.20145 $[M+H]^+$ corresponds to the formula $C_{20}H_{36}O_5ClSi^+$ (*m*/*z* = 419.20150) with a deviation of −0.1 ppm. IR (film) $\tilde{\nu}$ = 2935, 2900, 2860, 1760, 1730, 1630, 1450, 1370, 1255, 1145, 1115, 1085, 1005, 840, 780 $cm^{-1}$. Elemental analysis $C_{20}H_{35}ClO_5Si$ (419.03): calcd. C 57.33, H 8.42; found C 57.46, H 8.47.

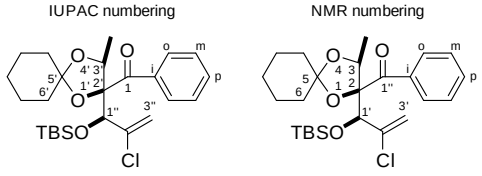
**Methyl (*rel*-2*R*,3*S*)-2-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-chloroprop-2-en-1-yl)-3-methyl-1,4-dioxaspiro[4.5]decane-2-carboxylate (*anti*-29)**




*anti*-**29**

At 0 °C *tert*-butyldimethylsilyl triflate (TBSOTf, 0.38 mL, 0.44 g, 1.7 mmol, 1.5 equiv.) was added dropwise to a solution of the alcohol *trans*,*anti*-**10b** (338 mg, 1.11 mmol) and 2,6-lutidine (0.39 mL, 0.36 g, 3.3 mmol, 3.0 equiv.) in $CH_2Cl_2$ (11 mL). The solution was allowed to warm to room temp. with stirring for 18 h. Brine (10 mL) and $CH_2Cl_2$ (10 mL) were added, the phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. Purification by flash chromatography [2.0 × 18 cm, 20 mL, cyclohexane/EtOAc = 50:1 (F1–8) → 30:1 (F9–19) → 30:1 (F15–28), F12–17] afforded compound *anti*-**29** (404 mg, 0.96 mmol, 87%) as a colorless oil. $^1$H NMR (400.13 MHz, $CDCl_3$) δ = 0.06 (s, 3H, $SiC^AH_3$), 0.07 (s, 3H, $SiC^BH_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 1.30 (d, $J_{3\text{-}CH_3,3}$ = 6.4 Hz, 3H, 3-$CH_3$), {1.31–1.64 (m, 7H) and 1.66–1.76 (m, 1H) and 1.77–1.93 (m, 2H)} (6-$H_2$, 7-$H_2$, 8-$H_2$, 9-$H_2$, 10-$H_2$), 3.72 (s, 3H, 2-$CO_2CH_3$), 4.24 (q, $J_{3,3\text{-}CH_3}$ = 6.4 Hz, 1H, 3-H), 4.60 ($m_c$, 1H, 1'-H), 5.56 (dd, $^2J_{A,B}$ = 1.3 Hz, $^4J_{3',1'}$ = 0.3 Hz, 1H, 3'-$H^A$), 5.65 (dd, $^2J_{B,A}$ = 1.2 Hz, $^4J_{3',1'}$ = 0.6 Hz, 1H, 3'-$H^B$). $^{13}$C NMR (100.61 MHz, $CDCl_3$) δ = −5.34 ($SiC^AH_3$), −4.50 ($SiC^BH_3$), 16.01 (3-$CH_3$), 18.16 ($SiC(CH_3)_3$), {23.91 and 24.08 and 25.30} (C-7, C-8, C-9), 25.77 ($SiC(CH_3)_3$), {35.98 and 36.52} (C-6, C-10), 51.83 (2-$CO_2CH_3$), 75.06 (C-3), 77.71 (C-1'), 89.64 (C-2), 110.25 (C-5), 118.18 (C-3'), 139.50 (C-2'), 171.03 (2-$CO_2CH_3$). HRMS (pos. APCI) *m*/*z* = 419.20148 $[M+H]^+$ corresponds to the formula $C_{20}H_{36}O_5ClSi^+$ (*m*/*z* = 419.20150) with a deviation of −0.1 ppm. IR (film) $\tilde{\nu}$ = 2935, 2860, 1765, 1730, 1635, 1450, 1370, 1255, 1145, 1110, 1080, 915, 840, 780 745 $cm^{-1}$. Elemental analysis $C_{20}H_{35}ClO_5Si$ (419.03): calcd. C 57.33, H 8.42; found C 57.50, H 8.48.

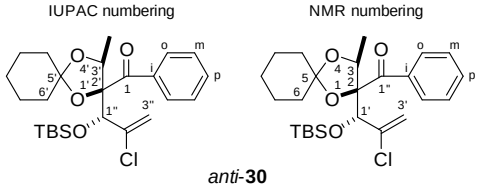
**((*rel*-2*R*,3*S*)-2-((*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-chloroprop-2-en-1-yl)-3-methyl-1,4-dioxaspiro[4.5]decan-2-yl)(phenyl)methanone (*syn*-30)**




*syn*-**30**

At −78 °C PhLi (1.8 M in $Bu_2O$, 4.3 mL, 7.7 mmol, 1.2 equiv.) was added dropwise to a solution of the ester *syn*-**29** (2.58 g, 6.16 mmol) in THF (48 mL) and the resulting solution was stirred at that temperature for 1 h. The reaction was quenched by pouring the cold solution on a mixture of aq. phosphate buffer (pH 6, 0.1 M, 200 mL) and $Et_2O$ (70 mL) and warming to room temp. with vigorous stirring. The phases were separated, the aqueous phase was extracted with $Et_2O$ (3 × 60 mL), and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Purification by flash chromatography [4.5 × 15 cm, 100 mL, cyclohexane/EtOAc = 100:1 (F1–15) → 50:1 (F16–25), F6–15] afforded compound *syn*-**30** (2.62 g, 5.63 mmol, 91%) as a colorless oil. $^1$H NMR (400.13 MHz, $CDCl_3$) δ = 0.11 (s, 3H, $SiC^AH_3$), 0.13 (s, 3H, $SiC^BH_3$), {0.89–0.97 (m, 1H) and 1.10–1.29 (m, 2H) and 1.36–1.76 (m, 6H), 1.96–2.04 (m, 1H)} (6-$H_2$, 7-$H_2$, 8-$H_2$, 9-$H_2$, 10-$H_2$), 0.95 (s, 9H, $SiC(CH_3)_3$), 1.31 (d, $J_{3\text{-}CH_3,3}$ = 6.5 Hz, 3H, 3-$CH_3$), 4.67 (q, $J_{3,3\text{-}CH_3}$ = 6.5 Hz, 1H, 3-H), 4.82 (d, $^4J_{1',3'B}$ = 0.6 Hz, 1H, 1'-H), 5.42 (d, $^2J_{A,B}$ = 1.2 Hz, 1H, 3'-$H^A$), 5.46 (dd, $^2J_{B,A}$ = 1.2 Hz, $^4J_{3',1'}$ = 0.8 Hz, 1H, 3'-$H^B$), 7.33–7.38 (m, 2H, Ar-$H^m$), 7.44 ($m_c$, 1H, Ar-$H^p$), 7.80–7.83 (m, 2H, Ar-$H^o$). $^{13}$C NMR (100.61 MHz, $CDCl_3$) δ = −5.11 ($SiC^BH_3$), −4.75 ($SiC^AH_3$), 16.74 (3-$CH_3$), 18.33 ($SiC(CH_3)_3$), {23.56 and 24.04 and 25.30} (C-7, C-8, C-9), 25.87 ($SiC(CH_3)_3$), {35.82 and 36.36} (C-6, C-10), 75.87 (C-3), 76.24 (C-1'), 94.59 (C-2), 110.53 (C-5), 116.40 (C-3'), 127.42 (Ar-$C^m$), 129.22 (Ar-$C^o$), 131.58 (Ar-$C^p$), 139.47 (Ar-$C^i$), 141.17 (C-2'), 205.64 (C-1''). HRMS (pos. ESI) *m*/*z* = 487.2043 $[M+Na]^+$ corresponds to the formula $C_{25}H_{37}O_4ClNaSi^+$ (*m*/*z* = 487.2042) with a deviation of +0.3 ppm. IR (film) $\tilde{\nu}$ = 2935, 2900, 2860, 1675, 1625, 1600, 1445, 1370, 1255, 1150, 1105, 945, 890, 840, 780, 700 $cm^{-1}$. Elemental analysis $C_{25}H_{37}ClO_4Si$ (465.10): calcd. C 64.56, H 8.02; found C 64.47, H 7.99.

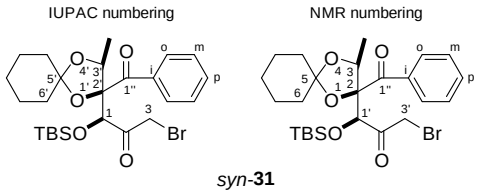
**((*rel*-2*R*,3*S*)-2-((*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-2-chloroprop-2-en-1-yl)-3-methyl-1,4-dioxaspiro[4.5]decan-2-yl)(phenyl)methanone (*anti*-30)**




*anti*-**30**

At −78 °C PhLi (1.8 M in $Bu_2O$, 0.80 mL, 1.4 mmol, 1.5 equiv.) was added dropwise to a solution of the ester *anti*-**29** (398 mg, 950 µmol) in THF (10 mL) and the resulting solution was stirred at that temperature for 1 h. The reaction was quenched by pouring the cold solution on a mixture of sat. aq. $NH_4Cl$ solution (10 mL), $H_2O$ (2 mL), and $Et_2O$ (10 mL), and warming to room temp. with vigorous stirring. The phases were separated, the aqueous phase was extracted with $Et_2O$ (3 × 10 mL), and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Purification by flash chromatography (2.0 × 18 cm, 20 mL, cyclohexane/EtOAc = 100:1) afforded compound *anti*-**30** (437 mg, 940 µmol, 99%) as a colorless oil. $^1$H NMR (400.13 MHz, $CDCl_3$) δ = −0.11 (s, 3H, $SiC^AH_3$), 0.06 (s, 3H, $SiC^BH_3$), {0.81–0.97 (m, 2H) and 1.19–1.70 (m, 8H)} (6-$H_2$, 7-$H_2$, 8-$H_2$, 9-$H_2$, 10-$H_2$), 0.79 (s, 9H, $SiC(CH_3)_3$), 1.39 (d, $J_{3\text{-}CH3,3}$ = 6.4 Hz, 3H, 3-$CH_3$), 4.29 (q, $J_{3,3\text{-}CH3}$ = 6.4 Hz, 1H, 3-H), 4.70 (br. s, 1H, 1'-H), 5.63 (d, $^2J_{A,B}$ = 1.2 Hz, 1H, 3'-$H^A$), 5.74 (dd, $^2J_{B,A}$ = 1.2 Hz, $^4J_{3',1'}$ = 0.5 Hz, 1H, 3'-$H^B$), 7.32–7.37 (m, 2H, Ar-$H^m$), 7.43 ($m_c$, 1H, Ar-$H^p$), 7.84–7.89 (m, 2H, Ar-$H^o$). $^{13}$C NMR (100.61 MHz, $CDCl_3$) δ = −5.48 ($SiC^AH_3$), −4.76 ($SiC^BH_3$), 16.00 (3-$CH_3$), 18.17 ($SiC(CH_3)_3$), {23.66 and 23.93 and 25.18} (C-7, C-8, C-9), 25.80 ($SiC(CH_3)_3$), {36.09 and 36.34} (C-6, C-10), 76.00 (C-3), 78.44 (C-1'), 93.82 (C-2), 109.79 (C-5), 118.16 (C-3'), 127.19 (Ar-$C^m$), 129.66 (Ar-$C^o$), 131.44 (Ar-$C^p$), 139.75 (Ar-$C^i$), 140.11 (C-2'), 205.53 (C-1''). HRMS (pos. APCI) *m*/*z* = 465.22223 $[M+H]^+$ corresponds to the formula $C_{25}H_{38}O_4ClSi^+$ (*m*/*z* = 465.22224) with a deviation of 0.0 ppm. IR (film) $\tilde{\nu}$ = 2935, 2860, 1685, 1445, 1370, 1255, 1145, 1115, 1065, 915, 840, 780, 750, 695 $cm^{-1}$.

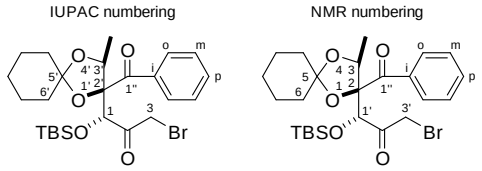
**(*rel*-1*S*)-1-((2*R*,3*S*)-2-Benzoyl-3-methyl-1,4-dioxaspiro[4.5]decan-2-yl)-3-bromo-1-((*tert*-butyldimethylsilyl)oxy)propan-2-one (*syn*-31)**




*syn*-**31**

A solution of $Ca(OBr)_2$ in $H_2O$ was prepared by dropwise addition of bromine (1.2 mL, 3.7 g, 23 mmol) at 0 °C within 15 min to a suspension of $Ca(OH)_2$ (5.6 g, 76.0 mmol) in $H_2O$ (48 mL). The suspension was stirred at 0 °C for 30 min and then used immediately. A portion of this suspension (0.24 M, 21 mL, 5.0 mmol, 2.4 equiv.) was added dropwise within 15 min to a solution of the chloroolefin *syn*-**30** (1.0 g, 2.1 mmol) and AcOH (11 mL, 12 g, 0.20 mol, 95 equiv.) in MeCN (28 mL) at 0 °C with a needleless syringe. After complete addition the resulting bright orange solution was stirred for further 45 min at 0 °C. The reaction was quenched by pouring the mixture on an aqueous solution of $Na_2S_2O_3$ and $K_2CO_3$ (1 M/2 M, 100 mL). $CH_2Cl_2$ (50 mL) was added and the mixture was stirred at room temp. for 10 min. The solids were filtered and brine (200 mL) was added to the filtrate. The mixture was extracted with $CH_2Cl_2$ (2 × 100 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography [3.5 × 15 cm, 50 mL, cyclohexane/EtOAc = 100:1 (F1–19) → 75:1 (F20–50), F27–38] afforded compound *syn*-**31** (1.0 g, 1.9 mmol, 89%) as a yellowish solid (mp 97–98 °C). $^1$H NMR (400.13 MHz, $CDCl_3$) δ = 0.13 (s, 3H, $SiC^AH_3$), 0.22 (s, 3H, $SiC^BH_3$), 0.93 (s, 9H, $SiC(CH_3)_3$), 1.16 (d, $J_{3\text{-}CH3,3}$ = 6.3 Hz, 3H, 3-$CH_3$), {1.23–1.48 (m, 5H) and 1.49–1.67 (m, 3H) and 1.67–1.75 (m, 1H) and 1.76–1.83 (m, 1H)} (6-$H_2$, 7-$H_2$, 8-$H_2$, 9-$H_2$, 10-$H_2$), 4.31 (d, $^2J_{A,B}$ = 14.7 Hz, 1H, 3'-$H^A$), 4.51 (d, $^2J_{B,A}$ = 14.7 Hz, 1H, 3'-$H^B$), 4.51 (s, 1H, 1'-H), 4.78 (q, $J_{3,3\text{-}CH3}$ = 6.3 Hz, 1H, 3-H), 7.35–7.39 (m, 2H, Ar-$H^m$), 7.48 ($m_c$, 1H, Ar-$H^p$), 7.75–7.80 (m, 2H, Ar-$H^o$). $^{13}$C NMR (100.61 MHz, $CDCl_3$) δ = −4.79 ($SiC^AH_3$), −4.00 ($SiC^BH_3$), 17.09 (3-$CH_3$), 18.13 ($SiC(CH_3)_3$), {23.76 and 23.94 and 25.09} (C-7, C-8, C-9), 25.93 ($SiC(CH_3)_3$), {35.00 and 35.40} (C-6, C-10), 36.28 (C-3'), 76.04 (C-3), 82.65 (C-1'), 95.49 (C-2), 110.83 (C-5), 127.59 (Ar-$C^m$), 129.29 (Ar-$C^o$), 132.09 (Ar-$C^p$), 138.70 (Ar-$C^i$), 202.09 (C-2'), 204.70 (C-1''). HRMS (pos. ESI) *m*/*z* = 547.14886 $[M+Na]^+$ corresponds to the formula $C_{25}H_{37}O_5BrNaSi^+$ (*m*/*z* = 547.14858) with a deviation of +0.5 ppm. IR (film) $\tilde{\nu}$ = 2940, 2860, 1730, 1675, 1600, 1465, 1450, 1370, 1255, 1145, 1115, 1085, 1010, 945, 880, 840, 780, 700 $cm^{-1}$.

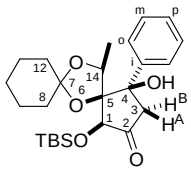
**(*rel*-1*R*)-1-((2*R*,3*S*)-2-Benzoyl-3-methyl-1,4-dioxaspiro[4.5]decan-2-yl)-3-bromo-1-((*tert*-butyldimethylsilyl)oxy)propan-2-one (*anti*-31)**




*anti*-**31**

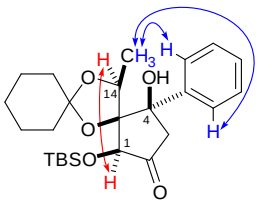
A solution of $Ca(OBr)_2$ in $H_2O$ was prepared by dropwise addition of bromine (0.3 mL, 1 g, 6 mmol) at 0 °C to a suspension of $Ca(OH)_2$ (1.4 g, 19 mmol) in $H_2O$ (12 mL). The suspension was stirred at 0 °C for 30 min and then used immediately. A portion of this suspension (0.25 M, 6.4 mL, 1.6 mmol, 2.5 equiv.) was added dropwise within 15 min to a solution of the chloroolefin *anti*-**30** (297 mg, 639 µmol) and AcOH (3.4 mL, 3.5 g, 59 mmol, 92 equiv.) in MeCN (8.5 mL) at 0 °C with a needleless syringe. After complete addition the resulting bright orange solution was stirred at room temp. for 18 h. The reaction was quenched by pouring the mixture on an aqueous solution of $Na_2S_2O_3$ and $K_2CO_3$ (1 M/2 M, 25 mL). $CH_2Cl_2$ (50 mL) was added and the mixture was stirred at room temp. for 10 min. The solids were filtered and brine (70 mL) was added to the filtrate. The mixture was extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography (2.0 × 15 cm, 20 mL, cyclohexane/EtOAc = 100:1, F18–27] afforded compound *anti*-**31** (261 mg, 497 µmol, 78%) as a yellowish solid (mp 100–101 °C). $^1$H NMR (400.13 MHz, $CDCl_3$) δ = −0.07 (s, 3H, $SiC^AH_3$), 0.01 (s, 3H, $SiC^BH_3$), 0.77 (s, 9H, $SiC(CH_3)_3$), {0.84 ($m_c$, 2H) and 1.17–1.59 (m, 8H)} (6-$H_2$, 7-$H_2$, 8-$H_2$, 9-$H_2$, 10-$H_2$), 1.40 (d, $J_{3\text{-}CH3,3}$ = 6.4 Hz, 3H, 3-$CH_3$), 4.24 (q, $J_{3,3\text{-}CH3}$ = 6.4 Hz, 1H, 3-H), 4.59 (s, 1H, 1'-H), AB signal (A: 4.64, B: 4.75, $^2J_{A,B}$ = 16.5 Hz, 2H, 3-$H_2$), 7.35–7.40 (m, 2H, Ar-$H^m$), 7.50 ($m_c$, 1H, Ar-$H^p$), 7.82–7.86 (m, 2H, Ar-$H^o$). $^{13}$C NMR (100.61 MHz, $CDCl_3$) δ = −5.69 ($SiC^AH_3$), −4.86 ($SiC^BH_3$), 15.77 (3-$CH_3$), 17.90 ($SiC(CH_3)_3$), {23.80 and 24.04 and 24.95} (C-7, C-8, C-9), 25.69 ($SiC(CH_3)_3$), {35.77 and 36.36} (C-6, C-10), 37.30 (C-3'), 75.62 (C-3), 80.24 (C-1'), 91.95 (C-2), 110.80 (C-5), 127.45 (Ar-$C^m$), 129.52 (Ar-$C^o$), 131.88 (Ar-$C^p$), 139.34 (Ar-$C^i$), 202.45 (C-2'), 203.43 (C-1''). HRMS (pos. APCI) *m*/*z* = 525.16650 $[M+H]^+$ corresponds to the formula $C_{25}H_{38}O_5BrSi^+$ (*m*/*z* = 525.16664) with a deviation of −0.3 ppm. IR (film) $\tilde{\nu}$ = 2935, 2860, 1735, 1685, 1450, 1390, 1255, 1140, 1080, 915, 900, 840, 780, 745, 700 $cm^{-1}$.

**(*rel*-1*S*,4*R*,5*R*,14*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-14-methyl-4-phenyl-6,13-dioxadispiro[4.1.5$^7$.2$^5$]tetradecan-2-one (*cis*-39)**



*cis*-**39**

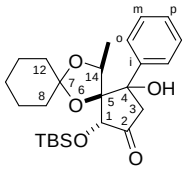
Crude brownish 1,2-diiodoethane was dissolved in $Et_2O$ and the orange solution was washed with sat. aq. $Na_2S_2O_3$ solution (2 ×), $H_2O$ and brine. The organic phase was dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure to give a white solid. The purified 1,2-diiodoethane (2.00 g, 7.1 mmol) was transferred to the reaction flask under argon, then samarium powder (2.13 g, 14.2 mmol, 2.0 equiv.) and degassed THF (71 mL) were added successively. The mixture was stirred vigorously under argon at room temp. for 18 h, buffering the initial temperature rise with a water bath. Stirring was stopped, the mixture was allowed to stand until the solids were settled (approx. 1 h) and titrated with 2-heptanone indicating a concentration of 0.075 M.[40] The freshly prepared solution of $SmI_2$ (0.075 M in THF, 43 mL, 3.2 mmol, 2.1 equiv.) was diluted with THF (25 mL) and cooled to −78 °C. A solution of the bromoketone *syn*-**31** (790 mg, 1.50 mmol) in THF (25 mL) was added dropwise within 15 min. The reaction mixture was stirred at −78 °C for 1 h and was then allowed to warm to room temp. within 3 h. Air was bubbled through the mixture until the blue color faded. Brine (50 mL), sat. aq. $NH_4Cl$ solution (50 mL), EtOAc (50 mL) and aq. HCl (1 M, 5 mL) were added, the phases were separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography [2.5 × 15 cm, 20 mL, cyclohexane/EtOAc = 20:1 (F1–35) → 10:1 (F36–47), F18–44) afforded compound *cis*-**39** (644 mg, 1.44 mmol, 96%) as a white solid (mp 118–119 °C). $^1$H NMR (400.13 MHz, $CDCl_3$) δ = 0.14 (s, 3H, SiC$^A$H$_3$), 0.22 (s, 3H, SiC$^B$H$_3$), 0.95 (s, 9H, SiC(CH$_3$)$_3$), {1.01–1.13 (m, 2H) and 1.15–1.28 (m, 1H) and 1.36–1.54 (m, 6H) and 1.83–1.91 (m, 1H)} (8-H$_2$, 9-H$_2$, 10-H$_2$, 11-H$_2$, 12-H$_2$), 1.60 (d, $J_{14\text{-}CH_3,14}$ = 6.9 Hz, 3H, 14-CH$_3$), 1.96–1.98 (m, 1H, 4-OH), 2.36 (dd, $^2J_{A,B}$ = 18.8 Hz, $^4J_{3,1}$ = 2.1 Hz, 1H, 3-H$^A$), 3.23 (d, $^2J_{B,A}$ = 18.8 Hz, 1H, 3-H$^B$), 4.43 (q, $J_{14,14\text{-}CH_3}$ = 6.8 Hz, 1H, 14-H), 4.80 (d, $^4J_{1,3}$ = 2.1 Hz, 1H, 1-H), 7.30 (m$_c$, 1H, Ar-H$^p$), 7.34–7.39 (m, 2H, Ar-H$^m$), 7.65–7.68 (m, 2H, Ar-H$^o$). $^{13}$C NMR (100.61 MHz, $CDCl_3$) δ = −4.77 (SiC$^A$H$_3$), −4.17 (SiC$^B$H$_3$), 14.74 (14-CH$_3$), 18.58 (Si*C*(CH$_3$)$_3$), {23.46 and 23.92 and 25.23} (C-9, C-10, C-11), 26.03 (SiC(*C*H$_3$)$_3$), {35.19 and 35.80} (C-8, C-12), 52.76 (C-3), 73.82 (C-14), 77.83 (C-1), 79.82 (C-4), 90.55 (C-5), 109.37 (C-7), 127.75 (Ar-C$^m$), 127.90 (Ar-C$^p$), 127.92 (Ar-C$^o$), 140.80 (Ar-C$^i$), 211.24 (C-2). The configuration at C-4 was assigned by a NOESY experiment. NOESY (400.13 MHz/400.13 MHz, 600 ms, $CDCl_3$) [δ ($^1$H) ↔ δ ($^1$H)]: [1.60 (14-CH$_3$) ↔ 7.65–7.68 (Ar-H$^o$) ↔ 3.23 (3-H$^B$)], [1.96–1.98 (4-OH) ↔ 2.36 (3-H$^A$)], [4.43 (14-H) ↔ 4.80 (1-H)]. Graphical representation of crucial NOESY cross peaks:



*cis*-**39**

HRMS (pos. APCI) *m*/*z* = 464.28271 [M+NH$_4$]$^+$ corresponds to the formula $C_{25}H_{42}O_5NSi^+$ (*m*/*z* = 464.28268) with a deviation of +0.1 ppm. IR (film) $\tilde{\nu}$ = 3440, 2935, 2900, 2860, 1760, 1470, 1445, 1375, 1255, 1205, 1125, 1050, 945, 915, 860, 840, 780, 745, 705 cm$^{-1}$.

**(*rel*-1*R*,5*R*,14*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-14-methyl-4-phenyl-6,13-dioxadispiro[4.1.5$^7$.2$^5$]tetradecan-2-one (*trans*-39:*dia*,*trans*-39 = 70:30)[41]**

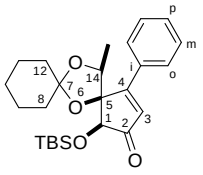


*trans*-**39**

A freshly prepared solution of $SmI_2$ (0.087 m in THF, 35 mL, 3.1 mmol, 2.0 equiv.) was diluted with THF (25 mL) and cooled to −78 °C. A solution of the bromoketone *anti*-**31** (858 mg, 1.54 mmol) in THF (20 mL) was added dropwise within 30 min. Towards the end of the addition the solution turned from dark blue to yellow. The reaction mixture was stirred at −78 °C for 1 h and was then allowed to warm to room temp. within 2.5 h. The reaction was quenched by addition of sat. aq. $NH_4Cl$ solution (75 mL). After addition of EtOAc (50 mL), $H_2O$ (20 mL) and aq. HCl (1 M, 10 mL), the phases were separated and the aqueous phase was extracted with EtOAc (2 × 50 mL). The combined organic phases were washed with brine (100 mL), dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography [3.5 × 17 cm, 50 mL, cyclohexane/EtOAc = 75:1 (F1–10) → 50:1 (F11–26) → 40:1 (F27–43), F21–41] afforded the target structure as a mixture of C-4 epimers (574 mg, 1.29 mmol, 84%, *trans*-**39**:*dia*,*trans*-**39** = 70:30). A pure sample of each diastereomer was isolated for analytics from F25 (*trans*-**39**, 37 mg, colorless oil) and F37–41 (*dia*,*trans*-**39**, 23 mg, yellowish oil), repectively. Major diastereomer (*trans*-**39**): $^1$H NMR (400.13 MHz, $CDCl_3$) δ = 0.23 (s, 3H, SiC$^A$H$_3$), 0.23 (s, 3H, SiC$^B$H$_3$), 0.95 (s, 9H, SiC(CH$_3$)$_3$), {1.28–1.43 (m, 3H) and 1.44–1.66 (m, 7H)} (8-H$_2$, 9-H$_2$, 10-H$_2$, 11-H$_2$, 12-H$_2$), 1.33 (d, $J_{14\text{-}CH_3,14}$ = 6.8 Hz, 3H, 14-CH$_3$), 2.79 (dd, $^2J_{A,B}$ = 19.3 Hz, $^4J_{3,1}$ = 0.8 Hz, 1H, 3-H$^A$), 3.18 (dd, $^2J_{B,A}$ = 19.2 Hz, $^4J_{3,1}$ = 0.6 Hz, 1H, 3-H$^B$), 3.95 (m$_c$, 1H, 1-H), 4.35 (s, 1H, 4-OH), 4.63 (q, $J_{14,14\text{-}CH_3}$ = 6.8 Hz, 1H, 14-H), 7.27 (m$_c$, 1H, Ar-H$^p$), 7.30–7.35 (m, 2H, Ar-H$^m$), 7.71–7.76 (m, 2H, Ar-H$^o$). $^{13}$C NMR (100.61 MHz, $CDCl_3$) δ = −5.15 (SiC$^A$H$_3$), −4.49 (SiC$^B$H$_3$), 17.59 (14-CH$_3$), 18.16 (Si*C*(CH$_3$)$_3$), {23.83 and 23.91 and 25.09} (C-9, C-10, C-11), 25.73 (SiC(*C*H$_3$)$_3$), {36.51 and 37.31} (C-8, C-12), 55.27 (C-3), 74.80 (C-14), 80.68 (C-1), 81.80 (C-4), 88.66 (C-5), 110.45 (C-7), 127.25 (Ar-C$^m$), 127.31 (Ar-C$^p$), 127.78 (Ar-C$^o$), 140.43 (Ar-C$^i$), 212.06 (C-2). HRMS (pos. ESI) *m*/*z* = 469.23810 [M+Na]$^+$ corresponds to the formula $C_{25}H_{38}O_5NaSi^+$ (*m*/*z* = 469.23807) with a deviation of +0.1 ppm. IR (film) $\tilde{\nu}$ = 3485, 2935, 2885, 2860, 1760, 1450, 1365, 1255, 1165, 1135, 1110, 1070, 1005, 915, 840, 745, 705 cm$^{-1}$. Minor Diastereomer (*dia*,*trans*-**39**): $^1$H NMR (400.13 MHz, $CDCl_3$) δ = 0.14 (s, 3H, SiC$^A$H$_3$), 0.23 (s, 3H, SiC$^B$H$_3$), 0.95 (s, 9H, SiC(CH$_3$)$_3$), 1.00 (d, $J_{14\text{-}CH_3,14}$ = 6.8 Hz, 3H, 14-CH$_3$), {1.37–1.49 (m, 2H) and 1.50–1.91 (m, 8H)} (8-H$_2$, 9-H$_2$, 10-H$_2$, 11-H$_2$, 12-H$_2$), 2.90 (m$_c$, 2H, 3-H$_2$), 3.77 (m$_c$, 1H, 4-OH), 4.66 (q, $J_{14,14\text{-}CH_3}$ = 6.9 Hz, 1H, 14-H), 4.84 (m$_c$, 1H, 1-H), 7.26–7.38 (m, 3H, Ar-H$^m$, Ar-H$^p$), 7.58–7.62 (m, 2H, Ar-H$^o$).$^{13}$C NMR (100.61 MHz, $CDCl_3$) δ = −4.80 (SiC$^A$H$_3$), −4.13 (SiC$^B$H$_3$), 15.76 (14-CH$_3$), 18.39 (Si*C*(CH$_3$)$_3$), {23.85 and 24.16 and 25.21} (C-9, C-10, C-11), 25.93 (SiC(*C*H$_3$)$_3$), {36.22 and 36.77} (C-8, C-12), 49.32 (C-3), 71.29 (C-14), 78.07 (C-4), 80.21 (C-1), 91.83 (C-5), 109.33 (C-7), 126.90 (Ar-C$^o$), 127.94 (Ar-C$^p$), 127.98 (Ar-C$^m$), 141.39 (Ar-C$^i$), 210.64 (C-2). HRMS (pos. ESI) *m*/*z* = 469.23822 [M+Na]$^+$ corresponds to the formula $C_{25}H_{38}O_5NaSi^+$ (*m*/*z* = 469.23807) with a deviation of +0.3 ppm. IR (film)

$\tilde{\nu}$ = 3505, 2935, 2855, 1760, 1450, 1375, 1255, 1110, 915, 840, 745, 700 cm$^{-1}$.

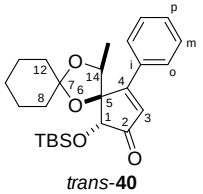
**(*rel*-1*S*,5*R*,14*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-14-methyl-4-phenyl-6,13-dioxadispiro[4.1.5$^7$.2$^5$]tetradec-3-en-2-one (*cis*-40)**




*cis*-**40**

At room temp. (methoxycarbonylsulfamoyl)triethylammonium hydroxide inner salt (Burgess reagent, 194 mg, 813 µmol, 3.0 equiv.) was added to a solution of the hydroxycyclopentanone *cis*-**39** (121 mg, 271 µmol) in toluene (3 mL). The mixture was stirred at 100 °C for 12 h and then cooled to room temp. Silica gel was added and the solvent was evaporated under reduced pressure. Purification by flash chromatography (1.0 × 16 cm, 7 mL, cyclohexane/EtOAc = 20:1, F5–10) afforded compound *cis*-**40** (113 mg, 263 µmol, 97%) as a white solid (mp 82–85 °C). $^1$H NMR (400.13 MHz, $CDCl_3$) δ = 0.17 (s, 3H, $SiC^AH_3$), 0.21 (s, 3H, $SiC^BH_3$), 0.95 (s, 9H, $SiC(CH_3)_3$), 1.16 (d, $J_{14\text{-}CH_3,14}$ = 6.7 Hz, 3H, 14-$CH_3$), {1.36–1.50 (m, 2H) and 1.51–1.59 (m, 8H)} (8-$H_2$, 9-$H_2$, 10-$H_2$, 11-$H_2$, 12-$H_2$), 4.02 (s, 1H, 1-H), 4.45 (q, $J_{14,14\text{-}CH_3}$ = 6.7 Hz, 1H, 14-H), 6.36 (s, 1H, 3-H), 7.37–7.45 (m, 3H, Ar-H$^m$, Ar-H$^p$), 7.80–7.86 (m, 2H, Ar-H$^o$). $^{13}$C NMR (100.61 MHz, $CDCl_3$) δ = −4.31 ($SiC^AH_3$), −3.99 ($SiC^BH_3$), 15.53 (14-$CH_3$), 18.64 ($SiC(CH_3)_3$), {23.90 and 24.11 and 25.26} (C-9, C-10, C-11), 26.10 ($SiC(CH_3)_3$), {35.80 and 36.32} (C-8, C-12), 75.58 (C-1), 77.10 (C-14, superimposed by $CDCl_3$), 88.59 (C-5), 110.89 (C-7), 128.39 (Ar-C$^m$), 128.99 (Ar-C$^o$), 129.71 (C-3), 130.38 (Ar-C$^p$), 134.75 (Ar-C$^i$), 170.27 (C-4), 202.31 (C-2). HRMS (pos. APCI) *m*/*z* = 429.24554 [M+H]$^+$ corresponds to the formula $C_{25}H_{37}O_4Si^+$ (*m*/*z* = 429.24556) with a deviation of 0.0 ppm. IR (film) $\tilde{\nu}$ = 2990, 2935, 2870, 1725, 1450, 1390, 1255, 1145, 1095, 1035, 915, 745 cm$^{-1}$. Elemental analysis $C_{25}H_{36}O_4Si$ (348.51): calcd. C 70.05, H 8.47; found C 69.72 H 8.06.

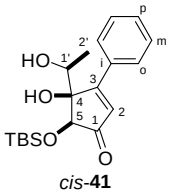
**(*rel*-1*R*,5*R*,14*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-14-methyl-4-phenyl-6,13-dioxadispiro[4.1.5$^7$.2$^5$]tetradec-3-en-2-one (*trans*-40)**




*trans*-**40**

At room temp. (methoxycarbonylsulfamoyl)triethylammonium hydroxide inner salt (Burgess reagent, 35 mg, 0.15 mmol, 2 equiv.) was added to a solution of a mixture of the hydroxycyclopentanones *trans*-**39** and *dia,trans*-**39** (d.r. 70:30, 121 mg, 271 µmol) in toluene (3 mL). The mixture was stirred at 100 °C for 12 h and then cooled to room temp. Silica gel was added and the solvent was evaporated under reduced pressure. Purification by flash chromatography (1.0 × 16 cm, 7 mL, cyclohexane/EtOAc = 20:1, F5–10) afforded compound *cis*-**40** (113 mg, 263 µmol, 99%) as a white solid (mp 94–95 °C). $^1$H NMR (400.13 MHz, $CDCl_3$) δ = 0.16 (s, 3H, $SiC^AH_3$), 0.27 (s, 3H, $SiC^BH_3$), 0.97 (s, 9H, $SiC(CH_3)_3$), 1.19 (d, $J_{14\text{-}CH_3,14}$ = 6.6 Hz, 3H, 14-$CH_3$), {1.33–1.47 (m, 2H) and 1.50–1.58 (m, 6H) and 1.72–1.87 (m, 2H)} (8-$H_2$, 9-$H_2$, 10-$H_2$, 11-$H_2$, 12-$H_2$), 4.70 (s, 1H, 1-H), 4.90 (q, $J_{14,14\text{-}CH_3}$ = 6.5 Hz, 1H, 14-H), 6.35 (s, 1H, 3-H), 7.37–7.44 (m, 3H, Ar-H$^m$, Ar-H$^p$), 7.68–7.75 (m, 2H, Ar-H$^o$). $^{13}$C NMR (100.61 MHz, $CDCl_3$) δ = −4.80 ($SiC^AH_3$), −3.74 ($SiC^BH_3$), 15.93 (14-$CH_3$), 18.49 ($SiC(CH_3)_3$), {23.82 and 23.96 and 25.29} (C-9, C-10, C-11), 26.00 ($SiC(CH_3)_3$), {35.10 and 36.56} (C-8, C-12), 73.07 (C-14), 81.70 (C-1), 91.46 (C-5), 109.78 (C-7), 128.25 (Ar-C$^m$), 129.17 (C-3), 129.27 (Ar-C$^o$), 130.11 (Ar-C$^p$), 134.36 (Ar-C$^i$), 170.98 (C-4), 199.76 (C-2). HRMS (pos. ESI) *m*/*z* = 451.22736 [M+Na]$^+$ corresponds to the formula $C_{25}H_{36}O_4NaSi^+$ (*m*/*z* = 451.22751) with a deviation of −0.3 ppm. IR (film) $\tilde{\nu}$ = 2935, 2860, 1725, 1560, 1450, 1260, 1180, 1105, 915, 835, 745 cm$^{-1}$.

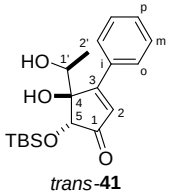
**(*rel*-4*R*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-4-((*S*)-1-hydroxyethyl)- 3-phenylcyclopent-2-en-1-one (*cis*-41)**




*cis*-**41**

At room temp. a solution of $H_2O$ (6 µL, 6 mg, 0.3 mmol, 1 equiv.) in trifluoroacetic acid (TFA, 0.30 mL, 0.44 g, 3.9 mmol, 13 equiv.) was added to a solution of the ketal *cis*-**40** (134 mg, 313 µmol) in $CH_2Cl_2$ (3 mL). The solution was stirred at room temp. for 1.5 h and then poured on a mixture of sat. aq. $NaHCO_3$ solution (10 mL), brine (20 mL) and $CH_2Cl_2$ (10 mL). The mixture was stirred vigorously at room temp. for 5 min until evolution of gas had ceased. The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography [1.5 × 15 cm, 7 mL, cyclohexane/EtOAc = 20:1 (F1–11) → 10:1 (F12–19) → 5:1 (F20–27) → 2:1 (F28–31), F22–28] afforded compound *cis*-**41** (109 mg, 313 µmol, 100%) as a white solid (mp 83–84 °C). $^1$H NMR (400.13 MHz, $CDCl_3$) δ = 0.28 (s, 3H, $SiC^AH_3$), 0.31 (s, 3H, $SiC^BH_3$), 0.95 (s, 9H, $SiC(CH_3)_3$), 1.26 (d, $J_{2',1'}$ = 6.4 Hz, 3H, 2'-$H_3$), 1.53 (br. d, $J_{1'\text{-}OH,1'}$ = 4.0 Hz, 1H, 1'-OH), 4.02 (s, 1H, 4-OH), 4.20 (br. qd, $J_{1',2'}$ = 6.4 Hz, $J_{1',1'\text{-}OH}$ = 3.7 Hz, 1H, 1'-H), 4.30 (s, 1H, 5-H), 7.40–7.48 (m, 3H, Ar-H$^m$, Ar-H$^p$), 7.80–7.87 (m, 2H, Ar-H$^o$). $^{13}$C NMR (100.61 MHz, $CDCl_3$) δ = −5.00 ($SiC^AH_3$), −3.55 ($SiC^BH_3$), 17.95 (C-2'), 18.39 ($SiC(CH_3)_3$), 26.96 ($SiC(CH_3)_3$), 69.04 (C-1'), 71.76 (C-5), 80.64 (C-4), 128.62 (Ar-C$^o$), 128.90 (Ar-C$^m$), 129.59 (C-2), 130.85 (Ar-C$^p$), 133.55 (Ar-C$^i$), 173.94 (C-3), 203.28 (C-1). HRMS (pos. APCI) *m*/*z* = 349.18311 [M+H]$^+$ corresponds to the formula $C_{19}H_{29}O_4Si^+$ (*m*/*z* = 349.18296) with a deviation of +0.4 ppm. IR (film) $\tilde{\nu}$ = 3470, 2990, 2870, 1710, 1600, 1575, 1450, 1390, 1260, 1140, 1075, 915, 840, 785 cm$^{-1}$. Elemental analysis $C_{19}H_{28}O_4Si$ (348.51): calcd. C 65.48, H 8.10; found C 65.45 H 8.08.

**(*rel*-4*R*,5*R*)-5-((*tert*-Butyldimethylsilyl)oxy)-4-hydroxy-4-((*S*)-1-hydroxyethyl)-3-phenylcyclopent-2-en-1-one (*trans*-41)**

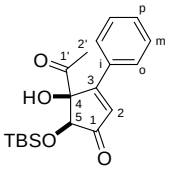



*trans*-**41**

At room temp. a solution of $H_2O$ (18 µL, 18 mg, 1.0 mmol, 14 equiv.) in trifluoroacetic acid (TFA, 87 µL, 0.13 g, 1.1 mmol, 15 equiv.) was added to a solution of the ketal *trans*-**40** (31 mg, 72 µmol) in $CH_2Cl_2$ (2 mL). The solution was stirred at room temp. for 14 h. The reaction was quenched by addition of sat. aq. $NaHCO_3$ solution (2 mL). The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated

under reduced pressure. Purification by flash chromatography [1.0 × 17 cm, 7 mL, cyclohexane/EtOAc = 30:1 (F1–8) → 20:1 (F9–14) → 10:1 (F15–22) → 5:1 (F23–30), F18–22] afforded compound *trans*-**41** (15 mg, 42 µmol, 58%) as white solid (mp 87–89 °C). $^1$H NMR (400.13 MHz, $CDCl_3$) δ = 0.21 (s, 3H, $SiC^AH_3$), 0.28 (s, 3H, $SiC^BH_3$), 0.92 (d, $J_{2',1'}$ = 6.5 Hz, 3H, 2'-H$_3$), 0.98 (s, 9H, $SiC(CH_3)_3$), 3.48 (br. d, $J_{1'\text{-OH},1'}$ = 4.0 Hz, 1H, 1'-OH), 3.93 (qd, $J_{1',2'}$ = 6.5 Hz, $J_{1',1'\text{-OH}}$ = 3.9 Hz, 1H, 1'-H), 3.95 (s, 1H, 4-OH), 4.64 ($m_c$, 1H, 5-H), 6.43 (s, 1H, 2-H), 7.37–7.45 (m, 3H, Ar-H$^m$, Ar-H$^p$), 7.83–7.90 (m, 2H, Ar-H$^o$). $^{13}$C NMR (100.61 MHz, $CDCl_3$) δ = −5.28 ($SiC^AH_3$), −4.23 ($SiC^BH_3$), 18.47 ($SiC(CH_3)_3$), 18.57 (C-2'), 25.90 ($SiC(CH_3)_3$), 73.03 (C-1'), 83.53 (C-4), 86.77 (C-5), 128.37 (C-2), 128.55 (Ar-C$^o$), 128.73 (Ar-C$^m$), 130.42 (Ar-C$^p$), 134.72 (Ar-C$^i$), 168.09 (C-3), 199.29 (C-1). HRMS (pos. ESI) *m*/*z* = 371.1650 [M+Na]$^+$ corresponds to the formula $C_{19}H_{28}O_4NaSi^+$ (*m*/*z* = 371.1649) with a deviation of +0.3 ppm. IR (film) $\tilde{\nu}$ = 3420, 3065, 2955, 2930, 2885, 2860, 1715, 1705, 1565, 1445, 1360, 1255, 1160, 1070, 885, 840, 780, 695 cm$^{-1}$. Elemental analysis $C_{19}H_{28}O_4Si$ (348.51): calcd. C 65.48, H 8.10; found C 65.41 H 8.08.

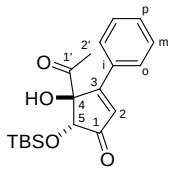
**(*rel*-4*S*,5*S*)-4-Acetyl-5-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-3-phenylcyclopent-2-en-1-one (*cis*-42)**




*cis*-**42**

At −78 °C a solution of DMSO (16 µL, 18 mg, 0.22 mmol, 2.9 equiv.) in $CH_2Cl_2$ (0.1 mL) was added dropwise to a solution of oxalyl chloride (10 µL, 14 mg, 0.11 mmol, 1.4 equiv.) in $CH_2Cl_2$ (1 mL) and the resulting solution was stirred at −78 °C for 15 min. A solution of the diol *cis*-**41** (27 mg, 77 µmol) in $CH_2Cl_2$ (1 mL) was added dropwise at −78 °C and the resulting solution was allowed to warm to −60 °C within 1.5 h. $NEt_3$ (0.05 mL, 0.04 g, 0.4 mmol, 5 equiv.) was added dropwise and the resulting suspension was allowed to warm to room temp. within 3 h. The reaction was quenched by addition of sat. aq. $NH_4Cl$ solution (2 mL). Brine (5 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography [1.0 × 18 cm, 7 mL, cyclohexane/EtOAc = 30:1 (F1–6) → 20:1 (F7–21), F15–20] afforded compound *cis*-**42** (25 mg, 72 µmol, 93%) as a white solid (90–91 °C). $^1$H NMR (400.13 MHz, $CDCl_3$) δ = 0.20 (s, 3H, $SiC^AH_3$), 0.26 (s, 3H, $SiC^BH_3$), 0.96 (s, 9H, $SiC(CH_3)_3$), 2.34 (s, 3H, 2'-H$_3$), 4.13 (s, 1H, 5-H), 4.31 (s, 1H, 4-OH), 7.39–7.48 (m, 3H, Ar-H$^m$, Ar-H$^p$), 7.65–7.77 (m, 2H, Ar-H$^o$). $^{13}$C NMR (100.61 MHz, $CDCl_3$) δ = −5.05 ($SiC^AH_3$), −4.11 ($SiC^BH_3$), 18.39 ($SiC(CH_3)_3$), 25.80 ($SiC(CH_3)_3$), 26.72 (C-2'), 75.96 (C-5), 84.29 (C-4), 128.11 (C-2), 128.25 (Ar-C$^o$), 129.15 (Ar-C$^m$), 131.52 (Ar-C$^p$), 132.44 (Ar-C$^i$), 171.26 (C-3), 201.90 (C-1), 210.68 (C-1'). HRMS (pos. ESI) *m*/*z* = 369.1494 [M+Na]$^+$ corresponds to the formula $C_{19}H_{26}O_4NaSi^+$ (*m*/*z* = 369.1493) with a deviation of +0.3 ppm. IR (film) $\tilde{\nu}$ = 3460, 2955, 2930, 2885, 2860, 1715, 1600, 1570, 1470, 1355, 1255, 1150, 1125, 840, 785, 770, 695 cm$^{-1}$. Elemental analysis $C_{19}H_{26}O_4Si$ (346.50): calcd. C 65.86, H 7.56; found C 65.95 H 7.54.

**(*rel*-4*S*,5*S*)-4-Acetyl-5-((*tert*-butyldimethylsilyl)oxy)-4-hydroxy-3-phenylcyclopent-2-en-1-one (*trans*-42)**




*trans*-**42**

At −78 °C a solution of DMSO (0.17 mL, 0.19 g, 2.4 mmol, 3.0 equiv.) in $CH_2Cl_2$ (1 mL) was added dropwise to a solution of oxalyl chloride (0.10 mL, 1.5 g, 1.2 mmol, 1.5 equiv.) in $CH_2Cl_2$ (5 mL) and the resulting solution was stirred at −78 °C for 15 min. A solution of the diol *trans*-**41** (280 mg, 803 µmol) in $CH_2Cl_2$ (4 mL) was added dropwise at −78 °C and the resulting solution was stirred at that temperature for 1 h. $NEt_3$ (0.54 mL, 0.39 g, 3.9 mmol, 4.8 equiv.) was added dropwise and the resulting solution was allowed to warm to −20 °C within 3 h. The cooling bath was removed and the mixture was stirred at room temp for 15 min. The reaction was quenched by addition of sat. aq. $NH_4Cl$ solution (20 mL). Brine (50 mL) was added and the mixture was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were dried over $Na_2SO_4$ and concentrated under reduced pressure. Purification by flash chromatography (2.0 × 16 cm, 7 mL, cyclohexane/EtOAc = 15:1, F14–32) afforded compound *trans*-**42** (247 mg, 713 µmol, 89%) as a white solid (mp 70–71 °C). $^1$H NMR (400.13 MHz, $CDCl_3$) δ = 0.11 (s, 3H, $SiC^AH_3$), 0.19 (s, 3H, $SiC^BH_3$), 0.90 (s, 9H, $SiC(CH_3)_3$), 2.15 (s, 3H, 2'-H$_3$), 4.60 ($m_c$, 1H, 5-H), 4.97 (s, 1H, 4-OH), 6.76 (s, 1H, 2-H), 7.37–7.49 (m, 5H, Ar-H). $^{13}$C NMR (100.61 MHz, $CDCl_3$) δ = −5.25 ($SiC^AH_3$), −4.57 ($SiC^BH_3$), 18.27 ($SiC(CH_3)_3$), 25.12 (C-2'), 25.68 ($SiC(CH_3)_3$), 84.83 (C-5), 88.85 (C-4), 128.20 (Ar-C$^o$), 129.14 (Ar-C$^m$), 129.36 (C-2), 131.53 (2C, Ar-C$^p$, Ar-C$^i$), 166.30 (C-3), 200.46 (C-1), 206.42 (C-1'). HRMS (pos. ESI) *m*/*z* = 369.1493 [M+Na]$^+$ corresponds to the formula $C_{19}H_{26}O_4NaSi^+$ (*m*/*z* = 369.1493) with a deviation of 0.0 ppm. IR (film) $\tilde{\nu}$ = 3430, 2955, 2930, 2890, 2860, 1720, 1595, 1570, 1360, 1260, 1150, 1120, 880, 840, 780, 770, 690 cm$^{-1}$. Elemental analysis $C_{19}H_{26}O_4Si$ (346.50): calcd. C 65.86, H 7.56; found C 65.63 H 7.43.

## Acknowledgements

We thank Stephanie Keller for experimental contributions.

**Keywords:** aldol reaction • α-bromoketones • cyclopentenone • natural products • samarium enolate

[1] N. V. S. Ramakrishna, K. H. S. Swamy, E. K. S. Vijayakumar, S. R. Nadkarni, K. Jayvanti, A. W. Herling, H. Kogler, L. Vertesy, R. M. Panshikar, K. Sridevi, M. Raman, R. M. Dalal (Hoechst Marion Roussel Deutschland GmbH), WO1998047888A1, **1998**.
[2] L. Vértesy, H.-J. Burger, J. Kenja, M. Knauf, H. Kogler, E. R. Paulus, N. V. S. Ramakrishna, K. H. S. Swamy, E. K. S. Vijaykumar, P. Hammann, *J. Antibiot.* **2000**, *53*, 677–686.
[3] L. K. Charkoudian, B. P. Farrell, C. Khosla, *Med. Chem. Commun.* **2012**, *3*, 926–931.
[4] T. Wüster, N. Kaczybura, R. Brückner, M. Keller, *Tetrahedron* **2013**, *69*, 7785–7809.
[5] Wedged bonds identify enantiomerically pure, straight bonds racemic compounds.
[6] D. Peter, R. Brückner, *Chem. Eur. J.* **2017**, *23*, 12104-12109.
[7] To the best of our knowledge C-functionalizations of 3-arylcyclopent-2-en-1-ones at C-2 are confined to the following examples: a) N.-H. Nam, Y. Kim, Y.-J. You, D.-H. Hong, H.-M. Kim, B.-Z. Ann, *Arch. Pharm. Res.* **2002**, *25*, 590–599: bromination; then Stille methylation; b) K. Thede, N. Diedrichs, J. P. Ragot, *Org. Lett.* **2004**, *6*, 4595–4597: bromination; then Suzuki arylation; c) D. L. Parker, R. R. Wilkening, D. Meng, R. W. Ratcliffe (Merck & Co., Inc.), WO 2004026887, **2004**: bromination; then Suzuki alkylation; d) T. Apelqvist, A. J. Loefstedt, T. A.

W. Norin, M. Wennerstal, X. Wu, L. Hagberg (Karo Bio AB), WO 2009012954, **2009**: bromination; then cyanation.

[8] The stereodescriptor $^{2,3}$*trans* refers to the orientation of the $C^3$–Me vs. $C^2$–$C^{1'}$ bond in the dioxolane ring of aldols **8**, **10** , and **18** (as imposed by induced diastereocontrol of an aldol addition). The stereodescriptor $^{2,1'}$*syn* – and $^{2,1'}$*anti* likewise – describes the orientation of the $C^2$–O vs. the $C^{1'}$–O bond (as imposed by simple diastereocontrol of an aldol addition) provided these aldols are drawn as in Scheme 1.

[9] The term "brominating hydrolysis" describes the overall change of substructure C(–Cl)C=C into substructure C(=O)C–C–Br. Formally (not mechanistically!), this transformation results from a hydrolysis C(–Cl)C=C → C(–OH)C=C, a tautomerization C(–OH)C=C → C(=O)C–C–H, and an α-bromination C(=O)C–C–H → C(=O)C–C–Br.

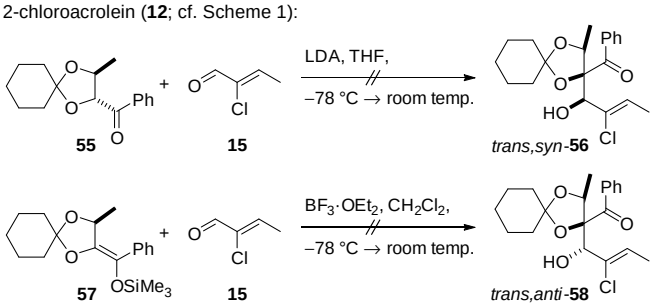
[10] Selected precedents: a) C.-N. Hsiao, M. R. Leanna, L. Bhagavatula, E. de Lara, T. M. Zydowsky, B. W. Horrom, H. E. Morton, *Synthetic Comm.* **1990**, *20*, 3507–3517: NBS, $H_2O$; b) R. A. Craig, J. L. Roizen, R. C. Smith, A. C. Jones, B. M. Stoltz, *Org. Lett.* **2012**, *14*, 5716–5719: NaOBr, aq. AcOH; c) V. Pace, L. Castoldi, M. J. Hernáiz, A. R. Alcántara, W. Holzer, *Tetrahedron Lett.* **2013**, *54*, 4369–4372: $Ca(OBr)_2$, aq. AcOH.

[11] Ref.[10b].

[12] Selected reviews: a) R. Mahrwald (Ed.), *Modern Methods in Stereoselective Aldol Reactions*, Wiley-VCH, Weinheim, New York, **2013**; b) G. L. Beutner, S. E. Denmark, *Angew. Chem. Int. Ed.* **2013**, *52*, 9086–9096; *Angew. Chem*. **2013**, 9256–9266; c) S. B. J. Kan, K. K. H. Ng, I. Paterson, *Angew. Chem. Int. Ed.* **2013**, *52*, 9097–9108; *Angew. Chem*. **2013**, 9267–9279; d) J.-i. Matsuo, M. Murakami, *Angew. Chem. Int. Ed.* **2013**, *52*, 9109–9118; *Angew. Chem.* **2013**, *125*, 9280–9289.

[13] a) Preparation including isolation: M. Hatano, T. Mizuno, A. Izumiseki, R. Usami, T. Asai, M. Akakura, K. Ishihara, *Angew. Chem. Int. Ed.* **2011**, *50*, 12189–12192; b) in situ preparation preceding an aldol addition: A. B. Smith, C. Sfouggatakis, D. B. Gotchev, S. Shirakami, D. Bauer, W. Zhu, V. A. Doughty, *Org. Lett.* **2004**, *6*, 3637–3640.

[14] We also considered installing the phenyl group *before* the aldol addition by using the phenyl ketone **55** as the source of the nucleophile instead of the ester **9**. In fact, we attempted both an aldol addition of the lithium enolate of ketone **55** and a Mukaiyama aldol addition of the corresponding enol silane **57** yet employed 2-chlorocrotonaldehyde (**15**) as the electrophile (cf. below) instead of 2-chloroacrolein (**12**; cf. Scheme 1):



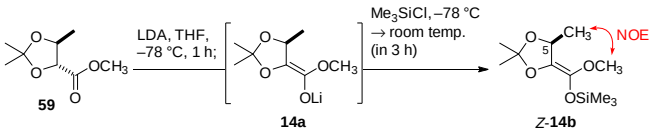

These reactions suffered from low reactivity at −78 °C and a lack of chemoselectivity at room temp., delivering nothing or complex mixtures. Considering **12** more prone to side-reactions than **15** we excluded ketone **55** and enol silane **57** from our planning.

[15] J. H. Dodd, R. S. Garigipati, S. M. Weinreb, *J. Org. Chem.* **1982**, *47*, 4045–4049.

[16] Previous additions of Li enolates of type-**9** esters to achiral electrophiles: a) R. Naef, D. Seebach, *Angew. Chem. Int. Ed. Eng.* **1981**, *20*, 1030–1031; *Angew. Chem.* **1981**, *93*, 1113–1114; b) W. Ladner, *Chem. Ber.* **1983**, *116*, 3413–3426; c) M. Pohmakotr, T. Junpirom, S. Popuang, P. Tuchinda, V. Reutrakul, *Tetrahedron Lett.* **2002**, *43*, 7385–7387; c) M. S. M. Timmer, B. L. Stocker, P. H. Seeberger, *J. Org. Chem.* **2006**, *71*, 8294–8297; d) E. Bette, A. Otto, T. Dräger, K. Merzweiler, N. Arnold, L. Wessjohann, B. Westermann, *Eur. J. Org. Chem.* **2015**, 2357–2365; e) K. C. Nicolaou, Q. Cai, H. Sun, B. Qin, S. Zhu, *J. Am. Chem. Soc.* **2016**, *138*, 3118–3124.

[17] Previous additions of silyl ketene acetals of type-**9** esters to achiral electrophiles: a) D. A. Evans, W. B. Trotter, J. C. Barrow, *Tetrahedron* **1997**, *53*, 8779–8794; b) V. K. Aggarwal, S. J. Masters, H. Adams, S. E. Spey, G. R. Brown, A. J. Foubister, *J. Chem. Soc., Perkin Trans. 1* **1999**, 155–162; c) Y. Hayashi, M. Shoji, J. Yamaguchi, K. Sato, S. Yamaguchi, T. Mukaiyama, K. Sakai, Y. Asami, H. Kakeya, H. Osada, *J. Am. Chem. Soc.* **2002**, *124*, 12078–12079.

[18] Deprotonating the related ester **59** under the same conditions (LDA, THF, −78 °C, 1 h) and quenching with $Me_3SiCl$ furnished the *Z*-configured silyl ketene acetal *Z*-**14b**. We inferred its configuration from NOE interactions between 5–$CH_3$ and $OCH_3$ [$CDCl_3/C_6D_6$ (3:2), 400.4 MHz].




[19] H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

[20] Examples of axial preferences in Zimmerman-Traxler transition states of aldol-equivalent additions of γ,γ-disubstituted allylmetals to aldehydes are summarized in T. Mejuch, N. Gilboa, E. Gayon, H. Wang, K. N. Houk, I. Marek, *Acc. Chem. Res.* **2013**, *46*, 1659–1669.

[21] C. H. Heathcock, S. K. Davidsen, K. T. Hug, L. A. Flippin, *J. Org. Chem.* **1986**, *51*, 3027–3037.

[22] S. E. Denmark, N. G. Almstead, *J. Am. Chem. Soc.* **1993**, *115*, 3133–3139.

[23] Aldol additions: S. E. Denmark, B. R. Henke, *J. Am. Chem. Soc.* **1991**, *113*, 2177–2194. This is a consequence of what is designated as an "endocyclic restriction" in a broader context (P. Beak, *Acc. Chem. Res.* **1992**, *25*, 215–222).

[24] Mukaiyama aldol additions: S. E. Denmark, W. Lee, *Chem. Asian J.* **2008**, *3*, 327–341 and literature cited therein.

[25] Y. Yang, X. Fu, J. Chen, H. Zhai, *Angew. Chem. Int. Ed.* **2012**, *51*, 9825–9828.

[26] J. Kadota, S. Komori, Y. Fukumoto, S. Murai, *J. Org. Chem.* **1999**, *64*, 7523–7527.

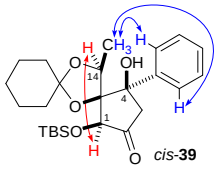
[27] a) Original report: D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155–4156; b) summary of applications: V. V. Zhdankin, *J. Org. Chem.* **2011**, *76*, 1185–1197.

[28] a) Original report: A. L. Gemal, J. L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459; b) application to a similar substrate: J. S. Clark, G. Yang, A. P. Osnowski, *Org. Lett.* **2013**, *15*, 1460–1463.

[29] H. Hoffmann, H. J. Dieter, *Angew. Chem.* **1964**, *76*, 944-953; *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 737-746.

[30] Prior to our work $SmI_2$-induced inter- and intramolecular aldol additions of α-haloketones have been used by a) Z. Yang, D. Shannon, V.-L. Truong, P. Deslongchamps, *Org. Lett.* **2002**, *4*, 4693–4696; b) D. Chapdelaine, J. Belzile, P. Deslongchamps, *J. Org. Chem.* **2002**, *67*, 5669–5672; c) B. A. Sparling, R. M. Moslin, T. F. Jamison, *Org. Lett.* **2008**, *10*, 1291–1294; d) E. J. Horn, J. S. Silverston, C. D. Vanderwal, *J. Org. Chem.* **2016**, *81*, 1819–1838.

[31] The *cis*-orientation of the $C^1$–OTBS and $C^4$–OH bonds in compound *cis*-**39** follows from the following cross peaks in the NOESY spectrum ($CDCl_3$, 400.13 MHz):




[32] a) Original report: G. M. Atkins, E. M. Burgess, *J. Am. Chem. Soc.* **1968**, *90,* 4744–4745; summaries of applications: b) S. Santra, *Synlett* **2009**, 328–329, c) M. M. Heravi, T. Ahmadi, A. Fazeli, N. M. Kalkhorani, *Curr. Org. Synth.* **2015**, *12*, 328–357.

[33] a) Original report: Mancuso, S.-L. Huang, D. Swern, *J. Org. Chem.* **1978**, *43*, 2480–2482; summaries of applications: b) T. T. Tidwell, *Synthesis* **1990**, 857–870; c) T. T. Tidwell, *Org. React*. **1990**, *39*, 297–572.

[34] Y. Ueno, L. D. S. Yadav, M. Okawara, *Chem. Lett.* **1983**, *12*, 831-834.

[35] Syntheses of the monomethyl ethers of dihydroxycyclopentenones with yet another position of an α-oxygenated side-chain were reported by P. Langer, V. Köhler, *Org. Lett.* **2000**, *2*, 1597–1599.

[36] a) M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.* **1999**, *64*, 4537–4538; b) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

[37] J. Suffert, *J. Org. Chem.* **1989**, *54,* 509-510.

[38] Due to the instability and volatility of 2-chloroacrolein (**12**), the distillation was performed quickly at a temperature as low as possible. The resulting small temperature gradient in the condenser and the high vapor pressure of **12** led to partial substance loss. The receiving flasks were cooled with dry ice.

[39] J. Kadota, S. Komori, Y. Fukumoto, S. Murai, *J. Org. Chem.* **1999**, *64*, 7523–7527.

[40] The $SmI_2$ solution was titrated according to A. Dahlén, G. Hilmersson, *Eur. J. Inorg. Chem.* **2004**, 3020–3024.

[41] The $C^4$-configurations in both isomers were not assigned.