A new Catalytic Route to Deoxypropionate Building Blocks

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Abstract

The deoxypropionate motif is found in many biologically active compounds and consists of stereogenic Me-centers in a 1,3-relationship (Figure 1). Although several methods exist to synthesize these building blocks, new catalytic approaches are warranted.

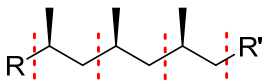


Figure 1. Deoxypropionate motif; three units shown.

A new catalytic route to deoxypropionate building blocks is presented here. The route relies on the Horner-Wadsworth-Emmons reaction, using a novel Horner-Wadsworth-Emmons-reagent, for the synthesis of α,β,γ,δ-unsaturated thioesters. Utilizing the asymmetric Cu-catalyzed 1,4- and 1,6-conjugate addition, Me-centers can be introduced in a 1,3-relation via an efficient iterative procedure.

Contents

1. Introduction

A valuable structural motif in biologically relevant compounds is the so-called deoxypropionate motif. It consists of stereogenic Me-centers in a 1,3-array (Figure 1). The deoxypropionate motif is abundant in natural products.[1, 2] The number of deoxypropionate subunits varies and also the structure of the molecules incorporating the deoxypropionate units are very diverse.

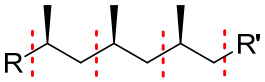


Figure 1. Deoxypropionate motif; three units shown.

The goal of this research project is to develop a new catalytic, generally applicable, easy to perform and time-efficient route to deoxypropionate building blocks.

It is interesting to note that in the majority of natural products bearing the recurring 1,3-dimethyl groups on acyclic chains, the relationship is all-*syn*. Examples of natural products (Figure 2) containing at least two *syn*-disposed deoxypropionate units are pectinatone,[3, 4] lardolure,[5, 6] TMC-151,[7] siphonarienolone[8, 9] and siphonarienal.[10, 11] Compounds that contain substructures with *syn*-disposed 2,4-dimethylbutane motifs are for example ionomycin,[12-15] zaragozic acid A,[16-19] rapamycin[20-23] and rakicidin C.[24] Furthermore, macrocycles that contain a *syn*-related 2,4,6-trimethylhexane motif are doliculide[25-27] and borrelidin.[28-31]

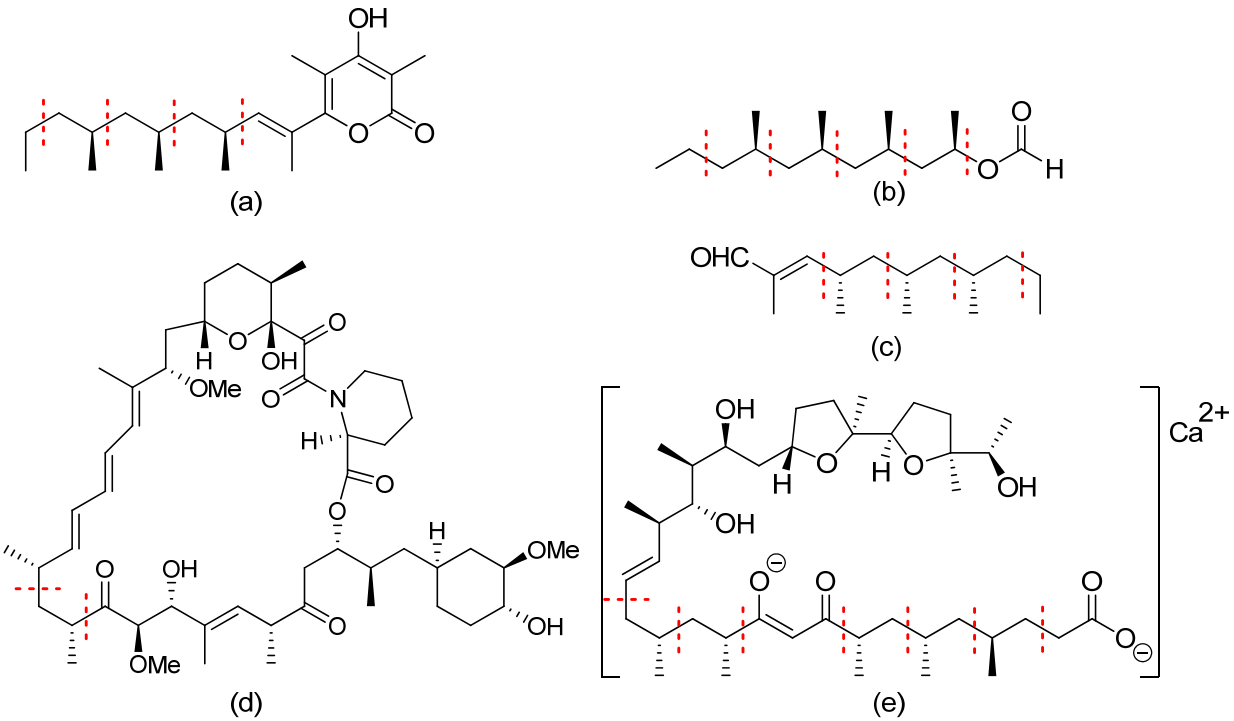


Figure 2. Natural products containing deoxypropionate subunits (marked with dotted lines). (a) (+)-pectinatone[3, 4] (b) (-)-lardolure[5, 6] (c) siphonarienal[10, 11] (d) rapamycin[20-23] (e) ionomycin.[12-15]

The abundance of the deoxypropionate motif in natural products has led to a number of methods for their stereocontrolled synthesis.[5, 6, 15, 32-47] Some of these methods

have been utilized to prepare acyclic (sub)structures, containing 2,4-dimethyl- and 2,4,6-trimethyldeoxypropionate units, in an iterative manner. The synthesis of the deoxypropionate building block of (-)-borrelidin will be discussed in more detail as an example.

Borrelidin (Figure 3) is a structurally distinct macrolide antibiotic produced by a variety of *Streptomyces*.[28-31] In addition to its long known inhibitory effect against infections caused by *Borrelia*, it also exhibits a diverse spectrum of other biological activities. The inhibition of cyclin-dependant kinase of *Saccharomyces cerevisiae*[48] and the potent antiangiogenesis activity[49, 50] in the rat aorta have attracted renewed attention for this structurally unique natural product.

The C1-C11 substructure contains four 1,3-alternating C-methyl groups consisting of three deoxypropionate and one propionate unit in a distinct *syn*/*syn*/*anti*-relationship (Figure 3).

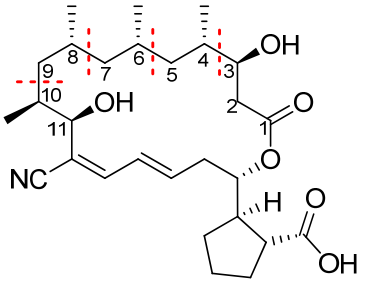
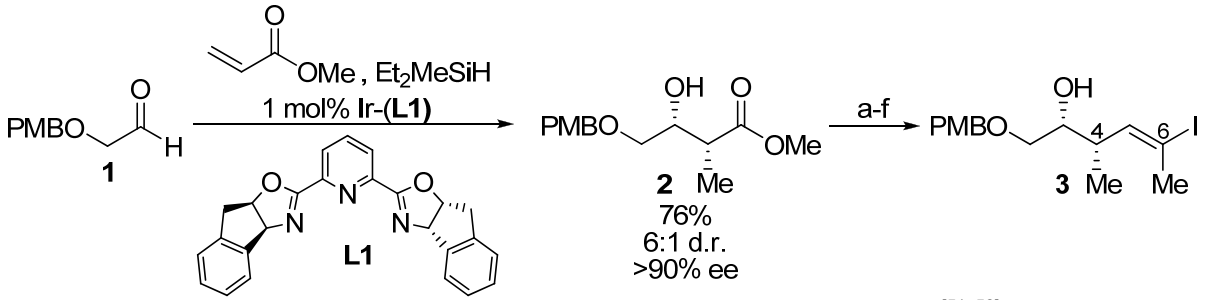


Figure 3. Structure of (-)-borrelidin (deoxypropionate subunits between dotted lines).

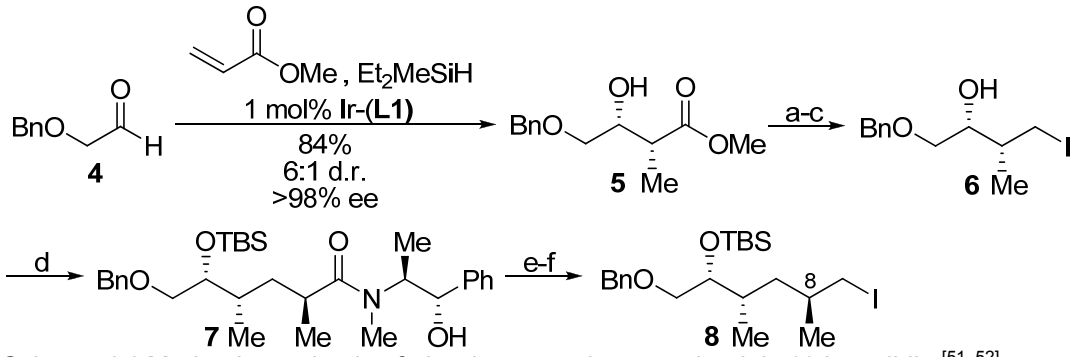
The first total synthesis of borrelidin, utilizing asymmetric methods to construct the deoxypropionate subunits was reported by Morken and coworkers.[51, 52] The synthesis starts with reductive aldol coupling of methyl acrylate and *p*-methoxybenzyloxyacetaldehyde to provide aldol aduct **2** (Scheme 1). After protection of **2**, the methyl ester was converted to the aldehyde and subsequently to a terminal alkyne by a Corey-Fuchs reaction. Hydro-zirconation and iodination of the alkyne gives vinyl iodide **3**.



Scheme 1.* Morken's synthesis of the deoxypropionate subunit in (-)-borrelidin.[51, 52]
* Reagents and conditions: (a) TBSOTf, 2,6-lutidine (90%); (b) DIBAL-H (79%); (c) Dess-Martin periodinane (92%); (d) CBr_4, PPh_3 (94%); (e) BuLi, MeI (97%); (f) (i) Cp_2ZrHCl, (ii) I_2 (89%).

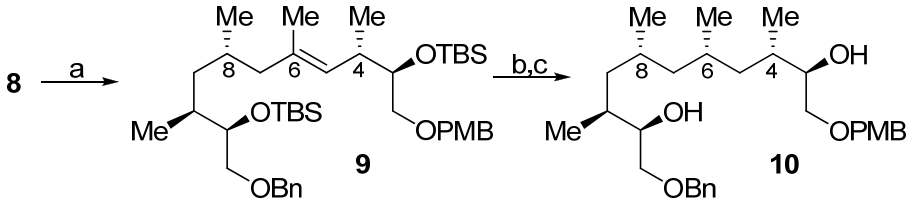
Reductive aldol coupling between methyl acrylate and benzyloxyacetaldehyde affords propionate **5** (Scheme 2). Compound **5** was converted to iodide **6**, which was

then used in a Myers' asymmetric alkylation to introduce the Me-center on C8. After reductive removal of the auxiliary, the alcohol was converted to alkyl iodide **8**.



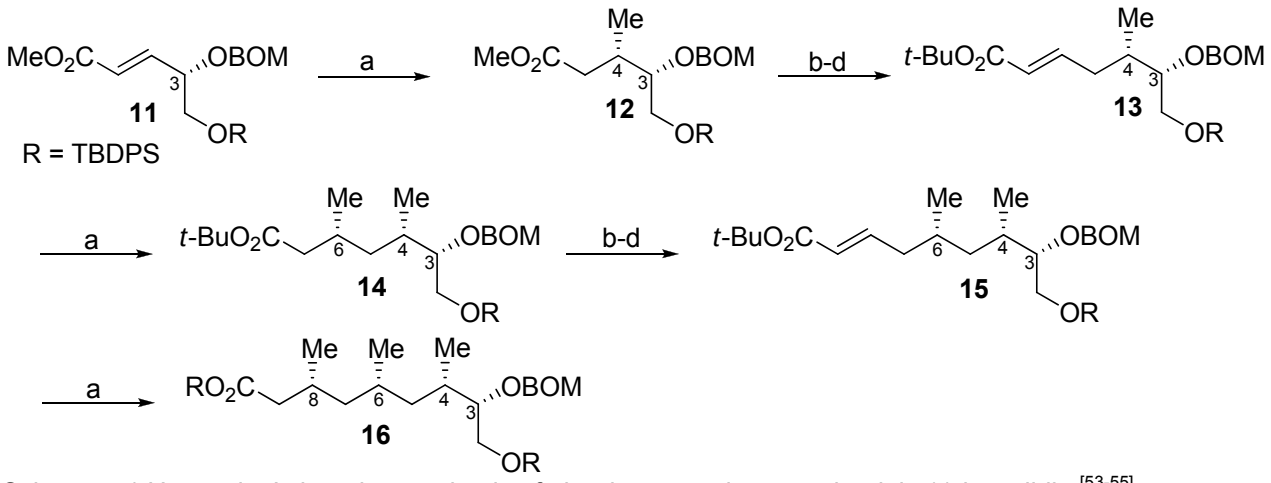
Scheme 2.* Morken's synthesis of the deoxypropionate subunit in (-)-borrelidin.[51, 52]
* Reagents and conditions: (a) TBSOTf, 2,6-lutidine (99%); (b) DIBAL-H (94%); (c) PPh_3, I_2 (96%); (d) pseudoephedrine propionamide, LDA (93%); (e) LAB (93%); (f) PPh_3, I_2 (95%).

Alkyl iodide **8** was subjected to a modified Negishi coupling with vinyl iodide **3** to give **9** (Scheme 3). After deprotection of the silyl ethers, the last stereogenic Me-center (on C6) was established through a direct hydrogenation to give building block **10**.



Scheme 3.* Morken's synthesis of the deoxypropionate subunit in (-)-borrelidin.[51, 52]
* Reagents and conditions: (a) (i) *t*-BuLi, $ZnCl_2$, (ii) $Pd(PPh_3)_4$, **3** (58%); (b) TBAF (87%); (c) H_2 (600 psi), 30 mol% Rh[(nbd)dppb]BF_4 (86%).

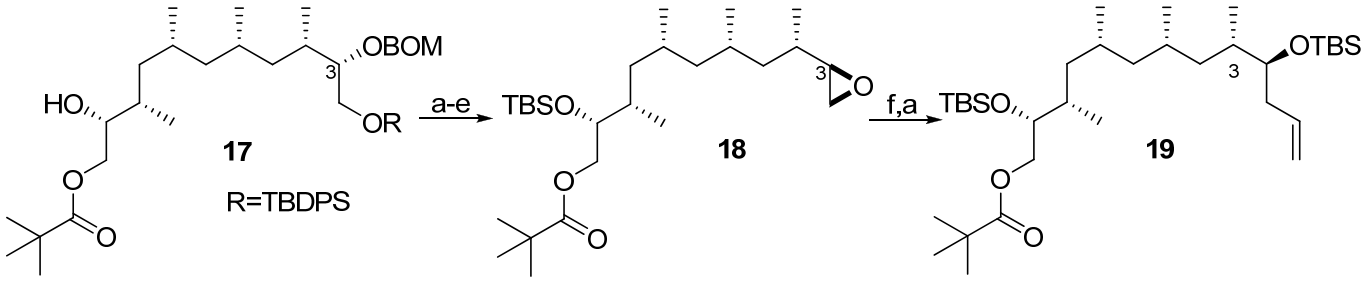
In another synthesis, Hanessian and coworkers[53] apply iterative cuprate additions to acyclic α,β-unsaturated esters to construct the deoxypropionate subunits (Scheme 4). Their method starts with D-glyceraldehyde as the chiral progenitor and uses stereoinduction by the substrate to control the formation of the two chiral Me-centers. Previously, they reported[54, 55] on the stereocontrolled synthesis of polypropionate subunits by an iterative protocol; an enantiopure γ-alkoxy-α,β-unsaturated ester undergoes a conjugate addition of lithium dimethylcuprate, followed by hydroxylation of the corresponding potassium enolate.



Scheme 4.* Hanessian's iterative synthesis of the deoxypropionate subunit in (-)-borrelidin.[53-55]
* Reagents and conditions: (a) MeLi·LiBr, CuI, TMSCl, THF, -78 °C (93%, >50:1 *anti*-**12**:*syn*-**12**); (b) DIBAL-H, CH_2Cl_2 (80%); (c) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 °C (96%); (d) PPh_3CHCO_2t-Bu, CH_2Cl_2 (91%); repeat a (93%, 4:1 *syn*-**14**:*anti*-**14**) ; repeat b (82%); repeat c (88%); repeat d (90%); repeat a (88%) [*syn*/*syn*:*syn*/*anti* >90% by chiral GC analysis of a derivative].

Highly selective conjugate addition of lithium dimethylcuprate in the presence of TMSCl to enoate **11**, gave adduct **12** in 93% yield and excellent diastereoselectivity (>50:1 *anti*:*syn* C3-C4). A second cuprate addition to **13** led to a mixture of **14** and its *anti*-isomer in a ratio of 4:1 in favor of the *syn*(C4-C6)-isomer. The third cuprate addition afforded *syn*/*syn* adduct **16** in high yield (88%) with good selectivity (>10:1 *syn*/*syn*:*anti*/*syn* C3-C4/C6-C8). Although a fourth conjugate addition to the homologated enoate proceeded in excellent yield, the resulting adduct was obtained as the minor isomer compared to the favored all-*syn*-product (*syn*:*anti* 2:1 for the fourth cuprate addition). Therefore, an alternative approach to install the Me-center at C10 with the correct configuration was used, which is outside the scope of this report.[53]

In a later stage of the synthesis, the stereogenic OH-center at C3 was inverted (Scheme 5).



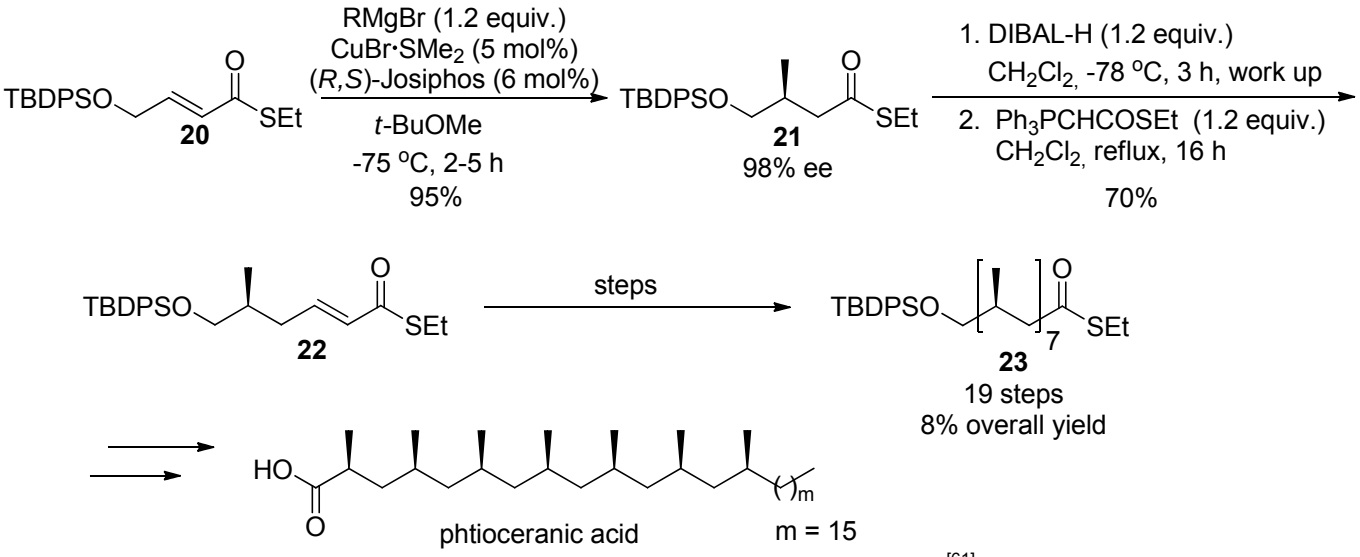
Scheme 5.* Inversion of the OH-stereocenter in Hanessian's synthesis of the deoxypropionate subunit in (-)-borrelidin.[54, 55]
* Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2 (90%); (b) H_2, Pd/C 10%, MeOH (80%); (c) MsCl, NEt_3, CH_2Cl_2 (82%); (d) TBAF, THF; (e) K_2CO_3, MeOH (88% over two steps); (f) vinylMgBr, CuI, THF, -78 °C (82%); repeat a (91%); DIBAL-H, CH_2Cl_2 (98%).

Protection of the hydroxyl group in **17** as a TBS ether, hydrogenolysis to remove the BOM ether, mesylation of the resulting alcohol, and selective cleavage of the TBDPS ether with Bu_4NF led to formation of the inverted epoxide **18**. Opening of the epoxide

with vinylmagnesiumcuprate and protection of the resulting alcohol as the TBS ether gives **19**, which can be hydrolyzed to the alcohol.

Classically, the synthesis of deoxypropionate subunits relies on chiral auxiliaries for asymmetric induction. For example, Sakai and coworkers[56] report a modest level of diastereoselectivity for the addition of lithium dimethylcuprate to α,β-unsaturated monoesters of (*R*,*R*)-1,2-cyclohexanediol prepared from *R*- and *S*-citronellal which resulted in *syn*:*anti*-ratios of up to 3:1 in 40% yield. Furthermore, Breit[57] and Demel[58] report conjugate addition of lithium dimethylcuprate to enantiopure α,β-unsaturated esters with a stereogenic Me-group and an adjacent directing group. Remarkably, they observe high preference for formation of the *anti*-deoxypropionate isomer. Williams and coworkers[59] describe the stereoselective synthesis of *syn*- and *anti*-1,3-dimethylarrays by conjugate addition of methylcopper reagents to enantiopure N-enoyloxazolidinones. Finally, Oppolzer *et al.*[60] synthesized *anti*-deoxypropionate units relying on stereoselective addition of an organocopper reagent harboring a stereogenic C-methyl group to chiral α,β-unsaturated camphorsultam amides.

Catalytic asymmetric routes have also been described for the synthesis of deoxypropionate units. A first example has been developed by the group of Feringa and Minnaard.[61] This route relies on an iterative protocol that applies asymmetric Cu-catalyzed 1,4-conjugate additions (1,4-ACA) as the key step. Utilizing this approach, phtioceranic acid (a fatty acid from *Mycobacterium Tuberculosis*) was synthesized (Scheme 6).

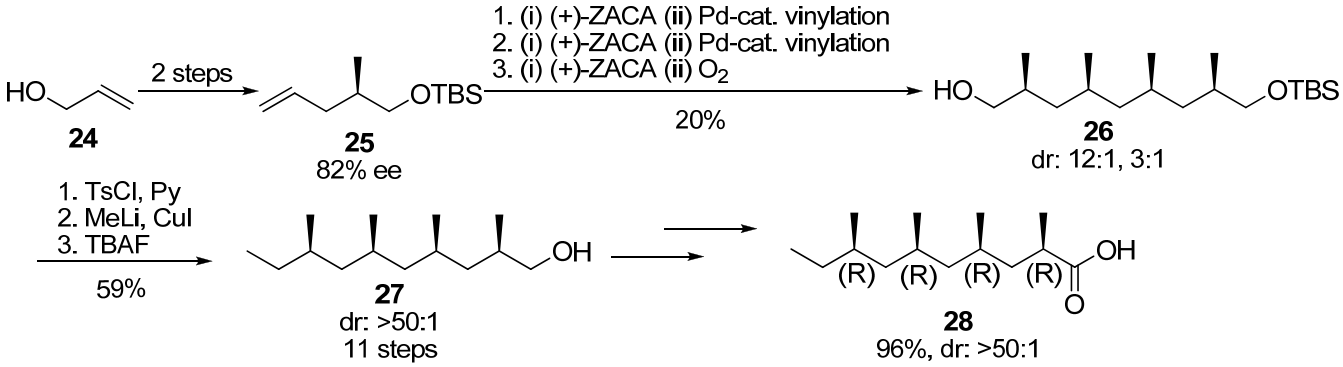


Scheme 6. Total synthesis of phtioceranic acid via an iterative 1,4-ACA protocol.[61]

Asymmetric 1,4-addition on substrate **20** yields the first stereogenic Me-center in 95% yield and with 98% ee. Selective reduction of the thioester to the aldehyde using DIBAL-H, followed by a Wittig reaction furnishes substrate **22**. This substrate undergoes the same three steps in an iterative protocol to yield thioester **23** from **20** in 19 steps and 8% overall yield. The diastereoselectivity of all iterative conjugate addition reactions was >96%. Overall, this protocol was used to synthesize phtioceranic acid. Although this procedure is very efficient with high overall yields and

excellent enantio- and diastereoselectivity, it is quite laborious for the synthesis of large molecules with multiple stereocenters.[61]

Another approach utilizes asymmetric zirconium-catalyzed carboalumination (ZACA).[62] Negishi and coworkers developed an iterative protocol for the synthesis of all-(*R*)-2,4,6,8-tetramethyldecanoic acid (Scheme 7), a major acid component of the preen-gland wax of the graylag goose, *Anser anser*.



Scheme 7. Total synthesis of all-(*R*)-2,4,6,8-tetramethyldecanoic acid via an iterative ZACA protocol.[62]

Compound **28** was synthesized from **25** in eight steps in 11.5% overall yield. The method of Negishi is very elegant and involves three one-pot reactions, but the stereoinduction by the zirconium catalyst requires improvement. Through purification the ratios can be greatly improved, but at the cost of overall yield.

The third route, developed by Burgess *et al.*[63] relies on asymmetric hydrogenation by the Ir-derived catalyst **L-2** depicted in figure 4. The first stereogenic Me-center is already present in the commercially available starting material; (*S*)-methyl-3-hydroxyisobutyrate. After a series of steps, deoxypropionate subunit **30** was prepared.[64] The selectivity for the hydrogenation is excellent (*syn*:*anti* 1:120 for the last Me-center). A drawback of this method is that for each new stereogenic Me-center, four steps are required (Scheme 8). For substrate **32**, containing 4 Me-centers, 12 steps are required from starting compound **29**.

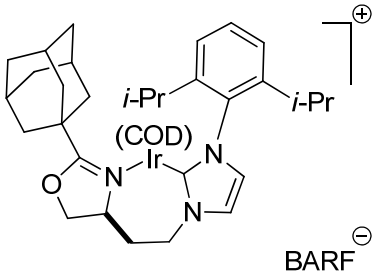
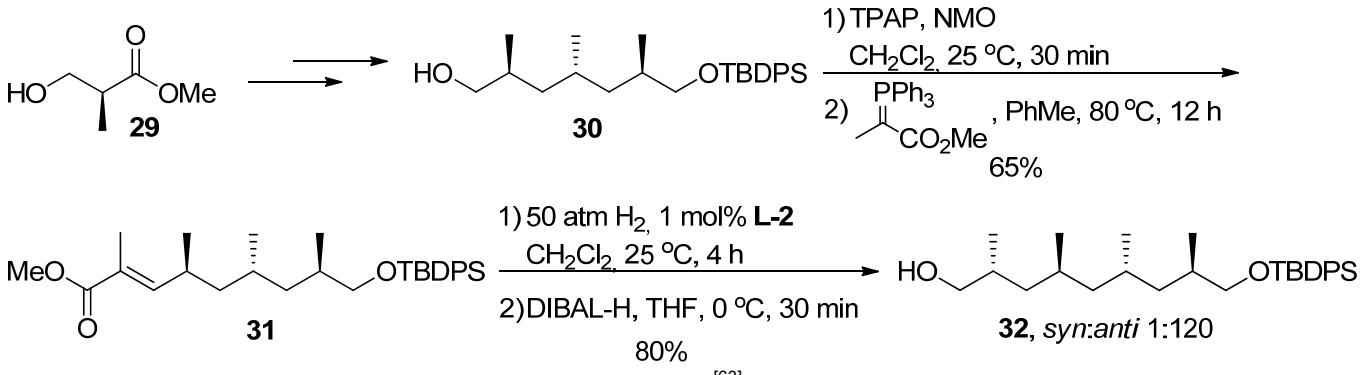
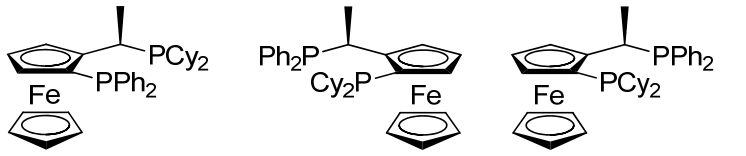


Figure 4. Burgess' Ir-catalyst **L-2**.[63]



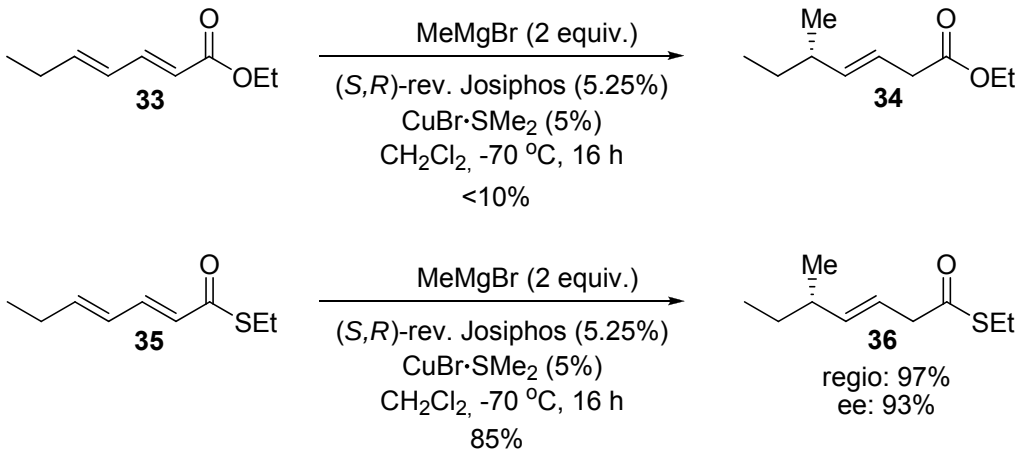
Scheme 8. Burgess' asymmetric Ir-catalyzed hydrogenation.[63]

As was shown recently,[65] asymmetric 1,6-additions of Grignard reagents to bisunsaturated enoates leads to δ-substituted β,γ-esters. The use of α,β,γ,δ-bisunsaturated substrates requires additional control of regioselectivity. Employing the (*R*,*S*)-reversed Josiphos ligand (Figure 5) and EtMgBr at -78 °C, the β,γ-unsaturated 1,6-product is obtained in excellent regio- (98:2) and enantioselectivity (95% for either (*S*)- or (*R*)-enantiomer). However, for the 1,6-addition of MeMgBr to α,β,γ,δ-bisunsaturated esters the 1,6-addition product was only obtained with low conversion. Use of a thioester substrate gives the anticipated product in high yield and excellent regio- and enantioselectivity (Scheme 9).[66]



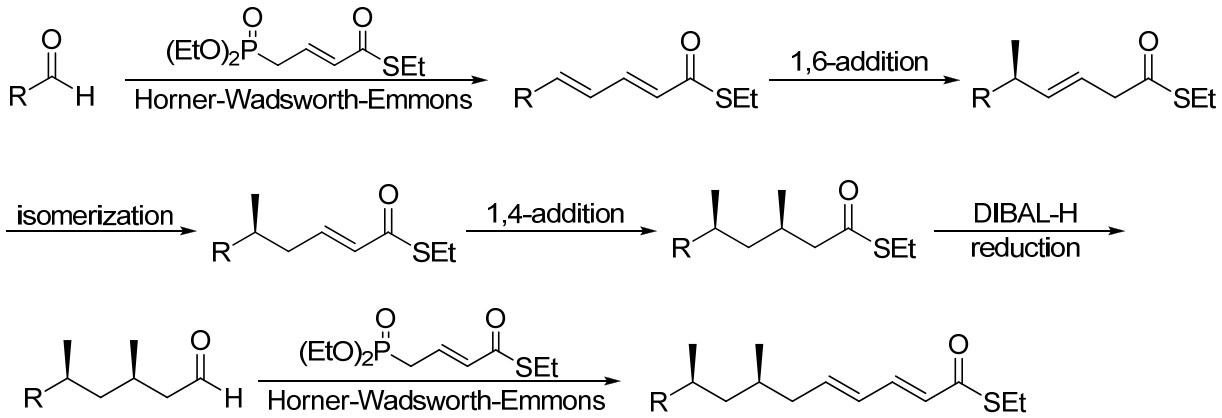
(*R*,*S*)-Josiphos (*S*,*R*)-Josiphos (*R*,*S*)-rev. Josiphos

Figure 5. Josiphos-family ligands.



Scheme 9. Increased reactivity of α,β-unsaturated thioesters in asymmetric catalytic 1,6-conjugate addition.[66]

We envisioned that a combined use of the 1,6- and 1,4-conjugate addition would allow an alternative and atom efficient way to introduce multiple stereogenic Me-centers in a 1,3-relationship. The general approach is depicted in scheme 10.



Scheme 10. Proposed route for the synthesis of deoxypropionate building blocks.

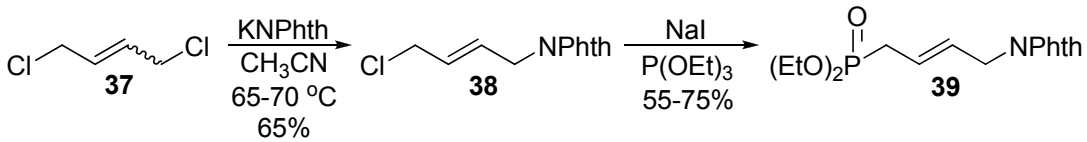
By introducing a double bond in the HWE-reagent, bisunsaturated substrates can be prepared in one step with the Horner-Wadsworth-Emmons reaction of an aldehyde. 1,6-Addition, followed by double bond isomerization and 1,4-addition installs two stereogenic Me-centers. Selective reduction to the aldehyde and a subsequent HWE-reaction furnishes a bisunsaturated thioester with two stereogenic Me-centers. This protocol can be repeated for the synthesis of additional Me-centers in a 1,3-fashion.

This report describes a new catalytic route towards deoxypropionate building blocks, utilizing a novel HWE-reagent and asymmetric 1,4- and 1,6-conjugate additions. In the second chapter of this report, the synthesis of the HWE-reagent will be discussed. Chapter 3 deals with the use of the HWE-reaction for the synthesis of α,β,γ,δ-bisunsaturated thioesters, followed by double bond isomerization (chapter 4) and the iterative steps in chapter 5. In chapter 6 all results will be discussed and conclusions will be drawn.

2. Synthesis of HWE-reagent

2.1 Introduction

The HWE-reaction is used extensively for the introduction of *E*-olefins in natural products. A lot of effort has therefore been made to optimize the synthesis of a wide variety of HWE-reagents. In general, most unsaturated HWE-reagents are made by an Arbuzov reaction of an allyl halide. One of the earliest examples is reported by Helquist and Åkermark in which the allyl chloride is replaced by the phosphonate group in the second step (Scheme 11).[67]



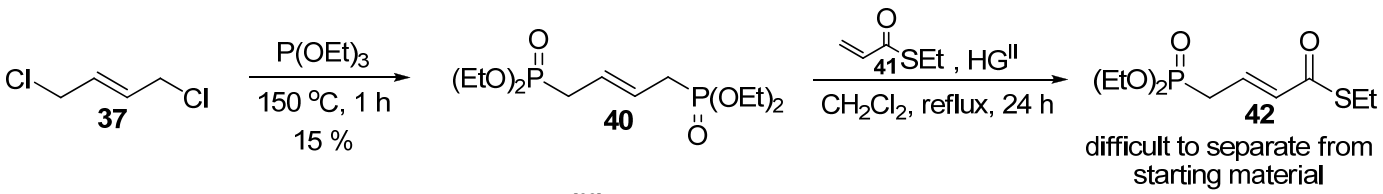
Scheme 11. Synthesis of unsaturated HWE-reagent **39**.[67]

2.2 Synthesis

There are numerous ways to construct the envisioned HWE-reagent (the attempted methods are described hereafter).

Route A

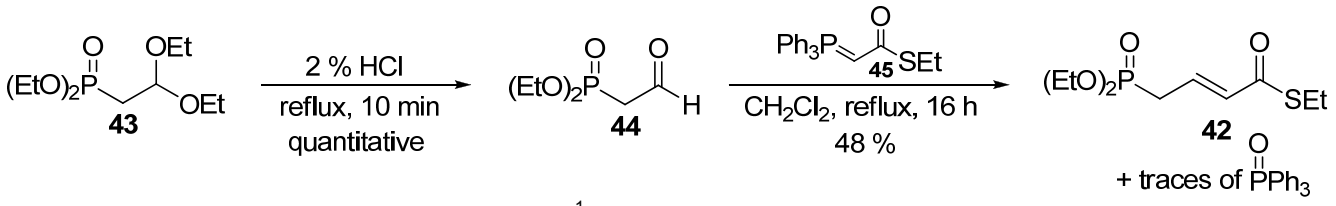
The synthesis starts by an Arbuzov reaction of (*E*)-1,4-dichloro-2-butene with triethyl phosphate[68] forming (*E*)-1,4-diphosponate-2-butene in low yield. The cross-metathesis reaction with ethyl-thioacrylate,[69] catalyzed by Hoveyda-Grubbs 2nd generation catalyst (HG^{II}) yields the HWE-reagent **42** (Scheme 12) as a mixture of starting material and product which proved difficult to separate. Due to the low yield and difficult separation, no further attempts were made to optimize and use this route.



Scheme 12. Synthesis of HWE-reagent; route A.[68]

Route B

The aldehyde **44** is unmasked from acetal **43**[70] in quantitative yield by refluxing in dilute HCl solution for 10 minutes. A Wittig reaction with ylid **45** yields the HWE-reagent **42** in moderate yield, contaminated with traces of triphenylphosphineoxide (Scheme 13). Because of this impurity this route was abandoned.

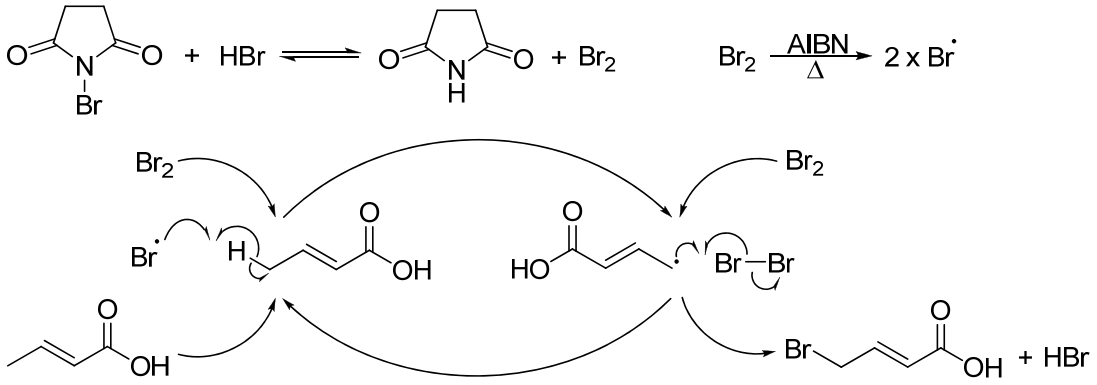


Scheme 13. Synthesis of HWE-reagent; route B.[1]

Route C

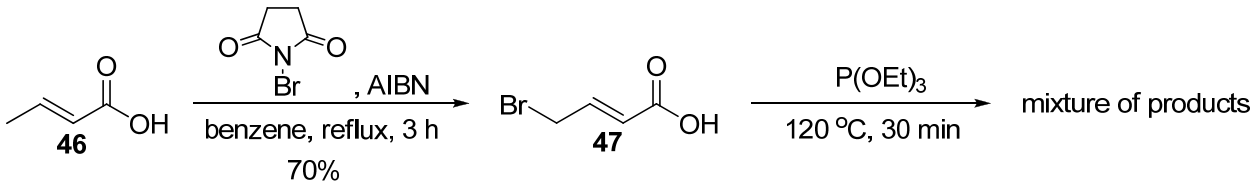
The first step in this route is the radical bromination of crotonic acid,[70] using N-bromosuccinimide (NBS) and azobis(isobutyronitile) (AIBN) under refluxing conditions in benzene. The original literature procedure describes toluene as solvent but this reaction proceeds via a radical pathway (Scheme 14). Toluene is not the optimal solvent since it can form benzylic radicals, which will react with NBS to give 1-bromotoluene so benzene is used instead.

[1] Only performed on preparative scale



Scheme 14. Mechanism of the radical bromination of crotonic acid.

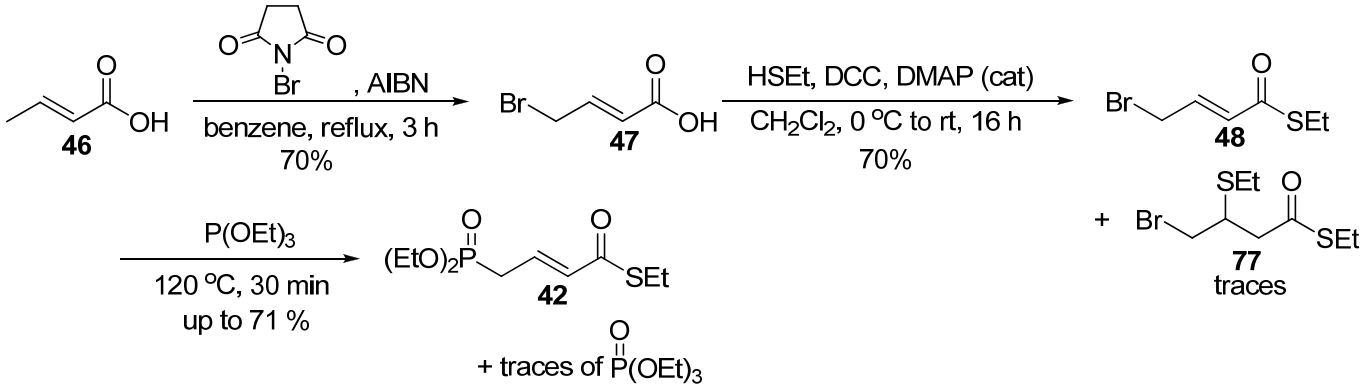
After recrystallization from toluene, 4-bromocrotonic acid **47** is obtained in good yield. The subsequent Arbuzov reaction with triethyl phosphite, gave an unidentified mixture of products (Scheme 15).



Scheme 15. Synthesis of HWE-reagent; route C.

Route D

As an alternative to route C, **47** can first be converted into the corresponding thioester via a N,N'-dicyclohexyldicarbodiimide (DCC) coupling with ethanethiol catalyzed by 4-dimethylaminopyridine (DMAP) in good yield, with traces of side product **77** (Scheme 16), formed by 1,4-addition of ethanethiol on the thioester. The Arbuzov reaction gives the HWE-reagent with inseparable traces of triethyl phosphite. Furthermore, the yields of this last step are irreproducible and vary from 25% to 75%. Therefore, the Arbuzov reaction was optimized.

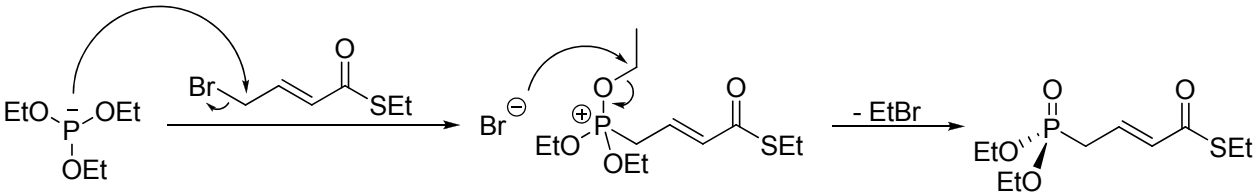


Scheme 16. Synthesis of HWE-reagent; route D.

Optimizing the Arbuzov reaction

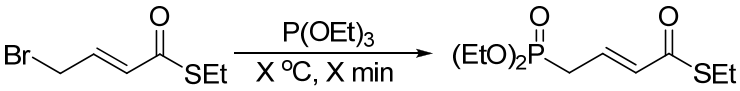
Standard reaction conditions for the Arbuzov reaction are addition of the alkylhalide to neat triethylphosphate at elevated temperature (typically 100-120 °C). After nucleophilic attack by the phosphorous on the alkylhalide, the halide ion dealkylates

the resulting trialkoxyphosphonium salt. The driving force for this reaction is the expellation of ethylbromide to give the phosphonate product (Scheme 17).



Scheme 17. Mechanism Arbuzov reaction.

The reaction temperature is important in this transformation. At 100 °C (Table 1, entry 2) full conversion is obtained in 30 min and the reaction proceeds in 65% yield reproducibly. At lower temperatures, both the conversion and yield drop (entries 3 and 4).



Entry	Temperature	Reaction time	Conversion	Yield
1	120 °C	15 min	100%	25 - 75%*
2	100 °C	30 min	100%	65%
3	80 °C	60 min	100%	40%
4	50 °C	5.5 h	75%	n.d.**

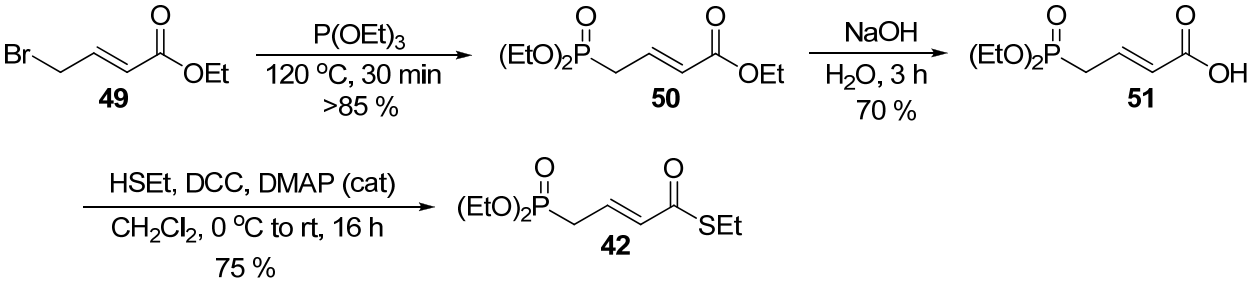
Table 1. Optimization Arbuzov reaction. * irreproducible ** $P(OEt)_3$ oxidized

Fast oxidation of triethyl phosphite at elevated temperatures causes the irreproducibility. Therefore, the best reaction conditions were repeated but now with prior removal of O_2 by degassing of the reaction mixture. Although the reaction time is identical, the ^1H NMR spectrum shows numerous side products. The desired product is only formed in low quantities.

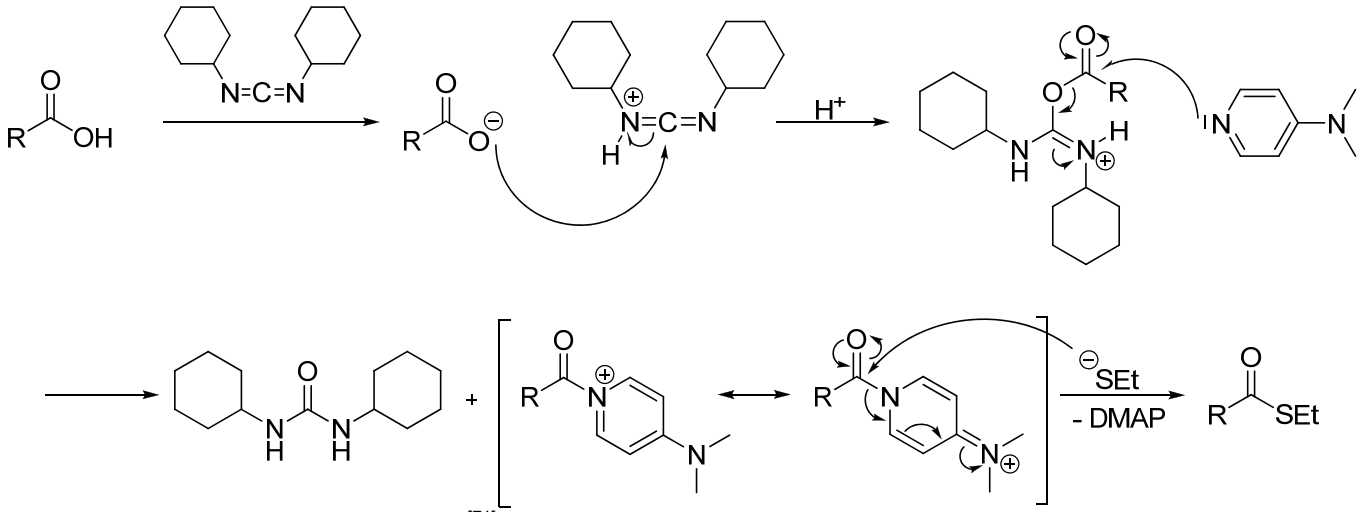
The Arbuzov reaction was optimized. Unfortunately, inseparable side products are still formed. Therefore, an alternative route is needed.

Route E

An alternative route (Scheme 18) starts from commercially available (*E*)-ethyl 4-bromobut-2-enoate **49**, an Arbuzov reaction furnishes phosphonate **50** in high yield and reproducibility. Saponification by aqeous sodiumhydroxide and subsequent DCC coupling of ethanethiol yields the HWE-reagent in good yield, with traces of dicyclohexylurea (the formation of which is shown in scheme 19).

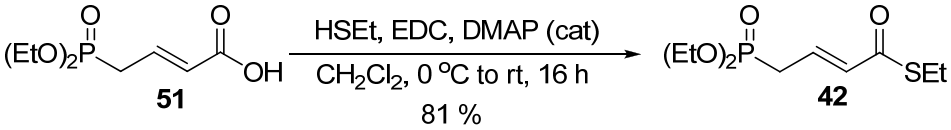


Scheme 18. Synthesis of HWE-reagent; route E.



Scheme 19. Mechanism DCC coupling.[71]

Unfortunately the urea is inseparable from the product. An alternative for DCC is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) (Scheme 20). The urea formed from EDC is water soluble and can thus be removed by aqueous extraction.



Scheme 20. Alternative last step in route E; using EDC instead of DCC.

2.3 Conclusions

Retrosynthetic analysis of the novel HWE-reagent provides numerous synthetic pathways. Problems for routes A to D were encountered in terms of reproducibility, long reaction times and impurities.

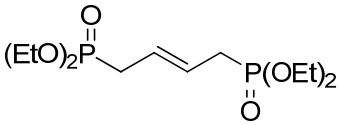
For route D, the optimal reaction temperature for the Arbuzov reaction was found to be 100 °C, reproducibly giving 65% of the desired product with traces of diethylphosphite.

Route E (Scheme 18 and 20) provides a quick and efficient synthetic route to the novel Horner-Wadsworth-Emmons reagent.

2.4 Experimental section

Route A:

Arbuzov reaction of (*E*)-1,4-dichloro-2-butene **37**:[68]

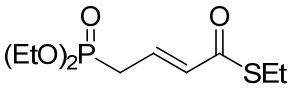


(*E*)-1,4-diphosphonate-2-butene (40):

In a round bottom flask equipped with stirring bar, (*E*)-1,4-dichloro-2-butene **37** (2.0 g, 16.0 mmol) and triethyl phosphite (6.86 mL, 40.0 mmol) were mixed at room temperature and this mixture was put in a preheated oil bath of 150 °C. The mixture

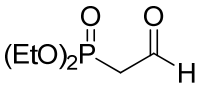
was stirred for 1 hour and allowed to cool down to room temperature. Flash column chromatography (100% Et_2O) yielded **40** in 15% yield as a yellowish oil.
Data in accordance with data described in ref [68].

Cross metathesis of **40** and ethyl-thioacrylate **41**:[69]



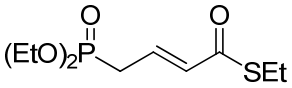
(*E*)-S-ethyl 4-(diethoxyphosphoryl)but-2-enethioate (42):
In a round bottom flask equipped with stirring bar, (*E*)-1,4-diphosponate-2-butene **40** (0.5 g, 1.5 mmol) and ethyl-thioacrylate **41** (0.12 mg, 1.0 mmol) were dissolved in CH_2Cl_2 (0.5 mL). Hoveyda-Grubbs catalyst 2nd generation (12.5 mg, 2 mol%) was added and the solution was brought to reflux. After 16 hours a second portion of HG^{II} (12.5 mg, 2 mol%) was added and refluxing was continued for another 6 hours. The mixture was concentrated in vacuo. The product was inseparable from the starting material by flash column chromatography.

Route B:[70]
Unmasking of aldehyde **44** from acetal **43**:



Diethyl 2-oxoethylphosphonate (44):
In a round bottom flask equipped with stirring bar, the acetal **43** (1.1 mL, 4.6 mmol) was dissolved in a 1% HCl solution in water (30 mL). After 8 h stirring at room temperature the reaction mixture was extracted with Et_2O (3x 15 mL). The combined organic extracts were washed with an aq. $NaHCO_3$ solution (saturated, 2x 30 mL), dried and carefully concentrated to a colorless oil (~30% yield) and immediately used for the Wittig reaction.
Data in accordance with data described in ref [70].

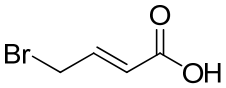
Wittig reaction of **44** with **45**:



(*E*)-S-ethyl-4-(diethoxyphosphoryl)but-2-enethioate (42):
In a round bottom flask equipped with stirring bar, **45** (1.49 g, 4.09 mmol, 1.3 equiv.) was dissolved in dry CH_2Cl_2 (30 mL). The aldehyde **44** (0.57 g, 3.15 mmol, 1.0 equiv.) was added and the reaction mixture was heated to reflux and stirred for 48 h, allowed to cool to room temperature and stirred for 4 days at room temperature. The reaction mixture was then concentrated and the remaining solid was washed with *n*-pentane (3x 10 mL). The combined organic extracts were concentrated to a yellow oil. Flash column chromatography (gradient 50% EtOAc/pentane to 100% EtOAc) yielded **42** as a colorless oil in ~60% yield with a minor impurity of triphenylphosphineoxide.
^{1}H NMR δ 6.85 – 6.67 (1 H, m), 6.20 (1 H, dd, J 15.5, 4.8), 4.20 – 3.98 (4 H, m), 2.92 (2 H, q, J 7.4), 2.70 (2 H, ddd, J 23.0, 7.8, 1.3), 1.30 (6 H, t, J 7.1), 1.25 (3 H, t, J 7.4). ; ^{13}C NMR δ 188.83 (0 H), 133.03 (1 H, d, 2JC-P 11.2), 132.24 (1 H, d, 3JC-P

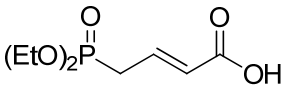
13.7), 62.04 (2 H, d, JC-P 6.6), 30.10 (2 H, d, 2JC-P 138.2), 22.86 (2 H), 16.11 (3 H, d 3JC-P 5.9), 14.40 (3 H); ^{31}P NMR δ 25.13 (t, J 13.6).; MS *m/z* 266 (M^+, 3), 205 (M-SEt, 62), 177 (M-COSEt, 33), 149 ($C_5H_{10}O_3$, 100); HRMS calcd. for $C_{10}H_{19}O_4PS$ 266.0742, found 299.0729.

Route C:
Bromination of crotonic acid **46**:[72]



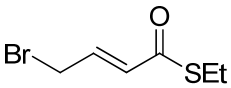
(*E*)-4-bromobut-2-enoic acid (4-bromocrotonic acid) (47):
In a round bottom flask equipped with stirring bar, crotonic acid **46** (20 g, 0.23 mol) and N-bromosuccinimide (46 g, 0.25 mol) were mixed in benzene (200 mL). After the solution was heated to reflux under nitrogen, AIBN (1.14 g, 6.97 mmol) was added and refluxing was continued for 2 h. Then the solution was cooled to 0 °C and filtered over celite and the residue was washed with benzene (50 mL). The filtrate was concentrated and recrystallized from toluene to yield a white solid in 70% yield.
Mp: 75 °C ; ^{1}H NMR δ 11.63 (1 H, s, br), 7.10 (1 H, dt, *J* 7.3, 15.3), 6.03 (1 H, d, *J* 15.4), 4.01 (2 H, d, *J* 7.3), spectrum contains traces of crotonic acid; ^{13}C NMR δ 171.3 (0 H), 144.65 (1 H), 123.99 (1 H), 28.86 (2 H) ; MS *m/z* 166 ($M^+[^{81}Br]$, 56), 164 ($M^+[^{79}Br]$, 56), 85 (M-Br, 100); HRMS calcd. for $C_4H_5BrO_2$ 163.9743, found 163.9471.

Arbuzov reaction of **47**:



(*E*)-4-diethoxyphosphorylbut-2-enoic acid (51):
In a round bottom flask equipped with stirring bar, (*E*)-4-bromobut-2-enoic acid **47** (90 mg, 0.55 mmol) and triethyl phosphite (0.1 mL, 0.60 mmol) were mixed at room temperature and this mixture was put in a preheated oil bath of 120 °C. The mixture was stirred for 30 minutes and allowed to cool down to room temperature. Flash column chromatography (50% EtOAc/pentane) yielded **51** as a yellowish oil in 11% yield as a mixture of products.

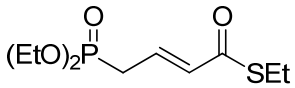
Route D:
Thioesterification of 4-bromocrotonic acid **47**:[69, 70]



(*E*)-S-ethyl 4-bromobut-2-enethioate (48):
In a round bottom flask equipped with stirring bar, 4-bromocrotonic acid **47** (3.47 g, 21.02 mmol), EtSH (1.55 mL, 21.02 mmol) and DMAP (0.26 g, 2.10 mmol) were dissolved in CH_2Cl_2 (120 mL), the solution was cooled to 0 °C using an ice bath and DCC (4.76 g, 23.12 mmol) was added. After addition, the ice bath was removed and the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was then filtered over celite and the residue washed with CH_2Cl_2 (30 mL). The combined organic extracts were washed with, subsequently, an aq. $NaHCO_3$ solution (saturated, 150 mL), H_2O (150 mL) and a saturated brine solution (100 mL), dried

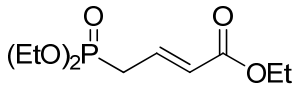
and carefully concentrated to a colorless oil. Flash column chromatography (1% Et_2O/pentane) yielded **48** as a colorless oil in 70% yield.
Data in accordance with data described in ref [69].

Arbuzov reaction of **48**:



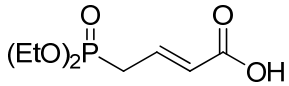
(*E*)-S-ethyl 4-(diethoxyphosphoryl)but-2-enethioate (42):
In a round bottom flask equipped with stirring bar, (*E*)-S-ethyl 4-bromobut-2-enethioate **48** (2.0 g, 9.57 mmol) and triethyl phosphite (2.33 mL, 13.40 mmol) were mixed at room temperature and then put in a preheated oil bath of 100 °C. The mixture was stirred for 30 minutes and allowed to cool down to room temperature. Flash column chromatography (66% EtOAc/pentane) yielded **42** in 65% yield as a yellowish oil.
For spectroscopic data see compound **42**.

Route E:
Arbuzov reaction of **49**:



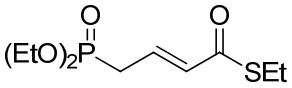
(*E*)-S-ethyl 4-(diethoxyphosphoryl)but-2-enoate (50):
In a round bottom flask equipped with stirring bar, (*E*)-ethyl 4-bromobut-2-eneoate (14.0 mL, 103.6 mmol) and triethyl phosphite (19.5 mL, 114 mmol) were mixed at room temperature and then put in a preheated oil bath of 120 °C. The mixture was stirred for 30 minutes and allowed to cool down to room temperature. Flash column chromatography (gradient 25% EtOAc/pentane to 100% EtOAc) yielded **50** as a colorless oil in >85% yield.
Data in accordance with data described in ref [73].

Saponification of triethylphosphonocrotonate **50**:



(*E*)-4-diethoxyphosphorylbut-2-enoic acid (51):
51 was obtained via a known procedure.[73]
Data in accordance with data described in ref [9] (4-diethoxyphosphoryl-2-butenoic acid).
[70% yield, colorless oil]
Data in accordance with data described in ref [73].

Thioesterification of **51**:

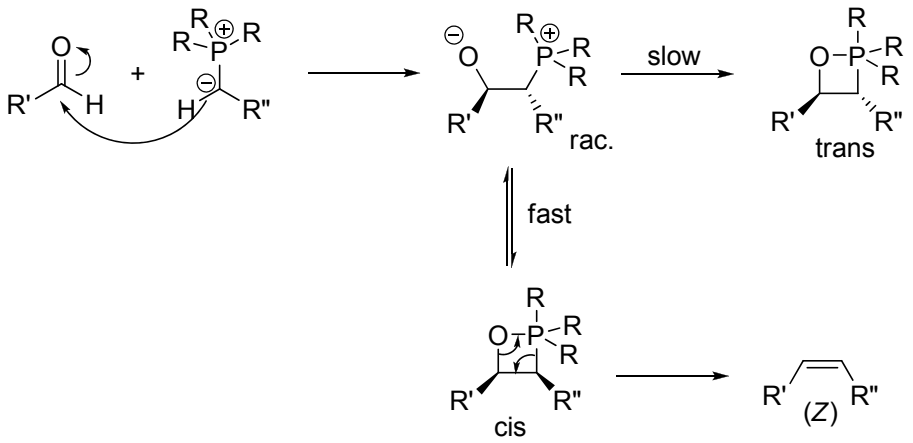


(*E*)-S-ethyl 4-(diethoxyphosphoryl)but-2-enethioate (42):
In a round bottom flask equipped with stirring bar, (*E*)-4-diethoxyphosphorylbut-2-enoic acid **51** (8.98 g, 40.42 mmol), EtSH (3.0 mL, 40.42 mmol) and DMAP (0.49 g, 4.04 mmol) were dissolved in CH_2Cl_2 (100 mL), the solution was cooled to 0 °C using an icebath and EDC (8.52 g, 44.46 mmol) was added. After addition the ice bath was removed and the reaction mixture was stirred for 16 h at room temperature. The reaction mixture was then filtered over celite and the residue washed with CH_2Cl_2 (30 mL). The combined organic extracts were washed with, subsequently, an aq. $NaHCO_3$ solution (saturated, 100 mL), H_2O (100 mL) and a saturated brine solution (75 mL), dried and carefully concentrated to a colorless oil. Flash column chromatography (gradient 20% EtOAc/pentane to 100% EtOAc) yielded **42** as a colorless oil in 81% yield.
For spectroscopic data see compound **42**.

3. Horner-Wadsworth-Emmons reaction

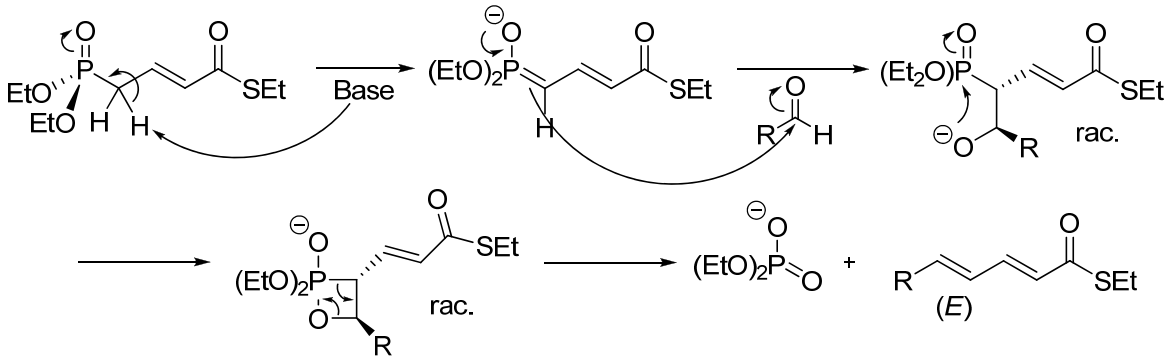
3.1 Introduction

In 1958 Horner published[74, 75] a modified Wittig reaction using a phosphonate-stabilized carbanion. Wadsworth and Emmons further improved this reaction.[76, 77] The reaction mechanism is very similar to that of the Wittig reaction (Scheme 21).[71] Both reactions form olefins by reaction of an aldehyde (or ketone) and a phosphorous containing nucleophile. For the Wittig reaction, the geometry of the resulting alkene depends on the reactivity of the ylid. Stabilized ylids in general give *E*-alkenes, whereas non-stabilized ylids give *Z*-alkenes.



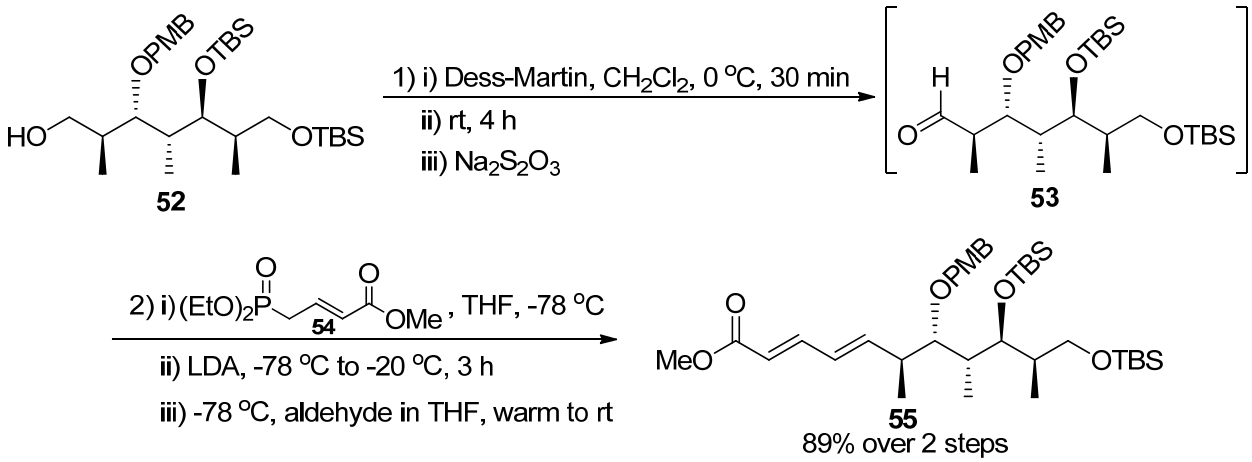
Scheme 21. Mechanism *Z*-selective Wittig reaction.

For the Horner-Wadsworth-Emmons reaction, the stereochemistry is controlled by sterics. In general, the HWE-reaction is *E*-selective. After deprotonation, the antiperiplanar approach of the carbanion to the carbonyl carbon is favored when the (small) aldehydic hydrogen eclipses the phosphoranyl group. After rotation to form the oxaphosphatene, the *E*-alkene product is formed (Scheme 22).



Scheme 22. Mechanism *E*-selective Horner-Wadsworth-Emmons reaction.

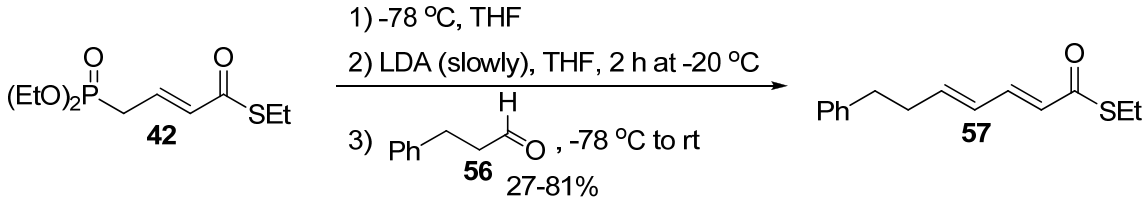
HWE-reactions with α,β-unsaturated phosphonate esters are known. A recent example by Mulzer *et al.* shows the transformation of an oxypropionate alcohol, via the aldehyde, to a bisunsaturated ester (Scheme 23).[78]



Scheme 23. Mulzer's synthesis of the propionate subunit of efomycine M.[78]

3.2 Synthesis

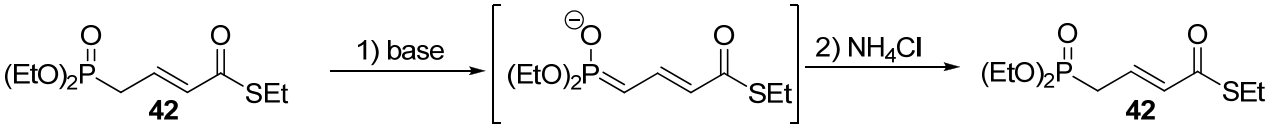
The HWE-reagent is dissolved in THF and cooled down to -78 °C. Then LDA (in THF) is slowly added to deprotonate the phosphonate. The reaction mixture is slowly allowed to warm to -20 °C to ensure carbanion formation and stirred for 2 hours. Subsequently the reaction mixture is cooled back to -78 °C and the aldehyde is slowly added in THF (Scheme 24). For initial screening 3-phenylpropionic aldehyde **56** was used because the anticipated bisunsaturated thioester product was believed to be non-volatile and stable. Using these conditions however, an irreproducible yield ranging from 27 to 81% was obtained.



Scheme 24. HWE-reaction with 3-phenylpropionic aldehyde **56**.

The irreproducible yield is believed to be due to minor impurities (HWE-reagent was obtained via route D). For further experiments, the HWE-reagent synthesized from route E was used. For the same reaction, the yield is 39-69%.

Optimization of the reaction conditions was performed. For the deprotonation, a strong base is required and possible candidates are LDA, *n*-BuLi, LHMDS and NaH. Degradation of HWE-reagent was investigated by deprotonating with base and reprotonating with NH_4Cl at low temperature (Table 2).

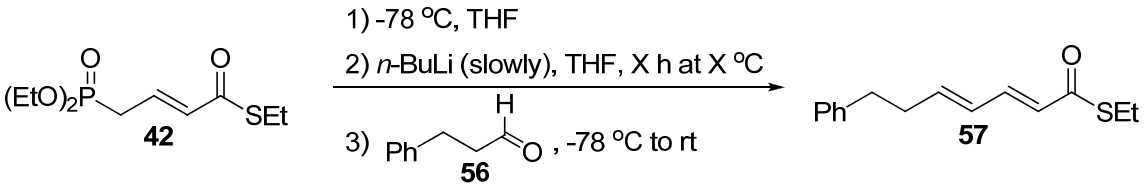


Entry	Base	Conditions	Degradation
1	LDA	-78 °C to -20 °C	<5%
2	*n*-BuLi	-78 °C, 2 h	<5%
3	*n*-BuLi	-78 °C to rt; 20 min	<5%
4	LHMDS	-78 °C; 30 min	<5%
5	LHMDS	-40 °C, 30 min	<5%
6	NaH	MeOH (2 mol%), -78 °C to -20 °C	>80%

Table 2. HWE-reagent degradation experiment.

The results in table 2 show that upon addition of NaH and a catalytic amount of MeOH, the HWE-reagent has degraded to a large extent after quenching with NH_4Cl. The other bases do not show a significant amount of degradation.

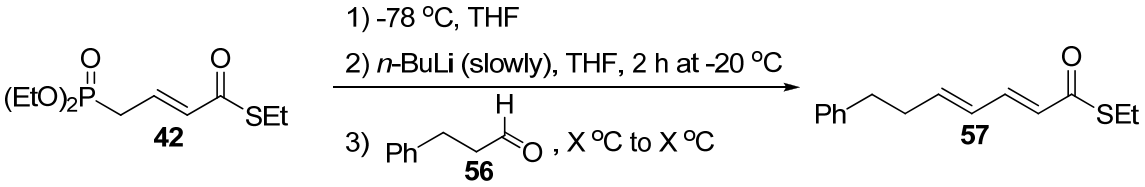
Furthermore, the deprotonation conditions (with *n*-BuLi as base) were screened. Stirring for 1.5 hours gives full conversion but the yield of the HWE-reaction varies from 39% to 69% (Table 3; entry 2). Higher temperatures lower the yield (entry 3).



Entry	Reaction time	Temperature	Yield	Notes
1	10 min	-78 °C	25%	conversion not full
2	1.5 h	-78 °C	39-69%	-
3	30 min	0 °C	30-34%	-

Table 3. Temperature dependency of the deprotonation.

The conditions of addition of aldehyde to the carbanion was also investigated (Table 4). Normally, the aldehyde is added at low temperature (usually -78 °C) and the reaction mixture is allowed to slowly warm up to room temperature.

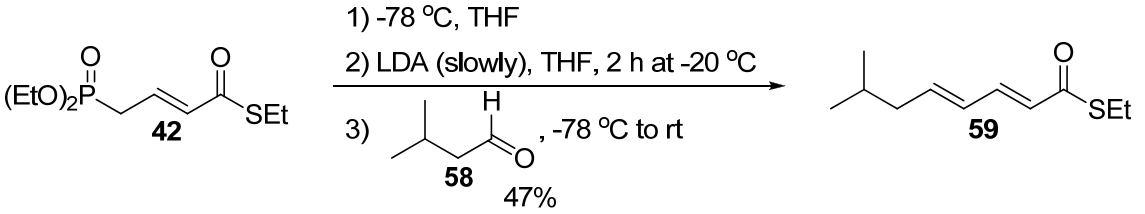


Entry	Conditions	Yield	Notes
1	-20 °C to rt	10%	side products
2	-78 °C to rt	26%	-
3	-78 °C overnight	<10%	conversion not full

Table 4. Temperature dependency of the aldehyde addition.

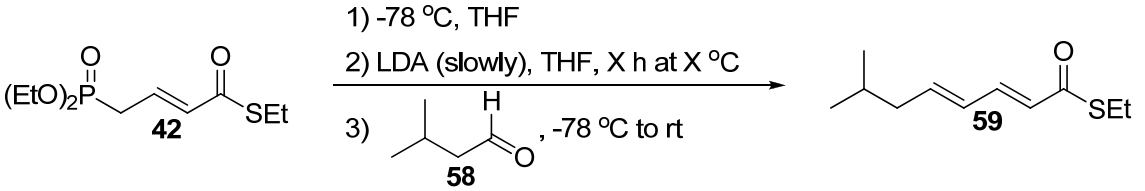
Addition of aldehyde at -20 °C leads to the formation of side products and the yield of the desired product is only 10% (Table 4; entry 1). Under standard conditions, the yield is 26% (entry 2). Keeping the temperature at -78 °C overnight gives low conversion and lowers the yield to 10% (entry 3).

From a recent article[79] by Davies *et al.* it was concluded that the model aldehyde **56**, gives lower yield than other aldehydes in HWE-reactions. Therefore, propionphenylaldehyde **56** was replaced by isovaleraldehyde **58** as the model aldehyde.



Scheme 25. Horner-Wadsworth-Emmons reaction with isovaleraldehyde **58**.

The HWE-reaction of **58** gives the desired product in 47% yield (Scheme 25). Again, optimization of conditions was performed.



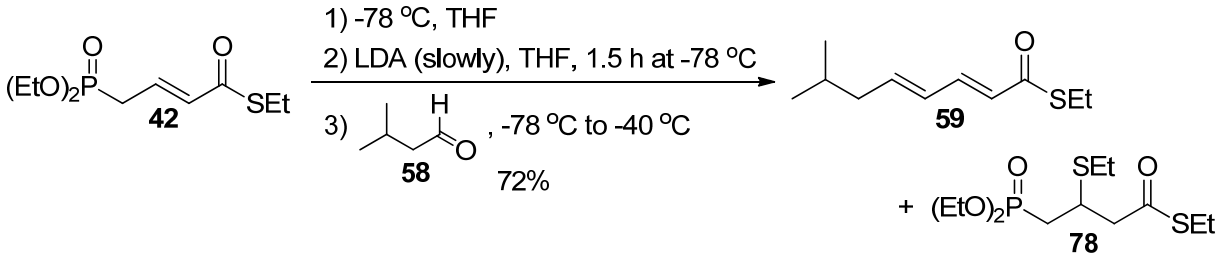
Entry	Conditions	Yield
1	1.5 h at -78 °C	53%
2	-78 °C to rt	47%

Table 5. Temperature dependency of the deprotonation.

The yields are in the same order of magnitude, whether the reaction mixture is kept at -78 °C or allowed to warm to room temperature (Table 5; entries 1 and 2).

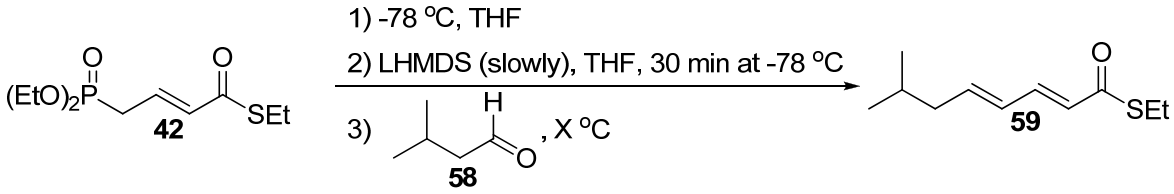
Using *n*-BuLi for the deprotonation, side product **78** is formed. Although to a lesser extent, **78** is also formed when using LDA. Adding the aldehyde at temperatures higher than -30 °C, more **78** is formed. After thorough examination, **78** could be

identified as the product of 1,4-addition of ethanethiol to the HWE-reagent (Scheme 26). The ethanethiol is liberated from the HWE-reagent by nucleophilic attack of the *n*-BuLi and attacks a second molecule of HWE-reagent to form side product **78** which can no longer participate in the HWE-reaction. LDA on the other hand forms diisopropylamine after deprotonating, which is still a base and may not be innocent. Therefore, LHMDS is the reagent of choice.



Scheme 26. Side product formation during the HWE-reaction.

The reaction conditions for the addition of aldehyde and the HWE-reaction were optimized hereafter.

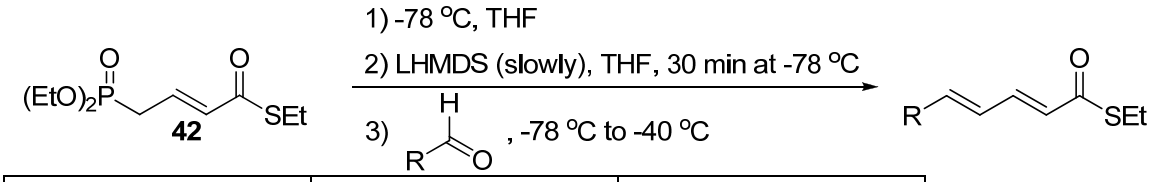


Entry	Conditions	Yield	Notes
1	-78 °C to rt	50%	-
2	-78 °C to -40 °C	72%	overnight
3	-78 °C to -20 °C	74%	overnight
4	-40 °C	70%	overnight
5	-30 °C to rt	35%	-
6	-78 °C to rt	<15%	excess aldehyde

Table 6. Temperature dependency of the aldehyde addition step.

For addition of isovaleraldehyde at -78 °C and allowing the reaction to warm up to room temperature slowly, the yield is 50% (Table 6; entry 1). Raising the final temperature or keeping the temperature at -40 °C increases the yield to ~70% (entries 2 to 4). Addition of isovaleraldehyde at a temperature higher than -40 °C decreases the yield (entry 5). Possibly, the aldehyde reacts away to form side products. This hypothesis was tested by adding an excess of aldehyde at -78 °C and allowing the reaction mixture to slowly warm to room temperature. The yield dropped to <15% (entry 6), the side reaction therefore occurs with the HWE-reagent, not with the aldehyde. As the risk of side reactions is increased at higher temperatures, the optimal conditions are adding the aldehyde at -78 °C and allowing it to warm to -40 °C overnight (72% yield).

To broaden the scope of the reactions, benzyl protected 1-hydroxybutanal was also subjected to the HWE-reaction under the optimal conditions. A summary of yields for the different aldehydes is given in table 7.



Entry	R	Yield
1	$Ph(CH_2)_2$	39-69%
2	*i*-Bu	72%
3	$BnO(CH_2)_3$	50%

Table 7. Optimized HWE-reaction for different aldehydes.

3.3 Conclusions

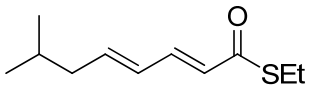
From a variety of bases, LHMDS was identified as optimal base. Furthermore, it was shown in a recent article[79] that the HWE-reaction with 3-phenylpropionic aldehyde gives lower yields than other aldehydes. Therefore, isovaleraldehyde **58** was chosen as the model aldehyde. The optimal conditions for the HWE-reaction are addition of the aldehyde at -78 °C and allowing the reaction mixture to warm to -40 °C overnight.

In conclusion, a new method to synthesize bisunsaturated thioesters was developed based on the HWE-reaction.

3.4 Experimental section

General procedure for the Horner-Wadsworth-Emmons reaction of an aldehyde and HWE reagent 42:

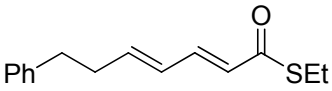
In a round bottom flask equipped with stirring bar (*E*)-S-ethyl 4-(diethoxyphosphoryl)but-2-enethioate **42** (200 mg, 0.75 mmol) was dissolved in dry THF (0.5 mL) and cooled to -78 °C. LHMDS (0.7 mL, 0.70 mmol) was added slowly and the mixture stirred for 30 minutes. Then, aldehyde (0.5 mmol) dissolved in dry THF (0.5 mL) was added slowly. After addition, the solution was allowed to warm to -40 °C and stirred for 16 h. A solution of NH_4Cl (1M, 1 mL) was added and the mixture extracted with Et_2O (3x 2 mL). The combined organic extracts were dried and concentrated. Flash column chromatography (1% Et_2O/pentane) yields the bisunsaturated thioester as a colorless oil.



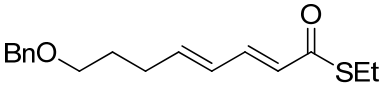
(2*E*,4*E*)-S-ethyl 7-methylocta-2,4-dienethioate (59):

[72% yield (0.5 mmol scale); 42% yield (2.0 mmol scale), colorless oil].

^{1}H NMR δ 7.16 (1 H, dd, *J* 15.2, 10.0), 6.20 – 6.01 (3 H, m), 2.93 (2 H, q, *J* 7.3), 2.03 (2 H, t, *J* 6.6), 1.68 (1 H, dt, *J* 13.3, 6.7), 1.25 (3 H, t, *J* 7.4), 0.88 (6 H, d, *J* 6.6); ^{13}C NMR δ 190.29 (0 H), 145.28 (1 H), 141.02 (1 H), 129.50 (1 H), 126.64 (1 H), 42.65 (2 H), 28.47 (1 H), 23.33 (2 H), 22.52 (3 H), 15.06 (3 H); MS *m/z* 198 (M^+, 18), 137 (M-SEt, 100); HRMS calcd. for $C_{11}H_{18}OS$ 198.1078, found 198.1087.



(2*E*,4*E*)-S-ethyl 7-phenylhepta-2,4-dienethioate (57):
[39-69% yield, colorless oil].
^{1}H NMR δ 7.33 – 7.25 (2 H, m), 7.23 – 7.13 (4 H, m), 6.25 – 6.11 (2 H, m), 6.07 (1 H, d, *J* 15.2), 2.96 (2 H, qd, *J* 7.4, 1.1), 2.75 (2 H, t, *J* 7.7), 2.50 (2 H, dd, *J* 14.5, 7.0), 1.28 (3 H, td, *J* 7.4, 1.2); ^{13}C NMR δ 190.07 (0 H), 144.80 (1 H), 141.10 (0 H), 140.63 (1 H), 128.92 (1 H), 128.54 (1 H), 128.48 (1 H), 126.93 (1 H), 126.20 (1 H), 35.13 (2 H), 34.96 (2 H), 23.28 (2 H), 14.99 (3 H); MS *m/z* 246 (M^+, 4), 185 (M-SEt, 63), 91 ($C_6H_5CH_2$, 100); HRMS calcd. for $C_{15}H_{18}OS$ 246.1078, found 246.1090.

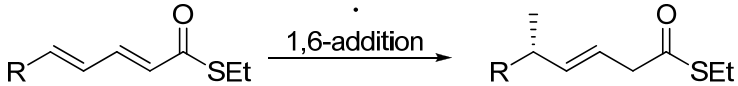


(2*E*,4*E*)-S-ethyl 6-(benzyloxy)hexa-2,4-dienethioate (61):[2]
[10% yield, colorless oil].
^{1}H NMR δ 7.30 – 7.15 (5 H, m), 7.09 (1 H, dd, *J* 15.2, 10.0), 6.15 – 6.01 (2 H, m), 5.98 (1 H, d, *J* 15.1), 4.40 (2 H, s), 3.39 (2 H, td, *J* 6.2, 1.5), 2.87 (2 H, qd, *J* 7.4, 1.7), 2.24 – 2.16 (2 H, m), 1.72 – 1.61 (2 H, m), 1.19 (3 H, td, *J* 7.4, 1.8); ^{13}C NMR δ 190.11 (0 H), 145.37 (1 H), 140.76 (1 H), 138.53 (0 H), 128.75 (1 H), 128.49 (1 H), 127.76 (1 H), 127.70 (1 H), 126.73 (1 H), 73.05 (2 H), 69.40 (2 H), 29.95 (2 H), 28.87 (2 H), 23.27 (2 H), 15.00 (3 H); MS *m/z* 229 (M^+-SEt, 1), 91 ($C_6H_5CH_2$, 100); HRMS calcd. for $C_{17}H_{22}O_2S$ (M+Na) 313.1238, found 313.1228.

4. Isomerization

4.1 Introduction

The product of a 1,6-addition on a bisunsaturated thioester is a β,γ-unsaturated thioester (Scheme 27). However, as described in the retrosynthetic analysis (see scheme 10), an α,β-unsaturated thioester is required for the subsequent 1,4-addition. Therefore, the isomerization step is important in the overall synthesis, and is required once for every new Me-group introduced.



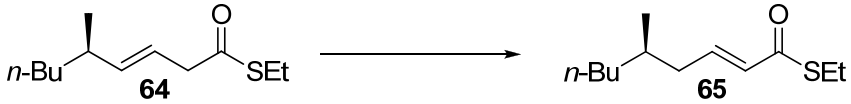
Scheme 27. 1,6-Addition yields a β,γ-unsaturated thioester.

Double bond isomerizations are well known and can usually be performed with heat, acid, base or transition metal catalysts.

4.2 Synthesis

The product of the isomerization step, the α,β-unsaturated thioester, is believed to be more stable than the starting β,γ-unsaturated thioester due to conjugation. β,γ-Unsaturated thioester substrate was exposed to a number of different conditions to verify the best method for isomerization (Table 8).

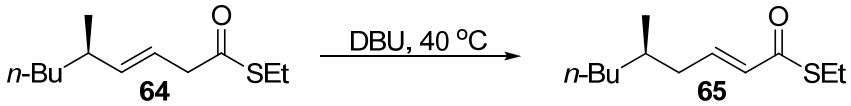
[2] The aldehyde was prepared via known procedures.[65, 80]



Entry	Conditions	% Isomerization	Combined yield (α,β + β,γ)
1	140 °C in xylene	<10%	n.d.
2	$RhCl(PPh_3)_3$ in CH_2Cl_2, rt	~10%	n.d.
3	$Pd(OAc)_2$, PPh_3 in CH_2Cl_2/MeCN, rt	~10%	n.d.
4	$RuCl_3$ in CH_2Cl_2/MeCN, rt	<10%	n.d.
5	NEt_3 (2 equiv.) in CH_2Cl_2, 40 °C	~10%	n.d.
6	in NEt_3, 40 °C	<10%	n.d.
7	0.1 equiv. DBU in CH_2Cl_2, 40 °C, 16 h	50%	88%

Table 8. Double bond isomerization.

Upon heating, starting material was the main product (Table 8; entry 1). When changing to transition metal catalysts like rhodium, palladium and ruthenium, the product was only formed in trace amounts (entries 2-4). When exposing the substrate to 2 equivalents of base (triethylamine) in CH_2Cl_2 at 40 °C (entry 5) or stirring the substrate in neat triethylamine at 40 °C (entry 6), the isomerized product was only formed in trace amounts. 0.1 Equivalents of DBU isomerizes 50% of the β,γ-unsaturated substrate to the α,β-unsaturated product in 88% combined yield (entry 7). Unfortunately, the α,β- and β,γ-isomers are inseparable. Optimization of the isomerization by DBU was performed.



Entry	Equivalents	Reaction time (40 °C)	% Isomerization	Combined yield (α,β + β,γ)
1	0.1	16 h	50%	88%
2	0.25	16 h	60%	n.d.
3	1.5	16 h	80%	87%
4	5	16 h	88%	88%
5	10	16 h	88%	88%
6	10	3 days	85%	90%

Table 9. Double bond isomerization using DBU.

When adding more equivalents of DBU to the substrate, the quantity isomerized product increases (Table 9; entries 2-4). When adding more than 5 equivalents (entry 5) or running the reaction for extended reaction times (3 days, entry 6), the isomerization percentage does not increase, indicating that the reaction reaches its equilibrium at 88% isomerization (entry 5). The enantiomeric excess of the Me-center is unchanged during the isomerization.

4.3 Conclusions

Catalytic amounts of transition metal catalysts such as rhodium, palladium or ruthenium as well as heat or use of a weak base did not give the desired product.

Upon addition of 5 equivalents of DBU however, the isomerization proceeds smoothly in 88%, yielding the desired product (with trace amounts of starting material) in 88%. The product and starting material however cannot be separated.

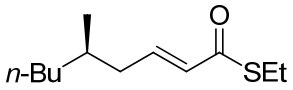
A good and reliable method was developed for the isomerization of β,γ-unsaturated thioesters to α,β-unsaturated thioesters.

4.4 Experimental section

General procedure for the isomerization of the β,γ-unsaturated thioester to the α,β-unsaturated thioester:[3]

(exemplified for the isomerization of **64**)

In a dried round bottom flask equipped with cooler and stirring bar under nitrogen, **64** (0.37 g, 1.7 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (18 mL). After 5 minutes stirring at room temperature, DBU (1.3 mL, 8.6 mmol, 5.0 equiv.) was added and the reaction mixture immediately turned yellow/orange. The reaction mixture was heated to reflux and stirred for 16 h. Subsequently an aq. NH_4Cl solution (1M, 20 mL) and 10 mL of CH_2Cl_2 were added and the layers were separated. After extraction with CH_2Cl_2 (2x 10 mL), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (1% Et_2O/pentane) yielded **65** as a colorless oil.



(*R*,*E*)-S-ethyl 5-methylnon-2-enethioate (65):

[91% yield of a mixture of x% α,β- and x% β,γ-unsaturated product, $[\alpha]_D^{20}$ = -1.0 (c = 1.0, CH_3Cl); colorless oil];

Data in accordance with data described in ref [81].

5. Iterative steps

5.1 Introduction

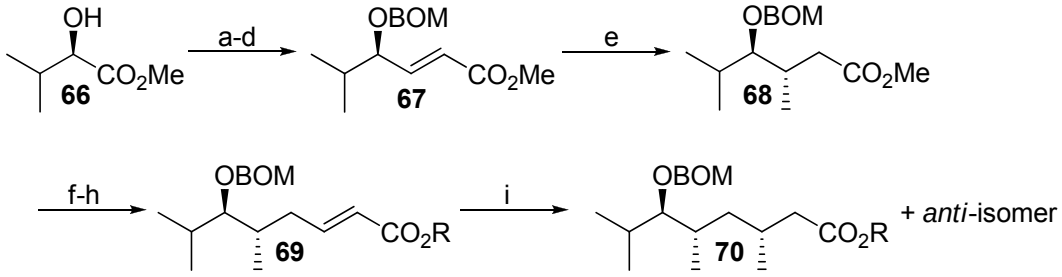
After optimization of the synthesis of the HWE-reagent, the HWE-reaction and the double bond isomerization, the iterative sequence could be studied. The synthesis of a deoxypropionate building block with three stereogenic Me-centers from a bisunsaturated thioester is described in this chapter.

5.1.1 Inductor effect

Most natural products containing deoxypropionate subunits have an all-*syn* configuration. In fact, it is often found that conjugate addition of lithium dimetyhlcuprate to acyclic α,β-unsaturated esters of various lengths and with either terminal alkyl or phenyl groups greatly favor the *syn*-diastereomer when a methyl is already present in the substrate. Hanessian and coworkers studied[82] the effect of end-group variation and the nature of the ester group on the diastereoselectivity of such conjugate additions. They find strong preferences for the formation of all-*syn*-

[3] This reaction was performed from 0.3 mmol up to 1.7 mmol scale.

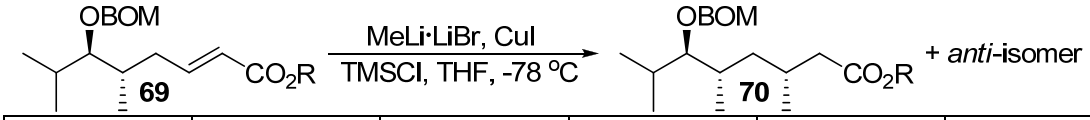
products. The results are rationalized as inductor effects that arise from an energetically favored folded conformation in the transition state that minimizes 1,5-pentane interactions. The nature and bulkiness of the ester group are of importance since *syn*-selectivity is still increasing when going from methyl to *t*-butyl to methylcyclopentyl (MCP) for the fourth cuprate addition (shown for the second cuprate addition in scheme 28 and table 10).



R = Me, *i*-Pr, *neo*-Pent, *t*-Bu, MCP

Scheme 28.* Effect of the ester group on *syn*-selectivity.[82]

* Reagents and conditions: (a) BOMCl, NEt(*i*-Pr)$_2$, CH_2Cl_2, 85%; (b) DIBAL-H, CH_2Cl_2, -78 °C, 92%; (c) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, -78 °C, 97%; (d) PPh_3=C(H)CO_2Me, CH_2Cl_2, *E*:*Z* >20:1, 91%; (e) MeLi·LiBr, CuI, TMSCl, THF, -78 °C, *syn*:*anti* >15:1, 96%; (f) repeat b, 93%; (g) repeat c, 97%, (h) PPh_3=C(H)CO_2R, CH_2Cl_2, for **69a**, 96%; **69b**, 85%; **69c**, 64%; **69d**, 91%; **69e**, 74%; (i) repeat e, see table 10 for yields and *syn*:*anti* ratios. MCP = 1-methyl-1-cyclopentyl.



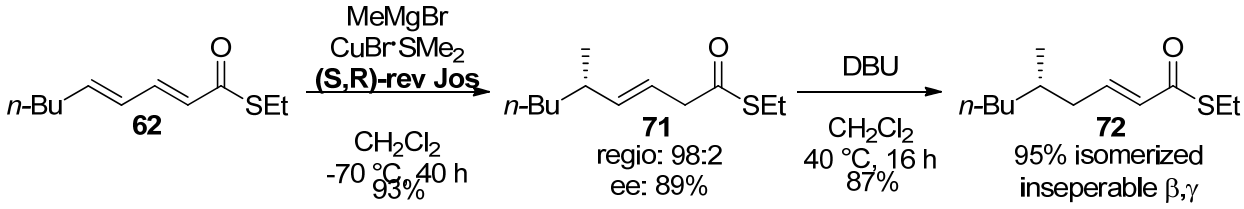
Entry	Compound	Product	R	*syn*:*anti*	yield
1	**69a**	**70a**	Me	75:25	80%
2	**69b**	**70b**	*i*-Pr	77:23	96%
3	**69c**	**70c**	*neo*-Pent	78:22	93%
4	**69d**	**70d**	*t*-Bu	89:11	87%
5	**69e**	**70e**	MCP	91:9	89%

Table 10. Effect of the ester group on *syn*-selectivity.[82]

Hanessian's research[82] shows that when a stereogenic Me-center is already present in the substrate, asymmetric conjugate addition is likely to show better *syn*- than *anti*-selectivity.

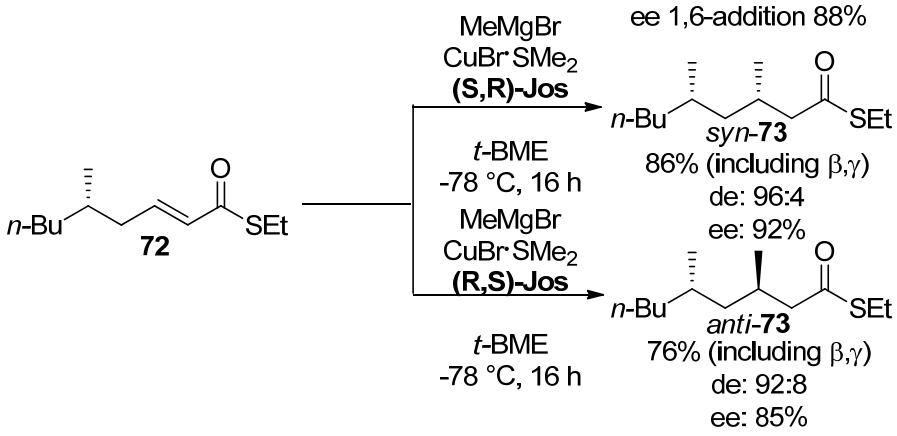
5.2 Synthesis

1,6-Addition of MeMgBr on substrate **62** introduces the first stereogenic Me-group in excellent yield (93%) and with excellent regio- and stereoselectivity (regio: 98:2 and 89% ee respectively). Subsequent isomerization with DBU furnishes the α,β-unsaturated thioester (Scheme 29). The product contains trace amounts of β,γ-unsaturated thioester.



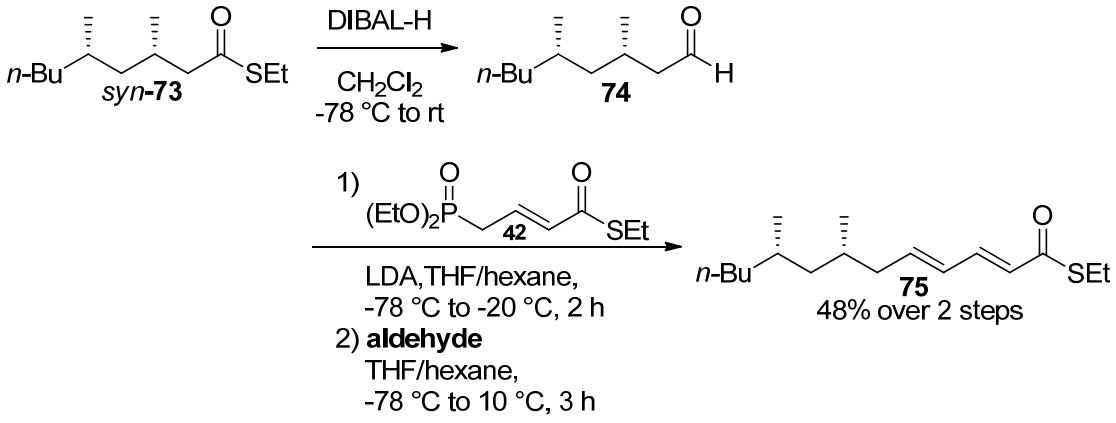
Scheme 29. Iterative sequence: first 1,6-addition and isomerization.

Subjecting **72** to the 1,4-addition using two different catalysts gives either the *syn*- or *anti*-isomer. Both in excellent enantiomeric and diastereomeric excess (92%, 96:4 and 85%, 92:8 respectively) as well as good to excellent yield (86% and 76% respectively). The substrate has a strong preference for the *syn*-motif as expected from the work of Hanessian,[82] and synthesis of this product proceeds with better diastereomeric ratios. It is important to note that the enantiomeric excess of the first stereogenic Me-center is unchanged (Scheme 30).



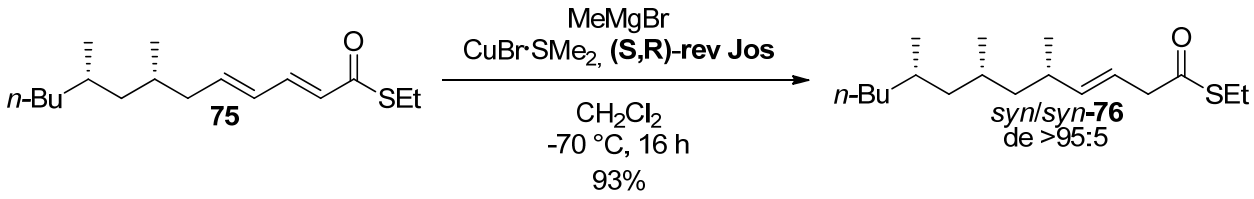
Scheme 30. Iterative sequence: 1,4-addition.

Consecutive reduction of the thioester with DIBAL-H and HWE-reaction gives bisunsaturated thioester **75** (Scheme 31).



Scheme 31. DIBAL-H reduction and subsequent HWE-reaction.

Another 1,6-addition furnishes the third stereogenic Me-center in excellent yield (93%) and diasteromeric excess (>95:5) (Scheme 32).



Scheme 32. Iterative sequence: third 1,6-addition.

More Me-centers can be introduced following the same sequence and based on literature,[61] the diastereomeric ratios is expected to follow the same trend for each new center.

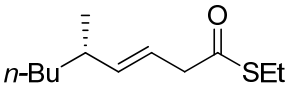
5.3 Conclusions

It was demonstrated that from a given aldehyde, up to three sterogenic Me-centers can be introduced in a 1,3-pattern. Repetition of the iterative steps allows introduction of Me-centers with good control over the relative configuration of each new Me-group.
An odd number of Me-groups can also be introduced by performing the reduction directly after the isomerization step, introducing the second double bond when there is still one present in the substrate.

5.4 Experimental section

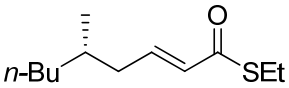
General procedure for the enantioselective 1,6-conjugate addition:[4]
(exemplified for the addition of MeMgBr to **62**)
In a dried Schlenk tube equipped with septum and stirring bar under nitrogen, CuBr•SMe_2 (5.14 mg, 25 µmol, 5.0 mol%) and (*R,S*)-reversed Josiphos (15.46 mg, 26 µmol, 5.25 mol%) were dissolved in dry CH_2Cl_2 (2 mL). After 5 min stirring at room temperature the mixture was cooled to -70 °C and MeMgBr (Aldrich, 3.0M solution in Et_2O, 0.33 mL, 1.0 mmol, 2.0 equiv.) was added. After stirring for an additional 10 min, a solution of **62** (70.1 mg, 0.5 mmol, 1.0 equiv.) in dry CH_2Cl_2 (additional 0.5 mL) was added with syringe pump over 2 h. The reaction mixture was stirred overnight (16 h including addition) at -70 °C and subsequently EtOH (0.1 mL) and an aq. NH_4Cl-solution (1M, 0.5 mL) were added. The mixture was warmed to room temperature and an additional 5 mL of the NH_4Cl solution and 5 mL of CH_2Cl_2 were added and the layers were separated. After extraction with CH_2Cl_2 (2x 5 mL), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (1% Et_2O/pentane) yielded **71** as a colorless oil.[5]

[4] This reaction has been performed up to 2.7 mmol scale. For larger scale reactions reaction time becomes longer. Typically >95% conversion was achieved in up to 40 h.
[5] Occasionally the product is polluted with a yellow coloured side product undetectable by GC/MS or NMR.



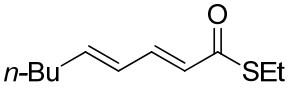
(*S*,*E*)-S-ethyl 5-methylnon-3-enethioate (71):
[83% yield, 89% ee, $[\alpha]_D^{20}$ = +9.0 (c = 1.0, CH_3Cl); colorless oil];
^{1}H NMR δ 5.50 – 5.39 (2 H, m), 3.19 (2 H, d, *J* 5.7), 2.84 (2 H, q, *J* 7.4), 2.18 – 2.04 (1 H, m), 1.31 – 1.16 (9 H, m), 0.96 (3 H, d, *J* 6.7), 0.86 (3 H, t, *J* 6.7); ^{13}C NMR δ 198.74 (0 H), 142.55 (1 H), 119.57 (1 H), 47.89 (2 H), 36.94 (1 H), 36.73 (2 H), 29.70 (2 H), 23.50 (2 H), 22.98 (2 H), 20.55 (3 H), 14.90 (3 H), 14.33 (3 H); MS *m/z* 214 (M^+, 10), 124 (M-SEt-Et, 34), 83 (C_6H_{11}, 46), 69 (C_5H_9, 100); HRMS calcd. for $C_{12}H_{22}OS$ 214.1391, found 214.1401.

For the general procedure for the isomerization of β,γ-unsaturated thioester to the α,β-unsaturated thioester the reader is reffered to chapter 4.



(*S*,*E*)-S-ethyl 5-methylnon-2-enethioate (72):
[91% yield of a mixture of x% α,β- and x% β,γ-unsaturated product, $[\alpha]_D^{20}$ = +1.0 (c = 1.0, CH_3Cl); colorless oil];
Data in accordance with data described in ref [81].

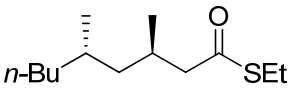
Wittig reaction of (*E*)-hept-2-enal **61** and **42**:



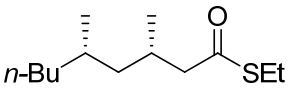
(2*E*,4*E*)-S-ethyl nona-2,4-dienethioate (62):
In a round bottom flask equipped with stirring bar, **42** (5.43 g, 14.9 mmol, 1.3 equiv.) was dissolved in dry CH_2Cl_2 (80 mL). The aldehyde **61** (1.5 mL, 11.5 mmol, 1.0 equiv.) was added, the reaction mixture was heated to reflux and stirred for 20 h. The reaction mixture was then concentrated and the remaining solid was washed with *n*-pentane (3x 10 mL). The combined organic extracts were concentrated to a yellow oil. Flash column chromatography (1% Et_2O/pentane) yielded **62** in 61% yield as a colorless oil.
^{1}H NMR δ 7.16 (1 H, dd, *J* 15.2, 10.1), 6.22 – 6.09 (2 H, m), 6.05 (1 H, d, *J* 15.2), 2.93 (2 H, q, *J* 7.4), 2.16 (2 H, dd, *J* 13.9, 6.7), 1.39 (2 H, dt, *J* 14.4, 7.2), 1.34 – 1.29 (2 H, m), 1.26 (3 H, td, *J* 7.4, 0.5), 0.88 (3 H, t, *J* 7.2); ^{13}C NMR δ 190.33 (0 H), 146.56 (1 H), 141.14 (1 H), 128.42 (1 H), 126.56 (1 H), 33.06 (2 H), 30.99 (2 H), 23.35 (2 H), 22.44 (2 H), 15.08 (3 H), 14.07 (3 H); MS *m/z* 198 (M^+, 14), 137 (M-SEt, 100), 81 (C_5H_5O, 39); HRMS calcd. for $C_{11}H_{18}OS$ 198.1078, found 198.1083.

General procedure for the enantioselective 1,4-conjugate addition:
(exemplified for the addition of MeMgBr to **72**)
In a dried Schlenk tube equipped with septum and stirring bar under nitrogen, the preprepared Josiphos-complex (5.54 mg, 7.5 µmol, 1.0 mol%) was dissolved in dry *t*-BuOMe (3.05 mL). After 5 min stirring at room temperature the mixture was cooled to -78 °C and MeMgBr (Aldrich, 3.0M solution in Et_2O, 0.38 mL, 1.1 mmol, 1.5 equiv.) was added. After stirring for an additional 10 min, a solution of **72** (0.16 mg, 0.75 mmol, 1.0 equiv.) in dry *t*-BuOMe (additional 0.75 mL) was added with syringe pump

over 30 minutes. The reaction mixture was stirred overnight (16 h including addition) at -78 °C and subsequently EtOH (0.1 mL) and an aq. NH_4Cl solution (1M, 0.5 mL) were added. The mixture was warmed to room temperature and an additional 5 mL of the NH_4Cl solution and 5 mL of Et_2O were added and the layers were separated. After extraction with Et_2O (2x 5 mL), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (1% Et_2O/pentane) yielded *anti*-**73** as a colorless oil.



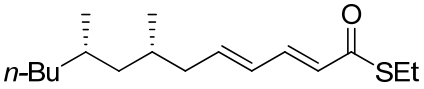
(3*R*,5*S*)-S-ethyl 3,5-dimethylnonanethioate (*anti*-73):
[X% yield of a mixture of x% ***syn*-73** and x% of ***anti*-73**, $[\alpha]_D^{20}$ = +13.9 (c = 1.0, CH_3Cl); colorless oil];
Data in accordance with data described in ref [65].



(3*S*,5*S*)-S-ethyl 3,5-dimethylnonanethioate (*syn*-73):
[X% yield of a mixture of x% ***syn*-73** and x% of ***anti*-73**, $[\alpha]_D^{20}$ = -1.3 (c = 1.0, CH_3Cl); colorless oil];
Data in accordance with data described in ref [65].

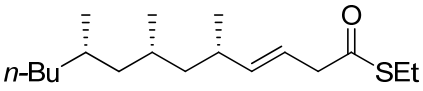
General procedure for the reduction of thioester to aldehyde:
In a dried Schlenk tube equipped with septum and stirring bar under nitrogen, ***syn*-73** (0.51 mg, 2.21 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (5 mL). After 5 minutes stirring at room temperature the mixture was cooled to -75 °C and DIBAL-H (1.0M solution in CH_2Cl_2, 2.66 mL, 2.66 mmol, 1.2 equiv.) was added. The solution turned pink/orange. The reaction mixture was stirred for 5 h at -75 °C. Subsequently the reaction mixture was poured into a round bottom flask with aq. Rochelle's salt-solution (saturated, 10 mL), stirred for 1 h at room temperature and the layers were separated. After extraction with CH_2Cl_2 (2x 5 mL), the combined organic extracts were washed with the aq. Rochelle's salt solution (2x 5 mL), dried and carefully concentrated. Flash column chromatography (10% Et_2O/pentane) yielded **74** as a highly odorous, colorless oil.

Chain prolongation:
Compound **75** was obtained via the general procedure for the Horner-Wadsworth-Emmons reaction of an aldehyde and HWE-reagent **42**:



(2*E*,4*E*,7*S*,9*S*)-*S*-ethyl 7,9-dimethyltrideca-2,4-dienethioate (75):
[X% yield, $[\alpha]_D^{20}$ = +9.4 (c = 1.0, CH_3Cl); colorless oil];
^{1}H NMR δ ; ^{13}C NMR δ ; MS *m/z*; HRMS calcd. for $C_{17}H_{30}OS$ ($M+H^+$) 283.2096, found 283.2090.

***Syn*-selective enantioselective 1,6-addition:**

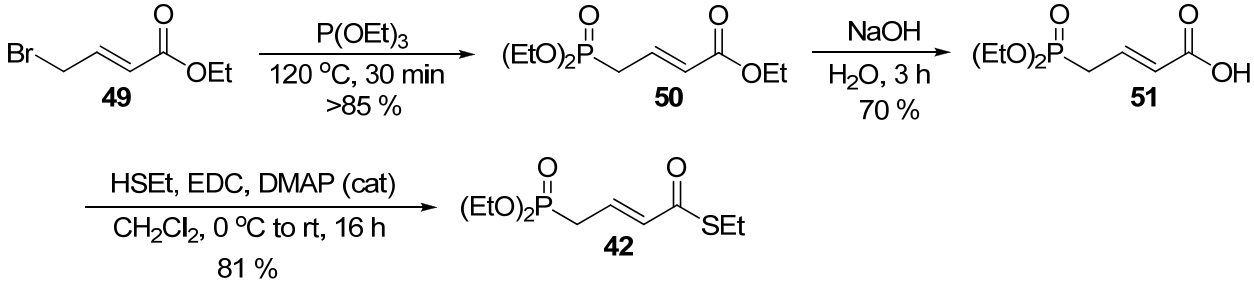


(5*S*,7*S*,9*S*,*E*)-*S*-ethyl 5,7,9-trimethyltridec-3-enethioate (*syn*/*syn*-76):
[X% yield, $[\alpha]_D^{20}$ = -2.4 (c = 1.0, CH_3Cl); colorless oil];
^{1}H NMR δ ; ^{13}C NMR δ ; MS *m/z* 319 (M^+-Et, 1), 91 ($C_6H_5CH_2$, 100); HRMS calcd. for $C_{21}H_{32}O_2S$ (M+Na) 371.2021, found 371.2010.

6. Conclusions

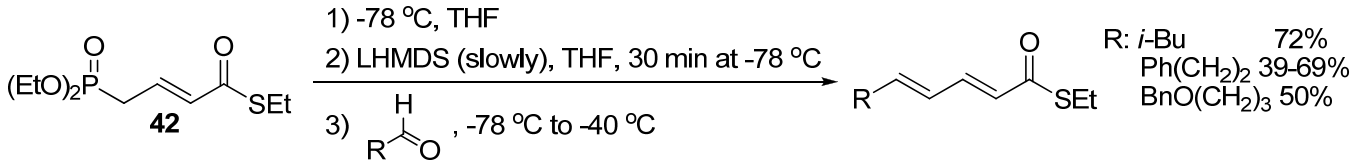
The goal of this research project was to develop a new catalytic route for the synthesis of deoxypropionate building blocks. Since natural products can contain numerous stereogenic Me-centers in a 1,3-fashion in a *syn*- as well as in an *anti*-relationship, a general method with high control over stereochemistry is required. The HWE-reaction with a novel unsaturated thioester seems ideally suited for the synthesis of bisunsaturated substrates.

The key reaction in this research project is the Horner-Wadsworth-Emmons reaction between HWE-reagent **42** and an aldehyde to produce an α,β,γ,δ-unsaturated thioester. A synthetic route to the HWE-reagent has been developed and **42** can now be prepared in >85% yield (Scheme 33).



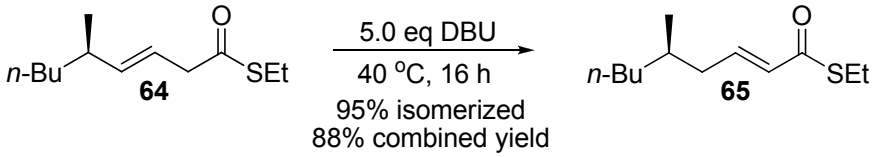
Scheme 33. Synthesis of HWE-reagent; route E.

Optimization of the HWE-reaction lead to a new efficient method for the synthesis of bisunsaturated thioesters. Important variables are the choice of base and the temperature profile of the aldehyde addition step. LHMDS is the best base for this particular HWE-reaction (Scheme 34). The optimal conditions for aldehyde addition are to add the aldehyde at -78 °C and allowing to warm up to -40 °C overnight (Scheme 34). The reaction is high yielding for a range of different aldehydes. However, some aldehydes give only moderate yields, such as 3-phenylpropionic aldehyde and 1-benzyloxybutanal. However, this is to be expected from literature.[79] The yields for the HWE-reaction with isovaleraldehyde and 1-benzyloxybutanal are 72% and 50% respectively.



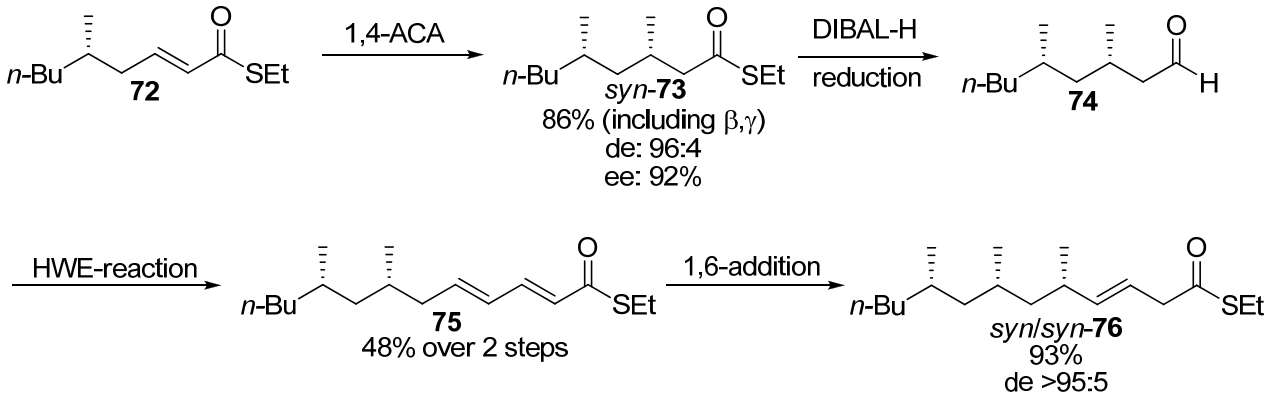
Scheme 34. Horner-Wadsworth-Emmons reaction with different aldehydes.

The subsequent iterative sequence involves an asymmetric 1,6-conjugate addition followed by an asymmetric 1,4-conjugate addition after isomerization. Upon addition of 5 equivalents of DBU (Scheme 35), the required isomerization proceeds in 88%, yielding the desired product (with trace amounts of starting material) in 88%. The applicability of this reaction appears to be quite broad.



Scheme 35. Double bond isomerization of the **64**.

1,4-Addition to install the next Me-group, followed by reduction to the aldehyde with DIBAL-H and subsequent HWE-reaction produces bisunsaturated substrate **75** containing two stereogenic Me-centers (Scheme 36).
Repetition of the iterative steps allows introduction of any number of Me-centers desired, with good control over the relative configuration of each new Me-group.



Scheme 36. Overall route for the introduction of 1,3-Me-arrays.

If an uneven number of Me-centers is required, the thioester needs to be reduced to the aldehyde after the first 1,6-addition. A HWE-reaction with the HWE-reagent then yields a bisunsaturated thioester with one Me-group already present. Following the iterative protocol, substrates can be obtained with three, five or in principal any odd number of Me-groups in a 1,3-array.
Alternatively the aldehyde can be subjected to a Wittig reaction, followed by 1,4-addition and another reduction as reported by the group of Feringa and Minnaard. In this way, any number of Me-centers can be introduced. The overall sequence for a number of Me-centers is longer, but selectivities are better.[61]

In conclusion, a new catalytic and time-efficient method for the synthesis of (poly)deoxypropionate building blocks has been described. The limitations and scope for the particular reactions have not yet been fully investigated.

In comparison to known methods for the synthesis of deoxypropionate building blocks, the stereoselective induction of the zirconium catalyst in the ZACA approach by Negishi[62] is inferior to that of the Josiphos ligand family and for the synthesis of

deoxypropionate building blocks, the method described in this report is preferred both in terms of selectivity and overall yield. Burgess' method[64] gives good control over selectivity, but for each Me-center four steps are required. The method described by the group of Feringa and Minnaard[61] gives higher overall yield and diastereoselectivity. It is the method of choice for the synthesis of deoxypropionate building blocks. The newly developed method may however be preferred if compounds with multiple Me-centers in a 1,3-array are required for screening purposes because it is more time-efficient.

Tim den Hartog is acknowledged for his share of work on the isomerization and iterative steps described in this report. The reactions described in chapter 4 and 5 were performed by him for the most part.

Abbreviations

ACA	asymmetric catalytic addition
AIBN	azobis(isobutyronitile)
Aq	aqueous
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	N,N'-dicyclohexylcarbodiimide
DIBAL-H	diisobutylalluminium hydride
DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
Et_2O	diethylether
EtOAc	ethylacetate
GC	gaschromatography
HG^{II}	Hoveyda-Grubbs catalyst 2nd generation
HRMS	high resolution mass spectrometry
HWE-reaction	Horner-Wadsworth-Emmons reaction
HWE-reagent	Horner-Wadsworth-Emmons reagent
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazane
m/z	mass / charge
Mp	melting point
MS	mass spectrometry
NBS	N-bromosuccinimde
n-BuLi	N-butyllithium
NMR	nuclear magnetic resonance
Phth	phtalimide
rt	room temperature
t-BuOMe	methyl *tert*-butyl ether
THF	tetrahydrofuran
TMSCl	trimethylsilyl chloride

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