An Improved Biomimetic Formal Synthesis of Abyssomicin C and *atrop*-Abyssomicin C.

Veroniki P. Vidali,*[a] Aleksander Canko, [a][b] Angelos D. Peroulias,[c] Evangelos T. Georgas,[a][d] Emmanuel Bouzas,[b] Julie M. Herniman[c] and Elias A. Couladouros[b]

Abstract: Biomimetic approaches towards the synthesis of abysssomicin C and *atrop*-abyssomicin C are based on a powerful intramolecular Diels–Alder reaction (IMDA) of a butenolide derivative attached to a keto-triene side chain, where the stereogenic centers and the carbon framework are established in one step. The synthesis of the IMDA precursor is based on an ionic coupling of methyl γ-methylene-β-tetronate with various aldehydes. However, the low yields of the coupling and the high sensitivity of the precursor hampered the efficiency of the developed routes and should be met. In the present work, a modified aldehyde is coupled with methyl γ-methylene-β-tetronate, in a substantially higher yield. Asymmetric synthesis of this aldehyde is based on the use of the widely available and cheap Amano lipase AK. In addition, the development of a highly convenient one-pot oxidation-IMDA reaction protocol obviates the isolation of the sensitive IMDA-precursor and augments the yield towards the carbocyclic skeleton of abysssomicin C and *atrop*-abyssomicin C.

Introduction

Class I spirotetronate polyketides (Figure 1) constitute an interesting class of natural products with fascinating structures and interesting biological activities.[1]

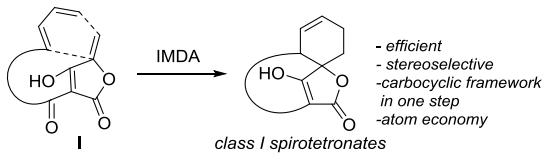
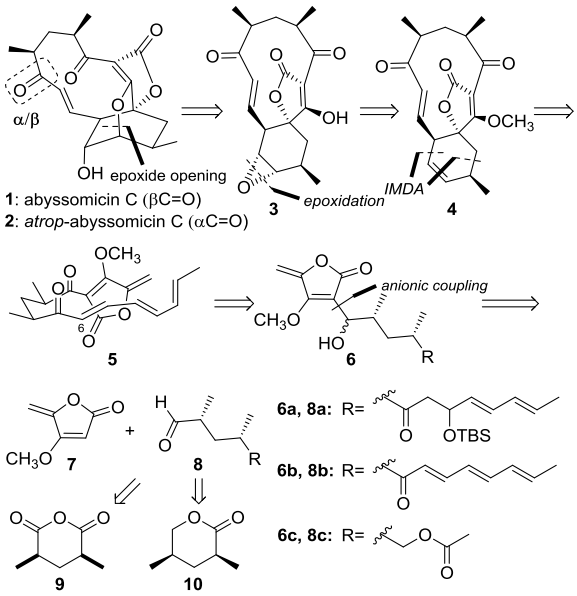


Figure 1. IMDA-reaction to class I spirotetronate polyketides.

Biosynthetically they derive from properly substituted derivatives of tetronic acid (**I**) via a stereoselective intramolecular Diels—Alder (IMDA) reaction, which establishes all stereogenic centers and the carbon framework of these molecules in one step. Consequently, this impressive and atom-efficient transformation has been utilized in many powerful bioinspired synthetic approaches.[1]

A representative sub-class of class I spirotetronates are naturally occurring abyssomicins. Among them, abyssomicin C (**1**) and its α-atropisomer (**2**) were the first members that caught-the-eye of the scientific community (Scheme 1).[2],[3] Their activity against methicillin-resistant *Staphylococcus aureus* mycobacteria and other Gram-positive bacteria, as well as their involvement in the inhibition of *p*-aminobenzoic acid (*p*-ABA) biosynthesis, brought the abyssomicin pharmacophore to the attention of researchers for the development of novel antifolates.[3] Many top researchers have developed impressive pathways to the abyssomicin scaffold and they reported syntheses of **1** and **2,** along with the hemisynthesis of other natural abyssomicins and analogs, pointing out the need for the development of efficient synthetic routes to these molecules.[1],[3-6]



[a] Dr. V. P. Vidali, A. Canko, E. T. Georgas
Institute of Nanoscience & Nanotechnology, NCSR "Demokritos" Patr. Grigoriou & Neapoleos 25, Athens 153 41, Greece
E-mail:v.vidali@inn.demokritos.gr, https://inn.demokritos.gr
[b] A. Canko, Dr. E. Bouzas, Prof. Dr. E. A. Couladouros
Department of Food Science and Human Nutrition, Agricultural University of Athens, Iera Odos 75, http://fst.aua.gr/en, Athens, Greece.
[c] A. D. Peroulias, Dr. J. M. Herniman
University of Southampton, School of Chemistry, United Kingdom, Southampton SO17 1BJ, UK . https://www.southampton.ac.uk/
[d] E. T. Georgas
Department of Chemistry, University of Athens, Panepistimioupolis, Zografou, Athens, Greece.
Supporting information for this article is given via a link at the end of the document

Scheme 1. Biomimetic approaches to abyssomicin C (**1**) and *atrop*-abyssomicin C (**2**).

Among them, biomimetic approaches to **1** and **2** featuring an efficient and stereoselective IMDA reaction of diketone **5** for the construction of key-intermediate **4**, are the most straightforward (Scheme 1). Sorensen et al. first developed a bioinspired total synthesis of abyssomicin C (**1**)[4a] and *atrop*-abyssomicin C (**2**) initially named *iso*-abyssomicin.[7] In his work, completion of synthesis from **4** was accomplished in three high-yielding steps, which involved an efficient stereoselective epoxidation, a demethylation, and an epoxide opening. Synthesis of the IMDA-precursor **5** was accomplished by condensation of the α-lithio salt of *γ*-methylene-*β*-tetronate **7** with the aldehyde **8a**, followed by an efficient oxidation-elimination reaction sequence to introduce the keto-triene side chain. Concurrent with Sorensen's synthesis, Snider & Zou[6a] and, shortly after, Couladouros' group[6b] developed efficient routes to **5** and **4** utilizing the condensation of **7** with aldehydes **8b** and **8c**, respectively. However, a number of issues arose in all methods.

Table 1. Previous approaches to aldehydes **8a-c** and the IMDA-adduct **4**.

Entry	Aldehyde	**8a**-**c** (%)	Coupling of **8a**-**c** with **7** (%)[c]	**6a**-**c** to **4** (%)[d]	Overall yield to **4** (%)[e]
1	**8a**	21[a]	35–55	58–65	3.5–5.6
2	**8b**	54[b]	30	59	9.5
3	**8c**	55[a]	45–58	27	6.5–8.5

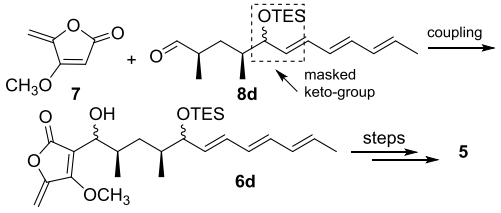
[a] Yields of **8a** and **8c**, prepaped from meso-anhydride **9**. [b] Yield of **8b** starting from asymmetric lactone **10**. [c] Coupling yield of aldehydes **8a**-**c** with the lithium salt of tetronate derivative **7**. [d] Yield from **6a**-**c** to **4**. [e] Overall yield to the IMDA-product **4** from the starting material **9** or **10**.

In particular, although aldehyde **8a** was prepared from anhydride **9** in 9 high-yielding steps (Table 1, entry 1), wide ranges and low to moderate yields of its coupling with **7** were major drawbacks, resulting in significant deterioration of the overall yield to **4** and consequently to **1** (15 steps, 0.9-1.7%).[4a] Coupling yield with **7** was even lower in the case of aldehyde **8b**, prepared from lactone **10** in 4 high-yielding steps (entry 2).[6a] In a different approach to **4**, aldehyde **8c** was coupled with **7** and introduction of the keto-triene side-chain was performed at a later stage, exploiting a Kishi reaction for the construction of **5**. However, both key-steps were characterized by low to moderate yields lowering the efficiency of the route to **4** (entry 3).[6b] Sensitivity of diketone **5**, which required special handling during isolation and purification, was an additional obstacle to its large-scale preparation. This motivated Sorensen et al. to develop an alternative sequence of *in-situ* formation and direct subjection of **5** to an IMDA-reaction.[4a] However, in the two formal syntheses that followed,[6] no attempts were reported towards this direction.

To address the above issues, herein we describe the use of a modified aldehyde which resulted in a high-yielding coupling with **7**. Moreover, completion of the sensitive diketone **5** synthesis, as well as its transformation to **4**, following a convenient one-pot oxidation-IMDA protocol, are presented in detail. Development of different synthetic approaches towards the aldehyde coupling-partner in racemic and homochiral form are also disclosed.

Results and Discussion

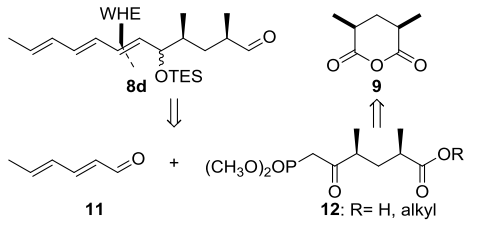
Aware of the aforementioned challenges of the biomimetic route, we first focused on the key-coupling step of aldehydes **8a-c** with tetronate **7**. We thought that low and wide ranges of the yields could be attributed to the presence of more than one carbonyl groups in the aldehyde coupling partners **8a-c**, as well as to the sensitivity of the products in the reaction conditions. Indeed, there are several reported examples of high-yielding anionic coupling reactions of tetronate derivative **7** with various aldehydes, even in cases of high sterical hindrance.[8] In contradiction to **8a-c**, these aldehydes lacked additional carbonyl groups. Accordingly, we designed the modified triene-aldehyde **8d**, where the keto group is masked as a silyl-protected alcohol which will be unmasked after coupling with **7** to provide diketone **5** (Scheme 2).



Scheme 2. Approach to **5** using aldehyde **8d** as a coupling partner.

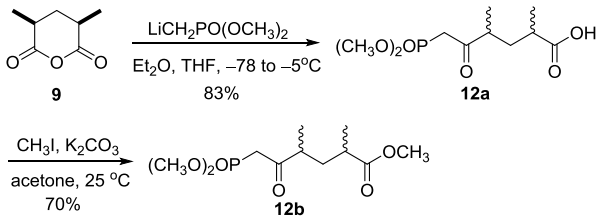
The synthesis of aldehyde **8d** relied on a Wadsworth-Horner-Emmons reaction (WHE) of (*E*,*E*)-2,4-hexadienal **11** with ketophosphonate **12**[6a] for the introduction of the triene moiety

(Scheme 3). The known anhydride **9**,[6b] easily prepared in gram scale, was chosen as the common starting material for the racemic and the asymmetric synthesis of ketophosphonate **12.**



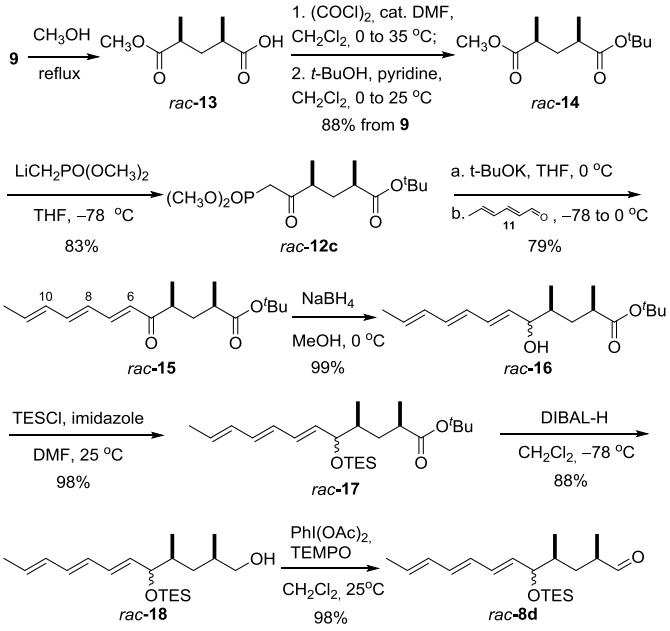
Scheme 3. Retrosynthetic plan to the targeted aldehyde **8d**.

Aiming to develop a short racemic synthesis, initial synthetic efforts were based on the direct opening of anhydride **9** with $LiCH_2PO(OCH_3)_2$ (Scheme 4). Although, this reaction would ensure a short route to the racemic form of ketophosphonate **12**, epimerization of the methyl groups observed under these conditions, led to an inseparable mixture of **12a** isomers. Their separation was not possible even after esterification to **12b**.



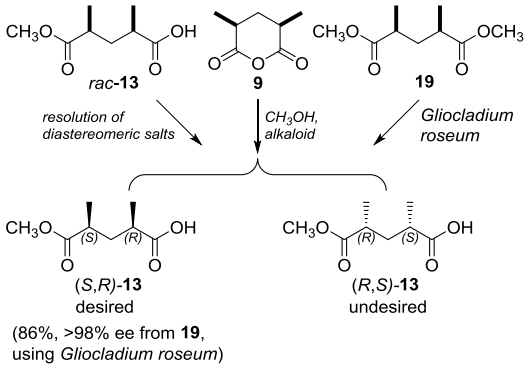
Scheme 4. Opening of **9** with $LiCH_2PO(OCH_3)_2$.

Hence, an alternative route was pursued, where *rac*-**13**, prepared by methanolysis of **9**, was esterified with *tert*-BuOH to afford diester *rac*-**14** in 88% overall yield (Scheme 5). Selective attack of $LiCH_2PO(OCH_3)_2$ on the methyl ester group of *rac*-**14**led to pure ketophosphonate *rac*-**12c** in 83% yield while no epimerization was observed. Introduction of the triene moiety to *rac*-**12c** was achieved *via* a WHE coupling utilizing 2,4-hexadienal **11**. A pure *E*-geometry at the C-6 double bond of rac-**15** was established while a 4.5:1 mixture of *E*- and *Z*-isomers at the terminal C-10 double bond was formed.[9] The ketone moiety of the derived *rac*-**15** was "masked" by conversion to alcohol *rac*-**16** and subsequent silylation to furnish *rac*-**17**. The latter was subjected to a reduction-oxidation reaction sequence to afford the targeted aldehyde *rac*-**8d** in 48% total yield from **9** (9 steps).



Scheme 5. Synthetic route to the *rac*-**8d**.

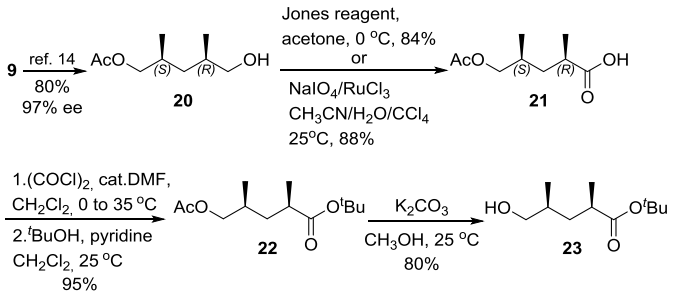
Following the above sequence, asymmetric synthesis of **8d** could be achieved employing the optically active ester (*S*,*R*)-**13** (Scheme 6). Preparation of the latter has been achieved via short routes from either **9** via enantioselective methanolysis using alkaloids[10] or from *rac*-**13** by separation of diastereomeric salts of the desired and the undesired antipode with an asymmetric amine.[11] These approaches, however, resulted in either moderate ee's or required tedious purification procedures which led to low yields.



Scheme 6. Approaches to (*S*,*R*)-**13**.

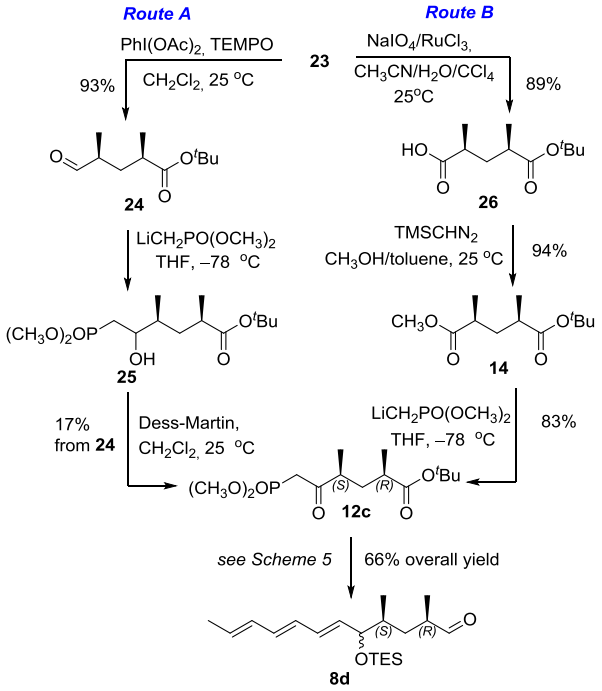
Conversely, asymmetric hydrolysis of diester **19** to the desired (*S*,*R*)-**13** has been successfully achieved in 86% yield and >98% ee, using microorganism *Gliocladium roseum*.[12] Obviously, this method would greatly facilitate our work resulting in a short asymmetric route to (*S*,*R*)-**13**, and consequently to aldehyde **8d** in 9 steps and ~42% overall yield from **19**. Nonetheless, the narrow availability of this organism and its special handling required prompted us to search for an alternative method.[13]

To this end, reduction of **9** and acetylation of the corresponding diol with vinyl-acetate and Amano-lipase AK, provided **20** in 80% overall yield and 97% ee (Scheme 7).[14]



Scheme 7. Synthesis of alcohol **23**.

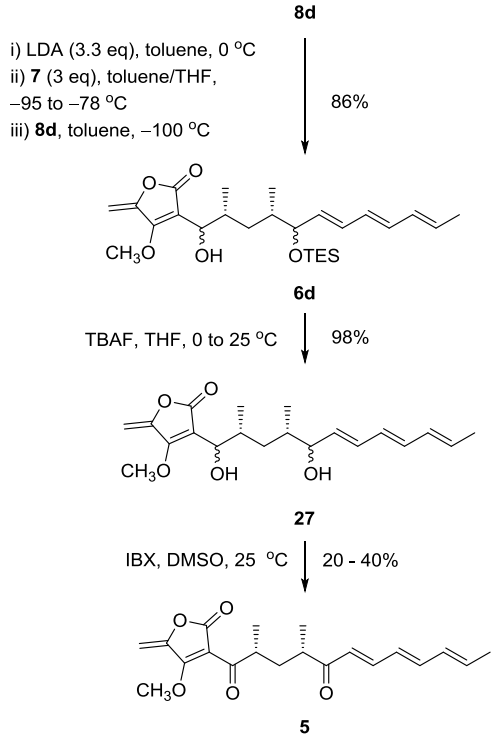
The wide availability and the low cost of Amano-lipase AK, as well as the simplicity of the method, allowed the multi-gram synthesis of **20**. Thus, applying a different approach towards the designed alcohol **8d**, oxidation of **20** to acid **21**, by using Jones reagent (84% yield) or $RuCl_3/NaIO_4$ (88% yield), followed by esterification of the latter with *tert*-BuOH (95% yield) and deacetylation of the resulting diester **22** (80% yield) provided alcohol **23** in 54% overall yield from **9**. Oxidation of **23** to the aldehyde **24** followed by addition of $LiCH_2OP(OCH_3)_2$ and oxidation of the secondary alcohol **25** led to the homochiral ketophosphonate **12c** (Scheme 8, route A). This route, however, was characterized by very low overall yield and laborious purification procedures. Consequently, we switched back to the racemic approach by applying oxidation of **23** with $RuCl_4/NaIO_4$ and subsequent methylation to secure homochiral **14** in 84% overall yield (Scheme 8, route B). Hence, the asymmetric synthesis of **8d** was completed in 25% overall yield from **9** (14 steps) following the chemistry described in Scheme 5. The asymmetric route from **9** to **14**, employing **20** as source of chirality, albeit obviously longer than the approach based on the use of (*S*,*R*)-**13** described above, was facile enough to allow a fast synthesis of key intermediate **14**, in large quantities, following simple reaction steps.



Scheme 8. Approaches to ketophosphonate **12c** and completion of the asymmetric synthesis of aldehyde **8d**.

Hence, having completed the asymmetric synthesis of **8d** we proceeded to its crucial coupling reaction with an excess of the α-lithio salt of **7** to ensure high yields and minimization of

unwanted side products (Scheme 9). Indeed, the best coupling conditions involved a three-fold excess of **7** in THF/toluene and using LDA as a base, resulting in **6d** in 86% yield, which was substantially higher than what it has been achieved with aldehydes **8a-c.** Lower **7**/**8d** ratios led to deteriorated yields, while the combination of THF/toluene was crucial for the reaction outcome. Alcohol **6d** was then subjected to desilylation to afford diol **27,** almost quantitatively. To avoid repeated purification procedures, excess of **7** was removed in this step. Thus, synthesis of diketone **5** could be completed by oxidation of **27** with IBX in DMSO, based on a previously described method.[6b]

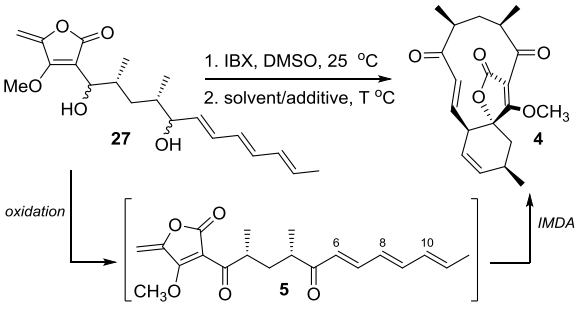


Scheme 9. Coupling of **8d** with **7** and synthesis of diketone **5**.

However, the known instability of **5** during purification along with its substantial decomposition during concentration of the ethereal extracts of the reaction mixture resulted in variable and low to moderate yields (20-40%). Based on the observation that **5** remained stable in the ethereal extracts for longer times, we sought an alternative protocol for its direct subjection to IMDA reaction, omitting concentration and isolation (see Table 2).

At a first attempt, a number of IMDA conditions were applied on the ethereal extracts of **5** followed by selective removal of Et_2O (entries 1-4). This would ensure that **5** would not exist in high concentration solutions. Following this protocol, application of Snider and Zou's conditions for IMDA ($CHCl_3$/hydroquinone)[6a] led to a very slow and incomplete conversion of **5** to **4**, the latter being isolated in only 25% yield (from **27**) after 48 h, while longer reaction times resulted in the formation of more polar decomposed products (entry 1). 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) was also tested as an IMDA solvent (entry 2), as its low nucleophilicity and its ability to act as a hydrogen bond donor has been shown to accelerate Diels–Alder reactions at lower temperatures.[16] Indeed, **5** was almost completely consumed in 48 h at 45 °C, leading to **4** in substantially higher yield. Aiming at less time-consuming conditions, we turned to toluene as a solvent, used also by Sorensen's and Couladouros' groups.[4a,6b] Thus, heating of the ethereal extracts of **5** in toluene for 4.5 h at 100 °C resulted in **4**, albeit an incomplete conversion of **5** was observed (entry 3). Moreover, only more polar by-products were formed with longer heating times. The presence of a catalytic amount of I_2, under the same conditions, resulted in a more rapid and almost complete conversion of **5** → **4**, although the yield was not substantially improved (entry 4). The establishment of a pure *E*-geometry at C-6 of **27** via a WHE reaction indicates that, as it has been also described theoretically,[17],[18] I_2 might accelerate the IMDA, and its role is not restricted to the isomerization of the 6*Z*-double bond of the triene-side chain formed by previous methods.[4a,6b]

Table 2. Oxidation of **27** to **5** and its IMDA to **4**.



Entry	Solvent/ additive	T (°C)	Time (h)	Yield[c] (%)
1	$CHCl_3$/hydroquinone[a]	67	48	25 (30)

2	HFIP[a]	45	48	66 (79)
3	toluene[a]	100	4.5	30 (36)
4	toluene/I_2[a]	100	3	38 (46)
5	toluene[b]	90	1.5	46 (55)
6	HFIP [b]	45	36	71 (85)

[a] Solvent added to the ethereal extract of **5**. [b] Solvent of IMDA directly added to the oxidation reaction mixture. [c] Overall yield from **27**. Yields in parentheses are calculated based on the 6*E*,8*E*,10*E*-isomer in **27**.[9]

The above results provoked us to attempt a more daring protocol, following a one-pot procedure of oxidation-IMDA. In particular, toluene (entry 5) or HFIP (entry 6) were simply added to the reaction mixture of oxidation of **27**. To our delight**,** conversion of **5** to **4** was achieved in higher yield. Notably, this protocol resulted in shorter times of conversion, indicating that the iodosocarboxylic acid, formed during the oxidation of **27** with IBX/DMSO, plays a crucial role in accelerating the reaction, probably due to its acidic properties. This one-pot oxidation-IMDA protocol ensured no loss of the unstable diketone **5** during work-up and purification and it resulted in **4** in an experimentally more straightforward manner.

Conclusions

In conclusion, two major improvements in the route to key-intermediate **4**, required for the biomimetic synthesis of abyssomicin C (**1**) and *atrop*-abyssomicin C (**2**) resulted in its preparation in 14.8% overall yield from anhydride **9**. First, the utilization of the modified aldehyde **8d,** prepared in racemic and homochiral form, led to a high and repeatable yield (86%) of the key-coupling reaction with tetronate derivative **7**, improving significantly on the results obtained with aldehydes **8a-c**. Second, a convenient and viable one-pot oxidation-IMDA protocol for the conversion of diol **27** to key-intermediate **4** was developed. This protocol obviated the need for work-up or isolation of the sensitive intermediate diketone **5** and decreased significantly the reaction times of its cycloaddition. In the IMDA-reaction, better results were obtained when HFIP was used as solvent at 45 °C, but toluene at 90 °C resulted in sufficiently lower reaction times. Aldehyde **8d** was prepared from *meso*-2,6-dimethylglutaric anhydride **9** in 14 convenient and scalable steps. Efforts to lower the number of steps to **8d** are currently underway, while the results of this work will be considered in the development of biomimetic routes to analogs and other members of this remarkable family of compounds.

Experimental Section

General Remarks: All reactions were carried out under anhydrous conditions and an argon atmosphere using dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone, dichloromethane (DCM) from CaH_2, and toluene from sodium. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. All reagents were purchased at highest commercial quality from Sigma-Aldrich or Alfa-Aesar and used without further purification, unless otherwise stated. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60 F254), using UV light as visualizing agent and ethanolic phosphomolybdic acid, p-anisaldehyde or potassium permanganate solutions and heat as developing agents. Purifications with flash column chromatography were carried out by using Merck silica gel (60, particle size 0.040–0.063 mm) and elution systems as stated in each experimental procedure. NMR spectra were recorded on Bruker Avance DRX-500 or Bruker Advance II 250 MHz instruments. The following abbreviations were used to explain NMR signal multiplicities: brs : broad singlet, s: singlet, d: doublet, t: triplet, q: quartet, h: hexaplet, m: multiplet, dd: doublet of doublets, ddd: doublet of doublets of doublets, dt: doublet of triplets, dq: doublet of quartets. In cases of diasteroisomers, where doublets or triplets overlap, *J* is reported when it is possible to be measured. Assignment of ^{1}H NMR spectra is based on COSY experiments. Samples were dissolved in $CDCl_3$. Optical rotations were recorded on a Perkin–Elmer 241 polarimeter. High resolution mass spectra were recorded using positive/negative ion electrospray ionisation. Samples were infused via a syringe driver at a flow rate of 5 uL/minute and analysed using a solariX (Bruker Daltonics, Bremen, Germany) FT-ICR mass spectrometer equipped with a 4.7T superconducting magnet. LCMS spectra were recorded on a Shimadzu 2010 EUV LC-MS instrument.

The experimental procedures which refer to the compounds **12c** (from **14**), **15**, **16, 17**, **18** and **8d** are described only for the homochiral forms, since substrates and applied conditions are the same for the racemic and the corresponding asymmetric routes.

6-(dimethoxyphosphoryl)-2,4-dimethyl-5-oxohexanoic acid (12a): A solution of dimethyl methylphosphonate (8.7 g, 70 mmol) in dry Et_2O (220 mL) was cooled at −78 °C and *n*-BuLi (1.6 M solution in hexanes, 37.4 mL, 59.8 mmol) was added. The mixture was stirred at this temperature for 1h and a solution of anhydride **9** (5 g, 35.0 mmol) in dry THF (25 mL) was added. Stirring was continued for 1 h and then the reaction temperature was allowed to increase up to −5 °C. A solution of oxalic acid (3.2 g) in MeOH (16 mL) was added to the reaction mixture (pH 2-3) and stirring was continued for 30 min. The mixture was then filtered through celite and the filtrate was concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, $CHCl_3$/MeOH 98:2 - 9:1) to afford phosphonate acid **12**a (mixture of two inseparable diasteroisomers in a ratio ~4:1, 7.8 g, 83%) as a light yellow oil. R_f = 0.38 ($CHCl_3$/MeOH 9:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.03 (brs, 1H; -COO*H* of both isomers), 3.80 (d, $J_{P\text{-}H}$ = 11.3 Hz, 6H; (CH_3O)$_2$PO- of minor isomer), 3.79 (d, $J_{P\text{-}H}$ = 11.2 Hz, 6H; (CH_3O)PO- of major isomer), 3.33 - 3.14 (m, 2H; (MeO)$_2$PO-CH_2CO of both isomers), 2.90 (m, 1H; -C*H*(CH)$_3$CO of minor isomer), 2.82 (m, 1H; -C*H*(CH)$_3$CO of major isomer), 2.52 (m, 1H; -C*H*(CH)$_3$CO- of major isomer), 2.43 (m, 1H; -C*H*(CH)$_3$CO- of minor isomer), 2.16-2.06 (m, 1H; -CH_aH$_b$- of major isomer), 1.88-1.80 (m, 1H; -CH_aH$_b$- of minor isomer), 1.68-1.57 (m, 1H; -CH$_a$*H*$_b$- of minor isomer), 1.37-1.29 (m, 1H; -CH$_a$*H*$_b$- of major isomer), 1.21 (d, *J* = 7.0 Hz, 3H; -CH(C*H*$_3$)- of major isomer), 1.20 (d, *J* = 7.0 Hz, 3H; -CH(C*H*$_3$)- of minor isomer), 1.13 (d, *J* = 7.0 Hz, 3H; -CH(C*H*$_3$)- of major isomer), 1.11 (d, *J* = 7.0 Hz, 3H; -CH(C*H*$_3$)- of minor isomer) ppm**;** HRMS (ESI) *m/z*: [*M*-H]$^-$ calcd for $C_{10}H_{19}O_6P$ 265.0846; found: 265.0844.

Methyl 6-(dimethoxyphosphoryl)-2,4-dimethyl-5-oxohexanoate (**12b**): To a solution of **12a** (0.71 g, 2.65 mmol) in acetone (10 mL), dry K_2CO_3 (0.44 g, 3.18 mmol) was added under argon at 25 °C. After stirring for 30 min, CH_3I (0.8 mL, 13.3 mmol) was added and the mixture was further stirred until **12a** was fully consumed (reaction monitored by TLC). The reaction mixture was concentrated *in vacuo*, ethyl acetate was added and the mixture was filtered through celite. The filtrate was then concentrated in vacuo and subjected in flash column chromatography (SiO_2, $CHCl_3$/MeOH 98:2) to afford compound **12b** ((mixture of two inseparable diasteroisomers in a ratio ~4:1, 522 mg, 70%) as yellow oil. R_f = 0.23 ($CHCl_3$/MeOH 98:2); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.74-3.69 (two doublets overlapping, J_{PH}=11.1 Hz, 6H; C*H*$_3$O-PO of both isomers), 3.67 (s, 3H; COOC*H*$_3$ of major isomer), 3.66 (s, 3H; COOC*H*$_3$ of minor isomer), 3.13-3.09 (two doublets overlapping, 1H; (CH_3O)$_2$POCH_aH$_b$CO of both isomers), 3.08-3.05 (two doublets overlapping, 1H; (CH_3O)$_2$POCH$_a$*H*$_b$CO of both isomers), 2.78-2.64 (two multiplets overlapping, 1H; -C*H*(CH)$_3$CO of both isomers), 2.50-2.40 (m, 1H; -C*H*(CH)$_3$CO of major isomer), 2.40-2.32 (m, 1H; -C*H*(CH)$_3$CO of minor isomer), 2.06-1.99 (m, 1H; -CH_aH$_b$- of major isomer), 1.75-1.69 (m, 1H; -CH_aH$_b$- of minor isomer), 1.64-1.57 (m, 1H; -CH$_a$*H*$_b$- of minor isomer), 1.29-1.21 (m, 1H; -CH$_a$*H*$_b$- of major isomer), 1.11 (d, *J* = 7.0 Hz, 3H; CH_3 of major isomer), 1.08 (d, *J* = 7.0 Hz, 3H; CH_3 of minor isomer), 1.05 (d, *J* = 7.0 Hz, 3H; CH_3 of major isomer), 1.04 (d, *J* = 7.0 Hz, 3H; CH_3 of minor isomer) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) (peaks are given for both isomers): δ = 205.0 (d, $J_{C\text{-}P}$ = 6.5 Hz), 204.6 (d, $J_{C\text{-}P}$ = 6.5 Hz), 176.5, 176.3, 52.9, 52.8 52.7 51.5, 51.4, 45.0 (d, $J_{C\text{-}P}$ = 2 Hz), 44.9 (d, $J_{C\text{-}P}$ = 2 Hz), 40.3, 39.8, 39.3, 38.7, 37.1, 37.0, 36.1, 35.8, 17.6, 17.5, 16.6, 15.8 ppm; HRMS (ESI) *m/z*: [*M*+Na]$^+$ calcd for $C_{11}H_{21}O_6P$ 287.1019; found 287.1017.

1-(*tert*-butyl) 5-methyl (2*R,4*S**)-2,4-dimethylpentanedioate** (*rac*-**14**). *Rac*-**13** was prepared according to literature.[4a] Thus, a solution of anhydride **9** (538 mg, 3.78 mmol) was refluxed with MeOH (5 mL) for 12 h, under argon. Reaction was monitored by TLC. After complete consumption of **9**, the mixture was concentrated under reduced pressure and dried in high vacuum to afford the corresponding acid *rac*-**13** as light yellow oil, which was used in the next step without further purification. Thus, to a solution of *rac*-**13**, obtained as described above, in CH_2Cl_2 (5 mL) a catalytic amount of DMF (0.378 mmol, 0.029 mL), followed by oxalyl chloride (18.9 mmol, 1.6 mL) was added at 0 °C, under argon. The reaction mixture was allowed to warm at 25 °C for 2 h and at 35 °C for 1 h. The reaction mixture was cooled at 25 °C, concentrated in vacuo to remove excess of $(COCl)_2$ and dried in a vacuum pump. To the residue CH_2Cl_2 (1 mL) was added and the solution was cooled at 0 °C. A solution of *tert*-BuOH (7.56 mmol, 0.72 mL) and pyridine (7.56 mmol, 0.6 mL) in CH_2Cl_2 (1 mL) was added and the reaction mixture was stirred at 40 °C for 30 min and at 25 °C for 16 h. The reaction was quenched with H_2O (5 mL), EtOAc (10 mL) was added and after separation of the two phases, the organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to a short flash column chromatography (SiO_2, *n*-hexane/ethyl acetate 9:1) to afford diester *rac*-**14** (763 mg, 88 % from **9**) as light yellow oil. R_f = 0.55 (*n*-hexane/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.66 (s, 3H; C*H*$_3$O), 2.50 (m, 1H; -C*H*(CH_3)-), 2.37 (m, 1H; -C*H*(CH_3)-), 2.04 (dt, *J* = 13.6, 7.6 Hz, 1H; -CH_aH$_b$-), 1.47-1.38 (brs and m overlapping, 10H; -C(C*H*$_3$)$_3$, -CH$_a$*H*$_b$-), 1.17 (d, *J* = 6.8 Hz, 3H; -CH(C*H*$_3$)-), 1.12 (d, *J* = 6.4 Hz, 3H; -C*H*(C*H*$_3$)-) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$, 25 °C): δ = 176.7, 175.4, 80.1, 51.6, 38.1, 37.2, 37.1, 28.0, 17.3, 17.0 ppm; HRMS (ESI) *m/z*: [*M*+Na]$^+$ calcd for $C_{12}H_{22}O_4$ 253.1410; found 253.1410.

(2*R*,4*S*)-5-acetoxy-2,4-dimethylpentanoic acid (**21**): **Method A. Oxidation of 20 with Jones reagent:** To a solution of

alcohol **20** (710 mg, 4.07 mmol) (prepared from **9** according to literature[14]) in acetone (30 mL) a solution of a freshly prepared Jones reagent (4.5 mL, 10.2 mmol) was added at 0 °C. The reaction mixture was stirred at this temperature for 30 min. After complete consumption of alcohol **20** (reaction monitored by TLC), the reaction was quenched with *i*PrOH and filtered. The solid was washed with EtOAc and the combined filtrates were concentrated *in* vacuo almost to dryness. To the residue EtOAc (10 mL) and H_2O (5 mL) were added, the organic phase was separated, and the aqueous phase was washed with EtOAc (2 × 10 mL). The organic extracts were washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 9:1 to 7:3) to afford acid **20** as a yellow oil (652 mg, 85%). **Method B. Oxidation of 20 with $RuCl_3$/$NaIO_4$.** To a well stirred solution of **20** (1.0 g, 5.74 mmol) in a mixture of $CH_3CN/H_2O/CCl_4$ (1:1.5:1) (21 mL), $NaIO_4$ (3.7 g, 17.3 mmol) and $RuCl_3$ (60 mg, 0.289 mmol) were added at 25 °C. After 12 h of stirring, the reaction mixture was filtered through Celite. Celite was washed with EtOAc and the filtrate was washed with a saturated aqueous solution of NH_4Cl (20 mL). The organic phase was separated and the aqueous layers were washed with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude mixture was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 8:2 to 7:3) to afford **21** (951 mg, 88%) as yellow oil. R_f = 0.39 (*n*-hexane/EtOAc 6:4); $[\alpha]_D^{25}$ = –16.6 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 11.18 (brs, 1H; -COO*H*), 3.88 (dd, *J* = 6.0, 1.8 Hz, 2H; -C*H*$_2$OAc), 2.57 (m, 1H; -(CH_3)C*H*-), 2.04 (s, 3H; C*H*$_3$CO-), 1.91-1.77 (m, 2H; -C*H*$_2$-), 1.24 – 1.15 (d and m overlapping , *J* = 6.9 Hz, 4H; (CH_3)C*H*-, C*H*$_3$-), 0.95 (d, *J* = 6.5 Hz, 3H; C*H*$_3$-) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 182.8, 171.3, 69.1, 37.4, 37.0, 30.6, 20.8, 17.8, 16.7 ppm; HRMS (ESI) *m/z*: $[M\text{-H}]^-$ calcd for $C_9H_{16}O_4$ 187.0976; found: 187.0973.

***tert*-butyl (2*R*,4*S*)-5-acetoxy-2,4-dimethylpentanoate** (**22**): To a stirred solution of acid **21** (1.78 g, 9.45 mmol) in CH_2Cl_2 (14 mL), DMF (0.075 mL, 0.94 mmol) and $(COCl)_2$ (3.9 mL, 47.0 mmol) were added at 0 °C, under an argon atmosphere and the reaction was stirred for 2 h. The reaction mixture was concentrated *in vacuo* and dried in a high vacuum pump to remove excess of oxalyl chloride. To the crude chloride of **21**, a solution of pyridine (0.75 mL, 14.1 mmol) in CH_2Cl_2 (9 mL) and *t*-BuOH (2 mL) were added successively, at 25 °C under argon. After stirring for 12 h at this temperature, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and the mixture was extracted with EtOAc (3 × 40 mL). The combined organic phases were washed with H_2O and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to provide pure *tert*-butyl ester **22** (2.2 g, 95%) as light yellow oil, which was used in the next step without further purification. R_f = 0.69 (*n*-hexane/EtOAc 7:3); $[\alpha]_D^{25}$ = –16.8 (*c* = 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.82 (m, 2H; AcOC*H*$_2$-), 2.38 (m, 1H; (CH_3)C*H*-), 1.99 (s, 3H; C*H*$_3$COOCH_2-), 1.83 – 1.64 (m, 2H; -(CH_3)CH-C*H*$_2$-(CH_3)CH-), 1.38 (s, 9H; -C(C*H*$_3$)$_3$), 1.06 (m, d overlapping, *J* = 6.0 Hz, 4H; -(CH_3)C*H*-, -(C*H*$_3$)CH-, 0.89 (d, *J* = 5.7 Hz, 3H; -(C*H*$_3$)CH-) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 175.7, 170.9, 79.8, 69.1, 38.0, 37.7, 30.6, 27.9, 20.8, 18.0, 16.5 ppm; HRMS (ESI) *m/z*: $[M\text{+Na}]^+$ calcd for $C_{13}H_{24}O_4$ 267.1567; found 267.1566.

***tert*-butyl (2*R*,4*S*)-5-hydroxy-2,4-dimethylpentanoate** (**23**): To a stirred solution of **22** (2.2 g, 9.00 mmol) in MeOH (31 mL), dry K_2CO_3 (1.24 g, 9.00 mmol) was added at 0 °C, under an argon atmosphere and the reaction mixture was stirred for 2 h. The reaction was quenched with H_2O and then it was extracted with Et_2O (20 mL) and EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by short flash column chromatography (SiO_2, *n*-hexane/EtOAc 9:1: to 8.2) to afford **23** (1.46 g, 80%) as colorless oil. R_f = 0.49 (*n*-hexane/EtOAc 7:3); $[\alpha]_D^{25}$ = –23.3 (*c* = 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.48-3.38 (m, 2H; -C*H*$_2$OH), 2.42 (m, 1H; -C*H*(CH_3)COO^{t}Bu), 1.78 (m, 1H; -C*H*$_a$H$_b$-), 1.70 (brs, 1H; -O*H*), 1.62 (m, 1H; -C*H*(CH_3)-), 1.44 (s, 9H; -C(C*H*$_3$)$_3$), 1.13 (d, *J* = 7.1 Hz, 3H; -CH(C*H*$_3$)-), 1.09 (m, 1H; -CH$_a$*H*$_b$-), 0.95 (d, *J* = 6.7 Hz; -CH(C*H*$_3$)-) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 176.5, 80.0, 67.6, 38.2, 37.4, 33.9, 27.9, 18.3, 16.6 ppm; HRMS (ESI) *m/z*: $[M\text{+Na}]^+$ calcd for $C_{11}H_{22}O_3$ 225.1461; found 225.1464.

2*S*,4*R*)-5-(*tert*-butoxy)-2,4-dimethyl-5-oxopentanoic acid (**26**): To a well-stirred solution of alcohol **23** (590 mg, 2.92 mmol) in a biphasic mixture of $CH_3CN/H_2O/CCl_4$ (1:1.5:1) (21 mL), $NaIO_4$ (1.87 g, 8.76 mmol) and $RuCl_3$ (30 mg, 0.145 mmol) were added at 25 °C. After 12 h of stirring the reaction mixture was filtered through Celite. Celite was washed with EtOAc (10 mL) and the filtrate was washed with a saturated aqueous solution of NH_4Cl (10 mL). The organic phase was separated and the aqueous layers were washed with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude mixture was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 8:2) to afford acid **26** as a pale yellow oil (562 mg, 89%). R_f = 0.48 (*n*-hexane/EtOAc 6:4); $[\alpha]_D^{25}$ = –24.2 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 2.52 (m, 1H; -C*H*(CH_3)-), 2.42 (m, 1H; -C*H*(CH_3)-), 2.07 (ddd, *J* = 14.8, 7.7, 7.7 Hz; -C*H*$_a$H$_b$-), 1.46 - 1.40 (brs and m overlapping, 10H; -C(C*H*$_3$)$_3$, -CH$_a$*H*$_b$-), 1.20 (d, *J* = 6.2 Hz, 3H; C*H*$_3$), 1.13 (d, *J* = 7.0 Hz, 3H;

CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 182.5, 175.5, 80.3, 38.2, 37.2, 36.9, 28.0, 17.4, 16.8 ppm; HRMS (ESI) *m/z*: [*M*-H]$^-$ calcd for $C_{11}H_{20}O_4$ 215.1289; found: 215.1285.

1-(*tert*-butyl) 5-methyl (2*R*,4*S*)-2,4-dimethylpentanedioate (**14**).$TMSCHN_2$ (2 M solution in hexanes, 3.9 mL, 7.74 mmol) was added dropwise to a stirred solution of acid **26** (1.12 g, 5.17 mmol) in a mixture of MeOH/toluene 1:1.5 (40 mL) at 25 °C under argon. After 3 h of stirring the reaction mixture was concentrated under vacuum and purified by flash column chromatography (SiO_2, *n*-hexane/EtOAc 9:1) to afford diester **14** (1.12 g, 94%) as a yellow oil. $[\alpha]_D^{25}$ = +2.0 (*c* = 3.0, $CHCl_3$); ^{1}H, ^{13}C NMR and HRMS data were identical to those reported above for *rac*-**14**.

***tert*-butyl (2*R*,4*S*)-2,4-dimethyl-5-oxopentanoate** (**24**): **Method A. With sulfur trioxide pyridine complex.** To a solution of alcohol **23** (218 mg, 1.08 mmol) in CH_2Cl_2 (2 mL), DMSO (1 mL, 14.1 mmol) and Et_3N (1 mL, 7.17 mmol) were added successively, at 0 °C, under argon. To the reaction mixture sulfur trioxide pyridine complex (554 mg, 3.48 mmol) was added portionwise and stirring was continued for 30 min. The reaction was quenched with a saturated aqueous NH_4Cl solution (5 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was dried in a high vacuum pump to afford aldehyde **24**, which was used directly in the next step without further purification. **Method B. With PhI(OAc)$_2$/TEMPO.** To a solution of alcohol **23** (100 mg, 0.494 mmol) in dry CH_2Cl_2 (1.3 mL), a mixture of $PhI(OAc)_2$ (264 mg, 0.820 mmol) and TEMPO (4 mg, 0.025 mmol) was added portionwise during 40 min, at 25 °C. The reaction was stirred for 2 h, where TLC monitoring showed complete consumption of **23**. The reaction was quenched with a saturated aqueous solution of sodium thiosulfate (1 mL) and the mixture was stirred for 15 min. The mixture was then extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed sequentially with a saturated aqueous solution of $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 9:1) to afford aldehyde **24** (93 mg, 94%) as yellow oil. R_f = 0.8 (*n*-hexane/EtOAc 7:3); $[\alpha]_D^{25}$ = −7.0 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 9.60 (d, *J* = 1.8 Hz, 1H; -C*H*=O), 2.47 – 2.35 (m, 2H; -C*H*(CH_3)), 2.11 (ddd, *J* = 13.9, 9.2, 6.1 Hz, 1H; -CH_aH$_b$-), 1.43 (s, 9H; -C(CH_3)$_3$), 1.31 (ddd, *J* = 13.9, 8.0, 5.5 Hz, 1H; -CH$_a$*H$_b$*-), 1.15 (d, *J* = 7.0 Hz, 3H; -CH(CH_3)-), 1.11 (d, *J* = 6.9 Hz, 3H; -CH(CH_3)-) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 204.2, 175.3, 80.4, 44.5, 38.0, 34.2, 28.0, 17.9, 13.4 ppm; HRMS (ESI) *m/z*: [*M*+Na]$^+$ calcd for $C_{11}H_{20}O_3$ 223.1305 ; found 223.1309.

***tert*-butyl (2*R*,4*S*)-6-(dimethoxyphosphoryl)-2,4-dimethyl-5-oxohexanoate** (**12c**): **Route A. From aldehyde 24.** To a solution of $CH_3PO(OCH_3)_2$ (0.44 mL, 4.06 mmol) in THF (5 mL), *n*-BuLi (1.6 M in hexanes, 2.18 mL, 3.48 mmol) was added at −78 °C and the mixture was stirred for 1 h at this temperature. To this mixture a solution of the aldehyde **24** (1.08 mmol) (prepared by method A, as described above) in THF (3 mL) was added and stirring was continued for 30 min at −78 °C. The reaction was quenched with a saturated aqueous NH_4Cl solution (5 mL) and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4, concentrated in vacuo and the residue was subjected to flash column chromatography (SiO_2, $CHCl_3$/MeOH 9:1) to afford crude alcohol **25** as mixture with an inseparable by-product (yellow oil, 199 mg) and it was used as such in the next step. Thus, crude **25** was dissolved in CH_2Cl_2 (0.8 mL) and Dess-Martin periodinane reagent (520 mg, 1.21 mmol) was added, at 25 °C. The reaction mixture was stirred for 30 min (TLC monitoring showed complete consumption of **25**) and a saturated aqueous solution of sodium thiosulfate (2 mL) was added. Stirring was continued for 20 min and the reaction mixture was extracted with EtOAc (4 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was subjected in flash column chromatography (SiO_2, *n*-hexane/EtOAc 3:7 to 1:9 and then $CHCl_3$/MeOH 9:1) to afford ketophosphonate **12c** (60 mg, 17% from alcohol **23**). **Route B. From diester 14.** To a stirred solution of dimethyl methylphosphonate (1.35 mL, 12.4 mmol) in dry THF (8.2 mL) at −78 °C was added *n*-BuLi (7.2 mL, 1.6 M in hexanes, 11.5 mmol) dropwise under an argon atmosphere and the reaction was stirred for 1 h and 20 min. A solution of diester **14** (950 mg, 4.12 mmol) in THF (8.2 mL) was added via a cannula and the reaction was stirred for 2 h. The reaction mixture was quenched with an aqueous saturated solution of NH_4Cl (10 mL) and then allowed to warm at room temperature. The mixture was extracted with EtOAc (3 × 40 mL) and the combined organic layers were washed with H_2O (40 mL) and brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude mixture was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 7:3 to 3:7) to afford pure ketophosphonate **12c** (1.1 g, 83%) as a yellow oil. R_f = 0.28 (*n*-hexane/EtOAc 6:4); $[\alpha]_D^{25}$ = +10.6 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.78 (d, $J_{H\text{-}P}$ = 11.2 Hz, 6H; CH_3O), 3.23 - 3.09 (m, 2H; -CH_2CO), 2.73 (m, 1H; -C*H*(CH_3)), 2.39 (m, 1H; -C*H*(CH_3)), 2.02 (m, 1H; -CH_aH$_b$-), 1.45 (s, 9H; C(CH_3)$_3$), 1.30-1.22 (m, 1H; -CH$_a$*H$_b$*-), 1.13 (d, *J* = 5.3 Hz, 3H; CH_3), 1.11 (d, *J* = 5.2 Hz, 3H; CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 204.9 (d, $J_{C\text{-}P}$

= 7.8 Hz), 175.4, 80.3, 53.0 (d, $J_{C\text{-}P}$ = 6.4 Hz), 52.9 (d, $J_{C\text{-}P}$ = 6.4 Hz), 45.2 (d, $J_{C\text{-}P}$ = 2.2 Hz), 39.9, 38.8, 38.1, 36.0, 28.0, 17.9, 15.6 ppm; HRMS (ESI) *m/z*: [*M*+Na]$^+$ calcd for $C_{14}H_{27}O_6P$ 345.1437 ; found 345.1438.

***tert*-butyl (2*R*,4*S*,6*E*,8*E*,10*E*/*Z*)-2,4-dimethyl-5-oxododeca-6,8,10-trienoate** (**15**): To a stirred solution of **12c** (1.03 g, 3.20 mmol) in dry THF (12 mL) at 0 °C under an argon atmosphere *t*-BuOK (464 mg, 4.13 mmol) was added and the reaction was stirred for 1.5 h. The solution was cooled at −78 °C and (2*E*,4*E*)-hexa-2,4-dienal **11** (commercially available as mixture with (2*E*,4*Z*)-isomer) (0.53 mL, 4.9 mmol) was added. The reaction mixture was allowed to warm at −20 °C over a period of 1 h and then it was stirred at 0 °C for 3 h, before quenching with a saturated aqueous solution of NH_4Cl (10 mL). EtOAc (10 mL) was added, the organic phase was separated and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 95:5) to afford **15** (mixture of *E*/*Z*-isomers at C-10, ~4.5:1, 735 mg, 79%)**,** as a yellow oil**.** R_f = 0.71 (*n*-hexane/EtOAc 9:1); $[\alpha]_D^{25}$ = −9.4 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.24 (dd, *J* = 14.9, 11.4 Hz, 1H; -C*H*=CH-), 6.57 (dd, *J* = 14.9, 10.7 Hz, 1H; -C*H*=CH-), 6.25 – 6.09 (m, 3H; -C*H*=CH-), 5.96 (dq, *J* = 14.9, 6.8 Hz, 1H; (CH_3)C*H*=CH-), 2.77 (m, 1H; -(CH_3)C*H*- of both isomers), 2.40 (m, 1H; -(CH_3)C*H*-C of both isomers), 2.04 (m, 1H; -CH_aH$_b$- of both isomers), 1.83 (d overlapping with d of Z-isomer, *J* = 6.8 Hz, 3H; CH_3-CH=CH-), 1.45 (brs overlapping with brs of Z-isomer, 9H; -C(CH_3)$_3$), 1.33 (m, 1H; -CH$_a$*H$_b$*-), 1.11 (d overlapping with d of Z-isomer, *J* = 6.8 Hz, 6H; -(CH_3)CH-) ppm; **Z-isomer (partial):** δ = 7.31 (dd, *J* = 11.5, 15.3 Hz, 1H; -C*H*=CH-), 6.92 (dd, *J* = 14.9, 11.4 Hz, 1H; -C*H*=CH-), 6.31 (dd, *J* = 14.6, 11.4 Hz, 1H; -C*H*=CH-), 5.76 (m, 1H; (CH_3)C*H*=CH-) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): ***E*-isomer:** δ = 203.1, 175.7, 143.1, 142.1, 135.4, 131.4, 128.2, 127.1, 80.1, 42.0, 38.2, 36.9, 28.1, 18.6, 17.8, 16.2. ppm; ***Z*-isomer (partial):** δ = 142.9, 136.6, 131.9, 130.1, 129.0, 127.5 ppm; HRMS (ESI) *m/z*: [*M*+Na]$^+$ calcd for $C_{18}H_{28}O_3$ 315.1931 ; found 315.1930.

***tert*-butyl(2*R*,4*S*,6*E*,8*E*,10*E*/*Z*)-5-hydroxy-2,4-dimethyldodeca-6,8,10- trienoate** (**16**): To a solution of **15** (800 mg, 2.74 mmol) in MeOH (20 mL), $NaBH_4$ (125 mg, 3.30 mmol) was added at 0 °C. After 1 h the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL), EtOAc was added (15 mL) and then it was allowed to warm at room temperature. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 9:1) to afford **16** [mixture of diasteroisomers at C-5 (c.a. 1:1), *E*/*Z* isomers at C-10 (~5:1), 799 mg, 99%) as a pale yellow oil]. R_f = 0.39 (*n*-hexane/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) ***E*-isomer** (peaks are reported for both diasteroisomers at C-5): δ = 6.25 – 6.14 (m, 2H; -C*H*=CH-), 6.13 – 6.00 (m, 2H; -C*H*=CH), 5.72 (m, , 1H; -C*H*=CH-), 5.64 (ddd, *J* = 15.1, 7.3, 2.8 Hz, 1H; -C*H*=CH-), 3.97 (m, 1H; -C*H*OH), 2.43 (m, 1H; -(CH_3)C*H*-COO^{t}Bu), 1.87 – 1.73 (m, d overlapping, *J* = 7.3 Hz, 4H; -CH_aH$_b$-, CH_3CH=CH-), 1.63 (m, 1H; -C*H*(CH_3)-)), 1.43 (s, 9H; -C(CH_3)$_3$), 1.12 (d, *J* = 7.1 Hz, 3H; -CH(CH_3)), 1.10 - 1.02 (m, 1H; -CH$_a$*H$_b$*-), 0.91 (d, *J* = 7.0 Hz, 3H; -CH(CH_3)) ppm; ***Z*-isomer** (partial, peaks are reported for both diastereoisomers at C-5): 6.51 (dd, *J* = 14.9, 11.2 Hz, 1H; -C*H*=CH-), 6.30 (m, 1H; -C*H*=CH-), 5.53 (m, 1H; (CH_3)C*H*=CH-) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) (peaks are reported for all isomers): δ = 176.2, 133.6, 133.4, 133.3, 133.1, 132.9, 132.0, 131.5, 131.5, 130.2, 130.1, 129.5, 129.4, 80.0, 76.8, 76.0, 38.5, 38.4, 37.4, 37.3, 37.0, 36.9, 28.1, 18.6, 18.5, 18.3, 15.1, 14.6 ppm; HRMS (ESI) *m/z*: [*M*+Na]$^+$ calcd for $C_{18}H_{30}O_3$ 317.2087; found 317.2083.

***tert*-butyl (2*R*,4*S*,6*E*,8*E*,10*E*/*Z*)-2,4-dimethyl-5-((triethylsilyl)oxy)dodeca-6,8,10-trienoate** (**17**): To a solution of **16** (500 mg, 1.7 mmol) in DMF (5.2 mL), imidazole (1.85 g, 27.2 mmol) and TESCl (1.6 mL, 9.53 mmol) were added sequentially, at room temperature, under an argon atmosphere. After being stirred for 3 h the reaction was quenched with MeOH (0.5 mL) and saturated aqueous solution of NH_4Cl (10 mL) was added. The mixture was extracted with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude residue was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 98:2) to afford **17** as a pale yellow oil [mixture of diastereoisomers at C-5 (c.a. 1:1), *E*/*Z* isomers at C-10 (~5:1), 681 mg, 98%]. R_f = 0.83 (*n*-hexane/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) (peaks are reported for all isomers unless defined otherwise)**:** δ = 6.48 (dd, *J* = 13.9, 11.2 Hz, 1H; -C*H*=CH- of Z-isomer), 6.24 – 5.99 (m, 4H; -C*H*=CH-), 5.74 - 5.45 (multiplets overlapping, *2*H; -C*H*=CH-), 4.03-3.92 (m, 1H; -C*H*(OTES)-), 2.41 (m, 1H; -C*H*(CH_3)-),1.84-1.69 (m, d overlapping *J*=7.0 Hz, 4H; CH_3CH=CH-, -C*H*(CH_3)-), 1.60 (m, 1H; -CH_aH$_b$-), 1.43 (s, 9H; -C(CH_3)$_3$), 1.14-1.07 (two doublets of diastereomers overlapping, 3H; -CH(CH_3)-), 1.07-0.98 (m of diasteroisomers overlapping, 1H; -CH$_a$*H$_b$*-), 0.97-0.90 (triplets overlapping, 9H; -Si(CH$_2$CH_3)$_3$), 0.89 - 0.84 (doublets overlapping, 3H; -CH(CH_3)-), 0.61-0.53 (doublets of diastereomers overlapping, 6H; -Si(CH_2CH$_3$)$_3$) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$, 25 °C) (peaks are reported for all isomers): δ = 176.2, 134.6, 134.4, 133.7, 132.4, 131.7, 130.9, 130.7, 129.9, 129.6, 129.4, 79.7, 77.3, 77.1 , 38.4, 38.2, 38.1, 37.9, 37.3, 37.2,

28.1 (2C), 18.4, 18.3, 18.2, 14.7, 14.6, 6.9, 5.0 (2C) ppm; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{24}H_{44}O_3Si$ 431.2952 ; found 431.2957**.**

(2*R*,4*S*,6*E*,8*E*,10*E*/*Z*)-2,4-dimethyl-5-((triethylsilyl)oxy)dodeca-6,8,10-trien-1-ol (**18**): To a stirred solution of **17** (550 mg, 1.35 mmol) in CH_2Cl_2 (5.5 mL), DIBAL-H (2.9 mL, 1 M in hexanes, 2.9 mmol) was added dropwise, at -95 °C under an argon atmosphere. The reaction mixture was allowed to warm to -20 °C over a period of 2 h. After 1 h of further stirring at this temperature, the reaction mixture was quenched with few drops of MeOH. EtOAc was added (20 mL) and the solution was poured to an aqueous saturated solution of potassium sodium tartrate (20 mL). The mixture was stirred vigorously until a sufficient separation of the two phases was observed (~2.5 h). The organic phase was separated and the aqueous phase was washed with EtOAc (3 × 20 mL). The combined organic extracts were washed successively with an aqueous saturated solution of NH_4Cl, water and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 9:1) to afford alcohol **18** [mixture of diasteroisomers at C-5 (c.a. 1:1), *E*/*Z* isomers at C-10 (~5:1), 402 mg, 88%] as a pale yellow oil. R_f = 0.25 (*n*-hexane/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) (peaks are reported for all isomers unless defined otherwise): δ = 6.48 (t, *J* = 12.1 Hz, 1H; -C*H*=CH- of Z isomer), 6.22 – 6.00 (m, 4H; -C*H*=CH), 5.71 (m, 1H; CH_3CH=CH-), 5.65 – 5.48 (m, 1H); -CH=C*H*-CH(OTES)-), 4.00 – 3.90 (m, t overlapping, 1H; -C*H*(OTES)-), 3.50 (dd, *J* = 10.6, 4.8 Hz, 1H); -CH_aH$_b$OH), 3.40 (dt, *J* = 10.6, 6.1 Hz, 1H; -CH$_a$*H$_b$*OH), 1.77 (d, *J* = 6.7 Hz, 3H; C*H*$_3$CH=CH-), 1.74 – 1.62 (m, *2*H; -C*H*(CH$_3$)-), 1.52 – 1.45 (m, 1H; -CH_aH$_b$-), 0.97 – 0.90 (t, d overlapping, 12H; -Si(CH$_2$C*H*$_3$)$_3$, -CH(C*H*$_3$)-), 0.89 - 0.83 (m, d (*J* = 6.9 Hz), d (*J* = 6.5 Hz) overlapping, 4H; -CH$_a$*H$_b$*-, -CH(C*H*$_3$)-), 0.61 - 0.53 (triplets overlapping, 6H; -Si(C*H*$_2$CH$_3$)$_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) (peaks are reported for all isomers): δ = 134.0, 133.8, 132.5, 131.6, 131.1, 131.0, 129.8, 129.4, 127.5, 126.8, 77.4, 77.3, 67.9, 67.6, 37.7, 36.8, 35.7, 33.4, 33.3, 18.3, 18.2, 18.0, 16.3, 15.9, 13.5, 6.8, 5.0 ppm; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{38}O_2Si$ 361.2533; found 361.2536.

(2*R*,4*S*,6*E*,8*E*,10*E*/*Z*)-2,4-dimethyl-5-((triethylsilyl)oxy)dodeca-6,8,10-trienal (**8d**): To a stirred solution of alcohol **18** (200 mg, 0.591 mmol) in CH_2Cl_2 (2 mL), a mixture of $PhI(OAc)_2$ (316 mg, 0.981 mmol) and TEMPO (4.7 mg, 0.030 mmol) was added portionwise, over a period of 40 min, at room temperature under an argon atmosphere. After stirring for 1h the reaction was completed and the mixture was quenched with an aqueous saturated solution of $Na_2S_2O_3$ and stirring was continued for 15 min. The mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed successively with a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 97:3) to afford aldehyde **8d** [mixture of diastereoisomers at C-5 (c.a. 1:1), *E*/*Z* isomers at C-10 ~5:1, 195 mg, 98%] as yellow oil. R_f = 0.63 (*n*-hexane/EtOAc 9:1); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) (peaks are reported for all isomers): δ = 9.53 (d, *J* = 2.9 Hz, 1H; -C*H*=O), 6.23 – 5.98 (m, 4H; -C*H*=CH-), 5.72 (dq, *J* = 13.9, 6.8 Hz, 1H); CH_3CH=CH-), 5.65 - 5.48 (m, 1H;-CH=C*H*-CH(OTES)-), 4.03-3.91 (triplets overlapping, 1H; -C*H*(OTES)-), 2.44 (m, 1H; -C*H*(CH$_3$)), 1.94-1.85 (m, 1H; -CH_aH$_b$-), 1.77 (d, *J* = 6.7 Hz, 3H; (C*H*$_3$)CH=CH-), 1.60 (m, 1H; -C*H*(CH$_3$)) 1.12-1.06 (2 doublets, *J* = 7.0 Hz, *J* = 7.0 Hz and 1 m overlapping , 4H; -CH$_a$*H$_b$*-, -CH(C*H*$_3$)), 0.97 - 0.90 (triplets overlapping, *J* = 7.9 Hz, 9H; -Si(CH$_2$C*H*$_3$)), 0.87-0.85 (doublets overlapping, *J* = 6.5 Hz, 3H; -CH(C*H*$_3$), 0.61 – 0.52 (quartets overlapping, *J* = 7.9 Hz, 6H; -Si(C*H*$_2$CH$_3$)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) (peaks are reported for all isomers): δ = 205.4, 205.3, 134.3, 133.6, 133.4, 132.7, 131.7, 131.6, 131.3, 131.2, 131.1, 129.9, 129.6, 129.3, 127.7, 126.9, 77.3, 44.2, 37.7, 33.9, 33.6, 18.2, 15.6, 15.5, 14. 6, 14.4, 13.5, 6.8, 5.0 (2C) ppm; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd for $C_{20}H_{36}O_2Si$ 359.2377; found 359.2374.

Alcohol 6d. LDA was prepared from *i*-Pr_2NH (0.170 mL, 1.21 mmol) and *n*-BuLi (0.740 mL, 1.6 M solution in hexanes, 1.18 mmol) in toluene (5.5 mL) at 0 °C for 1 h, under argon. The reaction mixture was then cooled at –95 °C and a solution of **7** (136 mg, 1.08 mmol) in a mixture of THF (7.7 mL) and toluene (2.4 mL) was added. The reaction mixture was stirred for 6 min, at –95 °C. A solution of aldehyde **8d** (120 mg, 0.357 mmol) in toluene (3.8 mL) was added dropwise. and stirring was continued at –78 °C for 1 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl and warmed at 25 °C. EtOAc (8 mL) was added, the organic phase was separated and the aqueous layer was extracted with EtOAc (3 × 8 mL). The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude mixture was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 9:1) to yield of the corresponding coupling product **6d** [mixture of 8 isomers, diastereoisomers at C-1 and C-5 (c.a. 1:1:1:1) and *E*/*Z* isomers at C-10 (~5:1), 142 mg, 86%] as a pale yellow oil. Complete separation of **6**d from excess of **7** was performed only for analytical purposes and in larger scales it was omitted. Thus, the mixture of **7** and **6d** could be used in the next step, where a more facile and complete removal of **7** was achieved without any negative effect in the total yield. R_f = 0.36 (*n*-hexane/EtOAc 8:2); ^{1}H NMR (500 MHz,

$CDCl_3$, 25 °C) (peaks are reported for all isomers unless defined otherwise): δ = 6.63 - 6.39 (multiplets overlapping, 0.3H; -CH=C*H*- of minor isomers), 6.28 – 5.98 (m, 4H; -CH=C*H*-), 5.96 - 5.81 (m, 0.1H; -CH=C*H*- of a minor isomer), 5.72 (m, 1H; -(CH_3)C*H*=CH-), 5.66-5.42 (multiplets overlapping, 1H; -CH=C*H*-), 5.12-4.98 (broad singlets overlapping, 2H; CH_2=C- attached on tetronate moiety), 4.52-4.36 (m, 1H; -C*H*(OH)-), 4.15-4.05 (4 singlets overlapping, 3H; CH_3O-), 4.05-3.90 (m, 1H; -C*H*(OTES)), 3.28-3.09 (broad singlets overlapping, 1H; -O*H*), 2.17-1.81 (m, 2H; -C*H*(CH_3)-, -CH_aH$_b$-), 1.77 (d, *J* = 6.9 Hz, 3H; (CH_3)CH=CH), 1.62 (m, 1H; -C*H*(CH_3)-), 1.10 - 1.01 (m, 1H, -CH$_a$*H$_b$*), 0.98-0.78 (m, 15H; -CH(CH_3)-, -CH(CH_3)-, -Si(CH_2CH_3)$_3$), 0.63-0.47 (m, 6H; Si(CH_2CH$_3$)$_3$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) (peaks are reported for all isomers): δ = 169.5, 161.6, 149.4 (2C), 134.0, 133.9, 133.8, 133.7, 133.4, 133.1, 132.7 (2C), 131.8, 131.6, 131.5, 131.4 (2C), 131.0, 130.9 (2C), 129.8, 129.7, 129.6, 129.5, 129.4 (2C), 129.3, 127.6 (2C), 126.8. 107. 0, 100.1, 93.4, 93.2, 93.0, 92.3, 77.1, 76.4 (2C), 72.0, 71.9, 70.5, 60.4 (2C), 60.3, 60.2, 41.9, 38.2, 38.1 (2C), 37.9 (2C), 37.5, 37.3, 36.8, 36.7, 35.9, 18.3, 17.8, 17.6 (2C), 17.3, 16.9, 16.5, 16.2, 6.8, 6.6, 5.8, 5.0 ppm; HRMS (ESI) *m/z*: [*M*+Na]$^+$ calcd for $C_{26}H_{42}O_5Si$ 485.2694; found 485.2688.

Diol 27. To a solution of **6d** (140 mg, 0.303 mmol) in THF (1.6 mL), TBAF (1.06 mL, 1M solution in THF, 1.06 mmol) was added, at 0 °C. The mixture was allowed to warm at 25 °C. After stirring for 2 h at this temperature, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl. EtOAc (15 mL) was added and the two phases were separated. The aqueous layer was washed with EtOAc (3 × 15 mL) and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 8:2 to 7:3) to afford diol **27** [mixture of diastereoisomers at C-1 and C-5 (c.a. 1:1:1:1) and *E*/*Z* isomers at C-10 (~5:1), 103 mg, 98%] as a pale yellow oil. R_f = 0.19 (*n*-hexane/EtOAc 7:3)**.** ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) (peaks are reported for all isomers unless defined otherwise): δ = 6.70 - 6.43 (m, 0.1H of minor isomers; -CH=C*H*-), 6.33-5.94 (m, 4H; -CH=C*H*-), 5.79 - 5.49 (m, 2H; CH_3C*H*=CH-, -CH=C*H*-), 5.10-4.99 (broad singlets overlapping, 2H; CH_2=C- attached on tetronate moiety), 4.58-4.38 (m, 1H; tetronate-C*H*(OH)-), 4.14-4.07 (singlets overlapping, 3H; CH_3O-), 4.08-3.86 (m, 1H; -C*H*(OH)CH=CH-), 3.25 (brs, 1H; -O*H*), 2.91 (brs, 1H; -O*H*), 2.15-1.84 (m, 2H; -C*H*-), 1.78 (d, *J* = 6.9 Hz, 4H; (CH_3)CH=CH-, -C*H*-), 1.55-1.35 (m, 1H; -C*H*-), 1.11-0.88 (doublets overlapping, 6H; -CH(CH_3)) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) (peaks are reported for all isomers): δ = 169.7, 169.5, 161.4, 149.3, 133.7, 133.6, 133.5, 133.2 (2C), 132.7, 132.4 (2C), 131.8, 131.5, 131.3 (2C), 131.1, 130.4 (2C), 130.2 (2C), 129.4, 129.3, 129.1, 127.3, 115.5, 107.0, 93.5 (3C), 93.4, 93.3, 76.6, 75.9, 74.8, 74.7, 71.7 (2C), 70.4 (2C), 60.5 (2C), 60.3 (2C), 37.7, 37.5, 37.4, 37.3 (2C), 37.2 (3C), 37.0, 36.9, 36.8 (2C), 36.6, 36.3 (2C), 23.0, 18.3, 18.0 (2C), 16.7, 16.2, 16.1, 16.0, 15.7, 15.1, 15.0, 14.9 ppm; HRMS (ESI) *m/z*: [*M*+Na]$^+$ calcd for $C_{20}H_{28}O_5$ 371.1829; found 371.1830.

Oxidation of 27 to 5 and IMDA to 4 via a two-step procedure (Table 1, entries 1-4)**. A. Oxidation to diketone 5.** In a typical procedure, to a solution of diol **27** (32 mg, 0.092 mmol) in DMSO (1.3 mL), IBX (77 mg, 0.276 mmol) was added in one portion, under argon and the reaction mixture was stirred at 25 °C for 3 h. Et_2O (20 mL) was added and the reaction mixture was poured in H_2O (20 mL) and a saturated aqueous solution of $NaHCO_3$ was added with vigorous stirring until pH ~8-9. The organic phase was separated and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. For the isolation of **5**, for analytical purposes, the dried extracts were concentrated *in vacuo*. At this point, a substantial amount of diketone **5** was decomposed (monitored by TLC). Immediate flash chromatography (SiO_2, *n*-hexane/EtOAc/Et_3N 95:5:0.1 to 85:15:0.1) led to **5** (*E*/*Z* isomers at C-10 ~5:1). R_f = 0.56 (*n*-hexane/EtOAc 7:3)**.** ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) (peaks are reported for both isomers, unless otherwise stated): δ = 7.35 - 7.14 (m, 2H; -COCH=C*H*-), 6.93 (m, 1H; -CH=C*H*- of *Z*-isomer), 6.64 - 6.52 (m, 1H; -CH=C*H*-), 6.35 - 6.08 (m, 4H; -CH=C*H*-). 5.96 (dq, *J* = 14.1, 7.0 Hz, 1H; CH_3C*H*=CH- of *E* isomer), 5.77 (dq, *J* = 10.6, 7.1 Hz, 1H; CH_3C*H*=CH- of *Z* isomer), 5.27 (d, *J* = 2.8 Hz, 1H; CH_aH$_b$=C- attached on tetronate moiety),), 5.21 (d, *J* = 2.8 Hz, 1H; CH$_a$*H$_b$*=C- attached on tetronate moiety), 4.12 (s, 3H; CH_3O- of *E* isomer), 4.10 (s, 3H; CH_3O- of *Z* isomer), 3.70 - 3.56 (m, 1H; -(CH_3)C*H*CO-CH=CH-), 2.82 (m, 1H; -C*H*(CH_3)- of *E*-isomer), 2.33 (m, -C*H*(CH_3)- of *Z* isomer), 2.28 - 2.14 (m, 1H; -CH_aH$_b$-), 1.83 (d, *J* = 6.9 Hz, 3H; CH_3C*H*=CH-), 1.39 - 1.28 (m, 1H; -CH$_a$*H$_b$*-), 1.15 (d, *J* = 7.3 Hz, 3H; -(CH_3)CHCO-CH=CH-), 1.13 (d, *J* = 6.7 Hz, 3H; -CH(CH_3)-) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C) (peaks are reported for both isomers): δ = 203.2, 200.5, 168.5, 166.2, 148.8, 143.2, 143.1, 142.2, 142.1, 136.7, 135.3, 134.0, 131.9, 131.4, 130.2, 129.0, 128.2, 127.7, 127.2, 105.8, 95.7, 62.8, 62.7, 42.3 (2C), 42.1, 42.0, 35.7, 35.5, 20.2, 18.6, 17.8, 17.0 (2C), 16.2 ppm; MS (ESI) *m/z*: 345.15 (100) [*M*+H]$^+$.

B. IMDA of 5 to 4. To avoid decomposition of **5** the above organic extracts were not concentrated and IMDA reaction was performed by direct addition of an appropriate solvent and/or an additive (Table 1, entries 1-4), purging the mixture with argon, removal of Et_2O with distillation and heating of the reaction mixture, under argon, with one of the following methods. In all

cases, **4** was isolated as a colorless liquid, after concentration of the reaction mixture and subjection of the residue to flash column chromatography (SiO_2, *n*-hexane/EtOAc 9:1 to 8:2). *Z*-isomer of **5** remained unreacted in these conditions. **Using $CHCl_3$/hydroquinone** (entry 1)**.** Following the procedure described above, IMDA of **5** was performed using $CHCl_3$ (25 mL) and hydroquinone (1 mg), at 67 °C for 48 h to afford **4** (8 mg, 25% from **27**, 30% based on *E*,*E*,*E*-isomer of **27**) and recovered **5** (20 mg). **1,1,1,3,3,3-Hexafluoroisopropanol** (entry 2)**.** Following the procedure described above, IMDA of **5** was performed using HFIP (13 mL), at 45 °C for 48 h, to afford 4 (21 mg, 66%, 79% based on *E*,*E*,*E*-isomer of **27**). **Toluene** (entry 3)**:** Following the procedure described above, IMDA of **5** was performed using toluene (18 mL), at 100 °C for 4.5 h, to afford **4** (9.5 mg, 30%, 36% based on *E*,*E*,*E*-isomer of **27**) and unreacted **5** (20 mg). **Using I_2/toluene** (entry 4). Following the above procedure, IMDA of **5** to **4** was performed using toluene (18 mL) and I_2 (1.5 mg, 0.006 mmol) and heating the reaction mixture at 100 °C for 3 h to afford **4** (12 mg, 38%, 46% based on *E*,*E*,*E*-isomer of **27**).

One-pot oxidation-IMDA reaction of 27 to 4 (Table 1, entries 5-6)**. A. Oxidation step of diol 27 to diketone 5.** Diol **27** (55 mg, 0.158 mmol) was dissolved in DMSO (2.2 mL), under argon. IBX (133 mg, 0.474 mmol) was added in one portion and the reaction mixture was stirred at 25 °C for 3 h. At this stage formation of diketone **5** was checked by TLC (a spot-to-spot conversion of **27** to **5** was observed) and the reaction mixture was immediately and directly subjected to the next step. **B. IMDA of 5 to 4. a. In toluene** (entry 5)**.** To the above reaction mixture, degassed toluene (25 mL) was added and heating at 90 °C was applied for 1.5 h. During this time formation of a white solid was observed in the reaction mixture. The mixture was poured to a saturated aqueous solution of $NaHCO_3$ (pH ~ 8-9) and extracted with Et_2O (20 mL). The two phases were separated and the aqueous phase was washed with Et_2O (2 × 15 mL). The combined organic extracts were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude residue was subjected to flash column chromatography (SiO_2, *n*-hexane/EtOAc 8:2 to 7:3) to afford adduct **4** (25 mg, 46%, 55% based on *E*,*E*,*E*-isomer of **27**). **b. In $(CF_3)_2CHOH$** (entry 6). The above procedure was followed, using $(CF_3)_2CHOH$ (25 mL) and heating the reaction mixture at 45 °C for 36 h to afford **4** (39 mg, 71% from **27**, 85% based on *E*,*E*,*E*-**27**) as pale yellow oil. Data of **4** were in accordance with literature.[4a],[6] R_f = 0.53 (*n*-hexane/EtOAc 7:3); $[\alpha]_D^{25}$ = –199 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 6.48 (dd, *J* = 16.8, 6.8 Hz, 1H; -COCH=C*H*- of 11-membered ring), 6.25 (dd, *J* = 16.8, 1.3 Hz, 1H; -COC*H*=CH- of 11-membered ring), 5.86 (ddd, *J* = 9.7, 3.0, 3.0 Hz, 1H; -CH=C*H*CH(CH_3)- of cyclohexene ring), 5.67 (ddd, *J* = 9.9, 2.5, 2.5 Hz, 1H; -C*H*=CHCH(CH_3)- of cyclohexene ring), 3.91 (s, 3H; CH_3O-), 3.44 (dd, *J* = 6.3, 3.1 Hz, 1H; -C*H*-CH=CHC- of cyclohexene ring), 3.12 (ddq, *J* = 11.1, 6.8, 4.4 Hz, 1H; -C*H*(CH_3)- of 11-membered ring), 2.95 (h, *J* = 6.2 Hz, 1H; -C*H*(CH_3)- of 11-membered ring), 2.64 (m, 1H; -C*H*(CH_3)- of cyclohexene ring), 2.40 (dd, *J* = 14.4, 7.9 Hz, 1H; -CH_aH$_b$- of cyclohexene ring), 1.87 (ddd, *J* = 15.2, 6.0, 4.2 Hz, 1H; -CH_aH$_b$- of 11-membered ring), 1.82 (dd, *J* = 14.4, 4.5 Hz, 1H; ; -CH_aH$_b$- of cyclohexene ring), 1.24 (m, 1H; -CH_aH$_b$- of 11-membered ring), 1.21 (d, *J* = 7.5 Hz, 3H; -CH(CH_3)- of 11-membered ring), 1.19 (d, *J* = 6.8 Hz, 3H; -C*H*(CH_3)- of 11-membered ring), 1.15 (d, *J* = 7.3 Hz, 3H; -CH(CH_3)- of cyclohexene ring) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$, 25 °C): δ = 204.1, 200.4, 178.1, 169.8, 141.3, 136.6, 131.5, 121.7, 106.8, 85.9, 61.5, 46.5, 46.4, 44.5, 38.8, 36.5, 29.1, 21.0, 16.9, 16.5 ppm; MS (ESI) *m/z*: 343.00 (100) [*M*-H]$^-$.

Acknowledgments ((optional))

This research is co-financed by Greece and the European Union (European Social Fund- ESF) through the Operational Programme «Human Resources Development, Education and Lifelong Learning» in the context of the project “Strengthening Human Resources Research Potential via Doctorate Research” (MIS-5000432), implemented by the State Scholarships Foundation (IKY).

Keywords: abyssomicin C • *atrop*-abyssomicin C • biomimetic synthesis • cycloaddition

[1] For related reviews, see: (a) M. H. Lacoske, E. A. Theodorakis, *J. Nat. Prod.* **2015**, *78*, 562–575; (b) A. Braddock, E. A. Theodorakis, *Mar. Drugs* **2019**, *17*, 232–247.

[2] For isolation and bioactivity of abyssomicin C and *atrop*-abyssomicin C, see: (a) B. Bister, D. Bischoff, M. Ströbele, J. Riedlinger, A. Reicke, F. Wolter, A. T. Bull, H. Zähner, H.-P. Fiedler and R. D. Süssmuth, *Angew. Chem. Int. Ed.* **2004**, *43*, 2574–2576; *Angew. Chem.* **2004**, *116*, 2628–2630; (b) J. Riedlinger, A. Reicke, H. Zähner, B. Krismer, A. T. Bull, L. A. Maldonado, A. C. Ward, M. Goodfellow, B. Bister, D. Bischoff, R. D. Süssmuth, H.-P. Fiedler, *J. Antibiot.* **2004**, *57*, 271–279; (c) S. Keller, H. S. Schadt, I. Ortel, R. D. Süssmuth, *Angew. Chem. Int. Ed.* **2007**, *46*, 8284–8286; *Angew. Chem.* **2007**, *119*, 8433–8435; (d) J. S. Freundlich,

M. Lalgondar, J.-R. Wei, S. Swanson, E. J. Sorensen, E. J. Rubin, J. C. Sacchettini, *Tuberculosis* **2010**, *90*, 298–300.

[3] For a related review, see: C. Sadaka, E. Ellsworth, P. R. Hansen, R. Ewin, P. Damborg, J. L. Watts, *Molecules* **2018**, *23*, 1371–1396.

[4] For total syntheses, hemisynthesis and synthesis of analogs, see: (a) C. W. Zapf, B. A. Harrison, C. Drahl, E. J. Sorensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 6533–6537; *Angew. Chem.* **2005**, *117*, 6691–6695 (b) K. C. Nicolaou, S. T. Harrison, *Angew. Chem. Int. Ed.* **2006**, *45*, 3256–3260; *Angew. Chem.* **2006**, *118*, 3334–3338; (c) K. C. Nicolaou, S. T. Harrison, *J. Am. Chem. Soc.* **2007**, *129*, 429–440; (d) K. C. Nicolaou, S. T. Harrison, J. S. Chen, *Synthesis* **2009**, 33–42; (e) F. Bihelovic, R. N. Saicic, *Angew. Chem. Int. Ed.* **2012**, 51, 5687–5691; *Angew. Chem.* **2012**, *124*, 1–6; (f) F. Bihelovic, I. Karadzic, R. Matovic, R. N. Saicic, *Org. Biomol. Chem.* **2013**, *11*, 5413–5424; g) Q. Wang, F. Song, X. Xiao, P. Huang, L. Li, A. Monte, W. M. Abdel-Mageed, J. Wang, H. Guo, W. He, F. Xie, H. Dai, M. Liu, C. Chen, H. Xu, M. Liu, A. M. Piggott, X. Liu, R. J. Capon, L. Zhang, *Angew. Chem. Int. Ed.* **2013**, *52*, 1231–1234*; Angew. Chem.* **2013**, *125*, 1269-1272; h) R. Matovic, F. Bihelovic, M. Gruden-Pavlovic, R. N. Saicic, *Org. Biomol. Chem.* **2014**, *12*, 7682–7685.

[5] For synthetic studies and construction of spirotetronate cores, see: (a) J. P. Rath, S. Kinast, M. E. Maier, *Org. Lett*. **2005**, *7*, 3089–3092; (b) J. P. Rath, M. Eipert,; S. Kinast, M. E. Maier, *Synlett* **2005**, 314–318; (c) A. L. Zografos, A. Yiotakis, D. Georgiadis, *Org. Lett.* **2005**, *7*, 4515–4518.

[6] For formal syntheses of abyssomicin C and *atrop*-abyssomicin C: (a) B. Snider, Y. Zou, *Org. Lett.* **2005**, *7*, 4939–4941; (b) E.A. Couladouros, E.A. Bouzas, A.D. Magos, *Tetrahedron* **2006**, 62, 5272–5279.

[7] The identity of isoabyssomicin C as *atrop*-abyssomicin C was confirmed later by Nicolaou et al.; see ref [4c] and ref. 21 cited therein. Interestingly interconversion of abyssomicin C and *atrop*-abyssomicin C occurs in acidic conditions.

[8] (a) F. F. Paintner, G. Bauschke, M. Kestel, *Tetrahedron Lett.* **2000**, *41*, 9977–9980; (b) D. Niu, T. R. Hoye, *Org. Lett.* **2012**, *14*, 828–831; (c) A.Chatzimpaloglou, M. Kolosov, T. K. Eckols, D. J. Tweardy, V. Sarli, *J. Org. Chem.* **2014**, *79*, 4043–4054; (d) N. R. Lees, L.-C. Han, M. J. Byrne, J. A. Davies, A. E. Parnell, P. E. J. Moreland, J. E. M. Stach, M. W. van der Kamp, C. L. Willis, P. R. Race, *Angew. Chem. Int. Ed.* **2019**, *58*, 2305–2309; *Angew. Chem.* **2019**, *131*, 1–6; (e) K. Hori, K. Nomura, S. Mori, E. Yoshii, *J. Chem. Soc. Chem. Comm.* **1989**, *11*, 712–713; (f) H. Hori, M. Inagaki, Y. Nomura, *J. Org. Chem.* **1992**, *57*, 2888–2902.

[9] Commercial sorbaldehyde (**11**) used in this work contains ~11% of the Z isomer at the terminal double bond. The 10*Z*-isomer of **5** remains unreacted in the IMDA reaction to **4**, as it is reported already (see ref. 6a) and it is not depicted in the schemes of the text for clarity. Details about the *E*:*Z* ratio are given in the supporting information.

[10] J. Hiratake, M. Inagaki, Y. Yamamoto, J. Oda, *J. Chem. Soc. Perkin Trans 1* **1987**, 1053–1058.

[11] U. C. Dyer, J. A. Robinson, *J. Chem. Soc. Perkin Trans 1* **1988**, 53–60.

[12] (a) C.-S. Chen, Y. Fujimoto, C. J. Sih, *J. Am. Chem. Soc.* **1981**, *103*, 3580–3582; (b) D. V. Patel, F. VanMiddlesworth, J. Donaubauer, P. Gannett, C. J. Sih, *J. Am. Chem. Soc.* **1986**, *108*, 4603–4614.

[13] Despite Prof. G. A. Strobel's kind offer to provide it.

[14] Y. Schmidt, K. Lehr, U. Breuninger, G. Brand, T. Reiss, B. Breit, *J. Org. Chem.* **2010**, *75*, 4424–4433.

[15] IMDA of diketone **5** has been also performed using a Diels-Alderase: C. Marsh, N. Lees, L.-C. Han, M. Byrne, S. Mbatha, L. Maschio, S. Pagden-Ratcliffe, P. Duke, J. Stach, P. Curnow, C. Willis, P. Race, *ChemCatChem* **2019**, *11*, 5027–5031.

[16] For examples of use of HFIP in Diels–Alder reactions, see: (a) E. Tzouma, I. Mavridis, V. P. Vidali, E. N. Pitsinos, *Tetrahedron Lett.* **2016**, *57*, 3643–3647; (b) C. Cativiela, J. I. García, A. J. Royo, L. Salvatella, *Tetrahedron: Asymmetry* **1993**, *4*, 1613–1618; (c) C. Cativiela, J. I. García, J. A. Mayoral, L. Salvatella, *Can. J. Chem.* **1994**, *72*, 308–311. (d) C. Cativiela,, J. I. García, J. Gil, R. M. Martínez, J. A. Mayoral, L. Salvatella, J. S. Urieta, A. M. Mainar, M. H. Abraham, *J. Chem. Soc., Perkin Trans. 2* **1997**, 653–660; (e) For an interesting review on the uses of HFIP, see: I. Colomer, A. E. R. Chamberlain, M. B. Haughey, T. J. Donohoe, *Nat. Rev. Chem.* **2017**, *1***,** 0088–0100.

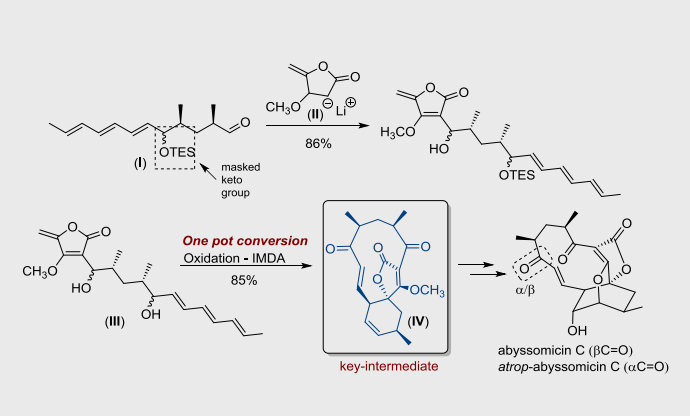
[17] S. Deuri, P. Phukan, *Struct. Chem*. **2011**, *22*, 1075–1085.

[18] For a review on iodine catalysis, see: M. Breugst, D. von der Heiden, *Chem. Eur. J.* **2018**, *24*, 9187–9199.

Entry for the Table of Contents (Please choose one layout)

Layout 2:

FULL PAPER



Natural Product Synthesis

*Veroniki P. Vidali**, *Aleksander Canko*, *Angelos D. Peroulias*, *Evangelos T. Georgas*, *Emmanuel Bouzas*, *Julie M. Herniman* and *Elias A. Couladouros*

Page No. – Page No.

An Improved Biomimetic Formal Synthesis of Abyssomicin C and *atrop*-Abyssomicin C

A high-yielding coupling of the modified aldehyde (**I**) with the α-lithio salt of *γ*-methylene-*β*-tetronate (**II**) and a one-pot oxidation-intramolecular Diels–Alder reaction of diol (**III**) to key-intermediate (**IV**), circumvent problems arosen by previous biomimetic approaches, towards abyssomicin C and *atrop*-abyssomicin C, and set the base for the development of improved synthetic routes to these molecules.