Tetrahedron 69 (2013) 7785–7809

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of enantiomerically pure model compounds of the glucose-6-phosphate-T_1-translocase inhibitors kodaistatins A–D. Inferences with regard to the stereostructure of the natural products

Thomas Wüster [†], Natasza Kaczybura [‡], Reinhard Brückner [*], Manfred Keller

Institut für Organische Chemie, Albert-Ludwigs-Universität, Albertstr. 21, 79104 Freiburg, Germany

ARTICLE INFO

Article history:
Received 6 April 2013
Received in revised form 18 May 2013
Accepted 20 May 2013
Available online 24 May 2013

Keywords:
Aldol addition
Cyclopentenone
Diabetes
Dienone
Horner–Wadsworth–Emmons reaction
Tetraalkylammonium enolate

ABSTRACT

The kodaistatins A and C (**5a**,**b**) inhibit a step in glucose-metabolism at ~100 nM concentrations. This makes them potential 'leads' in the therapy of diabetes. We elucidated the (*S*)-configuration of the side-chain stereocenter of kodaistatin A by ozonolysis/reduction. The ^{13}C NMR shifts of kodaistatin A model *cis*-**11** suggest that the diol moiety in the dihydroxycyclopentanone core of kodaistatin is *trans*-configured. This model was prepared from the Feringa lactone (**21**) and (*S*)-2-methylbutanal (**27**) in 23 steps (14 steps in the longest linear sequence). We employed the same strategy for the simplified kodaistatin A model *iso-cis*-**12**, which resulted from the same substrates in 11 steps (6 steps in the longest linear sequence). The cyclopentenone cores of both targets stemmed from a C_4+C_1 approach. The C_4 components were masked 'tartaric ketones' (**16a**,**b**) and a masked 'tartaric aldehyde' (**18**), respectively. The C_1 components were the lithium-derivatives of the side-chain bearing phosphonates **19** and **22**, respectively. The desired acylation/deprotonation/Horner–Wadsworth–Emmons tandem reaction succeeded in a single operation with the 'tartaric aldehyde' **18** but required partly or exclusively additional operations when we incorporated the 'tartaric ketones' **16a** or **16b**, respectively. The 'tartaric ketones' **16a**,**b** contained an α-siloxyethyl substituent. It is noteworthy that it had to be introduced by adding the benzyltrimethylammonium enolate of lactone **18** to acetaldehyde because the lithium enolate of this lactone fragmented by an acetone-releasing β-elimination.

1. Introduction

Natural products continue playing a major role in finding therapeutics and leads for novel medicines.[1] In recent years the certainty of this assessment has spurred many efforts at supplementing nature's stock of such materials by synthetic compounds dubbed 'natural product-like'.[2] Diabetes has been a major health disorder in virtually all societies. According to the 2012 numbers by the International Diabetes Federation more than 370 million people (=8.3% of the world's population) were affected by diabetes, the worldwide costs for the treatment of diabetes amounted to 470 billion US dollars, and nonetheless 4.8 million people died of this disease.[3] The largest numbers of patients in the populace of 20–79-year olds who suffered from diabetes were in China (92.3 million), India (63.0 million), and the United States (24.1 million).[3] The largest proportions of diabetes-sick in the same populace were citizens of the Pacific Islands of Micronesia (37.2%), Nauru (30.1%), and Marshall Islands (27.1%).[3] Considering the omnipresence and the commonness of this affliction, natural products with anti-diabetic activity have aroused great interest as conceivable cures.[4] Fig. 1 exemplifies compounds of that sort, such as chlorogenic acid (**1**),[5] ilicicolinic acid A (**3**),[5] and mumbaistatin[6] (**4**). Each of those inhibits the glucose-6-phosphate translocase[7] and is therefore a potential lead in the quest for effective anti-diabetes agents. An embellishment of the chlorogenic acid core structure led to the synthetic compound **2** as a veritable drug candidate.[8] To the best of our knowledge mumbaistatin is the currently most potent glucose-6-phosphate translocase inhibitor at all.[6] Little wonder that systematic studies of structure/activity relationships with modified mumbaistatins are underway also in academic environments.[9]

In 2000 a joint team of Aventis Pharma Deutschland and Indian chemists described several new glucose-6-phosphate translocase inhibitors. In a screening program of natural products they worked

* Corresponding author. Tel.: +49 7601 2036029; e-mail address: reinhard.brueckner@organik.chemie.uni-freiburg.de (R. Brückner).
† Current address: Glob. Dep. Process Development Chemicals, Boehringer Ingelheim Pharma GmbH & Co. KG, Binger Straße 173, 55216 Ingelheim am Rhein, Germany.
‡ Current address: GVX/P – C6, BASF SE, 67056 Ludwigshafen, Germany.

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http://dx.doi.org/10.1016/j.tet.2013.05.091

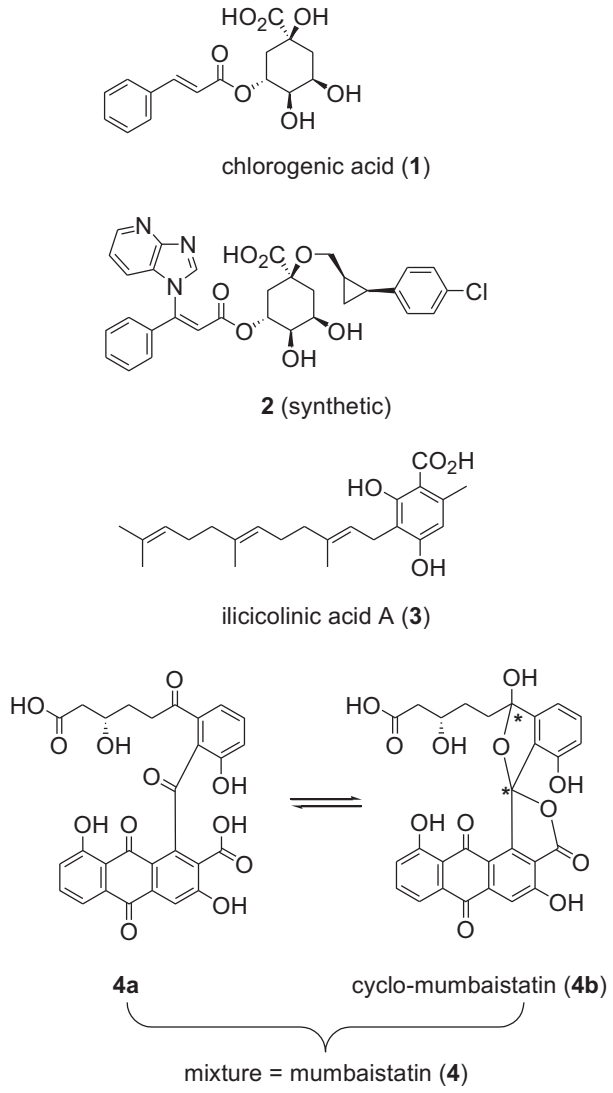


Fig. 1. Selected glucose-6-phosphate translocase inhibitors from natural product screenings (**1**,[5] **3**,[5] **4**,[6]) or from natural product-inspired laboratory syntheses (**2**[5]).

up 200 L of a culture solution of *Aspergillus terreus* Thom DSM 11247 and isolated two yellow solids: 120 mg of kodaistatin A and 11 mg of kodaistatin C.[10] A concomitant US patent[11] and a subsequent European patent[12] claimed protection for a total of four such compounds, namely for the kodaistatins A–D. The isolators designated kodaistatin B as a 'diastereomer' of kodaistatin A and kodaistatin D as a 'stereoisomer' of kodaistatin C.[11,13]

The structures of kodaistatins A ($C_{35}H_{34}O_{11}$) and C ($C_{35}H_{34}O_{12}$) were elucidated by mass spectrometry and intensive NMR studies.[10] Kodaistatin C turned out to be a hydroxy-kodaistatin A. Kodaistatins A and C comprise a cyclopentenone core, a dienone side-chain, and a pulvinone substituent (Fig. 2). HMBC spectra allowed identifying long-range H,C couplings and INADEQUATE spectra evidenced 1-bond C,C couplings. NOESY spectra revealed the (*E*)-configuration of the trisubstituted C=C bond in the acyclic 1,3-diene moiety. The disubstituted C=C bond is also (*E*)-configured because its protons shows a vicinal coupling of 16 Hz. The (*Z*)-configuration of the semicyclic C=C bond in the pulvinone moiety of kodaistatins A and C did not emerge directly from the spectra. It was assigned because of an indirect clue: there were conspicuous ^{1}H- and ^{13}C-NMR[14] similarities with analogous nuclei in a side-product from the same culture solution, which had been identified as aspulvinone E.[15] A crystal of this side-product was X-rayed[10] to reveal a (*Z*)-configuration of the semicyclic C=C bond. Consequently the same (*Z*)-configuration was attributed to the pulvinone moiety of the kodaistatins A and C.[10]

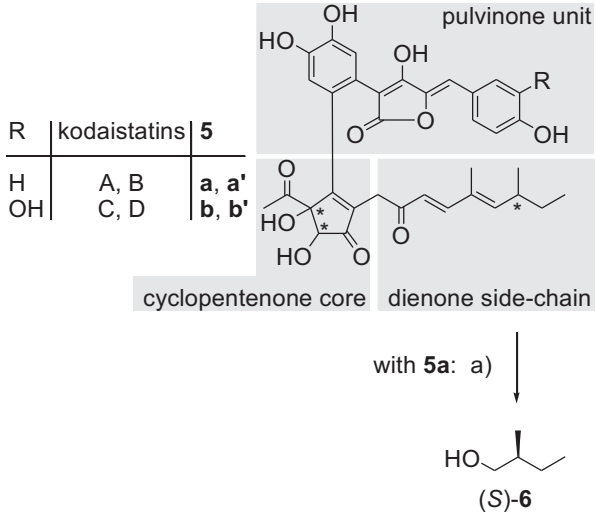


Fig. 2. Structurally novel glucose-6-phosphate translocase inhibitors from *Aspergillus terreus* Thom DSM 11247:[10] kodaistatins A (**5a**) and C (**5b**). The absolute and relative configurations of the stereocenters were left open by the original investigators.[10] We clarified the side-chain stereocenter by the oxidative degradation shown at the bottom. Reagents and conditions: (a) MeOH, −78 °C, O_3, 30 min; $NaBH_4$ (15.0 equiv), −78 °C, 30 min; −78 °C →room temperature, 4 h; scale too small for determining the yield.[18]

The original investigators did not determine the *relative* configuration of the stereocenters in the cyclopentenone moiety of the kodaistatins.[10] This is because the abundance of oxygen atoms in that zone made several NMR criteria inapplicable, which otherwise might have helped distinguishing a *cis*- from a *trans*-configured 1,2-diol moiety. Without derivatizing at least one of the OH groups there was neither a possibility of determining the *absolute* configuration of the OH-bearing stereocenters. Moreover, assessing the configuration of the stereocenter in the side-chain *relative* to the stereocenters in the diol moiety was an impossibility, and of course there is no NMR method for establishing its *absolute* configuration.

Having a small sample of kodaistatin A at our disposal[16] we determined the absolute configuration of its side-chain stereocenter by cleaving the adjacent C=C bond at −78 °C with ozone dissolved in methanol. After 30 min we added excess $NaBH_4$ and after another 30 min we discontinued feeding the cooling bath with dry ice. After the temperature had risen to ambient we injected an aliquot on a GLC apparatus charged with a 'chiral' capillary column.[17,18] Thereby we retrieved the alcohol **6** on a scale too small to determine the yield. The constitution and the (*S*)-configuration of the probe were inferred from coinjections with an authentic sample of (*S*)-(+)-**6** and an authentic sample of *rac*-**6**.[19]

Pondering synthetic pathways toward the kodaistatins their heavily substituted cyclopentenone core represents both a striking feature and a point of concern. This is because its substitution pattern is unique. Even similarly substituted cyclopentenones are scarce, and not just in natural products but in all of organic chemistry (Fig. 3).

2. Strategic considerations

An inference from the analysis of the introductory paragraphs was that we'd better attempt to synthesize not right away one of the kodaistatins but rather simpler model pounds. One reason was

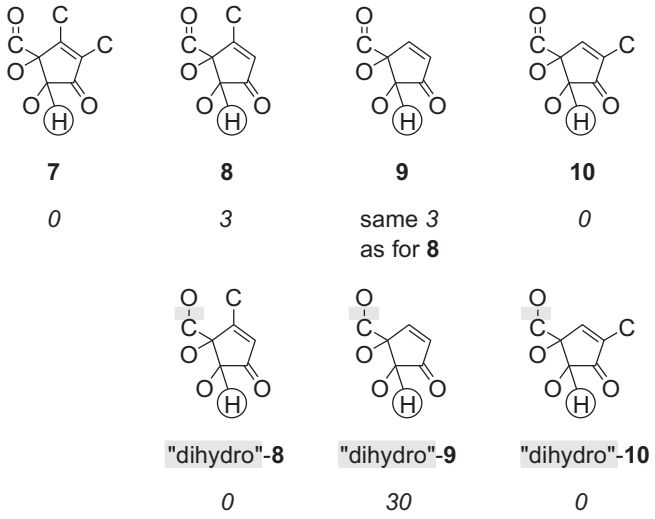


Fig. 3. Absence of the cyclopentenone substitution pattern identical (**7**) to that in the kodaistatins (**5**) and scarcity of several cyclopentenone substitution patterns related (**8**–**10**, 'dihydro' **8**–'dihydro' **10**) to that in the kodaistatins (**5**), as evidenced by the number of hits (in italics) for a search (February 28th, 2013) of the respective substructures with 'free substituents on all atoms' in the REAXYS database.

the incertitude about the relative and absolute configuration in the diol moiety of the natural products **5a**,**b**. Another consideration was the difficulty of attaching the sterically demanding *ortho*-substituted aryl moiety to the heavily substituted cyclopentenone core. Accordingly we selected our kodaistatin model(s) from the four diastereomers of the basic structure **11** (Fig. 4). They combine the (*S*)-configured side-chain stereocenter of kodaistatin A with the four permutations of the (*R*)- and (*S*)-configurations at the hydroxylated stereocenters. Moreover, they contain a phenyl ring stead of the pulvinone moiety of the kodaistatins.

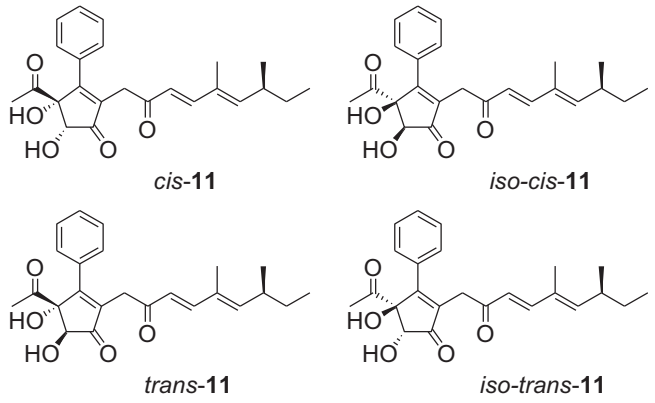


Fig. 4. Kodaistatin model compounds containing the correctly (cf. Fig. 2) configured dienone side-chain and either a *cis*-dihydroxylated cyclopentenone moiety (*cis*-**11**, *iso-cis*-**11**) or a *trans*-dihydroxylated cyclopentenone moiety (*trans*-**11**, *iso-trans*-**11**). A simplified analog *iso-cis*-**12** of the kodaistatin model *iso-cis*-**11** is depicted in Scheme 1 (upper right corner).

We hypothesized that once we would have gained an access to *one* of the **11**-diastereomers, which contains a *cis*-configured diol moiety (*cis*-**11**, *iso-cis*-**11**), and also an access to *one* of the **11**-diastereomers, which contains a *trans*-configured diol moiety (*trans*-**11**, *iso-trans*-**11**), NMR comparisons with the kodaistatins might allow to attribute a *cis*- or *trans*-configuration to the diol moiety of the *latter*. Whether *then* CD spectroscopy would suffice to unravel the absolute configuration of kodaistatin A (**5a**) would have to be tested. If it failed, the structural elucidation of kodaistatin A would have to be completed either by syntheses of the two diastereomers **5a** with the stereostructures of *cis*-**11** and *iso-cis*-**11** or by syntheses of the two diastereomers **5a** with the stereostructures of *trans*-**11** and *iso-trans*-**11**.

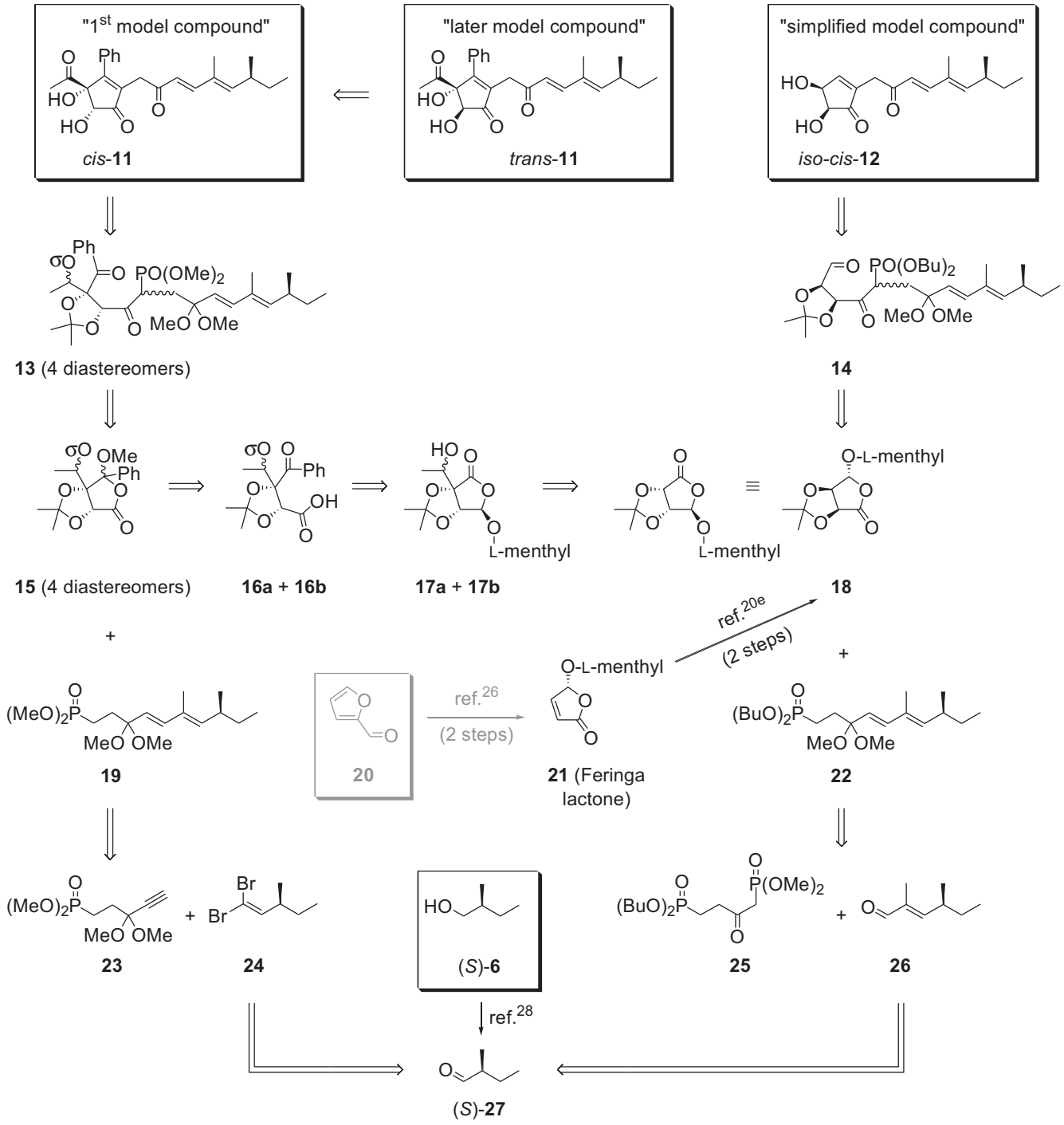
In principle *cis*-**11** and *trans*-**11** appear interconvertible by an oxidation/reduction sequence, and so do *iso-cis*-**11** and *iso-trans*-**11**. Hence, making one of a pair of the respective isomers available might provide the other in the sequel. In the current study we went for the model pair *cis*-**11** and *trans*-**11** when we recognized that *cis*-**11** (but not *iso-cis*-**11**) might result from the conveniently accessible[20e] Feringa[20] lactone,[21–23] i.e., from compound **21**. This is specified in the retrosynthetic analysis of Scheme 1.

Scheme 1 traces back model *trans*-**11** (classified as our 'later model compound') to model *cis*-**11** (considered as our '1st model compound') by a redox sequence. The cyclopentenone core of model *cis*-**11** should emerge from a C_4+C_1 approach envisaged as a phosphonate acylation/deprotonation/Horner–Wadsworth–Emmons tandem reaction.[24,25] A viable C_4 component of this approach would be whatever diastereomer of the masked ketoacid **15**. It would react as a bis-electrophile. The C_1 component of our cyclopentenone approach would be the phosphonate **19**. Due to an initial deprotonation at C-α and because of another deprotonation of C-α, which would occur after the acylation product **13** would have formed, phosphonate **19** would react as a bis-nucleophile. These serial deprotonations of **19** should be realized by letting **19** react with the masked ketoacid **15** in the presence of 2 equiv of a strong base.

The arbitrarily configured diastereomer of the masked ketoacid **15**, which our approach required, was expected to stem from an acid-catalyzed cyclocondensation of methanol with the ketoacid **16a** or with its epimer **16b** or with a mixture of the two compounds (Scheme 1). The ketoacids **16a** and **b** looked like resulting from the acylation of phenyllithium or a phenyl Grignard reagent by the silyl ethers of the aldol addition products **17a** and **b**. We planned to obtain them from the known lactone **18**[26] and acetaldehyde. This lactone is two synthetic steps away[26] from the Feringa lactone (**21**[20]). The latter is accessible from furfural (**20**) and L-menthol in another two steps.[20e] If the enolate of lactone **18** added to acetaldehyde with perfect simple diastereoselectivity,[27] a single adduct **17a** and **b** would be obtained. If no simple diastereocontrol occurred, the aldol adduct would be a diastereomeric mixture (**17a** and **b**). The latter would be as well suited as each of its constituents for synthesizing the kodaistatin models *cis*- and *trans*-**11**. Of course, attributing structures by NMR spectroscopy to synthetic intermediates with a homogenous C–O bond configuration would be easier.

Since many lactone enolates do not aldol-add with much simple diastereoselectivity we also targeted compound *iso-cis*-**12**, a simplified model compound of the kodaistatins (Scheme 1). In the context of the present project *iso-cis*-**12** offered a possibility of testing the viability of our C_4+C_1 strategy without having to deal with diastereomeric mixtures. Conveniently *iso-cis*-**12** might result from the metalated phosphonate **22** and the same lactone **18**,[26] which was meant to precede the more elaborate model compound *cis*-**12**.

The earlier mentioned phosphonate **19** and the last-mentioned phosphonate **22** display the acetal-protected side-chain of the kodaistatins linked with the C_1 constituent of our C_4+C_1 approach to the cyclopentenone cores of models *cis*- and *trans*-**11** and of model *iso-cis*-**12**, respectively (Scheme 1). Phosphonates **19** and **22** differ only with respect to their *O*-bound moieties. Nevertheless we simplified **19** and **22** retrosynthetically in two profoundly different manners. In our original thinking a crossed aldol condensation with the saturated aldehyde (*S*)-**27** should render the α,β-unsaturated aldehyde (*S*)-**26**.[28] The latter was supposed to undergo a *trans*-selective Horner–Wadsworth–Emmons reaction[29] with the



Scheme 1. Retrosynthetic analyses of kodaistatin models *cis*-**11**, *trans*-**11**, and *iso*-*cis*-**12**. σ=*t*-BuMe$_2$Si.

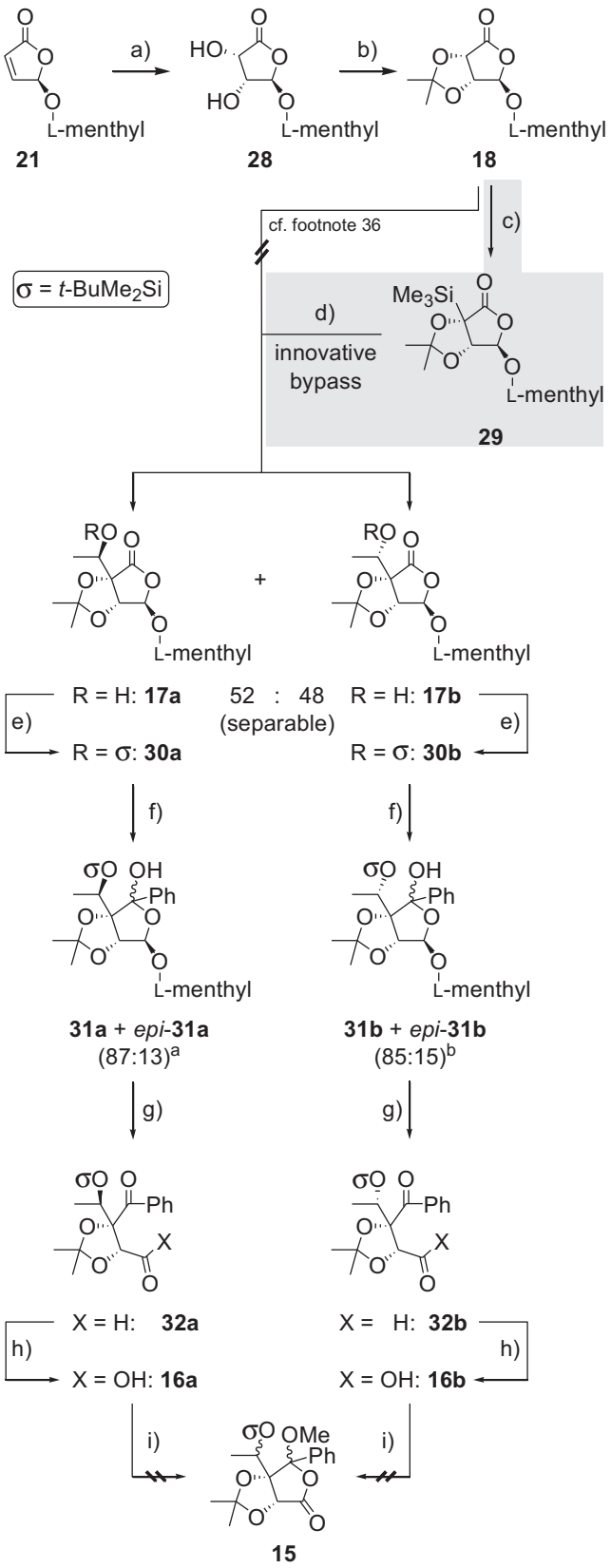
ketodiphosphonate **25**.[30] The resulting α,β,γ,δ-unsaturated ketophosphonate would be ketalized.

The last-mentioned step should have furnished the dimethylketal **22** uneventfully. In reality it tended to jeopardize the stereointegrity of the trisubstituted C=C bond. We circumvented this problem in the retrosynthetic analysis of phosphonate **19** as detailed in Scheme 1. In that access, the acetal moiety was implemented in the phosphonate **23** before the trisubstituted C=C bond was established. The latter was planned to originate from a three-step sequence: (1) a *trans*-selective hydrostannylation of the C≡C bond[31] of the precursor phosphonate **23**; (2) a *Z*-selective Stille-coupling between the resulting stannane and *gem*-dibromoolefin **24**[32,33] and (3) a stereo-retentive Negishi coupling of Me_2Zn with the resulting monobromodiene.[34]

3. Results and discussion

The synthesis of the C_4 bis-electrophile **18** from the Feringa lactone **21**[20] was straightforward following the description from Ref. 26 (Scheme 2, top line). The conversion of compound **18** into whatever suitable diastereomer of the *other* C_4 bis-electrophile **15** came to a halt one step before the last one, i.e., after reaching its γ-ketoacid precursors **16a** and **b** (Scheme 2). Fortunately, the latter intermediates lent themselves to a variation of our C_4+C_1 approach

to the cyclopentenone core of the kodaistatin model *cis*-**11** alright (cf. Scheme 6). Therefore we did not invest undue efforts for progressing to **15** in adherence to the original design.



Scheme 2. Conversion of the Feringa lactone (**21**) into the furanone **18** and into the γ-ketocarboxylic acid (**16a**,**b**) equivalents of the furanones **15**, precursors of the kodaistatin models *iso*-*cis*-**12** and *cis*-**11**, respectively (cf. Scheme 1). Reagents and conditions: (a) $KMnO_4$ (1.1 equiv), acetone/H_2O (10:1), −5 °C, 2.5 h; →50 °C, 10 min; 49% (Ref. 26: 62%). (b) acetone (1.2 equiv), $BF_3{\cdot}OEt_2$ (1.0 equiv), ethyl acetate, 0 °C, 6 h; →room temperature, 2 h; 97% (Ref. 26: 89%). (c) LDA (1.3 equiv), Me_3SiCl (1.5 equiv), THF, −78 °C, addition of **18** during 15 min, 1 h; 99%. (d) Acetaldehyde (8.0 equiv), THF, −78 °C, addition of $BnMe_3N^{\oplus}{}_2F^{\ominus}$ (1.1 equiv), →−10 °C during 2 h; 45% **17a** separated from 42% **17b** (X-ray structural analysis: Fig. 5). (e) *t*-$BuMe_2SiOTf$ (3.0 equiv), NEt_3 (7.5 equiv), CH_2Cl_2, room temperature, 2 h; 87% (**30a**); 97% (**30b**). (f) PhLi (2.0 equiv), LiCl (5.0 equiv), THF, −10 °C, 10 min. (g) *p*-TsOH (5 mol %), $CHCl_3$, room temperature, 1 h (induces liberation of menthol). (h) $RuCl_3{\cdot}H_2O$ (10 mol %), $NaIO_4$ (1.5 equiv), CCl_4/MeCN/H_2O (2:2:3), 0 °C, 45 min, →room temperature, 60 min; 34% over 3 steps (**16a**); 49% over the 3 steps (**16b**). (i) HCl-saturated MeOH/MeOH (1:4), −20 °C, 18 h; 0 °C, 15 h; room temperature, 12 h; no conversion. [a]At 300 MHz in $CDCl_3$ solution the major epimer displayed $\delta[HC(OR)_2]$=5.50 ppm and the minor epimer $\delta[HC(OR)_2]$=5.43 ppm. [b]At 300 MHz in $CDCl_3$ solution the major epimer displayed $\delta[HC(OR)_2]$=5.44 ppm and the minor epimer $\delta[HC(OR)_2]$=5.35 ppm.

Aldol additions of dioxolane mono- or diester enolates or the corresponding silylketene acetals have been described.[35] Hence we were surprised that treatment of the dioxolane-fused lactone **18** with LDA followed by the addition of acetaldehyde did not provide the aldols **17a** or **b** at all. The problem was that the lithium enolate of lactone **18** reacted prematurely. On the one hand it fragmented,[36] on the other hand it was acylated by the C=O bond of its not yet deprotonated progenitor **18**.[36,37]

Analogous lactone dimerizations are known.[38,39] For instance, the mono(lithium enolate) of a γ-substituted α,β-epoxy-γ-lactone dimerized by an acylation through the not yet deprotonated lactone in up to 65% yield.[39] Even the presence of propionaldehyde in the epoxylactone/LDA mixture *from the beginning* gave no opportunity for the desired aldol addition to compete.[39] Eventually, a dimerization was avoided by deprotonating the mentioned α,β-epoxy-γ-lactone by LDA in the presence of Me_3SiCl.[39] This provided the C^{α}-trimethylsilylated[40] α,β-epoxy-γ-lactone. The latter, 2 equiv of various aldehydes, and 10 mol % of $Bu_4N^{\oplus}\ F^{\ominus}$ (dried in situ by molecular sieves 4 Å) gave the desired aldol adducts in up to 62% yield.[39,41,42] The feasibility of such lactone enolate C^{α}-trimethylsilylations and reports on the advantageous use of *benzyltrimethyl*ammonium enolates[43] led *us* to implement a C^{α}-silylation **18**→**29** (99% yield) as the inaugural step of an ammonium enolate addition route to the desired aldol adducts **17a** and **b** (Scheme 2). Treatment of silyllactone **29** with acetaldehyde (8 equiv) and anhydrous $BnNMe_3F$ (1.1 equiv) at −78 °C to −10 °C provided a ca. 1:1 mixture of epimeric aldol adducts **17a** and **b**. The latter were separated by flash chromatography on silica gel,[44] **17a** (45% yield) eluting earlier than **17b** (42% yield).

The epimers **17a** and **b** were carried on separately (Schemes 2 and 6) until their follow-up products converged in our '1st model compound' *cis*-**11** (Scheme 6).[45] That observation proved the stereostructure of aldol adduct **17a** because the stereostructure of its epimer **17b** was elucidated by an X-ray structural analysis[46] (Fig. 5). The first

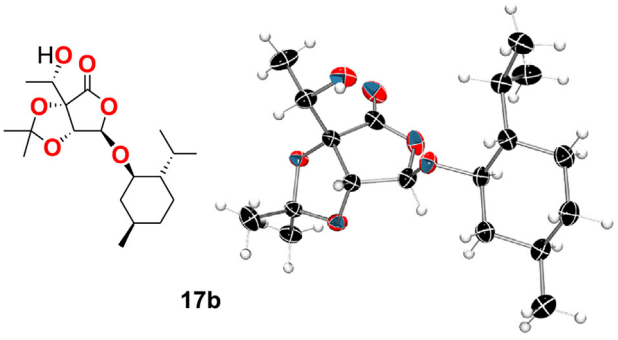
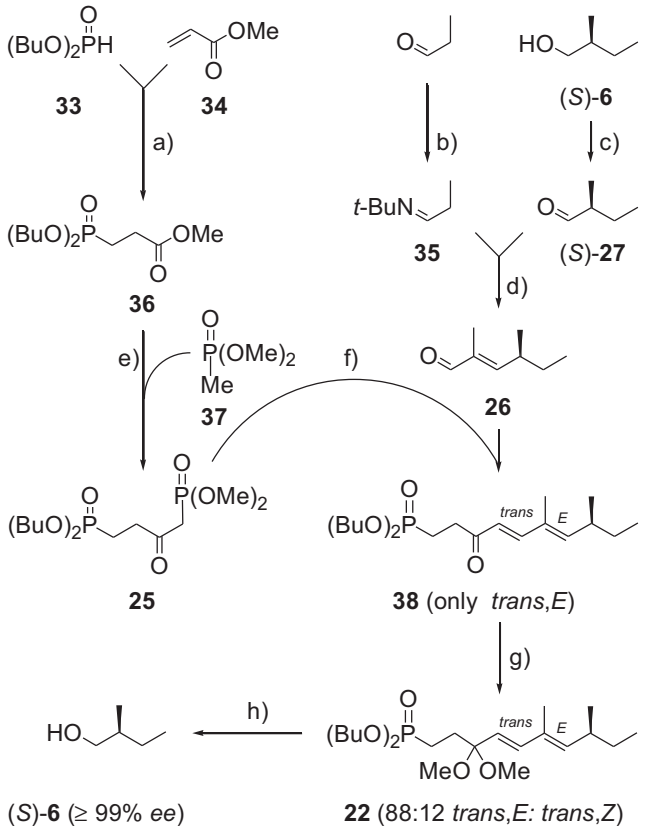


Fig. 5. ORTEP plot of the unit cell of an X-ray structure analysis of a single crystal of aldol **17b** (cf. Scheme 2) at 120 K.[46] All C-bound H atoms were refined while assuming perfectly staggered orientations with respect to the vicinal A–B bonds (B≠H). Only the H-atom of the OH group was localized and refined isotropically without a conformational constraint.

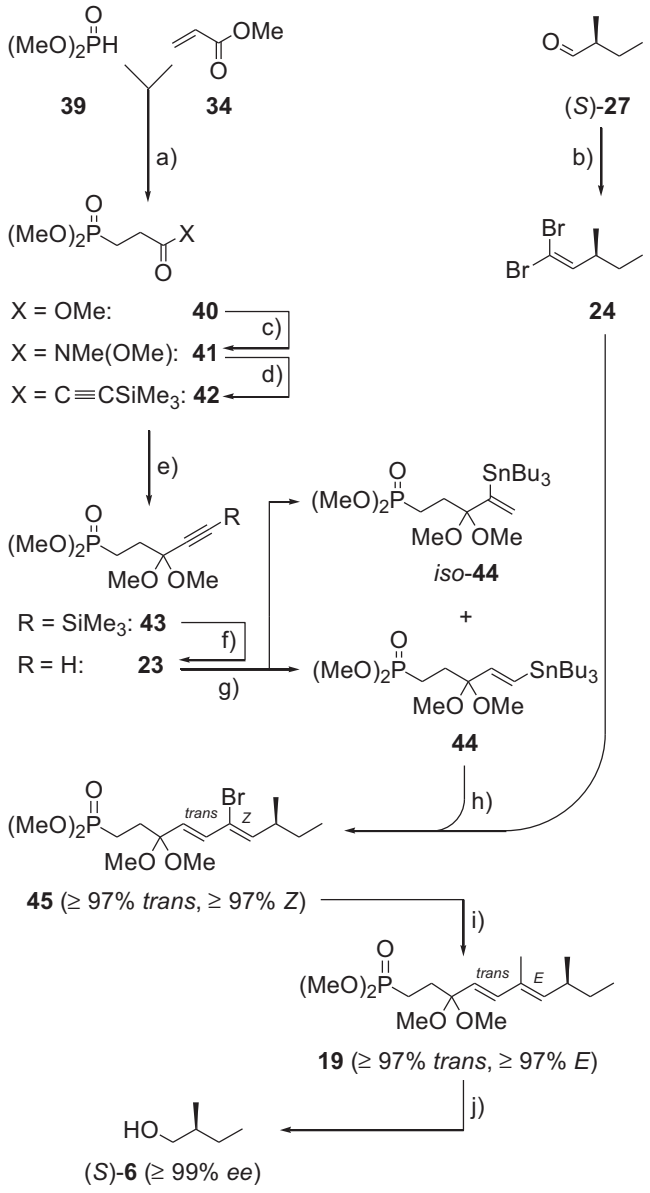
set of transformations of aldol adduct **17** comprised four steps both in the **a** and in the **b** series (Scheme 2). Protection of the OH groups gave the *tert*-butyldimethylsilylethers **30a**,**b**. Unable to acylate phenylmagnesium bromide even in refluxing THF either of the **30** epimers picked up phenyllithium, albeit in a 1:2 ratio. Speculating that the nucleophilicity of the latter might be modified by aggregate formation we attenuated the reactivity of 2 equiv of phenyllithium by 5 equiv of LiCl such that the **30** epimers accepted *that* phenyl donor in the desired 1:1 ratio. The ^{1}H NMR spectrum of the crude products evidenced more aliphatic protons than the expected ketoaldehyde structures **32a** and **b** would have contained. These excess protons indicated that in spite of the aqueous workup the initially formed hemiketal/acetal structures **31a** and **b** were still intact.[47] They decomposed when purified by flash chromatography on silica gel[44] in the presence of *p*-TsOH, though. The resulting ketoaldehydes **32a** and **b** exhibited minor signals, the slower the chromatography the more intensely. Concluding that epimerization α to the aldehyde function was a risk we chromatographed the ketoaldehydes **32a** and **b** as fast as possible and oxidized them immediately. This rendered the ketoacids **16a** ($\delta_{C=O}$ = 199.10 ppm, δ_{CO_2H} = 169.36 ppm) and **b** ($\delta_{C=O}$ = 201.39 ppm, δ_{CO_2H} = 172.75 ppm), in 34% and 49% overall yield from silyl ethers **30a** and **b**, respectively.



Scheme 3. Synthesis of the side-chain bearing phosphonate **22**, the other precursor (cf. Scheme 2) of the kodaistatin model *iso-cis*-**12** according to the retrosynthetic analysis of Scheme 1. Reagents and conditions: (a) $AlMe_3$ (1.0 equiv), CH_2Cl_2, 0 °C; addition of **34** (1.0 equiv), →room temperature, 12 h; 95%. (b) *t*-$BuNH_2$ (1.1 equiv), $MgSO_4$ (1.7 equiv), CH_2Cl_2, Rückfluss, 1 h; 91% (Ref. 49: 96%). (c) NaOCl (1.1 equiv), TEMPO (1 mol %), KBr (10 mol %), CH_2Cl_2/H_2O (5:1), 0 °C, 8 min; 89% (Ref. 28: 59–88%). (d) **35** (1.5 equiv), *n*-BuLi (1.4 equiv), THF, −78 °C; →0 °C, 20 min, →−78 °C; addition of (*S*)-**27**; →0 °C, 4 h; addition of aq oxalic acid, →room temperature, 14 h; 71%. (e) LDA (1.5 equiv), THF, −78 °C; addition of **37** (1.5 equiv); addition of **36**; →room temperature, 12 h; 77%. (f) **25** (2.0 equiv), K_2CO_3 (8 equiv), dioxane, 70 °C, 1 h; addition of **26**, H_2O (8 equiv), 40 h; 75%. (g) Trimethyl orthoacetate (1.0 equiv), *p*-TsOH (10 mol %), 2,6-di-*tert*-butyl-4-methylphenol (10 mol %), MeOH (degassed), 0 °C, 3 h; 87% of the indicated isomeric mixture. (h) Stream of ozonated oxygen, MeOH, −78 °C, 30 min; addition of $NaBH_4$ (6 equiv), →room temperature, 4 h; GLC analysis.

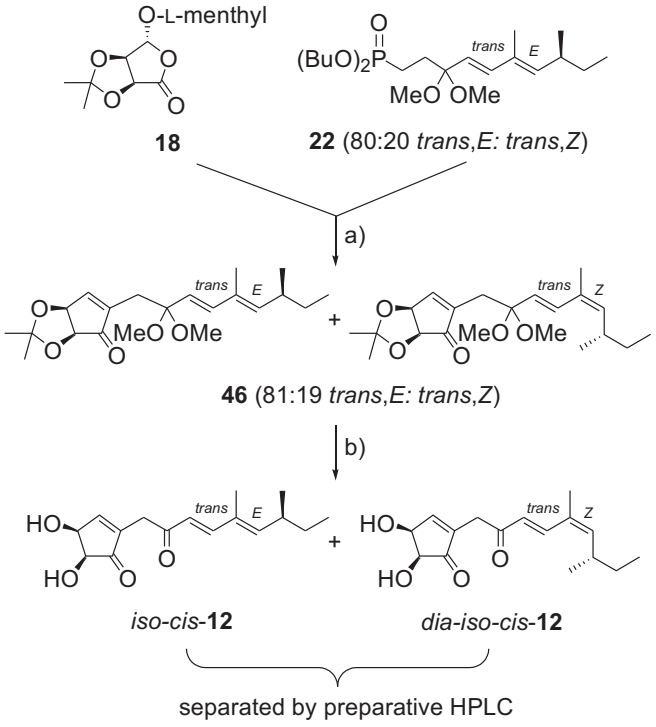
Following our retrosynthetic analysis of Scheme 1, the ketal-substituted phosphonate **22** was derived from the ketobis(phosphonate) **25** and the (*S*)-configured α,β-unsaturated aldehyde **26**. These compounds were prepared and combined as shown in Scheme 3. The 1,4-addition of dimethyl phosphite (**33**) to the acrylate **34** was induced by $AlMe_3$.[48] The resulting phosphorylated ester **36** allowed to acylate the lithiated phosphonic ester **37**. This rendered 77% of the ketobis(phosphonate) **25**. Condensation of *N*-*tert*-butylamine with propionaldehyde gave imine **35** in accordance with Ref. 49. Moreover, oxidation of alcohol (*S*)-**6** by NaOCl (stoichiom.), TEMPO (cat.), and KBr (cat.) gave aldehyde (*S*)-**27** as reported.[28] After lithiation with *n*-BuLi, imine **35** was added to aldehyde (*S*)-**27**. The crude product was treated with oxalic acid. This gave the (*S*)-configured α,β-unsaturated aldehyde **26** in 71% yield.[50] No Horner–Wadsworth–Emmons olefinations, which engage the ketobis(phosphonate) **25** or analogs thereof, have been described in the literature.[30] Nonetheless **25** underwent such an olefination with enal **26** without a problem (K_2CO_3 in dioxane and a small amount of H_2O at 70 °C). The ketophosphonate **38** resulted in 75% yield, the newly formed C=C bond being exclusively *trans*-configured.[51] The ensuing ketalization in MeOH with trimethyl formiate and cat. *p*-TsOH occurred at 0 °C within 3 h. It rendered the ketal-substituted phosphonate **22** in 87% yield. However, this reaction was hampered by a partial isomerization of the trisubstituted C=C bond. Usually **22** could not be obtained purer than as a 88:12 mixture of the *trans*,*E*- and the *trans*,*Z* isomer.[51] Gratifyingly, though, the stereocenter had stayed intact all the way from alcohol (*S*)-**6** into phosphonate **22**. This was proven by an ozonolysis of **22** followed by reduction of the crude product by $NaBH_4$ because the resulting alcohol **6** was ≥99% (*S*)-configured.

In the retrosynthetic analysis of Scheme 1 the isomerically pure ketal-substituted decadienyl phosphonate **19** was traced back to the ketal-substituted pentynyl phosphonate **23** and the *gem*-dibrominated alkene **24**. The latter materials were obtained and processed as detailed in Scheme 4. The 1,4-addition of dimethyl phosphite (**39**) to methyl acrylate (**34**) was made work like the addition of dibutyl phosphite (**33**) to the same acrylate (Scheme 3), namely by adding $AlMe_3$ (→74% **40**).[48] $AlMe_3$ also served for deprotonating the hydrochloride of *N*,*O*-dimethylhydroxylamine, the resulting amide converting the phosphorylated ester **40** into the Weinreb amide **41** (89% yield). The latter allowed the acylation of lithiated (trimethylsilyl)acetylene. The resulting ketone **42** was so sensitive that it was ketalized without prior purification. The ketalized and silyl-substituted phosphonate **43** resulted in 40% yield over the two steps. It was desilylated by a substoichiometric amount of borax in aqueous methanol.[52] This delivered the ketal-substituted pentynyl phosphonate **23** in 98% yield. Compound **23** was hydrostannylated with Bu_3SnH under $PdCl_2(PPh_3)_2$ catalysis.[53] To the extent that this provided the 1-(tributylstannyl)alkene **44** (66% yield) the reaction was *trans*-selective.[54] In addition we obtained the 2-(tributylstannyl) alkene *iso*-**44** (18% yield). These isomers could be separated by flash chromatography on silica gel,[44] *iso*-**44** eluting faster than **44**.[55,56] The counterpart of the terminally stannylated alkene **44** for the Stille coupling was the dibromoolefin **24**. It was prepared as described[32] from aldehyde (*S*)-**27**[28] (which was synthesized as shown in Scheme 3), PPh_3, and Zn. The Stille-coupling between **44** and (*S*)-**27** worked best in the presence of 10 mol % $Pd(dba)_2$ and 30 mol % P(2-Fur)$_3$ in toluene. It was chemoselective—because mono-coupling occurred—and stereoselective,[57] both as anticipated.[33] The *trans*,*Z*-configured bromodecadienyl phosphonate **45** resulted in 66% yield.[54] It underwent a stereo-retentive Negishi coupling with Me_2Zn in refluxing THF when 10 mol % of $Pd(P^tBu_3)_2$ were present. These conditions were adopted from a literature precedent where 2 mol % of $Pd(P^tBu_3)_2$ had sufficed.[34] Using such a small amount of the catalyst caused an incomplete conversion of the bromodecadienyl phosphonate **45**. This faced us with the problem of being unable to



Scheme 4. Synthesis of the side-chain bearing phosphonate **19**, the other precursor (cf. Scheme 2) of the kodaistatin model *cis*-**11** according to the retrosynthetic analysis of Scheme 1. Reagents and conditions: (a) $AlMe_3$ (1.0 equiv), CH_2Cl_2, 0 °C, 50 min; addition of **34** (1.0 equiv); →room temperature, 21 h; 74%. (b) CBr_4 (2.5 equiv), PPh_3 (2.5 equiv), Zn (3.0 equiv), CH_2Cl_2, room temperature, 96 h; →0 °C; addition of (*S*)-**27**, 30 min; →room temperature, 6 h; 81% (ref.32a: 81%). (c) HN(OMe)Me·HCl (4.0 equiv), $AlMe_3$ (4.0 equiv), CH_2Cl_2, −10 °C, 20 h; 89%. (d) Me_3Si-acetylene (1.25 equiv), *n*-BuLi (1.25 equiv), THF, −78 °C, 1 h; addition of **41**, →−40 °C, 4 h; the crude product was carried on without purification. (e) $HC(OMe)_3$/MeOH (1:1), *p*-TsOH (5 mol %), 80 °C, 7 h; 40% over the 2 steps. (f) $Na_2B_4O_7$ (15 mol %), MeOH/H_2O (3:1), 40 °C, 3 h; 98%. (g) Bu_3SnH (1.2 equiv), $PdCl_2(PPh_3)_2$ (5 mol %), THF (degassed), room temperature, 20 min; 66% **44** separated from 18% of regioisomer *iso*-**44**. (h) **24** (1.25 equiv), $Pd(dba)_2$ (30 mol %), $Pd[P(2\text{-furyl})_3]_3$ (10 mol %), 2,6-di-*tert*-butyl-4-methylphenol (5 mol %), toluene (degassed), 50 °C, 44 h; 66%. (i) $ZnMe_2$ (1.2 M in toluene, 2.0 equiv), $Pd(P^tBu_3)_2$ (10 mol %), 2,6-di-*tert*-butyl-4-methylphenol (5 mol %), THF (degassed), 0 °C→55 °C, 22 h; 87%. (j) Stream of ozonated oxygen, MeOH, −78 °C, 30 min; addition of $NaBH_4$ (6 equiv), →room temperature, 4 h; GLC analysis.

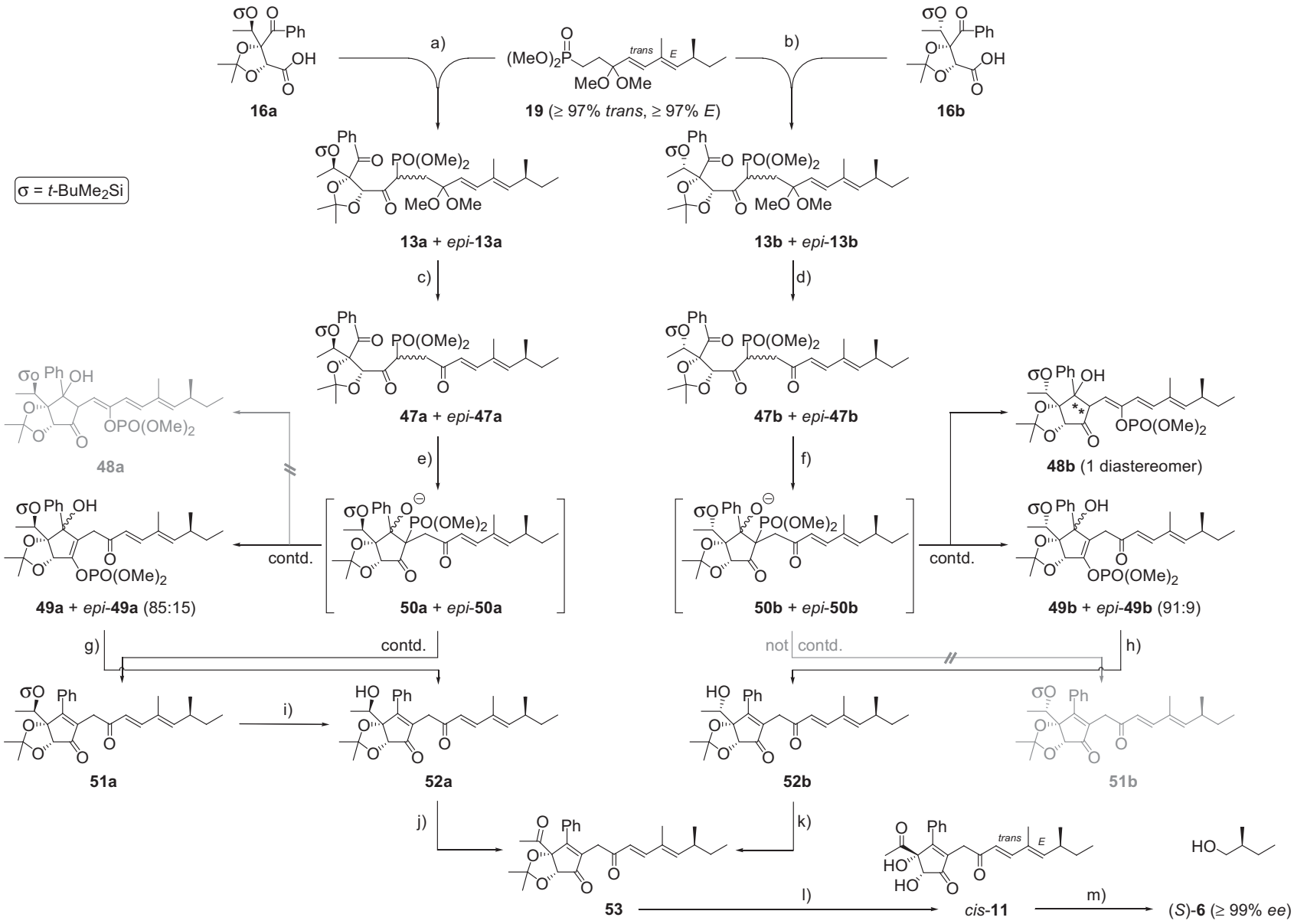
separate the coupling product **19** from residual bromide **45** by flash chromatography on silica gel.[44] Employing 10 mol % of the catalyst led to a complete conversion of **45** and an 87% yield of phosphonate **19**.[54,58] As in phosphonate **22** (Scheme 3) the stereocenter in **19** (Scheme 4) was ≥99% (*S*)-configured. This was proved by ozonolyzing **19**, reducing the crude product by $NaBH_4$, and analyzing the resulting alcohol **6** by chiral GLC.



Scheme 5. Completion of the simplified kodaistatin model *iso-cis*-**12**. Reagents and conditions: (a) **22**, *n*-BuLi (1.0 equiv), THF, −78 °C, 1 h; addition of LDA (1.0 equiv), −78 °C, 5 min; addition of **18** (1.0 equiv); →−45 °C, 18 h; 43%, 81:19 mixture *trans*,*E*-**46**:*trans*,*Z*-**46**. (e) *p*-TsOH (5 mol %), H_2O (101 equiv), acetonitrile, room temperature, 16 h; →60 °C, 3 h; additional H_2O (51 equiv), 60 °C, 1 h; 90%.

Consecutive additions of 1 equiv of *n*-BuLi and 1 equiv of LDA to a THF solution of an 80:20 *trans*,*E*:*trans*,*Z*-mixture of the decadienyl phosphonate **22** at −78 °C provided a 1:1 mixture the lithiated phosphonate and LDA, as we had hoped (Scheme 5). After adding 1 equiv of the C_4 bis(electrophile) **18**, we warmed to −45 °C and allowed the reaction to proceed for 18 h. This delivered the cyclopentenone **46** in 43% yield as an inseparable 81:19 *trans*,*E*:*trans*,*Z*-mixture.[51] Obviously both phosphonate stereoisomers had been equally reactive. The dimethylketal and acetonide moieties of compound **46** were cleaved in aqueous acetonitrile in the presence of a small amount of tosic acid. The dimethylketal seemed to disappear at room temperature while removing the acetonide required heating to 60 °C. The simplified kodaistatin model *iso-cis*-**12**[51] and its C=C bond stereoisomer *dia-iso-cis*-**12** resulted as an unchanged 81:19 *trans*,*E*:*trans*,*Z*-mixture in 90% combined yield.[51] The two isomers were separable by preparative HPLC, which allowed to characterize the constituents unambiguously. The accessibility of compound *iso-cis*-**12** suggested that the synthesis strategy, on which we had relied would probably be also viable for the synthesis of the more advanced kodaistatin models *cis*-**11** and *trans*-**11**.

Scheme 6 shows how we combined the decadienyl phosphonate **19**, which was our second latent C_1 bis(nucleophile), with the γ-ketoacid **16a** or its epimer **16b**, both of which were latent C_4 bis(electrophiles). These ketoacids were converted into the corresponding ketoacyl chlorides by treatment with 'chloroenamine' in THF.[59] Either of these ketoacyl chlorides was combined with an equimolar amount of a 1:1 mixture of LDA and the lithiated decadienyl phosphonate **19** at −78 °C. This provided, as we presumed, the diketophosphonates **13a**/*epi*-**13a**[60] and **13b**/*epi*-**13b**,[60] respectively, in 49% yield each, i.e., no Horner–Wadsworth–Emmons olefination had occurred. The dimethylketal moieties of the diketophosphonates **13** were cleaved by tosic acid in aqueous acetonitrile. This rendered what we surmised were the triketophosphonates **47a**/*epi*-**47a**[60] and **47b**/*epi*-**47b**,[60] respectively.



Scheme 6. Completion of the kodaistatin model *cis*-**11**. Treatment of the triketophosphonates **47a** and **b** with base did not induce the desired cyclopentenone-delivering Horner–Wadsworth–Emmons reactions only (**a**) or at all (**b**) since we observed competing (**a**) or exclusive (**b**) enol phosphate formations instead. Reagents and conditions: (a) (i) Activation of **16a**: 1-chloro-*N*,*N*,2-trimethylprop-1-en-1-ylamine ('chloroenamine'; 1.2 equiv), THF, room temperature, 1.5 h; (ii) lithiation of **19** (1.0 equiv): *n*-BuLi (1.0 equiv), −78 °C, 1 h; LDA (1.0 equiv); (iii) diketophosphonate formation: lithio-**19**/LDA added to activated **16a** at −78 °C, 25 min; 49% **13a**/*epi*-**13a** separated from 14% recovered **19**. (b) Same as (a) but starting from **16b** and admitting 30 min for step (iii); 49% **13b**/*epi*-**13b** separated from 31% recovered **19**. (c) *p*-TsOH (5 mol %), MeCN/H_2O (5:1), room temperature, 16 h; the resulting triketophosphonates **47a**/*epi*-**47a** were not purified. (d) Same as (c) but starting from **13b**/*epi*-**13b** and allowing for 16.5 h reaction time; the resulting triketophosphonates **47b**/*epi*-**47b** were not purified. (e) K_2CO_3 (2.0 equiv), 18-crown-6 (4.0 equiv), benzene, 60 °C, 2.5 h; 26% **51a**+(separately) 26% **49a**/*epi*-**49a** (over the 2 steps). (f) K_2CO_3 (2.2 equiv), 18-crown-6 (3.0 equiv), benzene, 60 °C, 3.5 h; 32% **48b**+(separately) 26% **49b**/*epi*-**49b** (over the 2 steps). (g) HBF_4 (3.0 equiv), H_2O (15 equiv), CH_2Cl_2, 40 °C, 100 min; 45% **52a**. (h) Same as (g) but starting from **49b**/*epi*-**49b**; 48% **52b**. (i) NH_4F (5.0 equiv), 1,4-dioxane/H_2O 7:2, 40 °C, 14 h; 64%. (j) Pr_4NRuO_4 (10 mol %), *N*-methylmorpholine-*N*-oxide (2.5 equiv), CH_2Cl_2 (degassed), room temperature, 3 h; 80%. (k) Same as (j) but starting from **52b**; 90%. (l) H_2O (110 equiv) in trifluoroacetic acid, room temperature, 3 h; 55%. (m) Stream of ozonated oxygen, MeOH, −78 °C, 10 min; addition of $NaBH_4$ (6 equiv), →room temperature, 4.5 h; GLC analysis.

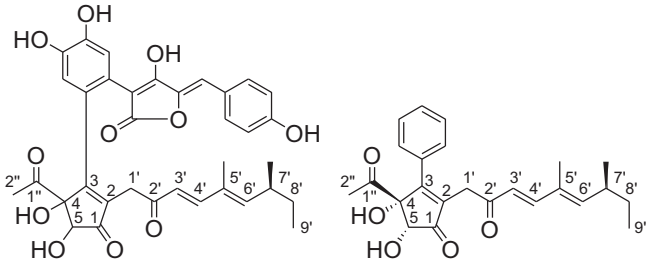
Each of the latter pairs of compounds was heated in a mixture of K_2CO_3 and 18-crown-6 in benzene. Workup after 2.5 and 3.5 h, respectively, gave a surprising result. A cyclopentenone (**51a**[54]) resulted only in the **a**-configured series (26% yield over the two steps from **13a**/*epi*-**13a**). It arose together with a 85:15 mixture of the cyclopentenyl phosphates **49a**[54] and *epi*-**49a** (again 26% yield from **13a**/*epi*-**13a**). Starting from the differently configured triketophosphonates **47b**/*epi*-**47b** none of the cyclopentenone **51b** formed. Instead, we isolated a 91:9 mixture of the cyclopentenyl phosphate epimers **49b**[54] and *epi*-**49b** (34% yield over the two steps from **13b**/*epi*-**13b**) and separately the side-chain based alkenyl phosphate **48b**[54] (32% yield from **13b**/*epi*-**13b**). This preference for alkenyl phosphate formation can be interpreted as follows (details: footnote[61]): (1) Horner–Wadsworth–Emmons ring-closures were slowed down due to steric hindrance. (2) Ring-closures by an aldol addition were kinetically competitive; they limited the role of the $P(=O)(OMe)_2$ group to that of a by-stander. (3) Enolate formation in the side-chain allowed a C→O and subsequently an O→O migration of the $P(=O)(OMe)_2$ moiety.

Only the side-chain based alkenyl phosphate **48b** was a genuine loss in our synthesis. In contrast, the cyclopentenyl phosphates **49a**/*epi*-**49a** and **49b**/*epi*-**49b** could be re-routed toward the kodaistatin model *cis*-**11**. This succeeded by exposure to HBF_4 in a 2-phase system composed of CH_2Cl_2/H_2O. Either of the mixtures underwent two structural changes: loss of the *tert*-butyldimethylsilyl group and 1,4-elimination of dimethyl phosphate. As a result, we obtained the cyclopentenones **52a**[54] and **52b**[54] in 45% and 48% yield, respectively. Cyclopentenone **52a** was also obtained by an NH_4F-mediated desilylation of the Horner–Wadsworth–Emmons product **51a** (64% yield). The hydroxydiketones **52a** and **52b** converged to the triketone **53**[54] upon oxidation with TPAP.[62] The yields of **53** were 80% and 90%, respectively. When we cleaved the acetonide ring of triketone **53** in aqueous trifluoroacetic acid the kodaistatin model *cis*-**11**[54] was attained in 55% yield. Ozonolysis of *cis*-**11** and an ensuing reduction with $NaBH_4$ furnished the alcohol (*S*)-**6** once more as a stereochemically integer compound. Accordingly none of the steps between the phosphonate **19** and the model *cis*-**11** had scrambled the side-chain stereocenter.

A Swern oxidation with trifluoroacetic anhydride as the activating agent left our kodaistatin model *cis*-**11** unaffected whereas TPAP or the Dess–Martin periodinane attacked the model but provided product mixtures. These exploratory experiments contrasted with our hope that an oxidation/reduction sequence might allow for converting at least some kodaistatin model *cis*-**11** into the epimeric model *trans*-**11**. No more efforts with that objective were undertaken at that stage.

Table 1 juxtaposes the ^1H- and ^{13}C NMR shifts of kodaistatin model *cis*-**11** and those the natural product kodaistatin A (**5a**[10]). The absolute values of the six largest ^{13}C-shift differences $\delta_{\mathbf{5a}}-\delta_{cis\text{-}\mathbf{11}}$ range from 8.95 to 1.92 ppm. They are associated with the nuclei of the cyclopentenone ring and with the carbonyl substituent of the quaternary stereocenter. These shift differences and the locations of their origin could mean that our kodaistatin model *cis*-**11** and the natural product (**5a**) contain diastereomeric cyclopentenone moieties. Since our model *cis*-**11** is a *cis*-1,2-diol, one would then conclude that **5a** is a *trans*-1,2-diol. The absolute values of the six largest ^1H NMR shift differences $\delta_{\mathbf{5a}}-\delta_{cis\text{-}\mathbf{11}}$ range from 0.43 to 0.21 ppm. They stem from protons other than the only proton (5-H), which is cyclopentenone-bound. In fact 5-H is only marginally deshielded in **5a** versus *cis*-**11** [$\delta_{\mathbf{5a}}-\delta_{cis\text{-}\mathbf{11}}$=0.06 ppm], which does not hint at the occurrence of a differently configured diol moiety in **5a** versus *cis*-**11**. Surprisingly, the mentioned larger ^1H NMR shift differences are associated with several protons located off and away from the diol moiety. For instance, the 6′-H resonance is shifted downfield by 0.28 ppm in **5a** versus *cis*-**11**. Indeed, this kind of observation is surprising no matter what the diol configuration. These remote substituent effects are unlikely to reflect configurational issues in the diol moiety. They might rather indicate that the unsubstituted phenyl ring in compound *cis*-**11** models the *ortho*-substituted phenyl ring of kodaistatin A (**5a**) poorly. An *ortho*-substituted instead of an unsubstituted phenyl substituent might be twisted more severely relative to the cyclopentenone ring. It is conceivable that differential twists expose side-chain protons in a different manner to the shielding/deshielding sections of the anisotropy tensor.

Table 1
Chemical shift comparisons between model compound *cis*-**11** (^1H NMR: 499.6 MHz; ^{13}C NMR: 125.6 MHz) and kodaistatin A[10] (**5a**; ^1H NMR: 600 MHz; ^{13}C NMR: 151 MHz) in DMSO-d_6 solutions at 300 K. Gray backgrounds point out ^1H NMR chemical shift differences with absolute values >0.20 ppm and ^{13}C NMR chemical shift differences with absolute values >3.00 ppm.



5a *cis*-**11**

Nucleus	$\delta(^1H)$/ppm		$[\delta(^1H)_{\mathbf{5a}}-\delta(^1H)_{cis\text{-}\mathbf{11}}]$/ppm	$\delta(^{13}C)$/ppm		$[\delta(^{13}C)_{\mathbf{5a}}-\delta(^{13}C)_{cis\text{-}\mathbf{11}}]$/ppm
	cis-**11**	**5a**		*cis*-**11**	**5a**	
1	Devoid of H	Devoid of H	—	204.43	200.01	−4.42
2	Devoid of H	Devoid of H	—	135.32	137.24	+1.92
3	Devoid of H	Devoid of H	—	165.30	161.61	−3.69
4	Devoid of H	Devoid of H	—	85.49	89.66	+4.17
5	4.20	4.26	+0.06	75.50	84.45	+8.95
1′	3.46+3.72	3.06+3.29	−0.40–0.43	36.03	36.91	+0.88
2′	Devoid of H		—	195.48	194.09	−1.39
3′	6.15	5.93	−0.22	123.68	122.60	−0.78
4′	7.28	6.92	−0.36	148.49	147.21	−1.28
5′	Devoid of H	Devoid of H	—	131.80	131.62	−0.18
6′	5.85	5.57	−0.28	149.64	148.67	−0.97
7′	2.44–2.50	2.44	−0.03	34.39	34.22	−0.17
8′	1.22–1.32+ 1.34–1.43	1.21+1.34	−0.06–0.05	29.38	29.35	−0.03
9′	0.81	0.78	−0.03	11.74	11.63	−0.11
5′-Me	1.76	1.70	−0.06	12.15	12.11	−0.04
7′-Me	0.96	0.97	+0.01	19.95	19.94	−0.01
1″	Devoid of H	Devoid of H	—	210.94	207.71	−3.23
2″	2.13	2.32	+0.21	27.27	27.69	+0.42

4. Conclusions

We achieved the first synthesis of the cyclopentenone *cis*-**11**. It exhibits the unprecedented substitution pattern of the cyclopentenone core of the glucose-6-phosphate-T_1-translocase inhibitor kodaistatin A (**5a**). A cornerstone of our synthesis is a C_4+C_1 approach to the cyclopentenone moiety. This approach worked without problems for reaching the simplified kodaistatin model *iso-cis*-**12**. It was not so straightforward for reaching the advanced kodaistatin model *iso-cis*-**11**. This is because the desired Horner–Wadsworth–Emmons ring-closures **47**→**52** were outcompeted by ring-closures based on aldol-additions. The latter were followed by $P(=O)(OMe)_2$ migrations. They provided alkenyl phosphates **48** and **49**. The latter of those were not lost on our way to *cis*-**11**. Seizable ^{13}C NMR shift differences between our model compound *cis*-**11** and kodaistatin A (**5a**) suggest that the latter—other than the former—contains a *trans*-1,2-diol moiety.

Unfortunately, we could not corroborate this inference by transforming our model compound *cis*-**11** into the hitherto elusive model

compound *trans*-**11** and by including ^{13}C NMR data of the latter in our comparisons. We believe that synthesizing the kodaistatin models *trans*-**11** or *iso-trans*-**11** remains conceivable on *variations* of the present route to *cis*-**11**. However, one would then protect the latent 1,2-diol moiety differently than as an acetonide: the 'dioxydiquinane' **51a** with the *cis*-annulated acetonide formed already so reluctantly in the present study that obtaining the diastereomeric 'dioxydiquinane' with a *trans*-annulated acetonide appears almost impossible.

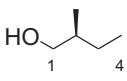
A while ago, Trost and Toste described a catalytic enantioselective synthesis of a compound, whose structure corresponds to an analog of the Feringa lactone **21**; therein the menthyloxy substituent gives way to a 2-naphthyloxy substituent.[63] The enantiomer of that analog should be equally readily accessible. It might be a cheaper progenitor of the cyclopentenone core of kodaistatin models like *iso-cis*-**11**, which exhibit the opposite diol configurations than the current models *cis*-**11** and *iso-cis*-**12**.

5. Experimental section

5.1. General information

Reactions were performed and reagents/solutions transferred in oven-dried (80 °C) glassware and plastic syringes/stainless steel cannulas, respectively, always under an atmosphere of N_2. 'Room temperature' refers to indoor temperatures in the absence of air-conditioning, i.e., to the range between 20 and 35 °C. THF was distilled over potassium prior to use, diethyl ether over Na/K-alloy, and dichloromethane, DMF, and diisopropylamine over calcium hydride. Most products were purified by flash chromatography[44] (column diameter, filling height, and eluents are given in parentheses) on Macherey-Nagel silica gel 60 (0.040–0.063 mm, 230–400 mesh, ASTM). Yields refer to analytically pure samples. ^1H NMR [TMS (δ=0.00) as internal standard in $CDCl_3$, C_6HD_5 as internal standard (δ=7.16[64]) in C_6D_6, DMSO-d_5 as internal standard (δ=2.50[64]) in DMSO-d_6]: Varian Mercury VX 300, Bruker Avance 400, and Bruker DRX 500. ^{13}C NMR [$CDCl_3$ as internal standard (δ=77.16[64]) in $CDCl_3$, C_6D_6 as internal standard (δ=128.06[64]) in C_6D_6, DMSO-d_6 as internal standard (δ=39.52[64]) in DMSO-d_6]: Bruker Avance 400 and Bruker DRX 500. Assignments of ^1H- and ^{13}C NMR resonances usually refer to the IUPAC nomenclature except within substituents, for which primed numbers may be used; exceptions from this rule are indicated in the formulas in the Experimental Part. MS, GLC/MS and HPLC/MS: Dr. J. Wörth and C. Warth, both Institut für Organische Chemie, Universität Freiburg. Chiral GLC: Carlo Erba gas chromatograph, with CP-7502 capillary (Chirasil-Dex) running on 50 kPa hydrogen. Combustion analyses: E. Hickl and F. Tönnies, Institut für Organische Chemie, Universität Freiburg. NMR: M. Schonhardt and F. Reinbold, Institut für Organische Chemie, Universität Freiburg. IR spectra: Perkin–Elmer Paragon 1000 spectrometer. Optical rotations α_{exp} were measured at 25 °C with a Perkin–Elmer polarimeter 341 MC at 589 with two exceptions, namely the kodaistatin model *cis*-**11** and compound **48b**, whose optical rotations were measured at λ=578 nm. The corresponding specific rotations $[\alpha]_D^{25}$ or $[\alpha]_{578}^{25}$ were calculated from the time-averaged value for α_{exp} furnished by the apparatus. X-ray crystal structure analyses: Dr. J. Geier, Institut für Organische Chemie, Universität Freiburg.

*5.1.1. (S)-2-Methylbutanol [(S)-**6**].*

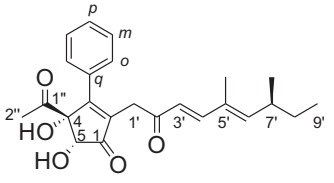


*5.1.2. Preparation by ozonolysis of kodaistatin A (**5a**) (Fig. 2).* A mixture of ozone and oxygen was bubbled through a solution of natural kodaistatin A (**5a**) (10 mg, 16 μmol) in MeOH (1.0 mL) at −78 °C. After 10 min the flow of ozone/oxygen was stopped and $NaBH_4$ (3.6 mg, 95 μmol, 5.9 equiv) was added in one portion. The dry-ice bath was removed and the mixture stirred for 3.5 h at room temperature. Aqueous, saturated solution of $NaHCO_3$ (1 mL) and Et_2O (1 mL) was added. After phase separation the aqueous phase was extracted with Et_2O (2×1 mL) and CH_2Cl_2 (2×1 mL) and the combined organic phases were dried over Na_2SO_4. The resulting solution was concentrated under reduced pressure and analyzed by 'chiral' GLC without further purification. GLC [CP-Chirasil-Dex CB, 25 m×0.25 mm (CP-7502), 35 °C isotherm, 45 min; +10 °C/min to 170 °C, 20 min; 50 kPa H_2 pressure—no additional carrier gas]: ≥99% ee for the detectable enantiomer of **6**, which was (*S*)-**6** and had R_t=18.39 min [R_t of (*R*)-**6**=17.55 min as read from the chromatogram obtained by coinjecting the described specimen of (*S*)-**6** and a reference specimen of *rac*-**6**].

*5.1.2.1. Preparation by ozonolysis of cis-**11** (Scheme 6).* A mixture of ozone and oxygen was bubbled through a solution of *cis*-**11** (3.0 mg, 7.6 μmol) in MeOH (1.0 mL) at −78 °C. After 10 min the flow of ozone/oxygen was stopped and $NaBH_4$ (1.7 mg, 46 μmol, 6.1 equiv) was added in one portion. The dry-ice bath was removed and the mixture stirred for 4.5 h at room temperature. Proceeding analogously as in the preceding paragraph we undertook an analogous analysis by 'chiral GLC' without prior purification [CP-Chirasil-Dex CB, 25 m×0.25 mm (CP-7502), 35 °C isotherm, 45 min; +10 °C/min to 170 °C, 20 min; 50 kPa H_2 pressure—no additional carrier gas]: ≥99% ee for the detectable enantiomer of **6**, which was (*S*)-**6** and had R_t=17.47 min [R_t of (*R*)-**6**=17.07 min as read from the chromatogram obtained by coinjecting the described specimen of (*S*)-**6** and a reference specimen of *rac*-**6**].

*5.1.2.2. Preparation by ozonolysis of **19** (Scheme 4).* A mixture of ozone and oxygen was bubbled through a solution of **19** (20 mg, 60 μmol) in MeOH (1.0 mL) at −78 °C. After 10 min the flow of ozone/oxygen was stopped and $NaBH_4$ (13.7 mg, 360 μmol, 6.00 equiv) was added in one portion. The dry-ice bath was removed and the mixture stirred for 3.5 h at room temperature. Proceeding analogously as in the preceding paragraph we undertook an analogous analysis by 'chiral GLC' without prior purification [CP-Chirasil-Dex CB, 25 m×0.25 mm (CP-7502), 35 °C isotherm, 45 min; +10 °C/min to 170 °C, 20 min; 50 kPa H_2 pressure—no additional carrier gas]: ≥99% ee for the detectable enantiomer of **6**, which was (*S*)-**6** and had R_t=17.84 min [R_t of (*R*)-**6**=17.87 min as read from the chromatogram obtained by coinjecting the described specimen of (*S*)-**6** and a reference specimen of *rac*-**6**].

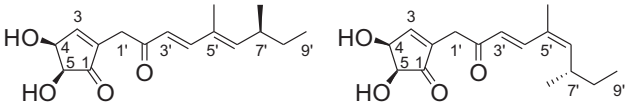
*5.1.3. (4R,5R)-4-Acetyl-2-[(S,3E,5E)-5,7-dimethyl-2-oxonona-3,5-dienyl]-4,5-dihydroxy-3-phenylcyclopent-2-en-1-one (cis-**11**).*



A solution of acetonide **53** (6.0 mg, 14 μmol) in CF_3CO_2H/H_2O (9:1, 500 μL; corresponds to 200 equiv of H_2O) was stirred at room temperature for 2.5 h. The solvent was removed at 30 °C in vacuo. Flash chromatography[44] (∅ 0.5 cm, 20 cm, packed with *c*-C_6H_{12}, then *c*-C_6H_{12}/AcOEt 2:1→1:1) gave the title compound (3.0 mg, 54%, ≥94% *trans*,*E*) as a yellow oil; R_f value (*c*-C_6H_{12}/AcOEt 1:1, impregnated with formic acid): 0.35; $[\alpha]_{578}^{25}$=+794, C_6D_6, *c*=0.24); IR (film): $\tilde{\nu}$=3415, 3060, 2955, 2925, 2865, 1720, 1690, 1675, 1665, 1640, 1620, 1590, 1490, 1480, 1460, 1445, 1410, 1390, 1355, 1305,

1255, 1205, 1185, 1150, 1125, 1080, 1020, 980, 930, 865 cm^{-1}; ^1H NMR (499.6 MHz, DMSO-d_6, sample contained ca. 6% of the *trans*,*Z* isomer of the title compound): δ=0.81 (3H, *t*, $J_{9',8'}$=7.4 Hz, 9′-H_3), 0.96 (3H, d, $J_{7'\text{-}CH3,7'}$=6.6 Hz, 7′-CH_3), 1.22–1.32 and 1.34–1.43 (2H, 2× m, 8′-H_2), 1.76 (3H, d, $J_{5'\text{-}CH3,6'}$=0.9 Hz, 5′-CH_3), 2.13 (3H, s, 2″-H_3), 2.44–2.52 (1H, m, 7′-H, superimposed by solvent signal), AB signal (2H, δ_A=3.46, δ_B=3.72, J_{AB}=17.3 Hz, 1′-H_2), 4.20 (1H, d, $J_{5,5\text{-}OH}$=7.3 Hz, 5-H), 5.85 (1H, br d, $J_{6',7'}$=9.8 Hz, 6′-H), 6.09 (1H, s, 4-O*H*), 6.15 (1H, d, $J_{3',4'}$=15.8 Hz, 3′-H), 6.19 (1H, d, $J_{5\text{-}OH,5\text{-}H}$=7.3 Hz, 5-O*H*), 7.28 (1H, d, $J_{4',3'}$=16.1 Hz, 4′-H), 7.40–7.45 (5H, m, Ph); ^{13}C NMR (125.6 MHz, DMSO-d_6, sample contained traces of a contaminant): δ=11.74 (C-9′), 12.15 (5′-CH_3), 19.95 (7′-CH_3), 27.27 (C-2″), 29.38 (C-8′), 34.39 (C-7′), 36.03 (C-1′), 75.50 (C-5), 85.49 (C-4), 123.68 (C-3′), 127.84 and 128.62 (*o*- and *m*-Ar), 129.65 (*p*-Ar), 131.80 (C-5′), 133.49 (*q*-Ar), 135.32 (C-2), 148.49 (C-4′), 149.64 (C-6′), 165.30 (C-3), 195.48 (C-2′), 204.43 (C-1), 210.94 (C-1″); HRMS (CI): MH^+, found *m*/*z*=397.20210, i.e., Δ=+1.5 ppm versus what $C_{24}H_{29}O_5$ requires (397.20150).

*5.1.4. (4S,5S)-2-[(7S,3E,5E)-5,7-Dimethyl-2-oxonona-3,5-dienyl]-4,5-dihydroxycyclopent-2-en-1-one (iso-cis-**12**) and (4S,5S)-2-[(7S,3E,5Z)-5,7-dimethyl-2-oxonona-3,5-dienyl]-4,5-dihydroxycyclopent-2-en-1-one (dia-iso-cis-**12**).*



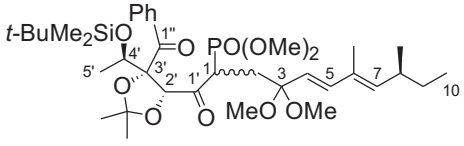
iso-cis-**12** *dia-iso-cis*-**12**

A suspension of dimethylketal **46** (81:19 *trans*,*E*:*trans*,*Z* mixture; 48.0 mg, 132 μmol), *para*-toluenesulfonic acid (1.2 mg, 7.0 μmol, 5 mol %), and H_2O (240 μL, 240 mg, 13.3 mmol, 101 equiv) in acetonitrile (1 mL) was stirred at room temperature for 16 h and at 60 °C for 3 h. More H_2O (120 μL, 120 mg, 6.77 mmol, 51 equiv) was added and stirring continued for 60 min. At room temperature AcOEt (5 mL) and satd aq $NaHCO_3$ (3 mL) were added. After phase separation the aq phase was extracted with AcOEt (3×2 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. Flash chromatography[44] (∅ 1.5 cm, 20 cm, *c*-C_6H_{12}/AcOEt 1:5→1:10) gave the title compounds (33 mg, 90%) as an orange oil and as an 80:20 *trans*,*E*:*trans*,*Z* mixture. 9 mg of this mixture were separated by preparative HPLC [stationary phase: Chiralpak AD-H; eluent: *n*-heptane/isopropanol (85:15); substrate concentration: 1.5 mg/mL; eluent flow: 16 mL/min] giving *iso-cis*-**12** (4 mg) and *dia-iso-cis*-**12** (1 mg).

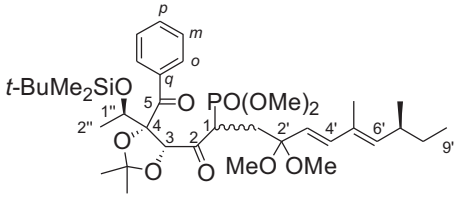
iso-cis-**12**: ^1H NMR (499.7 MHz, C_6D_6; sample contained residual AcOEt, isopropanol, and *n*-heptane): δ=0.71 (3H, *t*, $J_{9',8'}$=7.6 Hz, 9′-H_3), 0.79 (3H, d, $J_{7'\text{-}CH3,7'}$=6.6 Hz, 7′-CH_3), AB signal (2H, δ_A=1.08, δ_B=1.18, J_{AB}=13.3 Hz, A part additionally split by $J_{H(A),7'}$=7.2 Hz and $J_{H(A),9'}$=7.1 Hz, B part additionally split by $J_{H(B),9'}$=7.5 Hz and $J_{H(B),7'}$=5.8 Hz, 8′-H_2), 1.46 (3H, d, $J_{5'\text{-}CH3,6'}$=1.3 Hz, 5′-CH_3), 2.14 (1H, m_c, 7′-H), 2.80–3.24 (2H, 4- and 5-O*H*), AB signal (2H, δ_A=3.09, δ_B=3.23, J_{AB}=17.0 Hz, 1′-H_2), 3.73 (1H, d, $J_{5,4}$=5.7 Hz, 5-H), 4.21 (1H, dd, $J_{4,5}$=5.7, $J_{4,3}$=2.8 Hz, 4-H), 5.39 (1H, d, $J_{6',7'}$=9.8 Hz, 6′-H), 5.99 (1H, d, $J_{3',4'}$=15.8 Hz, 3′-H), 7.00 (1H, m_c, possibly interpretable as ddd, $J_{3,4}$=3.2 Hz, $J_{3,1'\text{-}H(A)}$=$J_{3,1'\text{-}H(B)}$=1.3 Hz, 3-H), 7.21 (1H, d, $J_{4',3'}$=15.8 Hz, 4′-H); ^{13}C NMR (125.7 MHz, C_6D_6): δ=12.05 (C-9′), 12.24 (5′-CH_3), 20.12 (7′-CH_3), 30.08 (C-8′), 35.12 (C-7′), 36.47 (C-1′), 67.99 (C-4), 71.23 (C-5), 123.84 (C-3′), 132.10 (C-5′), 139.98 (C-2), 148.67 (C-4′), 149.66 (C-6′), 156.99 (C-3), 194.55 (C-2′), 205.24 (C-1); MS (CI): *m*/*z*=279.1 (MH^+).

dia-iso-cis-**12**: ^1H NMR (499.7 MHz, C_6D_6; sample contained rests of isopropanol and *n*-heptane): δ=0.71 (3H, *t*, $J_{9',8'}$=7.6 Hz, 9′-H_3), 0.79 (3H, d, $J_{7'\text{-}CH3,7'}$=6.6 Hz, 7′-CH_3), AB signal (2H, δ_A=1.06, δ_B=1.17, J_{AB}=13.4 Hz, A part additionally split by $J_{H(A),9'}$=7.7 Hz and $J_{H(A),7'}$=7.6 Hz, B part additionally split by $J_{H(B),9'}$=7.5 Hz and $J_{H(B),7'}$=5.8 Hz, 8′-H_2), 1.61 (3H, d, $J_{5'\text{-}CH3,6'}$=1.3 Hz, 5′-CH_3), 2.37 (1H, 4-O*H*, assignment exchangeable with 5-O*H*), 2.47 (1H, m_c, 7′-H), 2.53 (1H, 5-O*H*, assignment exchangeable with 4-O*H*), AB signal (2H, δ_A=3.02, δ_B=3.23, J_{AB}=17.0 Hz, additional splitting not resolved, 1′-H_2), 3.59 (1H, d, $J_{5,4}$=5.4 Hz, 5-H), 4.08 (1H, m_c, 4-H), 5.32 (1H, d, $J_{6',7'}$=10.1 Hz, 6′-H), 6.07 (1H, dd, $J_{3',4'}$=15.8 Hz, $J_{unassignable}$=0.6 Hz, 3′-H), 6.93 (1H, ddd, $J_{3,4}$=2.9 Hz, $J_{3,1'\text{-}H(A)}$=$J_{3,1'\text{-}H(B)}$=1.3 Hz, 3-H), 7.81 (1H, d, $J_{4',3'}$=15.5 Hz, 4′-H); ^{13}C NMR (125.7 MHz, C_6D_6): δ=12.02 (C-9′), 20.01 (5′-CH_3), 20.96 (7′-CH_3), 30.36 (C-8′), 34.09 (C-7′), 36.96 (C-1′), 67.77 (C-4), 71.03 (C-5), 125.73 (C-3′), 130.15 (C-5′), 139.85 (C-4′), 139.91 (C-2), 147.47 (C-6′), 156.74 (C-3), 194.35 (C-2′), 205.76 (C-1); MS (CI): *m*/*z*=279.1 (MH^+).

5.1.5. Dimethyl {(1R,8S,4E,6E)-1-[(2R,3S,4R)-3-benzoyl-4-(tert-butyldimethylsiloxy)-2,3-(isopropylidenedioxy)-1-oxopentyl]-3,3-dimethoxy-6,8-dimethyldeca-4,6-dienyl}phosphonate (**13a**) and {(1S*,8S,4E,6E)-1-[(2R,3S,4R)-3-benzoyl-4-(tert-butyldimethylsiloxy)-2,3-(isopropylidenedioxy)-1-oxopentyl]-3,3-dimethoxy-6,8-dimethyldeca-4,6-dienyl}phosphonate (epi-**13a**; *these configurational descriptors are interchangeable).*



numbering in accordance with the IUPAC name

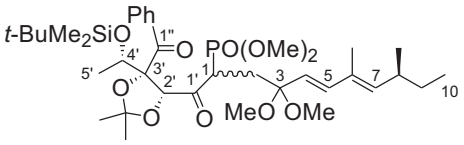


numbering for NMR assignments

A solution of acid **16a** (365 mg, 892 μmol) and 1-chloro-1-(*N*,*N*-dimethylamino)-2-methylprop-1-ene (131 mg, 981 μmol, 1.10 equiv) in THF (6 mL) was stirred at room temperature for 140 min and then cooled to −78 °C. In parallel, *n*-BuLi (2.4 M in hexane; 390 μL, 937 μmol, 1.05 equiv) was added at −78 °C to a solution of freshly dried (4 Å molecular sieves) phosphonate **19** (298 mg, 892 μmol, 1.00 equiv) in THF (3 mL); the resulting solution was stirred for 30 min at, which time LDA (0.31 M in THF, 3.00 mL, 937 μmol, 1.05 equiv) was added via cannula. The last-mentioned solution was added rapidly to the previously described solution (which contained the carboxylic chloride). After stirring the resulting mixture for 20 min at −78 °C it was poured into an ice-cold aq phosphate buffer (pH=5, 50 mL). After adding AcOEt (20 mL) the phases were separated, the aq phase was extracted with AcOEt (6×20 mL), the combined organic phases were dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was separated by flash chromatography[44] (∅ 4.0 cm, 20 cm, packed with *c*-C_6H_{12}/AcOEt 10:1+0.1 vol % NEt_3, eluted with *c*-C_6H_{12}/AcOEt 6:1→4:1) to give title compounds **13a**/*epi*-**13a** (315 mg, 49%) as an unquantified mixture of epimers [the ^1H NMR spectrum (300 MHz, C_6D_6) did not allow a more specific characterization due to signal overlap] and some reisolated phosphonate **19** (42 mg, 14%).

5.1.6. Dimethyl {(1R,8S,4E,6E)-1-[(2R,3S,4S)-3-benzoyl-4-(tert-butyldimethylsiloxy)-2,3-(isopropylidenedioxy)-1-oxopentyl]-3,3-dimethoxy-6,8-dimethyldeca-4,6-dienyl}phosphonate (**13b**) and*

{(1S,8S,4E,6E)-1-[(2R,3S,4S)-3-benzoyl-4-(tert-butyldimethylsiloxy)-2,3-(isopropylidenedioxy)-1-oxopentyl]-3,3-dimethoxy-6,8-dimethyldeca-4,6-dienyl}phosphonate (epi-**13b**; *these configurational descriptors are interchangeable).*



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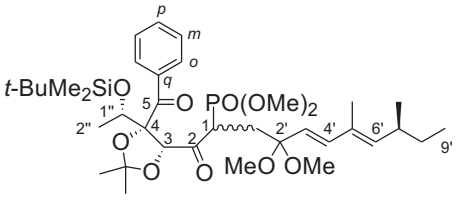
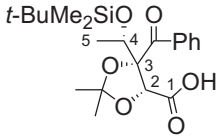


numbering for NMR assignments

The title compounds were prepared from acid **16b** (445 mg, 1.09 mmol) and 1-chloro-1-(*N*,*N*-dimethylamino)-2-methylprop-1-ene (160 mg, 1.20 mmol, 1.10 equiv) in THF (6 mL) on the one hand and from *n*-BuLi (2.4 M in hexane; 480 μL, 1.14 mmol, 1.05 equiv), phosphonate **19** (364 mg, 1.09 μmol, 1.00 equiv), and LDA (0.38 M in THF, 3.00 mL, 1.14 mmol, 1.05 equiv) in THF (3 mL) on the other hand after stirring at −78 °C for 30 min as described for the preparation of compounds **13a**/*epi*-**13a**. The crude product was separated by flash chromatography[44] like in the aforementioned case. It provided the title compounds **13b**/*epi*-**13b** (391 mg, 49%) as an unquantified mixture of epimers [the ^{1}H NMR spectrum (300 MHz, C_6D_6) did not allow a more specific characterization due to signal overlap] and some reisolated phosphonate **19** (113 mg, 31%); ^{31}P NMR (121.5 MHz, C_6D_6): δ=23.84 and 23.90 [2× *P*O(Me)$_2$].

*5.1.7. (2R,3S,4R)-3-Benzoyl-4-(tert-butyldimethylsiloxy)-2,3-(isopropylidenedioxy)pentanoic acid (**16a**).*



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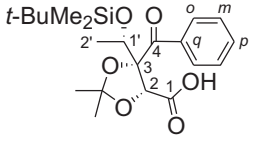
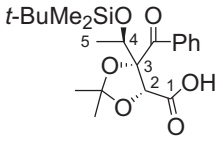


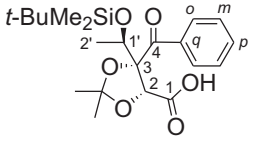
numbering for NMR assignments

At 0 °C $NaIO_4$ (543 mg, 2.55 mmol; 1.50 equiv) and $RuCl_3\cdot H_2O$ (35.3 mg, 170 μmol; 0.10 equiv) were added to a vigorously stirred solution of ketoaldehyde **32a** (670 mg, 1.70 mmol) in a biphasic mixture of CCl_4 (5 mL), MeCN (5 mL), and H_2O (7.5 mL). After 15 min the mixture was warmed to room temperature where stirring was continued for 3 h. After adding brine (15 mL) and AcOEt (10 mL) the phases were separated. The aq phase was extracted with AcOEt (4×10 mL). The combined organic phases were dried over Na_2SO_4. The solvent was removed in vacuo. Flash chromatography[44] (∅ 4 cm, 20 cm, *c*-C_6H_{12}/AcOEt 5:1 →4:1 →3:1: all eluents contained 0.2 vol % HCO_2H) furnished the title compound (543 mg, 78%) as a colorless resin; R_f value (*c*-C_6H_{12}/AcOEt 3:1, impregnated with HCO_2H): 0.25; $[\alpha]_D^{25}$=+52 ($CHCl_3$, *c*=2.70); IR (film): $\tilde{\nu}$=3055, 3015, 2930, 2855, 2660, 2545, 2355, 2335, 1730, 1675, 1595, 1575, 1470, 1445, 1415, 1370, 1320, 1255, 1215, 1190, 1135, 1155, 1095, 1020, 980, 940, 885, 835, 815, 775, 755 cm^{-1}; ^{1}H NMR (499.6 MHz, $CDCl_3$; because of line-broadening at 300 K the spectrum was registered at 280 K): δ=−0.17 and 0.00 [2× 3H, 2× s, Si(C*H*$_3$)$_2$], 0.82 [9H, SiC(C*H*$_3$)$_3$], 1.24[3H, s, 1× acetonide-C(C*H*$_3$)$_2$], 1.45 (3H, d, $J_{2',1'}$=6.3 Hz, 2′-H$_3$), 1.48[3H, s, 1× acetonide-C(C*H*$_3$)$_2$], 4.64 (1H, q, $J_{1',2'}$=6.4 Hz, 1′-H), 4.78 (1H, s, 2-H), 7.43 (2H, m$_c$, *m*-Ar), 7.55 (1H, *t*, $J_{p\text{-Ar},m\text{-Ar}}$=7.5 Hz, *p*-Ar), 8.12 (2H, d, $J_{o\text{-Ar},m\text{-Ar}}$=7.6 Hz, *o*-Ar); ^{13}C NMR (125.6 MHz, $CDCl_3$): δ=−5.24 and −4.52 [Si(*C*H$_3$)$_2$], 18.03 [SiC(CH$_3$)$_3$], 19.24 (C-2′), 25.66 [SiC(*C*H$_3$)$_3$], 26.52 and 27.37 [acetonide-C(*C*H$_3$)$_2$], 70.54 (C-1′), ca. 77.0 (C-2, superimposed by solvent signal), 92.79 (C-3), 111.63 [acetonide-*C*(CH$_3$)$_2$], 128.33 (*m*-Ar), 130.49 (*o*-Ar), 133.44 (*p*-Ar), 134.70 (*q*-Ar), 169.36 (C-1), 199.10 (C-4); combustion analysis: found C 61.45%, H 7.52%; calculated for $C_{21}H_{32}O_6Si$: C 61.73%, H 7.89%.

*5.1.8. (2R,3S,4S)-3-Benzoyl-4-(tert-butyldimethylsiloxy)-2,3-(isopropylidenedioxy)pentanoic acid (**16b**).*



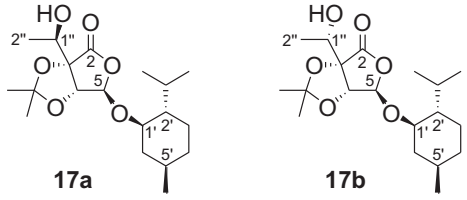
numbering in accordance with the IUPAC name



numbering for NMR assignments

The title compound was prepared from $NaIO_4$ (389 mg, 1.82 mmol; 1.50 equiv) and $RuCl_3\cdot H_2O$ (25.2 mg, 121 μmol; 0.10 equiv) were added to a vigorously stirred solution of ketoaldehyde **32b** (477 mg, 1.21 mmol) in a biphasic mixture of CCl_4 (5 mL), MeCN (5 mL), and H_2O (7.5 mL) as described for the preparation of compound **16a**. Flash chromatography[44] as in the preceding procedure delivered the title compound (325 mg, 66%) as a colorless resin; $[\alpha]_D^{25}$=+51 ($CHCl_3$, *c*=0.60); IR (film): $\tilde{\nu}$=3055, 3020, 2980, 2950, 2930, 2890, 2855, 2745, 2705, 2655, 2560, 2360, 2335, 1730, 1685, 1650, 1600, 1575, 1470, 1460, 1455, 1445, 1380, 1375, 1295, 1250, 1220, 1180, 1155, 1090, 1020, 975, 960, 935, 915, 880, 830, 810 cm^{-1}; ^{1}H NMR (499.6 MHz, $CDCl_3$; sample contained a trace of *t*-BuOMe; because of line-broadening at 300 K the spectrum was registered at 270 K): δ=−0.14 and 0.04 [2× 3H, 2× s, Si(C*H*$_3$)$_2$], 0.76 [9H, SiC(C*H*$_3$)$_3$], 1.11[3H, s, 1× acetonide-C(C*H*$_3$)$_2$], 1.32 (3H, d, $J_{2',1'}$=6.3 Hz, 2′-H$_3$), 1.45[3H, s, 1× acetonide-C(C*H*$_3$)$_2$], 4.60 (1H, q, $J_{1',2'}$=6.4 Hz, 1′-H), 4.62 (1H, s, 2-H), 7.38 (2H, m$_c$, *m*-Ar), 7.50 (1H, *t*, $J_{p\text{-Ar},m\text{-Ar}}$=7.4 Hz, *p*-Ar), 8.10 (2H, d, $J_{o\text{-Ar},m\text{-Ar}}$=7.9 Hz, *o*-Ar), 8.4–9.8 (1H, br s, CO_2H); ^{13}C NMR (125.6 MHz, $CDCl_3$): δ=−4.82 and −4.77 [Si(*C*H$_3$)$_2$], 18.01 [SiC(CH$_3$]$_3$, assignment exchangeable with C-2′), 18.36 [C-2′, assignment exchangeable with SiC(CH$_3$)$_3$], 25.80 [SiC(*C*H$_3$)$_3$], 26.80 and 27.21 (2× acetonide-*C*H$_3$), 69.68 (C-1′), 77.65 (C-2), 95.95 (C-3), 111.39 [acetonide-*C*(CH$_3$)$_2$], 127.85 (*m*-Ar), 130.93 (*o*-Ar), 132.88 (*p*-Ar), 136.19 (*q*-Ar), 172.79 (C-1), 201.39 (C-4); HRMS (CI): MH$^+$, found *m*/*z*=409.20470, i.e., Δ=+0.1 ppm versus what $C_{21}H_{33}O_6Si$ requires (409.20464).

*5.1.9. (3S,4R,5R)-3-[(R)-1-Hydroxyethyl]-5-{(1R,2S,5R)-[2-isopropyl-5-methylcyclohexyl]oxy}-3,4-(isopropylidenedioxy)-4,5-dihydro-3H-furan-2-one (**17a**) and (3S,4R,5R)-3-[(S)-1-hydroxyethyl]-5-{(1R,2S,5R)-[2-isopropyl-5-methylcyclohexyl]oxy}-3,4-(isopropylidenedioxy)-4,5-dihydro-3H-furan-2-one (**17b**).*

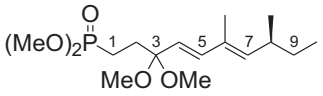


A mixture of benzyltrimethylammonium fluoride hydrate (266 mg, 1.57 mmol, 1.10 equiv), molecular sieves (4 Å), and THF (5 mL) was stirred at room temperature for 13 h. The resulting suspension was soaked up in a syringe and added at −78 °C in the course of 18 min to a solution of lactone **29** (550 mg, 1.43 mmol) and acetaldehyde (645 μL, 502 mg, 2.15 mmol, 8.00 equiv) in THF (10 mL). The mixture was allowed to warm to −10 °C over the course of 2 h. After stirring for 40 min the mixture was poured into ice-cold stirred satd aq NH_4Cl (50 mL). The phases were separated. The aq phase was extracted with Et_2O (5×10 mL). The combined organic phases were dried over Na_2SO_4. The solvent was removed in vacuo. Three successive purifications by flash chromatography[44] (∅ 4 cm, 20 cm, *c*-C_6H_{12}/AcOEt 15:1→10:1→5:1) gave diastereomer **17a** (229 mg, 45%) in the early fractions and diastereomer **17b** (214 mg, 42%) in the late fractions. The combined yield was 87% and the mass ratio of the isolated diastereomers 52:48. R_f value (*c*-C_6H_{12}/AcOEt 5:1): 0.25; combustion analysis: found C 64.19%, H 9.34%; calculated for $C_{19}H_{32}O_6$: C 64.02%, H 9.05%.

Compound **17a**: Colorless oil; $[\alpha]_D^{25}=-122$ ($CHCl_3$, *c*=1.08); IR (film): $\bar{\nu}$=2990, 2955, 2930, 2870, 2360, 1790, 1455, 1385, 1375, 1345, 1290, 1250, 1240, 1215, 1190, 1150, 1135, 1120, 1095, 1065, 1045, 1035, 1010, 985, 975, 930, 895, 875, 845, 815 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=0.74 (3H, d, ^3J=6.9 Hz, menthyl-CH_3), 0.82–1.04 (3H, m, menthyl-H), superimposed by 0.87 (3H, d, ^3J=6.9 Hz, menthyl-CH_3) and by 0.94 (3H, d, ^3J=6.3 Hz, menthyl-CH_3), 1.22–1.31 (1H, m, menthyl-H), 1.34–1.46 (1H, m, menthyl-H), superimposed by 1.41 (3H, d, $J_{2'',1''}$=6.6 Hz, 2″-H_3) and 1.44 as well as 1.45 [2× 3H, 2× s, acetonide-C(CH_3)$_2$], 1.62–1.72 (2H, m, menthyl-H), 1.94–2.08 (1H, m, menthyl-H), superimposed by 2.05 (1H, d, $J_{1''\text{-}OH,1''}$=9.2 Hz, 1″-O*H*), 2.11–2.18 (1H, m, menthyl-H), 3.58(1H, ddd, 2× ^3J=10.7 Hz, ^3J=4.2 Hz, 1′-H), 4.10 (1H, dq, $J_{1'',1''\text{-}OH}$=9.0 Hz, $J_{1'',2''}$=6.6 Hz, 1″-H), 4.49 (1H, s, 4-H), 5.60 (1H, s, 5-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=15.37 (menthyl-CH_3), 18.23 (C-2″), 21.09 (menthyl-CH_3), 22.34 (menthyl-CH_3), 22.90 (menthyl-CH_3), 25.49 (menthyl-*C*H), 26.98 and 27.28 [acetonide-C(CH_3)$_2$], 31.56 (menthyl-*C*H), 34.34 (menthyl-CH_2), 39.61 (menthyl-CH_2), 47.66 (menthyl-*C*H), 66.49 (C-1″), 78.12 (C-1′), 81.41 (C-4), 87.62 (C-3), 100.85 (C-5), 114.35 [acetonide-*C*(CH_3)$_2$], 174.93 (C-2).

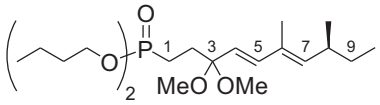
Compound·**17b**: Colorless crystals, mp 112–113 °C; $[\alpha]_D^{25}=-136$ ($CHCl_3$, *c*=1.00); IR (film):=2995, 2955, 2925, 2865, 2850, 2360, 2340, 1780, 1740, 1650, 1645, 1635, 1455, 1445, 1405, 1385, 1365, 1360, 1340, 1315, 1295, 1275, 1240, 1220, 1200, 1180, 1155, 1130, 1080, 1060, 1035, 1010, 985, 940, 920, 895, 870, 850, 810 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=0.74 (3H, d, ^3J=6.9 Hz, menthyl-CH_3), 0.80–0.88 (1H, m, menthyl-H), superimposed by 0.86 (3H, d, ^3J=7.0 Hz, menthyl-CH_3), 0.90–1.01 (2H, m, menthyl-H) superimposed by 0.95 (3H, d, ^3J=6.6 Hz, menthyl-CH_3), 1.23–1.31 (1H, m, menthyl-H), superimposed by 1.25 (3H, d, $J_{2'',1''}$=6.4 Hz, 2″-H_3), 1.34–1.46 (1H, m, menthyl-H), superimposed by 1.43 and 1.46 [2× 3H, 2× incompletely resolved q, ^4J=0.6 Hz, acetonide-C(CH_3)$_2$], 1.63–1.72 (2H, m, menthyl-H), 1.98–2.10 (1H, m, menthyl-H), 2.11–2.19 (1H, m, menthyl-H), 2.53 (1H, d, $J_{1''\text{-}OH,1''}$=2.5 Hz, 1″-O*H*), 3.58(1H, ddd, 2× ^3J=10.7 Hz, ^3J=4.2 Hz, 1′-H), 4.21 (1H, qd, $J_{1'',2''}$=6.6 Hz, $J_{1'',1''\text{-}OH}$=2.5 Hz, 1″-H), 4.41 (1H, s, 4-H), 5.62 (1H, s, 5-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=15.35 (menthyl-CH_3), 16.74 (C-2″), 21.12 (menthyl-CH_3), 22.36 (menthyl-CH_3), 22.83 (menthyl-CH_2), 25.33 (menthyl-CH), 27.25 and 27.26 [acetonide-C(CH_3)$_2$], 31.60 (menthyl-CH), 34.31 (menthyl-CH_2), 39.77 (menthyl-CH_2), 47.74 (menthyl-CH), 66.59 (C-1″), 78.74 (C-1′), 81.21 (C-4), 88.37 (C-3), 102.74 (C-5), 114.05 [acetonide-*C*(CH_3)$_2$], 174.91 (C-2); X-ray structural analysis: Fig. 5.

*5.1.10. Dimethyl (S,4E,6E-3,3)-dimethoxy-6,8-dimethyldeca-4,6-dienylphosphonate (**19**).*

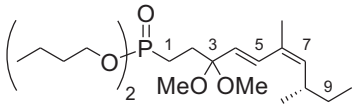


At room temperature $Pd(dba)_2$ (163 mg, 283 μmol, 0.10 equiv) was added under an atmosphere of Ar to a solution of P(*t*Bu)$_3$ (138 mg, 682 μmol, 0.24 equiv; weighed in a 'glovebox') in degassed THF (6 mL). After stirring for 10 min the solution was cannulated to a solution of bromoolefin **45** (1.13 g, 2.83 mmol) in degassed THF (24 mL). After cooling to 0 °C $ZnMe_2$ (1.2 M in toluene, 4.70 mL, 5.65 mmol, 2 equiv) was added slowly. The resulting mixture was stirred at 55 °C for 22 h. After re-cooling to 0 °C satd aq NH_4Cl (15 mL) was added *slowly*. Et_2O (30 mL) was added, the phases were separated, and the aq phase was extracted with AcOEt (4×10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. Flash chromatography[44] (∅ 4 cm, 20 cm, *c*-C_6H_{12}/acetone 4:1→*c*-C_6H_{12}/acetone 3:1→*c*-C_6H_{12}/acetone 2:1, →*c*-C_6H_{12}/acetone 1:1, 0.2 vol % NEt_3) yielded the title compound (823 mg, 87%, ≥97% *trans*,*E*) as a yellowish oil; $[\alpha]_D^{25}=22.7°$ ($CHCl_3$, *c*=2.50); IR (film): $\bar{\nu}$=3470, 2955, 2870, 2855, 2825, 1640, 1455, 1410, 1390, 1375, 1340, 1305, 1255, 1210, 1185, 1125, 1035, 980, 960, 930, 895, 880, 850, 815, 770, 750 cm^{-1}; ^1H NMR (400.1 MHz, C_6D_6, sample contained 3% of the *trans*,*Z* isomer and rests of *c*-C_6H_{12} and AcOEt): δ=0.77 (3H, *t*, $J_{10,9}$=7.4 Hz, 10-H_3), 0.86 (3H, d, $J_{8\text{-}CH3,8}$=6.7 Hz, 8-CH_3), 1.10–1.29 (2H, m, 9-H_2), 1.61 (3H, d, $J_{6\text{-}CH3,7}$=1.3 Hz, 6-CH_3), 1.76–1.89 (2H, m, 1-H_2), 2.20–2.31 (1H, m, 8-H), superimposed by 2.24–2.31 (2H, m, 2-H_2), 2×3.07 [2× 3H, 2× s, 3-(OCH_3)$_2$], 2×3.35 [2× 3H, 2× d, $^3J_{PO(OCH3)2,P}$=10.7 Hz, PO(OCH_3)$_2$], 5.27 (1H, d, $J_{7,8}$=9.6 Hz, 7-H), 5.34 (1H, dd, $J_{4,5}$=15.9 Hz, $^5J_{4,7}$=0.5 Hz, 4-H), 6.69 (1H, dd, $J_{5,4}$=15.9 Hz, $^4J_{5,7}$=0.8 Hz, 5-H); ^{13}C NMR (100.6 MHz, C_6D_6): δ=12.11 (C-10), 12.75 (6-CH_3), 20.40 (d, $^1J_{1,P}$=143.3 Hz, C-1), 20.67 (8-CH_3), 29.32 (d, $^2J_{2,P}$=3.9 Hz, C-2), 30.56 (C-9), 34.64 (C-8), 48.46 and 48.49 [2× 3-(OCH_3)$_2$], 51.74 [d, $^2J_{1,P}$=6.5 Hz, PO(OCH_3)$_2$], 102.10 (d, $^3J_{3,P}$=20.0 Hz, C-3), 125.56 (C-4), 131.87 (C-6), 139.18 (C-5), 140.98 (C-7); combustion analysis: found C 57.26%, H 9.52%; calculated for $C_{16}H_{31}O_5P$: C 57.47%, H 9.34%.

*5.1.11. Dibutyl (S,4E,6E-3,3)-dimethoxy-6,8-dimethyldeca-4,6-dienylphosphonate [(E,E)-**22**] in an 88:12 mixture with dibutyl (S,4E,6Z-3,3)-dimethoxy-6,8-dimethyldeca-4,6-dienylphosphonate [(E,Z)-**22**].*



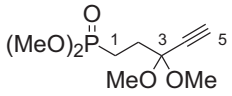
in an 88:12-mixture with



At 0 °C *para*-toluenesulfonic acid (9.0 mg, 52 μmol, 0.1 equiv) was added under an atmosphere of Ar to a solution of ketophosphonate **38** (181 mg, 486 μmol), 2,6-di-*tert*-butyl-4-methylphenol (11 mg, 50 μmol, 0.1 equiv), and trimethyl orthoacetate (62 μL, 59 mg,

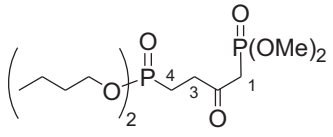
0.5 mmol, 1.0 equiv) in degassed MeOH (2 mL) in a Schlenk tube, which was protected from light. After stirring for 3 h triethylamine (7.0 μL, 5.1 mg, 50 μmol, 0.1 equiv) was added. The solution was allowed to reach room temperature Brine (2 mL) was added, the phases were separated, the aq phase was extracted with Et_2O (3×2 mL), the combined organic phases were dried over Na_2SO_4, and the solvent was removed in vacuo. Flash chromatography[44] (∅ 2.5 cm, 20 cm, degassed *c*-C_6H_{12}/acetone) gave the title compounds (177 mg, 87%) as an 88:12 mixture of (*E*,*E*)-**22** and (*E*,*Z*)-**22**; IR (film): $\overline{\nu}$=2960, 2875, 1745, 1675, 1645, 1625, 1600, 1460, 1415, 1380, 1300, 1250, 1215, 1190, 1130, 1060, 1030, 980 cm^{-1}; ^1H NMR (300.1 MHz, C_6D_6): δ=0.76 (3H, *t*, $J_{10,9}$=7.4 Hz, 10-H_3), coincides with 0.76 (6H, *t*, ^3J=7.4 Hz, 2× CH_3CH$_2$CH$_2$CH$_2$O), 0.86 (3H, d, $J_{8-CH_3,8}$=6.7 Hz, 8-CH_3), 1.10–1.29 (6H, 2× m, 9-H_2+ 2× CH$_3$CH_2CH$_2$CH$_2$O), 1.39–1.49 (4H, m, 2× CH$_3$CH$_2$CH_2CH$_2$O), 1.61 [3H, d, $^4J_{6-CH_3,7}$=1.0 Hz, 6-CH_3, (*E*,*E*)-**22**], 1.74 [3H, d, $^4J_{6-CH_3,7}$=0.9 Hz, 6-CH_3, (*E*,*Z*)-**22**], 1.93 (2H, m_c, 1-H_2), 2.25 (1H, m_c, 8-H), 2.32–2.41 (2H, m, 2-H_2), 3.11 [6H, s, 3-(OCH_3)$_2$], 3.88–4.03 (4H, m, 2× CH$_3$CH$_2$CH$_2$CH_2O), 5.14 [1H, d, $J_{7,8}$=9.8 Hz, 7-H, (*E*,*Z*)-**22**], 5.27 [1H, d, $J_{7,8}$=9.5 Hz, 7-H, (*E*,*E*)-**22**], 5.40 [1H, d, $J_{4,5}$=15.8 Hz, 4-H, (*E*,*E*)-**22**], 5.51 [1H, d, $J_{4,5}$=15.8 Hz, 4-H, (*E*,*Z*)-**22**], 6.72 [1H, d, $J_{5,4}$=15.8 Hz, 5-H, (*E*,*E*)-**22**]; ^{13}C NMR [100.6 MHz, C_6D_6/C_6D_6; this sample contained essentially sterically pure (*E*,*E*)-**22**]: δ=12.15 (C-10), 12.79 (6-CH_3), 13.75 (2× CH_3CH$_2$CH$_2$CH$_2$O), 19.11 (2× CH$_3$CH$_2$CH$_2$CH$_2$O), 20.71 (8-CH_3), 21.38 (d, $^1J_{1,P}$=143.7 Hz, C-1), 29.59 (d, $^2J_{2,P}$=3.9 Hz, C-2), 30.60 (C-9), 33.04 (d, $^3J_{C\text{-}2',P}$=5.8 Hz, 2× CH$_3$CH$_2$CH_2CH$_2$O), 34.68 (C-8), 48.52 and 48.55 (2× OCH$_3$), 65.18 (d, $^2J_{C\text{-}1',P}$=6.5 Hz, 2× CH$_3$CH$_2$CH$_2$CH_2O), 102.26 ($^3J_{3,P}$=20.3 Hz, C-3), 125.69 (C-4), 131.91 (C-6), 139.23 (C-5), 141.01 (C-7).

*5.1.12. Dimethyl (3,3-dimethoxypent-4-ynyl)phosphonate (**23**).*



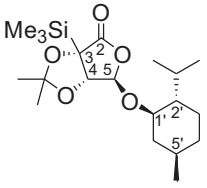
At 40 °C a solution of $Na_2B_4O_7{\cdot}10H_2O$ (13.8 mg, 68.4 μmol, 10 mol %) in H_2O (0.5 mL) was added to a solution of silylalkyne **43** (211 mg, 684 μmol) in MeOH (5 mL). After 3 h the solution was cooled to room temperature aq phosphate buffer (pH=7, 3 mL) was added, the phases were separated, and the aq phase was extracted with Et_2O (4×3 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. Flash chromatography[44] (∅ 2.5 cm, 20 cm, *c*-C_6H_{12}/acetone 3:1→*c*-C_6H_{12}/acetone 2:1→*c*-C_6H_{12}/acetone 1:1, 0.2 vol % NEt_3) gave the title compound (158 mg, 98%) as a colorless oil; R_f value (*c*-C_6H_{12}/acetone 2:1): 0.10; IR (film): $\overline{\nu}$ =3460, 3275, 3205, 2950, 2850, 2830, 2110, 1465, 1435, 1410, 1345, 1295, 1245, 1190, 1140, 1150, 965, 890, 845, 815, 755, 710, 665 cm^{-1}; ^1H NMR (400.1 MHz, C_6D_6): δ=2.04 (1H, 5-H), 2.05–2.15 (2H, m, 1-H_2), 2.26–2.33 (2H, m, 2-H_2), 3.12 [6H, s, 3-(OCH_3)$_2$], 3.34 [6H, d, $^3J_{PO(OCH_3)_2,P}$=10.7 Hz, PO(OCH_3)$_2$]; ^{13}C NMR (100.6 MHz, C_6D_6): δ=20.48 (d, $^1J_{1,P}$=143.6 Hz, C-1), 31.19 (d, $^2J_{2,P}$=3.4 Hz, C-2), 50.19 [3-(OCH_3)$_2$], 51.73 [d, $^2J_{1,P}$=6.5 Hz, PO(OCH_3)$_2$], 74.41 (C-5), 79.89 (C-4), 99.12 (d, $^3J_{3,P}$=21.7 Hz, C-3); combustion analysis: found C 46.15%, H 7.54%; calculated for $C_9H_{17}O_5P$: C 45.76%, H 7.25%.

*5.1.13. Dimethyl [4-(dibutoxyphosphoryl)-2-oxobutyl]phosphonate (**25**).*



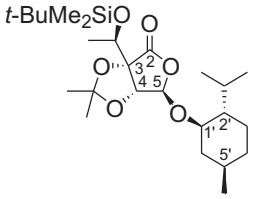
At −78 °C *n*-BuLi (2.50 M in hexane, 24.0 mL, 60.0 mmol, 1.50 equiv) was added to a solution of diisopropylamine (8.46 mL, 6.06 g, 60.0 mmol, 1.50 equiv) in THF (40 mL) while stirring. After 45 min phosphonate **37** (6.41 mL, 7.44 g, 60.0 mmol, 1.50 equiv) was added over the course of 2 h by a syringe pump and thereafter over the course of 1 h the phosphorylated propionate **36** (11.2 g, 40.0 mmol). The mixture was gradually warmed to room temperature. It was stirred for 17 h, at which time HCl (2 M, 75 mL) was added. The phases were separated. The aq phase was extracted with CH_2Cl_2(3×50 mL), the combined organic phases were dried over $MgSO_4$, and the solvent was removed in vacuo. The title compound (68% wt % of 16.9 g of a mixture with **36** and **37**, i.e., 11.5 g **25**, 77%) as a colorless oil; R_f value (acetone): 0.45; ^1H NMR (300.1 MHz, $CDCl_3$/TMS; sample contained 32 wt % of **36** and **37**): δ=0.94 (6H, *t*, ^3J=7.4 Hz, 2× CH_3CH$_2$CH$_2$CH$_2$O), 1.39 (4H, tq, ^3J=7.5 Hz, 2× CH$_3$CH_2CH$_2$CH$_2$O), 1.64 (4H, tt, ^3J=7.1 Hz, 2× CH$_3$CH$_2$CH_2CH$_2$O), 2.02 (2H, dt, $^1J_{4,P}$=18.0 Hz, $J_{4,3}$=7.7, 4-H_2), 2.90 (2H, dt, $^2J_{3,P}$=11.1 Hz, $J_{3,4}$=7.8 Hz, 3-H_2), 3.12 (2H, d, $^1J_{1,P}$=22.7 Hz, 1-H_2), 3.79 (6H, d, $^3J_{CH_3O,P}$=11.3 Hz, 2× CH$_3$O), AB signal (4H, δ_A=4.00, δ_B=4.03, J_{AB}=10.1 Hz, A part additionally split by $^3J_{H(A),P}$=10.1 Hz and $J_{H(A),CH_2CH_2CH_2}$=6.7 Hz, B part additionally split by $^3J_{H(B),P}$=10.0 Hz and $J_{H(B),CH_2CH_2CH_2}$=6.7 Hz, 2× CH$_3$CH$_2$CH$_2$CH_2O).

*5.1.14. (3R,4R,5R)-5-{(1R,2S,5R)-[2-Isopropyl-5-methylcyclohexyl] oxy}-3,4-(isopropylidenedioxy)-3-(trimethylsilyl)-4,5-dihydro-3H-furan-2-one (**29**).*



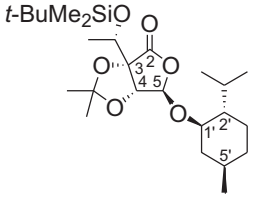
At −78 °C mit *n*-BuLi (2.08 M in hexane, 6.63 mL, 13.8 mmol, 1.30 equiv) was added to a solution of diisopropylamine (1.93 mL, 1.39 g, 13.8 mmol, 1.30 equiv) in THF (35 mL). After stirring for 30 min trimethylsilyl chloride (2.03 mL, 1.73 g, 15.9 mmol, 1.50 equiv) was added. After stirring for 5 min the solution was cannulated within 10 min to a −78 °C solution of lactone **18** (3.30 g, 10.6 mmol) in THF (15 mL). After 30 min the mixture was poured into ice-cold satd aq NH_4Cl (100 mL). The phases were separated and the aq phase was extracted with TBME (5×25 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. The crude product (4.04 g, 99%) was a highly viscous oil, which crystallized slowly; R_f value (*c*-C_6H_{12}/AcOEt 5:1): 0.65; mp 93–95 °C; $[\alpha]_D^{25}$=−129 ($CHCl_3$, *c*=1.00); IR (film): $\overline{\nu}$ =2960, 2920, 2865, 2340, 1780, 1455, 1385, 1375, 1345, 1250, 1160, 1150, 1120, 1085, 1055, 1005, 990, 935, 845 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$; sample contained a trace of *c*-C_6H_{12}): δ=0.22 [9H, s, Si(CH_3)$_3$], 0.75 (3H, d, ^3J=6.9 Hz, menthyl-CH_3), 0.81–0.90 (1H, m, menthyl-H), superimposed by 0.86 (3H, d, ^3J=7.1 Hz, menthyl-CH_3), 0.92–1.02 (2H, m, menthyl-H), superimposed by 0.94 (3H, d, ^3J=6.6 Hz, menthyl-CH_3), 1.18–1.27 (1H, m, menthyl-H), 1.32–1.42 (1H, m, menthyl-H), superimposed by 1.36 and 1.39 [2× 3H, 2× d, both ^4J=0.6 Hz, acetonide-C(CH_3)$_2$], 1.62–1.70 (2H, m, menthyl-H), 2.06–2.18 (2H, m, menthyl-H), 3.53(1H, ddd, 2× ^3J=10.7 Hz, ^3J=4.3 Hz, 1′-H), 4.24 (1H, s, 4-H), 5.56 (1H, s, 5-H); ^{13}C NMR (100.6 MHz, $CDCl_3$; sample contained a trace of *c*-C_6H_{12}): δ=−4.00 [Si(CH_3)$_3$], 15.47 (menthyl-CH_3), 21.15 (menthyl-CH_3), 22.34 (menthyl-CH_3), 22.78 (menthyl-CH_2), 25.09 (menthyl-CH), 27.02 and 27.23 [acetonide-C(CH_3)$_2$], 31.63 (menthyl-CH), 34.27 (menthyl-CH_2), 40.67 (menthyl-CH_2), 47.62 (menthyl-CH), 79.03 (C-3), 79.98 (C-1′), 83.42 (C-4), 103.33 (C-5), 113.21 [acetonide-C(CH$_3$)$_2$], 177.73 (C-2); combustion analysis: found C 62.17%, H 9.72%; calculated for $C_{20}H_{36}O_5Si$: C 62.46%, H 9.44%.

*5.1.15. (3R,4R,5R)-3-[(R)-1-(tert-Butyldimethylsiloxy)ethyl]-5-{[(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl]oxy}-3,4-(isopropylidenedioxy)-4,5-dihydro-3H-furan-2-one (**30a**).*



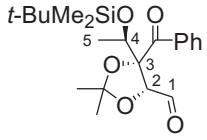
At 0 °C NEt_3 (1.12 mL, 818 mg, 8.00 mmol, 1.91 equiv) was added to a solution of alcohol **17a** (1.49 g, 4.19 mmol) and *tert*-butyldimethylsilyl triflate (2.89 mL, 3.32 g, 12.8 mmol, 3.05 equiv) in CH_2Cl_2 (8 mL). The solution was allowed to reach room temperature and stirred for 2.5 h. It was poured into ice-cold satd aq NH_4Cl (50 mL). The phases were separated and the aq phase was extracted with CH_2Cl_2 (4×15 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. Flash chromatography[44] (∅ 4 cm, 20 cm, *c*-C_6H_{12}/AcOEt 50:1→20:1) yielded the title compound (1.71 g, 87%) as a colorless oil; R_f value (*c*-C_6H_{12}/AcOEt 5:1): 0.65; (*c*-C_6H_{12}/AcOEt 20:1): 0.25; $[\alpha]_D^{25}=-68$ ($CHCl_3$, *c*=1.03); IR (film): $\bar{\nu}$ =2990, 2960, 2930, 2860, 1795, 1470, 1460, 1385, 1375, 1360, 1345, 1290, 1255, 1215, 1185, 1155, 1140, 1120, 1100, 1075, 1060, 1020, 1005, 975, 935, 880, 835, 815 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$): δ=0.07 and 0.09 [2× 3H, 2× s, Si(CH_3)$_2$], 0.75 (3H, d, ^3J=6.9 Hz, menthyl-CH_3), 0.82–0.91 (1H, m, menthyl-H), superimposed by 0.87 (3H, d, ^3J=6.9 Hz, menthyl-CH_3), 0.89 [9H, s, SiC(CH_3)$_3$], 0.91–1.01 (2H, m, menthyl-H), superimposed by 0.94 (3H, d, ^3J=6.6 Hz, menthyl-CH_3), 1.19–1.29 (1H, m, menthyl-H), 1.34–1.44 (1H, m, menthyl-H), superimposed by 1.36 (3H, d, $J_{2'',1''}$=6.2 Hz, 2″-H_3) as well as by 1.42 and 1.43 [2× 3H, 2× s, acetonide-C(CH_3)$_2$], 1.62–1.71 (2H, m, menthyl-H), 2.02–2.15 (2H, m, menthyl-H), 3.54(1H, ddd, 2× ^3J=10.7 Hz, ^3J=4.3 Hz, 1′-H), 4.10 (1H, q, $J_{1'',2''}$=6.3 Hz, 1″-H), 4.55 (1H, s, 4-H), 5.54 (1H, s, 5-H); ^{13}C NMR (100.6 MHz, $CDCl_3$; sample contained a trace of *c*-C_6H_{12}): δ=−4.78 and −4.47 [Si(CH_3)$_2$], 15.26 (menthyl-CH_3), 18.09 (C-2″), 18.16 [SiC(CH_3)$_3$], 21.15 (menthyl-CH_3), 22.34 (menthyl-CH_3), 22.75 (menthyl-CH_2), 25.34 (menthyl-*C*H), 25.88 [SiC(CH_3)$_3$], 26.72 and 27.25 [acetonide-C(CH_3)$_2$], 31.56 (menthyl-*C*H), 34.31 (menthyl-CH_2), 40.16 (menthyl-CH_2), 47.65 (menthyl-*C*H), 66.69 (C-1″), 78.60 (C-1′), 81.56 (C-4), 88.35 (C-3), 101.81 (C-5), 114.01 [acetonide-*C*(CH_3)$_2$], 174.89 (C-2); combustion analysis: found C 64.01%, H 10.10%; calculated for $C_{25}H_{46}O_6Si$; C 63.79% H 9.85%.

*5.1.16. (3R,4R,5R)-3-[(S)-1-(tert-Butyldimethylsiloxy)ethyl]-5-{[(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl]oxy}-3,4-(isopropylidenedioxy)-4,5-dihydro-3H-furan-2-one (**30b**).*

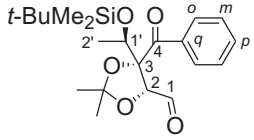


Alcohol **17b** (1.10 g, 3.09 mmol) was derivatized similarly as described for the silylation **17a**→**30a**, employing *tert*-butyldimethylsilyl triflate (2.13 mL, 2.45 g, 9.27 mmol, 3.00 equiv) in CH_2Cl_2 (8 mL) and NEt_3 (1.12 mL, 818 mg, 8.00 mmol, 2.59 equiv). Flash chromatography[44] (∅ 4 cm, 20 cm, *c*-C_6H_{12}/AcOEt 50:1→20:1) yielded the title compound (1.42 g, 98%) as a colorless solid; R_f value$_1$ (*c*-C_6H_{12}/AcOEt 5:1): 0.65; R_f value$_2$ (*c*-C_6H_{12}/AcOEt 20:1): 0.25; mp 70–72 °C; $[\alpha]_D^{25}=-90$ ($CHCl_3$, *c*=0.90); IR (film): $\bar{\nu}$ =2955, 2930, 2860, 1790, 1470, 1460, 1385, 1375, 1350, 1250, 1210, 1195, 1155, 1130, 1095, 1025, 1005, 950, 925, 870, 835, 815 cm^{-1}; ^1H NMR (400.1 MHz, $CDCl_3$; sample contained a trace of *c*-C_6H_{12}): δ=0.09 and 0.10 [2× 3H, 2× s, Si(CH_3)$_2$], 0.73 (3H, d, ^3J=6.9 Hz, menthyl-CH_3), 0.82–1.01 (3H, m, menthyl-H), superimposed by 0.85 (3H, d, ^3J=6.9 Hz, menthyl-CH_3) and by 0.90 [9H, SiC(CH_3)$_3$], 0.94 (3H, d, ^3J=6.6 Hz, menthyl-CH_3), 1.17 (3H, d, $J_{2'',1''}$=6.6 Hz, 2″-H_3), 1.23–1.32 (1H, m, menthyl-H), 1.33–1.45 (1H, m, menthyl-H), superimposed by 1.39 and 1.44 [2× 3H, 2× s, acetonide-C(CH_3)$_2$], 1.62–1.71 (2H, m, menthyl-H), 2.03–2.12 (1H, m, menthyl-H), 2.12–2.19 (1H, m, menthyl-H), 3.55(1H, ddd, 2× ^3J=10.7 Hz, ^3J=4.3 Hz, 1′-H), 4.22 (1H, q, $J_{1'',2''}$=6.6 Hz, 1″-H), 4.48 (1H, s, 4-H), 5.59 (1H, s, 5-H); ^{13}C NMR (100.6 MHz, $CDCl_3$; sample contained a trace of *c*-C_6H_{12}): δ=−4.70 and −4.19 [Si(CH_3)$_2$], 15.27 (menthyl-CH_3), 18.17 [SiC(CH_3)$_3$], 19.29 (C-2″), 21.12 (menthyl-CH_3), 22.33 (menthyl-CH_3), 22.75 (menthyl-CH_2), 25.15 (menthyl-*C*H), 26.01 [SiC(CH_3)$_3$], 27.34 and 27.47 [acetonide-C(CH_3)$_2$], 31.60 (menthyl-*C*H), 34.33 (menthyl-CH_2), 39.92 (menthyl-CH_2), 47.69 (menthyl-*C*H), 66.91 (C-1″), 78.89 (C-1′), 80.95 (C-4), 89.46 (C-3), 104.16 (C-5), 113.84 [acetonide-*C*(CH_3)$_2$], 175.57 (C-2).

*5.1.17. (2R,3S)-3-[(R)-1-(tert-Butyldimethylsiloxy)ethyl]-2,3-(isopropylidenedioxy)-4-oxo-4-phenylbutanal (**32a**).*



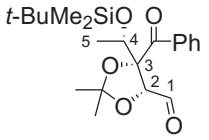
numbering in accordance with the IUPAC name



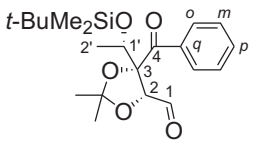
numbering for NMR assignments

LiCl (772 mg, 18.2 mmol, 5.01 equiv) was dried in vacuo while heating, cooled to room temperature, and dissolved in a solution of lactone **30a** (1.71 g, 3.63 mmol) in THF (35 mL). At −10 °C PhLi (2 M in nBu_2O; 3.63 mL, 7.26 mmol, 5.98 mmol; 2.00 equiv) was added. After 10 min the resulting mixture was poured into an ice-cold aq phosphate buffer (pH=7; 125 mL). The phases were separated and the aq phase was extracted with AcOEt (4×30 mL). The combined organic phases were dried over Na_2SO_4. The solvent was removed in vacuo. The residue, i.e., **31a** and/or *epi*-**31a**, was dissolved in *c*-$C_6H_{12}Cl_3$ (7 mL) at room temperature *p*-TsOH (16.0 mg, 93.9 μmol, 2.59 mol %) was added. After stirring for 1.5 the solution was poured directly on a flash chromatography[44] column (∅ 6 cm, 20 cm, *c*-C_6H_{12}/AcOEt 25:1→10:1→5:1) and purified to give the title compound (contaminated with 7 mol % M-menthol; 633 mg; 44% over the two steps from lactone **30a**) as a yellowish oil; R_f value (*c*-C_6H_{12}/AcOEt 5:1): 0.25; ^1H NMR (300.1 MHz, $CDCl_3$; sample contaminated with 7 mol % L-menthol): δ=−0.27 and −0.06 [2× 3H, 2× s, Si(CH_3)$_2$], 0.80 [9H, SiC(CH_3)$_3$], 1.25[3H, s, 1× acetonide-C(CH_3)$_2$], 1.42 (3H, d, $J_{2',1'}$=6.3 Hz, 2′-H_3), 1.50[3H, s, 1× acetonide-C(CH_3)$_2$], 4.55 (1H, q, $J_{1',2'}$=6.3 Hz, 1′-H), superimposed by 4.56 (1H, s, 2-H), 7.43 (2H, m_c, *m*-Ar), 7.57 (1H, *t*, $J_{p\text{-Ar},m\text{-Ar}}$=7.4 Hz, 1 H, *p*-Ar), 8.19 (2H, d, $J_{o\text{-Ar},m\text{-Ar}}$=8.2 Hz, 2 H, *o*-Ar), 9.79 (1H, s, 1-H).

*5.1.18. (2R,3S)-3-[(S)-1-(tert-Butyldimethylsiloxy)ethyl]-2,3-(isopropylidenedioxy)-4-oxo-4-phenylbutanal (**32b**).*



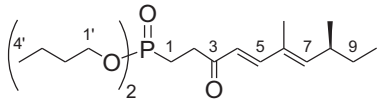
numbering in accordance with the IUPAC name



numbering for NMR assignments

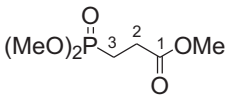
This reaction was performed similarly as described for the conversion **30a**→**31a** and/or *epi*-**31a**→**32a** yet employing LiCl (634 mg, 15.0 mmol, 5.02 equiv), lactone **30b** (1.41 g, 2.99 mmol), PhLi (2 M in nBu$_2$O, 2.99 mL, 5.98 mmol; 2.00 equiv), and *p*-TsOH (13.0 mg, 76.3 μmol, 2.55 mol %). Flash chromatography[44] (∅ 6 cm, 20 cm, *c*-C_6H_{12}/AcOEt 25:1→10:1→5:1) provided the title compound (contaminated with 9 mol % L-menthol; 865 mg, 74% over the two steps from lactone **30b**) as a yellowish oil; R_f value (*c*-C_6H_{12}/AcOEt 5:1): 0.25; ^{1}H NMR (300.1 MHz, $CDCl_3$; sample contaminated with 9 mol % L-menthol): δ=0.04 and 0.08 [2× 3H, 2× s, Si(CH_3)$_2$], 0.85 [9H, SiC(CH_3)$_3$], 1.18 (3H, d, $J_{2',1'}$=6.6 Hz, 2′-H$_3$), 1.22 [3H, s, 1× acetonide-C(CH_3)$_2$], 1.49[3H, s, 1× acetonide-C(CH_3)$_2$], 4.44 (1H, q, $J_{1',2'}$=6.5 Hz, 1′-H), 4.52 (1H, d, $J_{2,1}$=1.6 Hz, 2-H), 7.40–7.48 (2H, m, *m*-Ar), 7.53–7.61 (1H, m, *p*-Ar), 8.15–8.20 (2H, m, *o*-Ar), 9.85 (1H, d, $J_{2,1}$=1.5 Hz, 1-H).

*5.1.19. Dibutyl [(8S,4E,6E)-6,8-dimethyl-3-oxodeca-4,6-dienyl]phosphonate (**38**).*



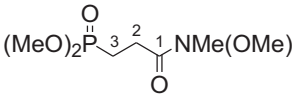
At 70 °C phosphonate **25** (8.75 g of a mixture with **36** and **37**, which contained 68% wt % of **38**, i.e., 5.95 g **25**, 16.0 mmol, 2.00 equiv) was added to a stirred suspension of K_2CO_3 (8.96 g, 64.0 mmol, 8.00 equiv) in 1,4-dioxane (30 mL). The mixture was stirred for 1 h, at which time enal **26** (1.01 g, 8.00 mmol) and H_2O (1.15 mL, 1.15 g, 64 mmol, 8.00 equiv) were added. Stirring was continued for 40 h. The mixture was cooled to room temperature H_2O (15 mL) and Et_2O (15 mL) added. The phases were separated, the aq phase was extracted with Et_2O (4×20 mL), the combined organic phases were dried over $NaSO_4$, and the solvent was removed in vacuo. Flash chromatography[44] (∅ 6 cm, 20 cm, *c*-C_6H_{12}/acetone 3:1) yielded the title compound (2.23 g, 75%) as a yellowish oil; R_f value (*c*-C_6H_{12}/acetone 3:1): 0.30; IR (film): $\bar{\nu}$ =2960, 2875, 1745, 1675, 1645, 1625, 1600, 1460, 1415, 1380, 1300, 1250, 1215, 1190, 1130, 1060, 1030, 980 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$/TMS): δ=0.85 (3H, *t*, $J_{10,9}$=7.5 Hz, 10-H$_3$), 0.94 (6H, *t*, $J_{4',3'}$=7.4 Hz, 2× 4′-H$_3$), 1.00 (3H, d, $J_{8\text{-}CH3,8}$=6.8 Hz, 8-CH_3), 1.26–1.36 (2H, m, 9-H$_2$), 1.40 (4H, qt, $J_{3',4'}$=$J_{3',2'}$=7.4 Hz, 2× 3′-H$_2$), 1.65 (4H, tt, $J_{2',1'}$=$J_{2',3'}$=7.3 Hz, 2× 2′-H$_2$), 1.79 (3H, s, 6-CH$_3$), 2.08 (2H, m$_c$, interpretable as dt, $^2J_{H,P}$=17.7 Hz, $J_{1,2}$=8.0 Hz, 1-H$_2$), 2.44–2.50 (1H, m, 8-H), 2.89 (2H, m$_c$, interpretable as dt, $^3J_{2,P}$=10.5 Hz, $J_{2,1}$=8.0 Hz, 2-H$_2$), 3.99–4.06 (m$_c$, 2× 1′-H$_2$), 5.74 (1H, d, $J_{7,8}$=9.8 Hz, 7-H), 6.10 (1H, d, $J_{4,5}$=15.8 Hz, 4-H), 7.23 (1H, d, $J_{5,4}$=15.8 Hz, 5-H); ^{13}C NMR (126 MHz, $CDCl_3$/$CDCl_3$): δ=11.94 (C-10), 12.44 (6-CH$_3$), 13.67 (2× C-4′), 18.82 (2× C-3′), 19.66 (d, $^1J_{C\text{-}1,P}$=144.4, C-1), 20.23 (8-CH$_3$), 30.01 (C-9), 32.63 (d, $^3J_{C\text{-}2',P}$=6.1 Hz, 2× C-2′), 33.15 (d, $^2J_{C\text{-}2,P}$=3.3 Hz, C-2), 35.13 (C-8), 65.50 (d, $^2J_{C\text{-}1',P}$=6.4 Hz, 2× C-1′), 123.59 (C-4), 131.86 (C-6), 148.79 (C-5), 150.17 (C-7), 197.87 (d, $^3J_{C\text{-}3,P}$=15.7 Hz, C-3); HRMS (EI, 70 eV): M$^+$, found m/z=372.2434, i.e., Δ=+1.2 ppm versus what $C_{20}H_{37}O_4P$ requires (372.2429).

*5.1.20. Methyl 3-(dimethylphosphoryl)propionate (**40**).*



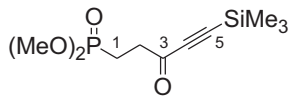
At 0 °C $AlMe_3$ (2 M in CH_2Cl_2, 100 mL, 200 mmol, 2.00 equiv) was cannulated to a solution of dimethylphospite (**39**, 18.3 mL, 22.0 g, 200 mmol) in dichloromethane (200 mL) such that the evolution of CH_4 was tolerable and such that the dichloromethane never boiled. Subsequently, the mixture was stirred for 50 min. The acrylate **34** (18.1 mL, 17.2 g, 200 mmol, 1.00 equiv) was added dropwise during 10 min. The cooling bath was removed up to 15 min later, such that the solution never warmed above room temperature. After stirring at room temperature for 21 h and recooling to 0 °C H_2O (ca. 150 mL in total) and HCl (4 M, ca. 150 mL in total) were added dropwise and in turns, until the phases separated and the aq phase had pH=1. The phases were separated, the aq phase was extracted with CH_2Cl_2(4×100 mL), the combined organic phases were dried over Na_2SO_4, and the solvent was removed in vacuo. Fractionating distillation (85–100 °C) in high vacuum yielded the title compound (29.0 g, 74%) as a colorless oil; ^{1}H NMR (300.1 MHz, $CDCl_3$/TMS): δ=2.01–2.17 (2H, m$_c$, 3-H$_2$), 2.54–2.66 (2H, m$_c$, 2-H$_2$), 3.70 (3H, s, CO_2CH_3), 3.74 [6H, d, $^3J_{PO(OCH3)2,P}$=10.8 Hz, PO(OCH$_3$)$_2$].

*5.1.21. 3-(Dimethylphosphoryl)-N-methoxy-N-methylpropionamide (**41**).*



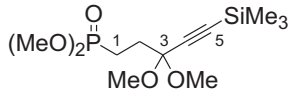
At −10 °C $AlMe_3$ (2 M in CH_2Cl_2, 38.3 mL, 76.6 mmol, 3.00 equiv) was added dropwise and slowly (!) to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (7.50 g, 76.5 mmol, 3.00 equiv) in CH_2Cl_2 (50 mL). When the addition was complete, we warmed to room temperature and stirred for 30 min. After recooling to −10 °C ester **40** (5.00 g, 25.5 mmol) was added. Stirring was continued for 20 h. The reaction was quenched by the slow (!) addition of satd aq NH_4Cl (100 mL). The phases were separated, the aq phase was extracted with CH_2Cl_2(5×100 mL), and the combined organic phases were dried over Na_2SO_4. Removal of the solvent under reduced pressure furnished a crude product (5.10 g, 89%), which was used without further purification; IR (film): $\bar{\nu}$ =3525, 3470, 3310, 2950, 2850, 2820, 1665, 1460, 1385, 1320, 1245, 1175, 1095, 1025, 990, 950, 850, 815, 745, 710 cm^{-1}; ^{1}H NMR (400.1 MHz, $CDCl_3$; sample contained residual CH_2Cl_2): δ=2.10 (2H, m$_c$, 3-H$_2$), 2.74 (2H, m$_c$, 2-H$_2$), 3.19 (3H, s, NCH_3), 3.71 (3H, s, N–OCH$_3$), 3.76 [6H, d, $^3J_{PO(OCH_3)_2,P}$=10.7 Hz, PO(OCH$_3$)$_2$]; ^{13}C NMR (100.6 MHz, $CDCl_3$): δ=19.25 (d, $^1J_{3,P}$=144.1 Hz, C-3), 25.19 (C-2), 32.41 (NCH_3), 52.42 [d, $^2J_{C,P}$=6.3 Hz, PO(OCH$_3$)$_2$], 61.33 (N–OCH$_3$), 172.64 (d, $^3J_{C\text{-}1,P}$=20.3 Hz, C-1); combustion analysis: found C 37.34%, H 7.29%, N 6.11%; calculated for $C_7H_{16}NO_5P$: C 37.34%, H 7.16%, N 6.22%.

*5.1.22. Dimethyl 3-oxo-5-(trimethylsilyl)pent-4-ynylphosphonate (**42**).*



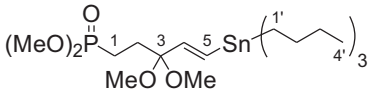
At −78 °C *n*-BuLi (2.3 M in hexane, 19.3 mL, 44.4 mmol, 1.25 equiv) was added to a solution of (trimethylsilyl)acetylene (4.36 g, 44.4 mmol, 1.25 equiv) in THF (100 mL). After stirring for 1 h a solution of Weinreb amide **41** (8.00 g, 35.5 mmol) in THF (100) was added dropwise. The resulting mixture was allowed to warm to −40 °C in the course of 30 min and stirred for 4 h. It was poured into ice-cold HCl (4 M, 500 mL). The phases were separated, the aq phase was extracted with AcOEt (4×150 mL), the combined organic phases were dried over Na_2SO_4, and the solvent was removed in vacuo. Due to the lability of title compound versus silica gel or heat it was immediately used for preparing **43**.

*5.1.23. Dimethyl 3,3-dimethoxy-5-(trimethylsilyl)pent-4-ynylphosphonate (**43**).*

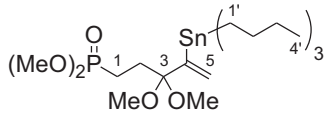


At room temperature *p*-toluenesulfonic acid (305 mg, 1.78 mmol, 5.01 mol %) was added to a solution of the crude alkynone **42** in MeOH (60 mL) and trimethyl orthoformiate (60 mL). The resulting mixture was refluxed for 6 h and then cooled to room temperature. NEt_3 (740 μL, 5.33 mmol, 15.0 mol %) was added and Et_2O (100 mL) and H_2O (200 mL) as well. The phases were separated and the aq phase was extracted with Et_2O (4×100 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed in vacuo. Flash chromatography[44] (∅ 5 cm, 20 cm, *c*-C_6H_{12}/acetone 4:1→*c*-C_6H_{12}/acetone 3:1→*c*-C_6H_{12}/acetone 2:1, 0.2 vol % NEt_3) yielded the title compound (4.39 g, 40% over the two steps from Weinreb amide **41**) as a colorless oil; R_f value (*c*-C_6H_{12}/acetone 2:1): 0.20; IR (film): $\bar{\nu}$ =3470, 2955, 2500, 2845, 2830, 2150, 2050, 1635, 1465, 1435, 1410, 1345, 1300, 1250, 1180, 1135, 1050, 965, 900, 850, 830, 760, 700, 645 cm^{-1}; ^1H NMR (400.1 MHz, C_6D_6): δ=0.07 [9H, s, $Si(CH_3)_3$], 2.14–2.24 (2H, m, 1-H_2), 2.33–2.40 (2H, m, 2-H_2), 3.19 [6H, s, 3-$(OCH_3)_2$], 3.35 [6H, d, $^3J_{PO(OCH_3)_2,P}$=10.6 Hz, $PO(OCH_3)_2$]; ^{13}C NMR (100.6 MHz, C_6D_6): δ=−0.35 [$Si(CH_3)_3$], 20.59 (d, $^1J_{1,P}$=143.4 Hz, C-1), 31.25 (d, $^2J_{2,P}$=3.6 Hz, C-2), 50.27 [3-$(OCH_3)_2$], 51.71 [d, $^2J_{C,P}$=6.5 Hz, $PO(OCH_3)_2$], 91.12 and 101.95 (C-4, C-5), 99.33 (d, $^3J_{3,P}$=21.5 Hz, C-3); combustion analysis: found C 47.12%, H 8.27%; calculated for $C_{12}H_{25}O_5PSi$: C 46.74%, H 8.17%.

*5.1.24. Dimethyl [trans-3,3-dimethoxy-5-(tributylstannyl)]pent-4-enylphosphonate (**44**) in a separable 79:21 mixture with dimethyl [3,3-dimethoxy-4-(tributylstannyl)]pent-4-enylphosphonate (iso-**44**).*



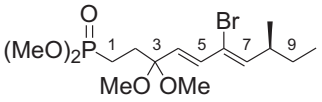
44



iso-**44**

At room temperature Bu_3SnH (680 μL, 734 mg, 2.54 mmol, 1.20 equiv) was added slowly to a stirred solution of phosphonate **23** (500 mg, 2.12 mol) and $PdCl_2(PPh_3)_2$ (74.4 mg, 106 μmol, 5.00 mol %) in degassed THF (10 mL). Stirring was continued for 20 min. The solvent was removed under reduced pressure. Two passages through flash chromatography[44] columns [∅ 2.5 cm, 20 cm, pure *c*-C_6H_{12} (for the separation of tin-containing products like Bu_3SnBr)→*c*-C_6H_{12}/acetone 5:1, 0.2 vol % NEt_3] gave a 79:21 mixture (900 mg, 84%) of the terminal stannane **44** (738 mg, 66%) and its regioisomer *iso*-**44** (162 mg, 18%);[65] R_f value (*c*-C_6H_{12}/acetone 2:1): 0.40; IR (film): $\bar{\nu}$ =3540, 3480, 2945, 2925, 2870, 2850, 1465, 1415, 1375, 1340, 1290, 1255, 1210, 1180, 1125, 1035, 1000, 960, 920, 895, 850, 810, 690, 665 cm^{-1}; ^1H NMR (400.1 MHz, C_6D_6): δ=0.91 (9H, *t*, $J_{4',3'}$=7.3 Hz, 3× 4′-H_3), 0.93 (6H, *t*, $J_{1',2'}$=8.0 Hz, flanked by Sn isotope satellites, which were incompletely resolved, 3× 1′-H_2), 1.33 (6H, tq, $J_{3',2'}=J_{3',4'}$=7.3 Hz, 3× 3′-H_2), 1.50–1.60 (6H, m, flanked by Sn isotope satellites, which were incompletely resolved, 3× 2′-H_2), 1.80–1.90 (2H, m, 1-H_2), 2.20–2.28 (2H, m, 2-H_2), 3.10 [6H, s, 3-$(OCH_3)_2$], 3.38 [6H, d, $^3J_{PO(OCH_3)_2,P}$=10.6 Hz, $PO(OCH_3)_2$], 5.91 (1H, d, $J_{4,5}$=19.6 Hz, each peak flanked by Sn isotope satellites as two interwoven doublets, $^3J_{4\text{-}H,^{117}Sn}$=63.5 Hz, $^3J_{4\text{-}H,^{119}Sn}$=66.4 Hz, 4-H), 6.69 (1H, d, $J_{5,4}$=19.6 Hz, each peak flanked by Sn isotope satellites as two interwoven doublets, $^2J_{5\text{-}H,^{117}Sn}$=72.0 Hz, $^2J_{5\text{-}H,^{119}Sn}$=75.4 Hz, 5-H); ^{13}C NMR (100.6 MHz, C_6D_6): δ=9.82 (flanked by Sn isotope satellites as two interwoven doublets, $^1J_{C\text{-}1',^{117}Sn}$=327.9 Hz, $^1J_{C\text{-}1',^{119}Sn}$=343.3 Hz, 3× C-1′), 13.93 (3× C-4′), 20.47 (d, $^1J_{1,P}$=143.9 Hz, C-1), 27.64 (flanked by Sn isotope satellites as two superimposing doublets, $^3J_{C\text{-}3',^{117}Sn}=$ $^3J_{C\text{-}3',^{119}Sn}$=53.1 Hz, 3× C-3′), 28.53 (d, $^2J_{2,P}$=3.6 Hz, C-2), 29.60 (flanked by Sn isotope satellites as two superimposing doublets, $^2J_{C\text{-}2',^{117}Sn}=^2J_{C\text{-}2',^{119}Sn}$=21.0 Hz, 3× C-2′), 48.61 [3-$(OCH_3)_2$], 51.80 [d, $^2J_{1,P}$=6.5 Hz, $PO(OCH_3)_2$], 102.31 (d, $^3J_{3,P}$=20.5 Hz, C-3), 133.23 (flanked by Sn isotope satellites as two interwoven doublets, $^1J_{5\text{-}C,^{117}Sn}$=346.7 Hz, $^1J_{5\text{-}C,^{119}Sn}$=362.1 Hz, C-5), 147.13 (C-4); combustion analysis: found C 48.17%, H 9.21%; calculated for $C_{21}H_{45}O_5PSn$: C 47.84%, H 8.60%; HRMS (Method): $[M-Bu]^+$, found *m*/*z*=471.13240, i.e., Δ=+0.3 ppm versus what $C_{17}H_{36}O_5PSn$ requires (471.13224).

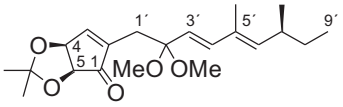
*5.1.25. Dimethyl [(S,4E,6Z)-6-bromo-3,3-dimethoxy-8-methyldeca-4,6-dienyl]phosphonate (**45**).*



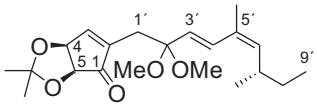
At room temperature $Pd(dba)_2$ (232 mg, 404 μmol, 0.10 equiv) under an atmosphere of Ar to a solution of P(2-furyl)$_3$ (280 mg, 1.21 mmol, 0.30 equiv) in degassed toluene (5 mL). After stirring for 10 min a green solution was obtained. We added successively the freshly distilled dibromoolefin **24** (1.22 g, 5.05 mmol, 1.25 equiv), a solution of pure stannane **44**[66] (2.13 g, 4.04 mmol), and a solution of 2,6-di-*tert*-butyl-4-methylphenol (44.0 mg, 202 μmol, 5.00 mol %) in degassed toluene (10 mL). The mixture was stirred at 50 °C under seclusion from light for 44 h. After cooling to room temperature the solution was transferred directly onto a flash chromatography[44] column (∅ 6 cm, 20 cm, *c*-C_6H_{12}/acetone 4:1→*c*-C_6H_{12}/acetone 3:1→*c*-C_6H_{12}/acetone 2:1, 0.2 vol % NEt_3). The title compound (1.07 g, 66%, ≥97% *trans,Z*) eluted as an orange-red oil. When stored in a refrigerator at 3 °C it solidified rendering orange-red platelets, which melted between 3 and 20 °C; R_f value (*c*-C_6H_{12}/acetone 2:1): 0.25; $[\alpha]_D^{25}$=+19.2 ($CHCl_3$, *c*=1.28); IR (film): $\bar{\nu}$ =3465, 2955, 2870, 2855, 2825, 1650, 1610, 1460, 1410, 1380, 1340, 1305, 1250, 1180, 1125, 1105, 1050, 1035, 965, 935, 910, 890, 850, 815 cm^{-1}; ^1H NMR (400.1 MHz, C_6D_6, sample contained 3% of the *trans,Z* isomer and NEt_3): δ=0.75 (3H, *t*, $J_{10,9}$=7.4 Hz, 10-H_3), 0.82 (3H, d, $J_{8\text{-}CH_3,8}$=6.7 Hz, 8-CH_3), 1.12–1.21 (2H, m, 9-H_2), 1.71–1.82 (2H, m, 1-H_2), 2.18–2.26 (2H, m, 2-H_2), 2.67 (1H, dqdd, $J_{8,7}$=9.1 Hz, $J_{8,8\text{-}CH_3}=J_{8,9\text{-}H(A)}=J_{8,9\text{-}H(B)}$=6.8 Hz, 8-H), 3.01 and 3.02 [2× 3H, 2× s, 3-$(OCH_3)_2$], 3.32 [6H, d, $^3J_{PO(OCH_3)_2,P}$=10.7 Hz, $PO(OCH_3)_2$],

5.50 (1H, d, $J_{7,8}$=9.2 Hz, 7-H), 5.99 (1H, dd, $J_{4,5}$=14.9 Hz, $^5J_{4,7}$=0.6 Hz, 4-H), 6.69 (1H, d, $J_{5,4}$=14.8 Hz, $^4J_{4,7}$=0.7 Hz, 5-H); ^{13}C NMR (100.6 MHz, C_6D_6; sample contained residual NEt_3): δ=11.87 (C-10), 19.26 (8-CH_3), 20.16 (d, $^1J_{1,P}$=143.4 Hz, C-1), 29.16 (d, $^2J_{2,P}$=3.9 Hz, C-2), 29.56 (C-9), 38.25 (C-8), 48.63 and 48.66 [2× 3-(OCH_3)$_2$], 51.79 [d, $^2J_{PO(OCH_3)_2,P}$=6.5 Hz, PO(OCH_3)$_2$], 101.74 (d, $^3J_{3,P}$=20.0 Hz, C-3), 123.51 (C-6), 132.84 (C-4), 133.92 (C-5), 142.14 (C-7); combustion analysis: found C 45.15%, H 7.10; calculated for $C_{15}H_{28}BrO_5P$: C 45.12%, H 7.07%.

*5.1.26. (4R,5R)-2-[(S,3E,5E)-5,7-Dimethyl-2-oxonona-3,5-dienyl]-4,5-dihydroxycyclopent-2-en-1-one [(3E,5E)-**46**] in an 81:19 mixture with (4R,5R)-2-[(S,3E,5Z)-5,7-dimethyl-2-oxonona-3,5-dienyl]-4,5-dihydroxycyclopent-2-en-1-one [(3E,5Z)-**46**].*



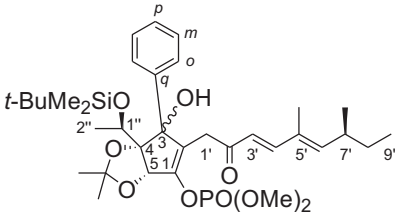
(3*E*,5*E*)-**46**



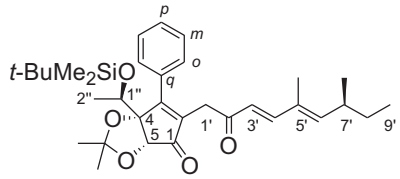
(3*E*,5*Z*)-**46**

At −78 °C *n*-BuLi (2.25 M in hexane, 220 μL, 0.50 mmol, 1.00 equiv) was added to a solution of an 80:20 mixture of phosphonates (*E*,*E*)-**22** and (*E*,*Z*)-**22** (209 mg, 0.50 mmol) in THF (1 mL); the solution was stirred for 1 h. In a parallel experiment *n*-BuLi (2.25 M in hexane, 220 μL, 0.50 mmol, 1.00 equiv) was added at −78 °C to a solution of diisopropylamine (70 μL, 50 mg, 0.5 mmol, 1.0 equiv) in THF (1 mL); it was also stirred for 1 h. The resulting solution of LDA was transferred dropwise via cannula to the solution of the lithiated phosphonates (*E*,*E*)-**22** and (*E*,*Z*)-**22**. After stirring for 5 min a solution of lactone **18** (156 mg, 0.50 mmol, 1.00 equiv) in THF (1 mL) was added dropwise. The mixture was allowed to warm to −45 °C in the course of 2 h. It was stirred for 18 h. The reaction was quenched by adding H_2O (3 mL). The mixture was gradually warmed to room temperature while continuing to stir. It was diluted with Et_2O (3 mL) and the phases were separated. The aq phase was extracted with Et_2O (3×5 mL), the combined organic phases were dried over Na_2SO_4, and the solvent was removed in vacuo. Flash chromatography[44] (∅ 1.5 cm, 20 cm, *c*-C_6H_{12}/AcOEt 10:1, 0.2 vol % NEt_3) gave the title compounds (79 mg, 43%) as an 81:19 mixture of isomers (3*E*,5*E*)-**46** and (3*E*,5*Z*)-**46**; ^{1}H NMR (400.1 MHz, C_6D_6; an unassignable peak superimposes with the resonance $\delta_{A\,part}$=2.68): δ=0.76 [3H, *t*, $J_{9',8'}$=7.4 Hz, 9′-H_3, (3*E*,5*E*)-**46**], 0.77 [3H, *t*, $J_{9',8'}$=7.4 Hz, 9′-H_3, (3*E*,5*Z*)-**46**], 0.84 [3H, d, $J_{7'\text{-}CH_3,7'}$=6.7 Hz, 7′-CH_3, (3*E*,5*E*)-**46**], 0.86 [3H, d, $J_{7'\text{-}CH_3,7'}$=6.7 Hz, 7′-CH_3, (3*E*,5*Z*)-**46**], 1.08−1.24 (2H, m, 8′-H_2), in part superimposed by 1.21 and 1.29 [2× 2H, 2× s, acetonide-C(CH_3)$_2$], 1.64 [3H, s, 5′-CH_3, (3*E*,5*E*)-**46**], 1.75 [3H, s, 5′-CH_3, (3*E*,5*Z*)-**46**], 2.24 [1H, m_c, 7′-H, (3*E*,5*E*)-**46**], 2.51 [1H, m_c, 7′-H, (3*E*,5*Z*)-**46**], AB signal (2H, δ_A=2.68, δ_B=2.78, J_{AB}=15.6 Hz, A part additionally split by $J_{H(A),3}$=1.1 Hz, B part additionally split by $J_{H(B),3}$=1.1 Hz, 1′-H_2), 3.05 [6H, s, 2′-(OCH_3)$_2$], 4.06 [1H, d, $J_{5,4}$=5.4 Hz, 5-H, (3*E*,5*E*)-**46**], 4.09 [1H, d, $J_{5,4}$=5.4 Hz, 5-H, (3*E*,5*Z*)-**46**], 4.53−4.56 [1H, m, 4-H, (3*E*,5*E*)-**46**], 4.60−4.62 [1H, m, 4-H, (3*E*,5*Z*)-**46**], 5.11 [1H, d, $J_{6',7'}$=10.6 Hz, 6′-H, (3*E*,5*Z*)-**46**], 5.23 [1H, d, $J_{6',7'}$=9.6 Hz, 6′-H, (3*E*,5*E*)-**46**], 5.36 [1H, d, $J_{3',4'}$=15.9 Hz, 3′-H, (3*E*,5*E*)-**46**], 5.46 [1H, d, $J_{3',4'}$=15.9 Hz, 3′-H, (3*E*,5*Z*)-**46**], 6.57 [1H, d, $J_{4',3'}$=15.9 Hz, 4′-H, (3*E*,5*E*)-**46**], 7.00 [1H, d, $J_{4',3'}$=15.9 Hz, 4′-H, (3*E*,5*Z*)-**46**], 7.05−7.07 [1H, m, 3-H, (3*E*,5*E*)-**46**], 7.07−7.09 [1H, m, 3-H, (3*E*,5*Z*)-**46**]; combustion analysis: found C 69.08%, H 8.87%; calculated for $C_{21}H_{32}O_5$: C 69.20%, H 8.85%.

*5.1.27. Deprotection of ketals **13a** and epi-**13a** and subsequent Horner–Wadsworth–Emmons reaction: synthesis of a 85:15 mixture of (3R*,4R,5R)-4-[(1R)-1-(tert-butyldimethylsiloxy)ethyl]-2-[(S,3E,5E)-5,7-dimethyl-2-oxonona-3,5-dienyl]-3-hydroxy-4,5-(isopropylidenedioxy)-3-phenylcyclopent-1-enyl dimethyl phosphate (**49a**) and (3S*,4R,5R)-4-[(1R)-1-(tert-butyldimethylsiloxy)ethyl]-2-[(S,3E,5E)-5,7-dimethyl-2-oxonona-3,5-dienyl]-3-hydroxy-4,5-(isopropylidenedioxy)-3-phenylcyclopent-1-enyl dimethyl phosphate (epi-**49a**; *these configurational descriptors are interchangeable) and of (4R,5R)-4-[(R)-1-(tert-butyldimethylsiloxy)ethyl]-2-[(S,3E,5E)-5,7-dimethyl-2-oxonona-3,5-dienyl]-4,5-(isopropylidenedioxy)-3-phenylcyclopent-2-en-1-one (**51a**).*



49a + *epi*-**49a**



51a

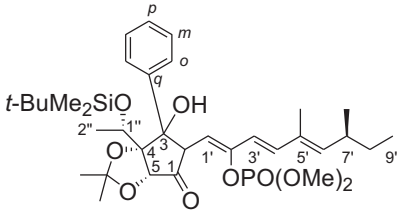
At room temperature a solution of *p*-TsOH (3.0 mg, 18 μmol, 5.1 mol %) and a mixture of the dimethoxy phosphonate epimers **13a** and *epi*-**13a** (255 mg, 352 μmol) in acetonitrile/H_2O [5:1 (vol:vol), 3.83 mL, tantamount to 100 equiv H_2O] was stirred for 16 h. AcOEt (4 mL) and satd aq $NaHCO_3$ (2 mL) were added. The phases were separated, the aq phase was extracted with AcOEt (5×5 mL), and the combined organic phases were dried over Na_2SO_4. The solvent was removed in vacuo and the residue (which must have contained the phosphonate epimers **47a** and *epi*-**47a**) dissolved in benzene (3 mL). K_2CO_3 (106 mg, 774 μmol, 2.20 equiv) was dried in vacuo under heating. Benzene (4 mL) and 18-crown-6 (280 mg, 1.06 mmol, 3.01 equiv) were added. The resulting suspension was heated to 60 °C and stirred for 10 min. The solution containing the crude phosphonate epimers **47a** and *epi*-**47a** (vide supra) was added. After stirring at 60 °C for 3.5 h we cooled to room temperature and added AcOEt (7 mL) and aq phosphate buffer (pH 7, 10 mL). The phases were separated, the aq phase was extracted with AcOEt (5×7 mL), the combined organic phases were dried over Na_2SO_4, and the solvent was removed in vacuo. Flash chromatography[44] (∅ 2.5 cm, 20 cm, packed with *c*-C_6H_{12}/AcOEt 10:1+0.2 vol % NEt_3, eluted with *c*-C_6H_{12}/AcOEt 5:1→3:1) led separately (first) to **51a** (50 mg, 26%) and (thereafter) to what we hold for an 85:15 mixture of C-3-epimers **49a** and *epi*-**49a** (62 mg, 26%), both as yellowish oils; R_f value **51a** (*c*-C_6H_{12}/AcOEt 5:1): 0.55; R_f value **49a**/*epi*-**49a** (*c*-C_6H_{12}/AcOEt 3:1): 0.25.

85:15 **49a**:*epi*-**49a** mixture: $[\alpha]_D^{25}$=+117 (C_6D_6, *c*=3.10); IR (film): $\tilde{\nu}$ =3320, 2960, 2930, 2860, 1690, 1675, 1650, 1620, 1490, 1460, 1450, 1375, 1325, 1290, 1245, 1215, 1205, 1190, 1150, 1045, 1020, 975, 945, 930, 900, 870, 845, 835 cm^{-1}; ^{1}H NMR (499.6 MHz, C_6D_6; sample contained traces of *c*-C_6H_{12} and *tert*-BuOMe): δ=0.13 and 0.26 [2× 3H, 2× s, Si(CH_3)$_2$], 0.65 (3H, *t*, $J_{9',8'}$=7.4 Hz, 9′-H_3), 0.74 (3H, d, $J_{7'\text{-}CH3,7'}$=6.6 Hz, 7′-CH_3), 1.05 [9H, s, SiC(CH_3)$_3$], 0.98−1.19 (2H, m, 8′-H_2), 1.29 (3H, d, $J_{2'',1''}$=6.0 Hz, 2″-H_3), 1.31 (3H, d, $J_{5'\text{-}CH_3,6'}$=1.1 Hz, 5′-CH_3), 1.68 and 1.73 [2× 3H, 2× s, 2× acetonide-(CH_3)$_2$], 2.08 (1H, m_c, 7′-H), AX signal (2H, δ_A=2.92, δ_X=4.12, J_{AX}=18.1 Hz, 1′-H_2), 3.48 and 3.51 [2× 3H, 2× d, $^3J_{PO(OCH_3)_2,P}$=11.3 Hz, PO(OCH_3)$_2$], 5.26 (1H, br d, $J_{6',7'}$=10.4 Hz, 6′-H), superimposed by 5.28 (1H, q, $J_{1'',2''}$=6.2 Hz, 1″-H), 5.77 (1H, d, $J_{3',4'}$=15.8 Hz, 3′-H), superimposed by 5.79 (1H, s, 5-H), 6.69 (1H, br s, 3-O*H*), 7.05 (1H, d, $J_{4',3'}$=15.8 Hz, 4′-H), 7.08−7.12 (1H, m, *p*-Ar), 7.25−7.29 (2H, m, *m*-Ar), 7.86 (2H, br s, *o*-Ar); ^{13}C NMR (125.6 MHz, C_6D_6; sample contained trace of *c*-C_6H_{12}): δ=−4.82 and −3.91 [Si(CH_3)$_2$], 12.00 and

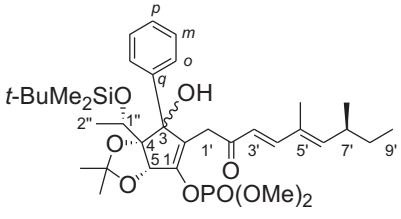
12.09 (C-9′, 5′-*C*H$_3$), 18.42 [Si*C*(CH$_3$)$_3$], 19.50 (C-2″), 20.02 (7′-*C*H$_3$), 26.22 [SiC(*C*H$_3$)$_3$], 28.47 and 29.63 [acetonide-C(*C*H$_3$)$_2$], 30.04 (C-8′), 35.19 (C-7′), 37.54 (C-1′), 54.62 [d, $^2J_{PO(OCH_3)_2,P}$=6.4 Hz, 1× PO(O*C*H$_3$)], 54.75 [d, $^2J_{PO(OCH_3)_2,P}$=5.4 Hz, 1× PO(O*C*H$_3$)], 69.24 (C-1″), 83.44 (C-3), 83.86 (C-5), 96.08 (C-4), 113.67 [acetonide-*C*(CH$_3$)$_2$], 123.08 (C-3′), 124.91 (d, $^3J_{2,P}$=7.5 Hz, C-2), 127.42 (*p*-Ar), 127.60 (*m*-Ar), 129.50 (*o*-Ar), 132.11 (C-5′), 141.60 (*q*-Ar), 149.72 (C-4′), 150.56 (C-6′), 151.86 (d, $^2J_{1,P}$=8.6 Hz, C-1), 199.16 (C-2′); HRMS (CI): M+H$^+$, found *m*/*z*=679.34310, i.e., Δ=±0.0 ppm versus what $C_{35}H_{56}O_9PSi$ requires (679.34312).

Compound **51a**: $[\alpha]_D^{25}$=+297 (C_6D_6, *c*=0.70); IR (film): $\bar{\nu}$ =3415, 3060, 2955, 2930, 2885, 2855, 1715, 1690, 1675, 1610, 1590, 1495, 1472, 1465, 1445, 1405, 1375, 1350, 1300, 1250, 1210, 1185, 1150, 1105, 1085, 1075, 1030, 1005, 970, 935, 865, 835, 815 cm^{-1}; ^{1}H NMR (499.6 MHz, C_6D_6; sample contained trace of *c*-C_6H_{12}): δ=−0.24 and −0.17 [2× 3H, 2× s, Si(C*H*$_3$)$_2$], 0.71 (3H, *t*, $J_{9',8'}$=7.4 Hz, 9′-H$_3$), 0.78 (3H, d, $J_{7'\text{-}CH_3,7'}$=6.9 Hz, 7′-C*H*$_3$), 0.84 [9H, s, SiC(C*H*$_3$)$_3$], 1.04–1.22 (2H, m, 8′-H$_2$), 1.24 (3H, d, $J_{2'',1''}$=6.3 Hz, 2″-H$_3$), 1.48 (3H, s, 1× acetonide-C*H*$_3$), 1.49 (3H, d, $J_{5'\text{-}CH_3,6'}$=1.3 Hz, 5′-C*H*$_3$), 1.52 (3H, s, 1× acetonide-C*H*$_3$), 2.15 (1H, m$_c$, 7′-H), AB signal (2H, δ_A=3.44, δ_B=3.71, J_{AB}=15.6 Hz, 1′-H$_2$), 4.22 (1H, q, $J_{1'',2''}$=6.3 Hz, 1″-H), 4.82 (1H, s, 5-H), 5.34 (1H, br d, $J_{6',7'}$=9.8 Hz, 6′-H), 6.22 (1H, d, $J_{3',4'}$=15.8 Hz, 3′-H), 7.07–7.12 (1H, m, *p*-Ar), 7.17–7.21 (2H, m, *m*-Ar), 7.27 (1H, d, $J_{4',3'}$=15.1 Hz, 4′-H), 7.96–7.99 (2H, m, *o*-Ar); ^{13}C NMR (125.6 MHz, C_6D_6; sample contained trace of *c*-C_6H_{12}): δ=−4.99 and −3.81 [Si(*C*H$_3$)$_2$], 12.00 (C-9′), 12.24 (5′-*C*H$_3$), 18.00 [Si*C*(CH$_3$)$_3$], 19.22 (C-2″), 20.14 (7′-*C*H$_3$), 26.04 [SiC(*C*H$_3$)$_3$], 28.32 and 28.49 [acetonide-C(*C*H$_3$)$_2$], 30.13 (C-8′), 35.07 (C-7′), 37.27 (C-1′), 68.87 (C-1″), 78.95 (C-5), 92.57 (C-4), 115.39 [acetonide-*C*(CH$_3$)$_2$], 124.13 (C-3′), 128.58 (*m*-Ar), 129.41 (*o*-Ar), 129.83 (*p*-Ar), 132.31 (C-5′), 134.04 (*q*-Ar), 137.55 (C-2), 148.36 (C-4′), 149.13 (C-6′), 167.60 (C-3), 194.40 (C-2′), 203.07 (C-1); HRMS (CI): M+H$^+$, found *m*/*z*=553.33420, i.e., Δ=−1.3 ppm versus what $C_{33}H_{49}O_5Si$ requires (553.33493).

*5.1.28. Deprotection of ketals **13b** and epi-**13b** and (attempted) subsequent Horner–Wadsworth–Emmons reaction: synthesis of (2R,3R,4R,5R)- or (2S,3S,4R,5R)-4-[(1S)-1-(tert-butyldimethylsiloxy) ethyl]-2-[(S,1Z,3E,5E)-5,7-dimethyl-2-(dimethylphosphatyl)nona-1,3,5-trienyl]-4,5-(isopropylidenedioxy)-3-phenylcyclopentane (**48b**) and a 91:9 mixture of (3R*,4R,5R)-4-[(1S)-1-(tert-butyldimethylsiloxy) ethyl]-2-[(S,3E,5E)-5,7-dimethyl-2-oxonona-3,5-dienyl]-3-hydroxy-4,5-(isopropylidenedioxy)-3-phenylcyclopent-1-enyl dimethyl phosphate (**49b**) and (3S*,4R,5R)-4-[(1S)-1-(tert-butyldimethylsiloxy)ethyl]-2-[(S,3E,5E)-5,7-dimethyl-2-oxonona-3,5-dienyl]-3-hydroxy-4,5-(isopropylidenedioxy)-3-phenylcyclopent-1-enyl dimethyl phosphate (epi-**49b**; *these configurational descriptors are interchangeable).*



48b (1 diastereomer)



49b + *epi*-**49b**

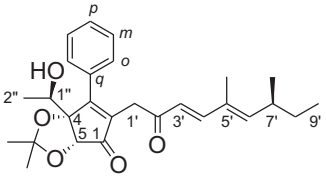
p-TsOH (4.2 mg, 24 μmol, 4.9 mol %) and a mixture of the dimethoxy phosphonate epimers **13b** and *epi*-**13b** (353 mg, 487 μmol) in acetonitrile/H_2O [5:1 (vol:vol), 5.28 mL, tantamount to 100 equiv H_2O] provided a crude product (which must have contained the phosphonate epimers **47b** and *epi*-**47b**) under analogous conditions as described for the conversion **13a**/*epi*-**13a**→**47a**/*epi*-**47a**. **47b**/*epi*-**47b** was carried on jointly with K_2CO_3 (134 mg, 974 μmol, 2.00 equiv) and 18-crown-6 (515 mg, 1.95 mmol, 4.00 equiv) in benzene (8.3 mL) at 60 °C (2.5 h) as described for the analogous reaction of **47a**/*epi*-**47a**. Flash chromatography[44] (∅ 4.0 cm, 20 cm, packed with *c*-C_6H_{12}/AcOEt 10:1, eluted with *c*-C_6H_{12}/AcOEt 5:1→3:1) led separately (first) to what we hold for a 91:9 mixture of epimers **49b** and *epi*-**49b** (114 mg, 34%) and (thereafter) to **48b** (105 mg, 32%), each of which was a yellowish oil.

Compound **48b**: R_f value (*c*-C_6H_{12}/AcOEt 2:1): 0.30; $[\alpha]_{578}^{25}$=+56 (C_6H_6, *c*=0.52); IR (film): $\bar{\nu}$ =3375, 3055, 2955, 2930, 2860, 1760, 1720, 1690, 1680, 1645, 1625, 1460, 1450, 1410, 1375, 1340, 1260, 1235, 1185, 1140, 1120, 1075, 1040, 1005, 960, 945, 855, 840, 830 cm^{-1}; ^{1}H NMR (499.6 MHz, C_6D_6; sample contained traces of *c*-C_6H_{12} and *tert*-BuOMe): δ=−0.13 and −0.09 [2× 3H, 2× s, Si(C*H*$_3$)$_2$], 0.71 (3H, *t*, $J_{9',8'}$=7.4 Hz, 9′-H$_3$), 0.80 (3H, d, $J_{7'\text{-}CH_3,7'}$=6.6 Hz, 7′-C*H*$_3$), 0.85 [9H, s, SiC(C*H*$_3$)$_3$], 0.98 (3H, d, $J_{2'',1''}$=6.6 Hz, 2″-H$_3$), 1.02–1.12 and 1.14–1.22 (2H, 2× m, 8′-H$_2$), 1.31 (3H, s, 1× acetonide-C*H*$_3$), 1.43 (3H, d, $J_{5'\text{-}CH_3,6'}$=1.3 Hz, 5′-C*H*$_3$), 1.91 (3H, s, 1× acetonide-C*H*$_3$), 2.18 (1H, m$_c$, 7′-H), 3.40 and 3.53 [2× 3H, 2× d, $J_{PO(OCH_3)_2,P}$=11.3 Hz, PO(O*C*H$_3$)$_2$], 4.34 (1H, q, $J_{1'',2''}$=6.7 Hz, 1″-H), 4.96 (1H, br s, 5-H), 5.23 (1H, br d, $J_{6',7'}$=9.5 Hz, 6′-H), AB signal [2H, δ_A=5.54, δ_B=5.66, J_{AB}=9.1 Hz, B part additionally split by $J_{1',P}$=2.2 Hz (splitting vanishes upon ^{31}P-decoupling), H$_A$=2-H, H$_B$=1′-H], 5.83 (1H, d, $J_{3',4'}$=15.8 Hz, 3′-H), 6.58 [1H, d, $J_{3\text{-}OH,P}$=1.3 Hz (splitting—through space—vanishes upon ^{31}P-decoupling), 3-O*H* (vanishes upon treatment with D_2O)], 6.70 (1H, d, $J_{4',3'}$=15.4 Hz, 4′-H), 7.06–7.10 (1H, m, 1H, *p*-Ar), 7.24–7.28 (2H, m, *m*-Ar), 8.17–8.22 (2H, m, *o*-Ar); ^{13}C NMR (125.6 MHz, C_6D_6; sample contained traces of *c*-C_6H_{12} and *tert*-BuOMe): δ=−5.64 and −4.43 [Si(*C*H$_3$)$_2$], 12.15 (C-9′), 12.51 (5′-*C*H$_3$), 17.86 [Si*C*(CH$_3$)$_3$], 18.79 (C-2″), 20.67 (7′-*C*H$_3$), 25.68 [SiC(*C*H$_3$)$_3$], 28.82 and 29.89 [acetonide-C(*C*H$_3$)$_2$], 30.57 (C-8′), 34.81 (C-7′), 54.66 [d, $^2J_{PO(OCH_3)_2,P}$=6.4 Hz, 1× PO(O*C*H$_3$)], 55.10 [d, $^2J_{PO(OCH_3)_2,P}$=5.4 Hz, 1× PO(O*C*H$_3$)], 59.42 (C-2), 73.78 (C-1″), 82.45 (C-3), 83.74 (C-5), 89.01 (C-4), 110.73 (d, $^3J_{1',P}$=5.4 Hz, C-1′), 115.05 [acetonide-*C*(CH$_3$)$_2$], 121.24 (d, $^3J_{3',P}$=2.1 Hz, C-3′), 127.61 (*p*-Ar), 127.69 (*o*-Ar), between 127.70 and 127.90 (superimposed by solvent signal; *m*-Ar), 132.46 (C-5′), 135.54 (C-4′), 141.73 (C-6′), 142.02 (*q*-Ar), 150.68 (d, $J_{2',P}$=8.6 Hz, C-2′), 209.85 (C-1); ^{31}P NMR (202.3 MHz, C_6D_6): δ=−3.38 [O*P*(OMe)$_2$]; ^{29}Si NMR (99.3 MHz, C_6D_6): δ=23.63 (O*Si*Me$_2$*t*Bu); HRMS (EI): M•$^+$, found *m*/*z*=678.33480, i.e., Δ=−0.7 ppm versus what $C_{35}H_{55}O_9PSi$ requires (678.33530).

Compound **49b**/*epi*-**49b**: R_f value (*c*-C_6H_{12}/AcOEt 2:1): 0.35; $[\alpha]_D^{25}$=+5.2 (C_6D_6, *c*=0.50); IR (film): $\bar{\nu}$ =3445, 2985, 2950, 2935, 2860, 3355, 2100, 1670, 1625, 1595, 1490, 1460, 1450, 1370, 1345, 1300, 1250, 1185, 1110, 1080, 1040, 1005, 955, 920, 890, 835, 810 cm^{-1}; ^{1}H NMR (499.6 MHz, C_6D_6): δ=0.08 and 0.27 [2× 3H, 2× s, Si(C*H*$_3$)$_2$], 0.68 (3H, *t*, $J_{9',8'}$=7.4 Hz, 9′-H$_3$), 0.76 (3H, d, $J_{7'\text{-}CH_3,7'}$=6.9 Hz, 7′-C*H*$_3$), 1.05 [9H, s, SiC(C*H*$_3$)$_3$], 1.09–1.19 (2H, m, 8′-H$_2$), 1.24 (3H, s, 1× acetonide-C*H*$_3$), 1.41 (3H, d, $J_{5'\text{-}CH_3,6'}$=1.0 Hz, 5′-C*H*$_3$), 1.57 (3H, s, 1× acetonide-C*H*$_3$), 1.64 (3H, d, $J_{2'',1''}$=6.6 Hz, 2″-H$_3$), 2.12 (1H, m$_c$, 7′-H), AB signal (2H, δ_A=3.29, δ_B=3.65, J_{AB}=17.0 Hz, 1′-H$_2$), 3.57 and 3.58 [2× 3H, 2× d, $^3J_{PO(OCH_3)_2,P}$=11.4 Hz, PO(O*C*H$_3$)$_2$], 4.28 (1H, q, $J_{1'',2''}$=6.5 Hz, 1″-H), 5.21 (1H, br d, $J_{6',7'}$=9.8 Hz, 6′-H), 5.38 (1H, s, 3-O*H*), 5.89 (1H, br s, 5-H), 5.97 (1H, d, $J_{3',4'}$=15.8 Hz, 3′-H), 7.09 (1H, d, $J_{4',3'}$=15.8 Hz, 4′-H), 7.12–7.16 (1H, m, superimposed by solvent resonance *p*-Ar), 7.30–7.34 (2H, m, *m*-Ar), 7.92–8.00 (2H, br d, *o*-Ar); ^{13}C NMR (125.6 MHz, C_6D_6): δ=−5.04 and −4.26 [Si(*C*H$_3$)$_2$], 12.05 (C-9′, assignment exchangeable with 5′-*C*H$_3$), 12.30 (5′-*C*H$_3$, assignment

exchangeable with C-9′), 18.16 [SiC(CH_3)$_3$], 18.89 (C-2″), 20.19 (7′-CH_3), 26.14 [SiC(CH_3)$_3$], 28.20 and 29.31 [acetonide-C(CH_3)$_2$], 30.17 (C-8′), 35.08 (C-7′), 37.56 (C-1′), 54.57 [d, $^2J_{PO(OCH_3)_2,P}$=6.4 Hz, 1× PO(OCH_3)], 54.72 [d, $^2J_{PO(OCH_3)_2,P}$=6.4 Hz, 1× PO(OCH_3)], 74.98 (C-1″), 85.03 (C-5), 88.03 (C-3), 91.54 (C-4), 113.84 [acetonide-C(CH_3)$_2$], 124.40 (C-3′), 127.40 (d, $^3J_{2,P}$=7.5 Hz, C-2), 127.40 (*p*-Ar), 127.60 (*m*-Ar), 129.62 (*o*-Ar), 132.26 (C-5′), 141.73 (*q*-Ar), 147.48 (C-4′), 148.16 (d, $^2J_{1,P}$=6.4 Hz, C-1), 148.45 (C-6′), 194.87 (C-2′); HRMS (EI): [M-*t*Bu]$^+$, found *m*/*z*=621.26540, i.e., Δ=+0.8 ppm versus what $C_{31}H_{46}O_9PSi$ requires (621.26487).

*5.1.29. (4R,5R)-2-[(S,3E,5E)-5,7-Dimethyl-2-oxonona-3,5-dienyl]-4-[(R)-1-hydroxyethyl]-4,5-(isopropylidenedioxy)-3-phenylcyclopent-2-en-1-one (**52a**).*

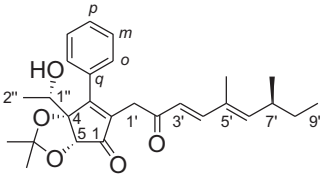


*5.1.29.1. Preparation of **52a** from the surmised 85:15 mixture of **49a** and epi-**49a**.* At room temperature HBF_4 (50% in H_2O, 17.0 μL, 23.8 mg, 138 μmol, 3.00 equiv, tantamount to 14.4 equiv H_2O) was added to a solution of the surmised 85:15 mixture of **49a** and *epi*-**49a** (27 mg, 46 μmol) in CH_2Cl_2 (2 mL). The mixture was stirred at 40 °C for 100 min. Addition of CH_2Cl_2 (3 mL) and aq phosphate buffer (pH=7, 5 mL) was followed by phase separation. The aq phase was extracted with CH_2Cl_2 (5×3 mL), the combined organic phases were dried over Na_2SO_4, and the solvent was removed in vacuo. Flash chromatography[44] (∅ 1.5 cm, 20 cm, *c*-C_6H_{12}/AcOEt 6:1→4:1) yielded the title compound (9 mg, 45%) as a slightly yellow oil; R_f value (*c*-C_6H_{12}/AcOEt 3:1): 0.30.

*5.1.29.2. Preparation of **52a** from **51a**.* A solution of **51a** (20.0 mg, 36.2 μmol) in 1,4-dioxane (500 μL) was cooled to 0 °C (ice-bath) and diluted with water (100 μL). Ammonium fluoride (3.4 mg, 92 μmol, 2.5 equiv) was added in one portion. The resulting mixture was stirred at 0 °C for 90 min. No conversion was observed by TLC. Accordingly, the mixture was warmed to 40 °C. After stirring for 1 h more ammonium fluoride (3.3 mg, 89 μmol, 2.5 equiv) was added in one portion. The resulting suspension was diluted with water (100 μL) and 1,4-dioxane (200 μL) and stirred at 40 °C for 13 h. The mixture was diluted with aq phosphate buffer (pH 7, 1 mL) and ethyl acetate (1 mL). After phase separation the aqueous phase was extracted with ethyl acetate (5×1 mL). The combined organic phases were dried over Na_2SO_4. The solvent was removed under reduced pressure. Flash chromatography[44] (∅ 1.5 cm, 20 cm, *c*-C_6H_{12}/AcOEt 6:1→4:1→2:1) furnished the title compound (9.9 mg, 64%).

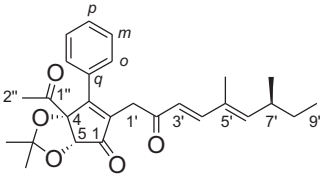
Compound **52a**: $[\alpha]_D^{25}$=+437 (C_6D_6, *c*=0.90); IR (film): $\bar{\nu}$ =3450, 3050, 2960, 2925, 2870, 1715, 1670, 1620, 1590, 1495, 1455, 1445, 1375, 1355, 1305, 1245, 1210, 1185, 1155, 1095, 1080, 1030, 985, 955, 925, 890, 855 cm^{-1}; ^{1}H NMR (499.6 MHz, C_6D_6; sample contained ca. 6% of the *trans*,*Z* isomer and traces of *c*-C_6H_{12} and *tert*-BuOMe): δ=0.71 (3H, *t*, $J_{9',8'}$=7.4 Hz, 9′-H_3), 0.79 (3H, d, $J_{7'\text{-}CH_3,7'}$=6.6 Hz, 7′-CH_3), 1.04–1.22 (2H, m, 8′-H_2), 1.11 (3H, d, $J_{2'',1''}$=6.3 Hz, 2″-H_3), 1.40 (3H, s, superimposed by *c*-C_6H_{12}, 1× acetonide-CH_3), 1.43 (3H, d, $J_{5'\text{-}CH_3,6'}$=0.9 Hz, 5′-CH_3), 1.55 (3H, s, 1× acetonide-CH_3), 2.15 (1H, m_c, 7′-H), AB signal (2H, δ_A=3.31, δ_B=3.60, J_{AB}=16.4 Hz, 1′-H_2), 3.88 (1H, q, $J_{1'',2''}$=6.3 Hz, 1″-H), 4.70 (1H, s, 5-H), 5.35 (1H, br d, $J_{6',7'}$=9.8 Hz, 6′-H), 6.06 (1H, d, $J_{3',4'}$=15.8 Hz, 3′-H), 7.07–7.11 (1H, m, *p*-Ar), 7.14–7.19 (3H, m, superimposed by *c*-C_6H_{12}, *m*-Ar+4′-H), 7.72–7.77 (2H, m, *o*-Ar); ^{13}C NMR (125.6 MHz, C_6D_6; sample contained traces of *c*-C_6H_{12}): δ=12.04 (C-9′), 12.25 (5′-CH_3), 18.13 (C-2″), 20.17 (7′-CH_3), 28.36 and 28.49 [acetonide-C(CH_3)$_2$], 30.18 (C-8′), 35.15 (C-7′), 36.45 (C-1′), 67.41 (C-1″), 78.35 (C-5), 92.57 (C-4), 115.37 [acetonide-C(CH_3)$_2$], 124.07 (C-3′), 128.62 (*o*-Ar), 128.77 (*m*-Ar), 129.57 (*p*-Ar), 132.30 (C-5′), 134.41 (*q*-Ar), 138.23 (C-2), 148.65 (C-4′), 149.39 (C-6′), 166.11 (C-3), 195.06 (C-2′), 202.59 (C-1); HRMS (CI): M+H$^+$, found *m*/*z*=439.24870, i.e., Δ=+0.6 ppm versus what $C_{27}H_{35}O_5$ requires (439.24845).

*5.1.30. (4R,5R)-2-[(S,3E,5E)-5,7-Dimethyl-2-oxonona-3,5-dienyl]-4-[(S)-1-hydroxyethyl]-4,5-(isopropylidenedioxy)-3-phenylcyclopent-2-en-1-one (**52b**).*



This compound was prepared analogously as described for epimer **52a** from HBF_4 (50% in H_2O, 22.0 μL, 30.8 mg, 172 μmol, 3.02 equiv, tantamount to 15.0 equiv H_2O) and the surmised 91:9 mixture of **49b** and *epi*-**49b** (39 mg, 57 μmol). Flash chromatography[44] (∅ 1.5 cm, 20 cm, *c*-C_6H_{12}/AcOEt 6:1→4:1) yielded the title compound (12 mg, 48%) as a slightly yellow oil; R_f value (*c*-C_6H_{12}/AcOEt 3:1): 0.30; $[\alpha]_D^{25}$=+496 (C_6D_6, *c*=1.17); IR (film): $\bar{\nu}$ =3575, 3480, 3035, 2960, 2925, 2870, 2355, 2280, 1720, 1690, 1665, 1620, 1590, 1495, 1480, 1460, 1455, 1445, 1400, 1370, 1350, 1310, 1250, 1210, 1185, 1160, 1125, 1080, 1045, 985, 900, 860 cm^{-1}; ^{1}H NMR (400.1 MHz, C_6D_6; sample contained ca. 5% of the *trans*,*Z* isomer and traces of *c*-C_6H_{12} and *tert*-BuOMe): δ=0.71 (3H, *t*, $J_{9',8'}$=7.4 Hz, 9′-H_3), 0.80 (3H, d, $J_{7'\text{-}CH_3,7'}$=6.6 Hz, 7′-CH_3), 1.02 (3H, d, $J_{2'',1''}$=6.6 Hz, 2″-H_3), 1.04–1.24 (2H, m, 8′-H_2), 1.36 (3H, s, 1× acetonide-CH_3), 1.45 (3H, d, $J_{5'\text{-}CH_3,6'}$=1.1 Hz, 5′-CH_3), 1.48 (3H, s, 1× acetonide-CH_3), 2.16 (1H, m_c, 7′-H), AB signal (2H, δ_A=3.19, δ_B=3.66, J_{AB}=16.3 Hz, 1′-H_2), 3.94 (1H, q, $J_{1'',2''}$=6.6 Hz, 1″-H), 4.79 (1H, s, 5-H), 5.38 (1H, br d, $J_{6',7'}$=9.6 Hz, 6′-H), 6.09 (1H, d, $J_{3',4'}$=15.8 Hz, 3′-H), 7.05–7.16 (3H, m, superimposed by solvent signal, *p*-Ar+*m*-Ar), 7.20 (1H, d, $J_{4',3'}$=15.9 Hz, 4′-H), 7.74–7.79 (2H, m, *o*-Ar); ^{13}C NMR (100.6 MHz, C_6D_6; sample contained traces of *c*-C_6H_{12}): δ=12.02 (C-9′), 12.25 (5′-CH_3), 17.09 (C-2″), 20.15 (7′-CH_3), 28.34 and 28.39 [acetonide-C(CH_3)$_2$], 30.17 (C-8′), 35.16 (C-7′), 36.31 (C-1′), 67.57 (C-1″), 77.48 (C-5), 92.74 (C-4), 114.85 [acetonide-C(CH_3)$_2$], 124.17 (C-3′), 128.61 (*o*-Ar), 128.92 (*m*-Ar), 129.94 (*p*-Ar), 132.30 (C-5′), 134.23 (*q*-Ar), 137.84 (C-2), 148.68 (C-4′), 149.48 (C-6′), 166.22 (C-3), 195.04 (C-2′), 201.73 (C-1); HRMS (CI): M+H$^+$, found *m*/*z*=439.24770, i.e., Δ=−1.7 ppm versus what $C_{27}H_{35}O_5$ requires (439.24845).

*5.1.31. (4R,5R)-4-Acetyl-2-[(S,3E,5E)-5,7-dimethyl-2-oxonona-3,5-dienyl]-4,5(-isopropylidenedioxy)-3-phenylcyclopent-2-en-1-one (**53**).*



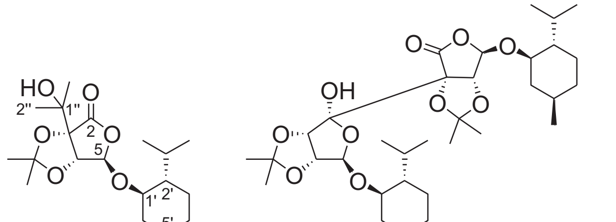
*5.1.31.1. Preparation of **53** from **52a**.* At room temperature a solution of alcohol **52a** (10 mg, 23 μmol) in degassed CH_2Cl_2 (500 μL) was added under an atmosphere of argon to a stirred mixture of *N*-

methylmorpholin-N-oxide monohydrate (7.8 mg, 58 μmol, 2.5 equiv) and molecular sieves (4 Å) in CH_2Cl_2 (250 μL). After 15 min tetrapropylammonium perruthenate (0.8 mg, 2.3 μmol, 10 mol %) was added. After stirring at room temperature for 3 h CH_2Cl_2 (2 mL) and aq phosphate buffer (pH=7, 3 mL) were added. The aq phase was extracted with CH_2Cl_2 (4×2 mL), the combined organic phases were dried over Na_2SO_4, and the solvent was removed at 30 °C in vacuo. Flash chromatography[44] (∅ 0.5 cm, 20 cm, c-C_6H_{12}/AcOEt 5:1→3:1) gave the title compound (8.0 mg, 80%, ≥97% *trans*,*E*) as a yellow oil.

*5.1.31.2. Preparation of **53** from **52b**.* A solution of alcohol **52b** (20 mg, 46 μmol) in degassed CH_2Cl_2 (750 μL), N-methylmorpholin-N-oxide monohydrate (15.5 mg, 115 μmol, 2.50 equiv), and tetrapropylammonium perruthenate (1.6 mg, 4.6 μmol, 10 mol %) was processed as described for the oxidation of alcohol **52a**. Flash chromatography[44] (∅ 1.5 cm, 20 cm, c-C_6H_{12}/AcOEt 5:1→3:1) gave the title compound (18 mg, 90%, ≥97% *trans*,*E*) as a yellow oil.

R_f value (c-C_6H_{12}/AcOEt 3:1): 0.35; $[\alpha]_D^{25}$=+96 (C_6D_6, c=0.20); IR (film): $\bar{\nu}$ =2960, 2925, 2870, 2360, 2335, 2720, 1690, 1675, 1665, 1645, 1620, 1595, 1460, 1440, 1415, 1375, 1355, 1305, 1250, 1210, 1185, 1110, 1080, 1025, 985, 850 cm^{-1}; ^1H NMR (499.6 MHz, C_6D_6; sample contained ca. 3% of the *trans*,*Z* isomer and contaminant signals at δ=1.02 and 4.88 ppm): δ=0.71 (3H, t, $J_{9',8'}$=7.4 Hz, 9′-H_3), 0.78 (3H, d, $^4J_{7'-CH_3,7'}$=6.6 Hz, 7′-CH_3), 1.04–1.13 and 1.13–1.20 (2H, 2× m, 8′-H_2), 1.36 (3H, s, 1× acetonide-CH_3), 1.44 (3H, d, $^4J_{5'-CH_3,6'}$=0.9 Hz, 5′-CH_3), 1.57 (3H, s, 1× acetonide-CH_3), 1.91 (3H, s, 2″-H_3), 2.10–2.19 (1H, m_c, 7′-H), AB signal (2H, δ_A=3.42, δ_B=3.46, J_{AB}=16.6 Hz, 1′-H_2), 4.50 (1H, s, 5-H), 5.35 (1H, br d, $J_{6',7'}$=10.1 Hz, 6′-H), 6.04 (1H, d, $J_{3',4'}$=15.4 Hz, 3′-H), 6.97–7.01 (1H, m, p-Ar), 7.04–7.08 (2H, m, m-Ar), 7.16 (1H, d, $J_{4',3'}$=15.8 Hz, 4′-H, superimposed by solvent signal), 7.66–7.69 (2H, m, o-Ar); ^{13}C NMR (125.6 MHz, C_6D_6; sample contained contaminant signals at δ=27.24, 28.53, and 94.24 ppm): δ=12.04 (C-9′), 12.24 (5′-CH_3), 20.14 (7′-CH_3), 26.91 (C-2″), 27.91 and 28.04 [acetonide-C(CH_3)$_2$], 30.16 (C-8′), 35.14 (C-7′), 36.51 (C-1′), 82.09 (C-5), 95.03 (C-4), 117.39 [acetonide-C(CH_3)$_2$], 123.95 (C-3′), 128.55 (o-Ar), 128.94 (m-Ar), 130.07 (p-Ar), 132.26 (C-5′), 133.93 (q-Ar), 138.38 (C-2), 148.61 (C-4′), 149.43 (C-6′), 166.36 (C-3), 194.34 (C-2′), 201.25 (C-1), 206.30 (C-1″); HRMS (CI): M+H^+, found m/z=437.23210, i.e., Δ=−1.6 ppm versus what $C_{27}H_{33}O_5$ requires (437.23280).

*5.1.32. (3R,4R,5R)-3-(1-Hydroxy-1-methylethyl)-5-{[(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl]oxy}-3,4-(isopropylidenedioxy)-4,5-dihydro-3H-furan-2-one (**62**) and hexacyclic dimer **64** of lactone **18**.*



62 64

5.1.32.1. Preparation A. At −50 °C n-BuLi (2.31 M in hexane, 65.0 μL, 150 μmol, 1.00 equiv) was added to a solution of diisopropylamine (22.0 μL, 15.8 mg, 157 μmol, 1.05 equiv) in THF (500 μL). The mixture was stirred for 30 min. A solution of lactone **18** (47.0 mg, 150 μmol) in THF (500 μL) was pre-cooled to −50 °C and added to the previously mentioned mixture via cannula. The resulting mixture was stirred for 45 min. It was quenched by one drop of H_2O. Et_2O (2 mL) and brine (2 mL) were added. After phase separation the aq phase was extracted with Et_2O (3×1 mL). The combined organic phases were dried over $NaSO_4$, the solvent was removed under reduced pressure, and the crude product separated by flash chromatography[44] (∅ 2 cm, 20 cm, c-C_6H_{12}/AcOEt 50:1→25:1→15:1→5:1) into dimer **64** (7.0 mg, 11 μmol, 15%; X-ray crystal structure: footnote,[37] Fig. 6) and a mixture (12 mg) of **62** and L-menthol. The latter was removed from that mixture in oil-pump vacuum. What remained was **62** (8.0 mg, 22 μmol, 15%).

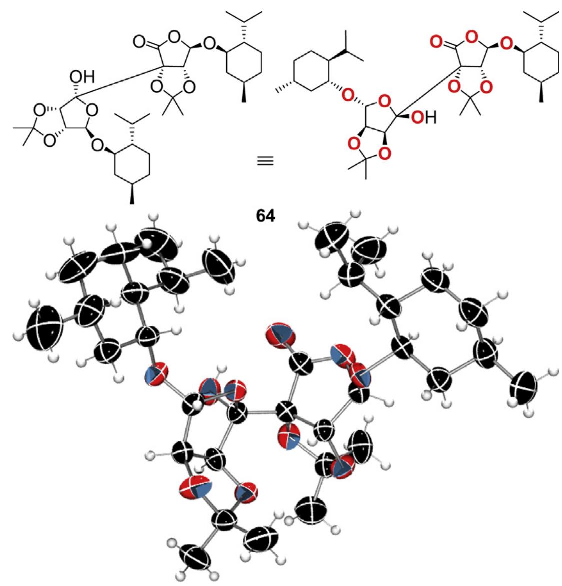


Fig. 6. ORTEP plot of the unit cell of an X-ray structure analysis of a single crystal of dimer **64** at 298 K.[46] Hydrogen atoms were restrained to idealized positions and refined isotropically based on a riding model.

5.1.32.2. Preparation B. At −40 °C n-BuLi (2.31 M in hexane, 130 μL, 300 μmol, 1.00 equiv) was added to a solution of diisopropylamine (44.0 μL, 31.7 mg, 314 μmol, 1.05 equiv) in THF (1 mL). The resulting mixture was stirred for 30 min. A solution of lactone **18** (94.0 mg, 300 μmol) in THF (500 μL) was pre-cooled to −40 °C and added to the previously mentioned mixture via cannula. The resulting mixture was stirred for 50 min. A solution of pre-cooled acetaldehyde (17.0 μL, 13.3 mg, 301 μmol, 1.00 equiv) in THF (255 μL) was added via cannula. The mixture was stirred at −40 °C for 25 h until it was poured into satd aq NH_4Cl (2 mL). Et_2O (2 mL) was added. After phase separation the aq phase was extracted with Et_2O (4×1 mL). The combined organic phases were dried over $NaSO_4$ and the solvent was removed under reduced pressure. Purification by flash chromatography[44] (∅ 2.5 cm, 20 cm, c-C_6H_{12}/AcOEt 15:1→10:1→5:1) provided dimer **64** (30 mg, 48 μmol, 32%) and a mixture (33 mg) of **62** and L-menthol. The latter was removed under oil-pump vacuum leaving **62** (20 mg, 54 μmol, 18%).

Acknowledgements

We thank Stefan Malsch for skillful technical assistance, Patrick Kasper, Christian Schubert, and Charles Tchoubun for their contributions in the course of their diploma or bachelor laboratory works, Dr. Jens Geier (Universität Freiburg) for performing the X-ray analyses,[46] Dr. Horst Hemmerle (at the time Aventis Pharma Deutschland) for a sample of kodaistatin A,[16] and Prof. Dr. Klaus Ditrich (BASF SE, Ludwigshafen) for a donation of (S)-2-methylbutanol.

Supplementary data

Reproductions of ^{1}H and ^{13}C NMR data of compounds prepared in this study and high-resolution representations of the X-ray structures of compounds **17b** (CCDC 932028) and **18** (CCDC 932027) can be found. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.05.091.

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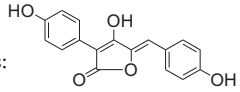
13. Ref. 10 mentions the occurrence of kodaistatins B and D, too, yet more vaguely: 'The strain *Aspergillus terreus* Thom DSM 11247 produces kodaistatin A as the main component, with smaller quantities of kodaistatin C. The components B and D, which occur only in traces, are isomers of compounds A and C, respectively.'
14. Aspulvinone E was isolated in the course of the kodaistatin study of Ref. 10. It resembles the pulvinone moiety of the kodaistatins but was not considered in terms of a biosynthetic relationship but appreciated as a 'pulvinone sample for free' for an unambiguous structural analysis, which one would have preferably executed with one of the kodaistatins. However, they eluded structure elucidation by X-ray analysis:



Z-aspulvinone E

15. (a) Sugiyama, H.; Ojima, N.; Kobayashi, M.; Senda, Y.; Ishiyama, J.-i.; Seto, S. *Agric. Biol. Chem.* **1979**, *43*, 403–404; (b) A crystal structure analysis for aspulvinon D was reported by Begley, M. J.; Gedge, D. R.; Knight, D. W.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 77–83 too. The two findings together show that two of the earliest described naturally occurring pulvinones contain an (*E*)-configured semicyclic C]C bond. This lends some plausibility to the ocurrence of a (*Z*)-configured semicyclic C]C bond in the kodaistatins as well.
16. We are grateful to Dr. Horst Hemmerle, who at the time was a member of the Hoechst Marion Roussel's kodaistatin team for a donation of kodaistatin A (thereafter Hoechst Marion Roussel developed into Aventis Pharma).
17. A CP-Chirasil-Dex CB column was employed.[18] Its stationary phase consists of poly(dimethylsiloxane)-bound β-cyclodextrin.
18. The enantiomeric composition of alcohol **6** was determined by GLC analysis [CP-Chirasil-Dex CB 25 m×0.25 mm (CP-7502; coating: Ref. 17) capillary; 35 °C isothermal; 45 min; +10 °C/min to 170 °C; 20 min; 50 kPa H_2 pressure—no additional carrier gas]: Several compounds eluted from the column, one of them being (*S*)-**6**. The latter eluted with R_t=20.9 min. When we injected the same ozonolysis products and co-injected *rac*-**6**, the peak attributed to (*S*)-**6** (R_t=20.9 min) was reinforced and an additional peak – which we attributed to (*R*)-**6**—showed up after R_t=19.6 min.
19. Reproductions of the GLCs of this analysis are included in the Supplementary Data file.
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21. Other early preparations and uses of the Feringa lactone were described by (a) Martel, J., Demoute, J.-P., Tessier, J., U.S. Patent 4769478 A1 (Roussel-Uclaf), September 6, 1988; (b) Hoffmann, N.; Scharf, H.-D.; Runsink, J. *Tetrahedron Lett.* **1989**, *30*, 2637–2638; (c) Pelter, A.; Ward, R. S.; Jones, D. M.; Maddocks, P. *Tetrahedron: Asymmetry* **1990**, *1*, 857–860.
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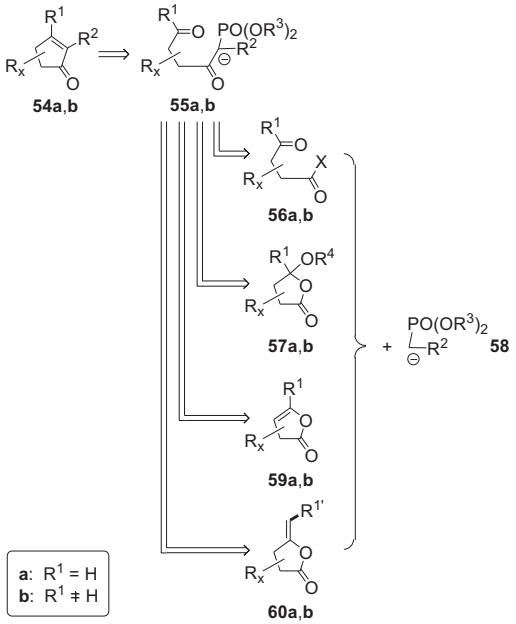
24. Established C_4+C_1 approaches to cyclopentenones **54a,b** following such a synthetic strategy comprise the following variations when the C_4 component (**56**–**60**) is a 3-formyl-(**a**) or a 3-acylcarboxylic acid equivalent (**b**) and the C_1 component a deprotonated phosphonate **58**:



a) **56**+**58** strategy (for X = OMe): Lin, C. -H.; Aristoff, P. A.; Johnson, P. D.; McGrath, J. P.; Timko, J. M.; Robert, A., *J. Org, Chem* **1987**, *52*, 5594–5601; b) **57**+**58** strategy: ref. 26; c) **59**+**58** strategy: Canevet, J. C.; Sharrard, F.; *Tetrahedron Lett* **1982**, *23*, 181–184; a) **60**+**58** strategy: Aristoff, P. A.; Johnson, P. D.; Harrison, A. W.; *J. Am. Chem. Soc* **1985**, *107*, 7967–7974.

25. Variations of the C_4+C_1 approach to substituted cyclopentenones **54a,b** delineated in footnote 24 include uses of a protected 3-acylcarboxylic acids as the C_4 component (e.g. Lard, R. D., Kozar, L. G., Heathcock, C. H. *Synth. Commun.* **1975**, *5*, 1–5) or of a 3-(α-hydroxyalkyl)carboxylic acid derivative, which gives a ketophosphonate intermediate, which must be oxidized before the Horner–Wadsworth–Emmons cyclization takes place (e.g. Altenbach, H.-J., Holzapfel, W., Smerat, G., Finkler, S. H. *Tetrahedron Lett.* **1985**, *26*, 6329–6332).
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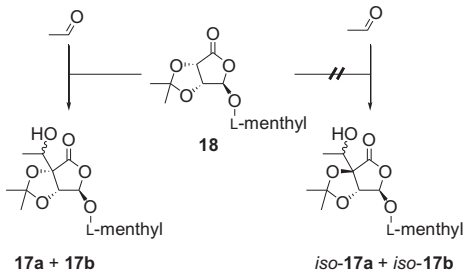
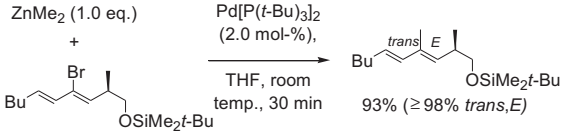
27. We were confident that the bicyclic core of lactone **18** (cf. Scheme 2) would exert induced diastereoselectivity in the desired sense, i.e., without allowing aldolization products *iso*-**17a** and *iso*-**17b** to form. This expectation was based

on the effectiveness of product development control in favoring a continued *cis*- vs a *trans*-fusion of the five-membered rings.

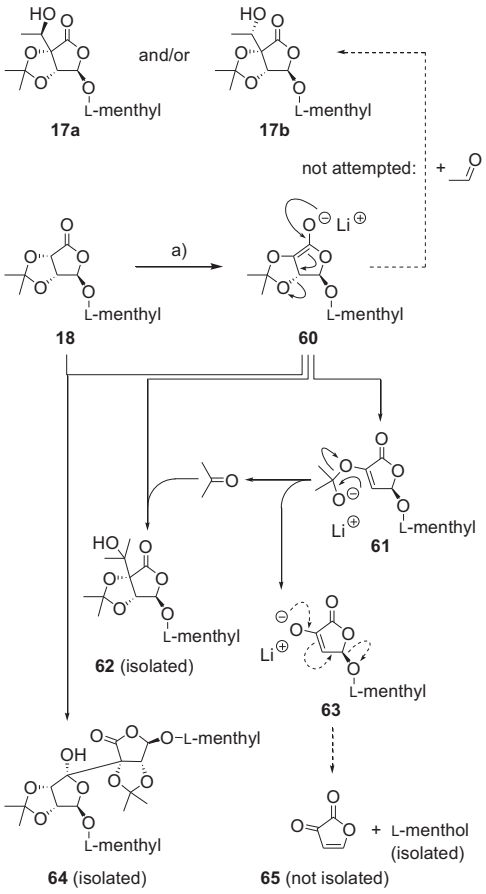


28. (a) Anelli, P. L.; Montanari, F.; Quici, S. *Org. Synth.* **1990**, *69*, 212–219 and; Org. Synth.Collect Vol. 8; 1993; Collect Vol. 8367–371 (82–84% yield); (b) Jauch, J.; Szesla, H.; Schurig, V. *Tetrahedron* **1999**, *55*, 9787–9792 (59% yield); (c) Davies, J. R.; Kane, P. D.; Moody, C. J.; Slawin, A. M. Z. *J. Org. Chem.* **2005**, *70*, 5480–5481 (72% yield); (d) Pouysegu, L.; Margguerit, M.; Gagnepain, J.; Lyvinec, G.; Quideau, S.; Eatherton, A. J. *Org. Lett.* **2008**, *10*, 5211–5214 (88% yield).
29. Cf., e g.: (a) Jessen, H. J.; Gademann, K.; Barbaras, D.; Hamburger, M. *Org. Lett.* **2009**, *11*, 3446–3449; (b) Raffier, L.; Piva, O. *Beilstein J. Org. Chem.* **2011**, *7*, 151–155; (c) Jessen, H. J.; Schumacher, A.; Shaw, T.; Pfaltz, A.; Gademann, K. *Angew. Chem* **2011**, *123*, 4308–4312; *Angew. Chem., Int. Ed.* **2011**, *50*, 4222–4226.
30. The only 2-oxobutane-1,4-bisphosphonates described prior to **25** were tetraisopropyl 2-oxobutane-1,4-bisphosphonate and tetraisopropyl 1,1-difluoro-2-oxobutane-1,4-bisphosphonate: Jakeman, D. L.; Ivory, A. J.; Andrew; Williamson, M. P.; Blackburn, G. M. *J. Med. Chem.* **1998**, *41*, 4439–4452.
31. Such hydrostannylations can be brought about via a radical chain reaction, using Pd catalysis or introducing the Bu_3Sn group by mixed cyanocuprates: Barbero, A.; Pulido, F. J. *Chem. Soc. Rev.* **2005**, *34*, 913–920 and references cited therein.
32. Compound **24** had been prepared from (*S*)-**27**, PPh_3, and Zn by (a) Rossi, R.; Carpita, A.; Cossi, P. *Tetrahedron* **1992**, *48*, 8801–8824 (81% yield); (b) Tietze, L.-F.; Singidi, R. R.; Gericke, K. M.; Böckemeier, H.; Laatsch, H. *Eur. J. Org. Chem.* **2007**, 5875–5878 (79% yield); (c) Knott, K. E.; Auschill, S.; Jäger, A.; Knölker, H.-J. *Chem. Commun.* **2009**, 1467–1469 (77% yield).
33. Selected examples for *Z*-selective Stille-coupling reactions between *trans*-alkenyl stannanes and *gem*-dibromoolefins: (a) Xu, C.; Negishi, E.-i. *Tetrahedron Lett.* **1999**, 431–434; (b) Wong, L.; Shepburn, S. *Org. Lett.* **2003**, *5*, 3603–3606; (c) Langille, N. F.; Panek, J. S. *Org. Lett.* **2004**, *6*, 3203–3206; (d) Marjanovic, J.; Kozmin, S. A. *Angew. Chem.* **2007**, *119*, 9010–9013; *Angew. Chem., Int. Ed.* **2007**, *46*, 8854–8857.
34. The following precedence encouraged relying on this methodology (Zeng, X., Qian, M., Hu, Q., Negishi, E.-i. *Angew. Chem.* **2004**, *116*, 2309–2313; *Angew. Chem., Int. Ed.* **2004**, *43*, 2259–2263):



The essential for achieving stereoretention rather than stereoinversion (which had previously been observed!) was using $(t\text{-Bu})_3P$ or NHCs as ligands.

35. Aldol additions of the mono(lithium enolate) from 1,3-dioxolane-4,5-diesters: (a) Naef, R.; Seebach, D. *Angew. Chem* **1981**, *93* 1113–1113; *Angew. Chem., Int. Ed. Engl* **1981**, *20*, 1030–1031; (b) Evans, D. A.; Trotter, B. W.; Barrow, J. C. *Tetrahedron* **1997**, *53*, 8779–8794; aldol additions of the mono (lithium thioenolate) from 1,3-dioxolane-4,5-dithioesters: (c) Barros, M. T.; Maycock, C. D. :; Ventura, M. R. *Org. Lett.* **2003**, *5*, 4097–4099; (d) Nakamura, S.; Sato, H.; Hirata, Y.; Watanabe, N.; Hashimoto, S. *Tetrahedron* **2005**, *61*, 11078–11106; aldol additions of lithium enolates from 1,3-dioxolane-4-monoesters: (e) Ladner, W. *Angew. Chem* **1982**, *94*, 459–460; *Angew. Chem., Int. Ed. Engl* **1982**, *21*, 449–450; (f) Timmer, M. S. M.; Stocker, B. L.; Seeberger, P. H. *J. Org. Chem.* **2006**, *71*, 8294–8297; (g) Mukaiyama aldol additions of the mono(silylketene-O, O-acetal) from a 1,3-dioxolane-4,5-diester: Ref. b; (h) Mukaiyama aldol additions of silylketene-O, S-acetal from a 5-substituted 1,3-dioxolane-4-thioester: Ref. d.
36. On the one hand the lithium enolate **60** of lactone **18** fragmented by an $E1_{cb}$ elimination, which released acetone. This was evidenced by isolating the aldol addition product **62** (pure diastereomer, configurational assignment tentative) of residual lithium enolate **60** to this acetone (and by isolating L-menthol, a plausible follow-up product of the acetone-releasing fragmentation; (lower right corner). Moreover we isolated the acylation (=dimerization) product **64** of lithium enolate **60** and lactone **18**, which served as its progenitor; **64** was identified by an X-ray monocrystal structural analysis.[37,46] The formation of aldol adduct **62** meant that we should have scavenged the enolate **60** as aldol addition products **17a**,**b** by adding acetaldehyde *earlier*. However, the formation of acylation product **64** implied that we should have *continued waiting* before adding acetaldehyde because the deprotonation of the substrate had not yet gone to completion. These requirements were irreconcilable.

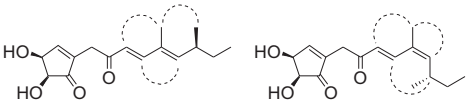


Reagents and conditions: a) LDA (1.0 equiv.), THF, −50 °C, 45 min; 15% **62** separated from 15% **64** and from an unquantified amount of L-menthol.

37. This was proven by an X-ray diffraction analysis of a single crystal of the respective compound **64** (Fig. 6).
38. Related lactone dimerizations were described by Csuk, R.; Schaade, M.; Schmidt, A. *Tetrahedron* **1994**, *50*, 11885–11892.
39. (a) Kuramochi, K.; Itaya, H.; Nagata, S.; Takao, K.-i.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 7367–7370; (b) Kuramochi, K.; Nagata, S.; Itaya, H.; Matsubara, Y.; Sunoki, T.; Uchiro, H.; Takao, K.-i.; Kobayashi, S. *Tetrahedron* **2003**, *59*, 9743–9758.
40. The C^2- and C^α silylation, respectively, of ester enolates including butyrolactone enolate was first described by Larson, G. L.; Fuentes, L. M. *J. Am. Chem. Soc.* **1981**, *103*, 2418–2419.
41. The C^2-trimethylsilylation of diethyl *trans*-2,3-epoxysuccinate and subsequent ammonium enolate formations therefrom were first described by Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1990**, *55*, 4835–4840.
42. Similarly, the dimerization the mono(lithium enolate) of a γ-substituted α,β-[*N*-(3,4-dimethoxylbenzyl)aziridino]-γ-lactone by acylation through its not yet deprotonated precursor was observed in 35% yield (Valle, M. S., Tarrade-Matha, A., Dauban, P., Dodd, R. H. *Tetrahedron* **2008**, *64*, 419–432). Nevertheless carbonyl compounds could be aldol-added in 15–66% yield. Alternatively, the identical aldol adducts were obtained – yet in slightly lower yields – after (1) the respective α,β-[N-(3,4-dimethoxylbenzyl)aziridino]-γ-lactone was *C*-, i.e., α-trimethylsilylated with a mixture of LDA and Me_3SiCl and after (2) the resulting lactones were combined with carbonyl compounds in the presence of $Bu_4N^{\oplus}$ $SiPh_3F_2^{\ominus}$
43. (a) First description of the generation of ammonium enolates from silyl enol ethers and ammonium fluorides: Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 1025–1030. This publication emphasized the advantage of employing benzyltrimethylammonium fluoride rather than, e. g., tetrabutylammonium fluoride (b) First description of aldol additions of ammonium enolates generated from silyl enol ethers and ammonium fluorides: Nakamura, E.; Shimizu, M.; Kuwajima, I.; Sakata, J.; Yokoyama, K.; Noyori, R. *J. Org. Chem.* **1983**, *48*, 932–945; (c) First description of aldol additions of ammonium enolates generated from [α-(trimethylsilyl)cyclopropyl]ketones or -esters and ammonium fluorides: Paquette, L. A.; Blankenship, C.; Wells, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 6442–6443.
44. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
45. This would have allowed to carry on the preceding aldol addition product as a mixture of diastereomers **17a/b**. We did not check this possibility in the present investigation, though.
46. CCDC 932028 (**17b**) and CCDC 932027(**64**) contain the crystallographic data for this paper. These data can be obtained free of charge from the

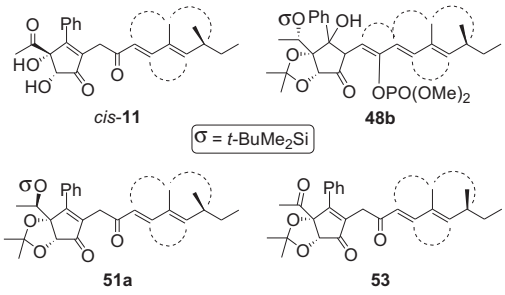
Cambridge Crystallographic Data Centre via the link www.ccdc.cam.ac.uk/data_request/cif.

47. Related hemiketal/acetals were reported inter alia by: (a) Mulzer, J.; Riether, D. *Tetrahedron Lett.* **1999**, *40*, 6197–6200; (b) Tanaka, K.; Pimentel, M.; Berova, N.; Nakanishi, K. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1843–1850.
48. This reagent had been described for effecting the 1,4-addition of phosphite **39** to (phthalimidoylmethyl)vinylketone: Perumal, S. K.; Pratt, R. F. *J. Org. Chem.* **2006**, *71*, 4778–4785.
49. The preparation of imine **35** from propionaldehyde was described by De Kimpe, N.; De Smaele, D.; Hofkens, A.; Dejaegher, Y.; Kesteleyn, B. *Tetrahedron* **1997**, *53*, 10803–10816 in 96% yield.
50. Condensation of imine **35** with *rac*-**27** under the same conditions allowed Moore, M. C.; Cox, R. J.; Duffin, G. R.; O'Hagan, D. *Tetrahedron* **1998**, *54*, 9195–9206 to isolate enal *rac*-26 "crude" in 95% yield.
51. The *trans*-configuration of the disubstituted C=C bond of the kodaistatin models *iso*-*cis*-**12** and *dia*-*iso*-*cis*-**12** and their precursors *trans*,*E*- and *trans*,*Z*-**22**, **38**, and *trans*,*E*- and *trans*,*Z*-**46** followed from the magnitude of the respective $J_{H-C=C-H}$ values. The latter were 15.8 Hz, 15.7 Hz, 15.8 Hz (both isomers), 15.8 Hz, and 15.9 Hz (both isomers), respectively. The configuration of the respective methylated C=C bond was proved in the kodaistatin models *iso*-*cis*-**12** and *dia*-*iso*-*cis*-**12** by the following ROESY crosspeaks:



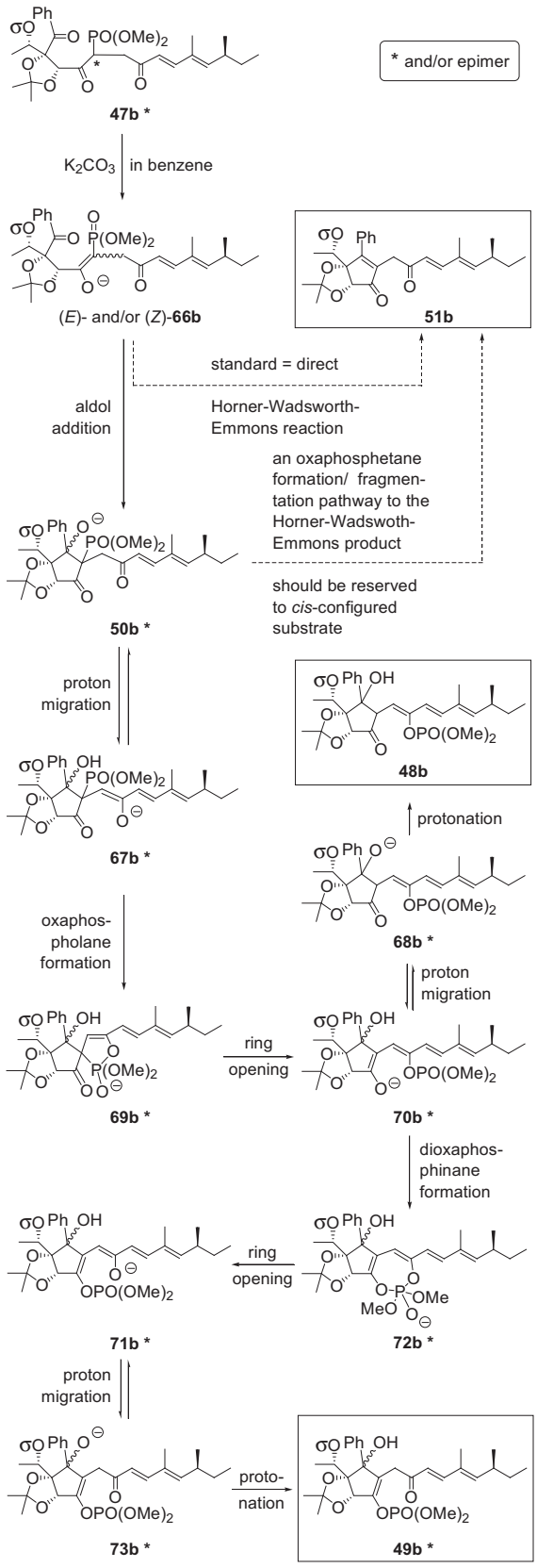
iso-*cis*-**12** *dia*-*iso*-*cis*-**12**

52. Method: Watson, D. R. M.; Waugh, F. *J. Organomet. Chem.* **1972**, *37*, 45–56.
53. Conditions: Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857–1867.
54. The *trans*-configuration of the disubstituted C=C bond of the kodaistatin model *cis*-**11** and its precursors **44**, **45**, **19**, **48b** (lies off-route), **49a**, **49b**, **51a**, **52a**, **52b**, and **53** followed from the magnitude of the respective $J_{H-C=C-H}$ values. The latter were 16.0 Hz, 19.6 Hz, 14.9 Hz, 15.9 Hz, 15.6 Hz, 15.8 Hz, 15.8 Hz, 15.5 Hz, 15.8 Hz, 15.9 Hz, and 15.4 Hz, respectively. The (*E*)-configuration of the methylated C=C bond was proved in the kodaistatin model *cis*-**11** and in **48b** (lies off-route), **51a**, and **53** by the following NOESY or ROESY correlations:



cis-**11** **48b** **51a** **53**

55. The attempted stannylcupration of pentynyl phosphonate **23** adopting a procedure from Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768–7780 failed; an unidentified mixture instead of the 1-(tributylstannyl)alkene **44** was obtained.
56. Effecting this separation could be avoided since it turned out that using the mixture of **44**/*iso*-**44** in the Stille coupling with dibromoalkene **24** a kinetic resolution took place: **44** coupled while *iso*-**44** proved inert. The latter was easily separable from the resulting **45**/*iso*-**44** mixture by flash chromatography.[44]
57. The isomeric purity of bromodecadienyl phosphonate **45** with respect to the newly formed C=C bond was assessed as the integral ratio of the singlets of 4-$H_{trans,E\text{-}45}$ (δ=5.99 ppm) and 4-$H_{trans,Z\text{-}45}$ (δ=6.14 ppm; this resonance was barely visible) in the ^{1}H NMR spectrum (400.1 MHz, C_6D_6).
58. In going from **45** to **19** the Cahn–Ingold–Prelog descriptor for the configuration of the trisubstituted C=C bond changes from *Z* to *E* although the stereostructure does not change.
59. Method: Devos, A.; Remion, J.; Frisque-Hesbain, A.-M.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* **1979**, 1180–1181.
60. The formation of these compounds was inferred from the synthetic context but not corroborated spectroscopically.
61. Pathways from the deprotonated Horner–Wadsworth–Emmons reagent **47** not just to the desired olefination product, i.e., to the cyclopentenone **51** (if at all) but competitively (if not exclusively) to the enol phosphates **48** and **49** are rationalized in the ensuing Scheme. Side-chain configurations are exemplified for the **b** series but the transformations of the epimeric Horner–Wadsworth–Emmons reagent **47a** abide to an analogous mechanistic analysis. While plausible in principle, the steps as shown do not allow to understand why we did not find **48a** but **48b** or obtained **51a** as opposed to not obtaining **51b**. A 1,4 *C*→*O* migration of a dimethylphosphoryl group—i.e., a step akin to **67b**→**68b**—was involved in an enol phosphate formation described by Moradei, O. M., du Mortier, C. M., Fernàndez Cirelli, A. *Tetrahedron* **1997**, *53*, 7397–7402 and by Moradei, O. M., du Mortier, C. M., Fernàndez Cirelli, A. *J. Carbohydr. Chem.* **1999**, *18*, 709–719.



62. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.
63. Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 3543–3544.
64. This calibration is listed by Gottlieb, H. E., Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512–7515 as 'solvent residual peak' [for δ(^{1}H)] or as 'solvent signal' [for δ(^{13}C)], respectively.

65. If the polarity of the eluent was increased incrementally (pure *c*-C_6H_{12} → *c*-C_6H_{12}/acetone 15:1 → 10:1 → 5:1) the terminal stannane **44** could be enriched in the later fractions until pure; *iso*-**44** preceded **44** but was not isolated as a pure compound.

66. Exceptionally, this experiment started from the pure stannane **44**. Normally we employed **44**/*iso*-**44** mixtures. This particular experiment is described in the Experimental Section because it was run at a larger scale than the Stille couplings performed with the mixtures.