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ORIGINAL ARTICLE

Modular total syntheses of thymifodioic/incanic acids

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Abstract The first total synthesis of the bioactive natural product 2,6-(*E*,*E*)-thymifodioic acid, also called incanic acid, and its stereoisomers is described. An unified, iterative and modular strategy was envisioned, achieving the synthesis of the goals products after five reaction steps in an overall yield ranging from 8% to 16%. The key step is a non-expensive easy to perform Horner–Wadsworth–Emmons condensation.

1. Introduction

Terpenes derive biosynthetically from units of isoprene, and they are the largest and most diverse class of natural products, with more than 55,000 compounds isolated to date (Maimone and Baran, 2007). Diterpenes comprise four isoprene units, and they constitute a vast family of secondary metabolites with diverse molecular architecture. Isolation (Li et al., 2015; Huang et al., 2014; Chen et al., 2013), synthesis (Serra and Lissoni, 2015; Zheng et al., 2014; Ishihara et al., 2013), varied biological studies (He et al., 2015; Sun et al., 2013; Su et al., 2012), biotransformation (Rico-Martínez et al., 2014) and even computational predictions (Liu et al., 2015) related to diterpenes appear continuously in the bibliography, highlighting the interest of these compounds. Thymifodioic acids or incanic acids (**1**–**4**) (Fig. 1) are linear diterpenoids containing a furan unit and two α,β-unsaturated acids. 2,6-(*E*,*E*)-thymifodioic acid (**1**) was first isolated in 1987 (Saad et al., 1987) from the aerial parts of the Argentinean bush *Baccharis thymifolia* Hook & Arn., and later from the aerial parts of Saudi Arabian plant *Conyza incana* (Galal et al., 1998). At the same time, Galal and co-workers isolated the natural product **2** from the same Saudi Arabian plant and named those products as 2,6-(*E*,*E*)-incanic acid and 2,6-(*Z*,*E*)-incanic acid (Galal et al., 1998). In 2008, it was also published the isolation of **2** from the *Baccharis thymifolia* Hook & Arn (Juan Hikawczuk et al., 2008). Both thymifodioic/incanic acids were originally named as 6,10-(*E*,*E*) and 6,10-(*E*,*Z*), although in this work we have numbered them according to the IUPAC name (for original numeration, see Electronic Supplementary Material).

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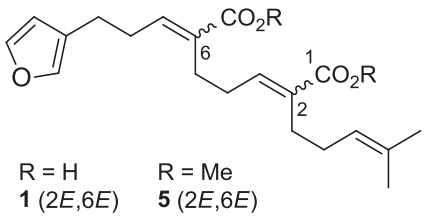

R = H | R = Me
1 (2*E*,6*E*) | **5** (2*E*,6*E*)
2 (2*Z*,6*E*) | **6** (2*Z*,6*E*)
3 (2*E*,6*Z*) | **7** (2*E*,6*Z*)
4 (2*Z*,6*Z*) | **8** (2*Z*,6*Z*)

Figure 1 Stereoisomers of thymifodioic/incanic acids and their dimethyl diesters.

Compound **1** and some synthetic derivatives, such as its dimethyl diester (**5**) (Fig. 1), showed insect growth inhibitory activity against *Tenebrio molitor* larvae. They produced developmental deficiencies in the larvae in assays using topical application on fifth instar larvae (Juan Hikawczuk et al., 2008), so their use as selective insecticide is worthy of consideration. For our biological studies, and for possible further applications, we needed an alternative to the limited bioavailability from the natural source. In consequence, we considered their stereocontrolled syntheses that should allow us their access in multi-milligram scale.

Thymifodioic/incanic acids (**1**–**4**) and their dimethyl diesters (**5**–**8**) show inherently modular structures. In natural products, this modularity, common to many biosynthetic systems, is based on the iterative coupling of bifunctional building blocks, for example in the building of polyterpenes from isopentenyl pyrophosphate or dimethylallyl pyrophosphate (Gillis and Burke, 2009). By contrast, in synthetic organic chemistry, the strategies based on the iterative coupling of bifunctional building blocks are not so widespread, especially when these building blocks bear two opposite functionalities. Thus, in recent literature we can find several total synthesis of terpenes that, far for showing an unified synthetic strategy, are subjected to the particular characteristics of each molecule (Pérez et al., 2009; Barrero et al., 2006; Barma et al., 2002; Li et al., 1998; Bando and Shishido, 1996). However, to the best of our knowledge, there are no reported syntheses of acyclic furanoterpenoids bearing α,β-unsaturated acids or esters, although several products with these characteristics have been found in the nature (Wang et al., 2014; Liu et al., 2006).

The linearity and the modularity found in compounds **1**–**4** inspired us to propose a unified synthesis based on iterative Horner–Wadsworth–Emmons (HWE) reactions (Horner et al., 1959; Wadsworth and Emmons, 1961).

2. Experimental

2.1. General experimental methods

All reagents were commercially available and used as received. Compounds **9** (Davis et al., 2005) and **15** (Ando, 1997) were prepared according to the cited literature, and all analytic data were consistent with those previously published. Compounds **1** (Saad et al., 1987), **2** (Galal et al., 1998), **5** and **6** (Juan Hikawczuk et al., 2008) have been previously described in the literature, although we found some differences regarding the assignment of several signals with very closely chemical shifts (a full discussion is provided at the end of the Electronic Supplementary Material). All solvents were dried and distilled under Ar immediately prior to use, or stored appropriately. THF and Et_2O were refluxed over sodium and benzophenone. DCM was distilled from CaH_2. Thin-layer chromatography (TLC) was run on silica gel 60 F_{254} aluminum sheets. Reactions were monitored by TLC analysis employing UV light (365 nm), a phosphomolybdic acid solution 10 wt.% in methanol or a vanillin solution (6 g of vanillin, 450 mL of ethanol, 40 mL of AcOH and 30 mL of H_2SO_4). Flash chromatography was performed with silica gel (230–400 mesh) as the stationary phase and mixtures of *n*-hexane and EtOAc, in different proportions given in each case, as the mobile phase. Chemical nomenclature was generated using ChemBioDraw Ultra 13.0, and atoms of all the compounds are numbered according to the IUPAC name. ^{1}H NMR (400, 500 or 600 MHz) and ^{13}C NMR (100, 125 or 150 MHz) spectra were recorded at room temperature and data were processed using Topspin software (version 2.1). Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (J) are quoted in Hertz (Hz). ^{1}H NMR spectra are referenced to the resonance from residual $CHCl_3$ at 7.26 ppm. Multiplicity is expressed by the abbreviations m (multiplet), br (broad signal), s (singlet), d (doublet), t (triplet), q (quartet), and combinations thereof for more highly coupled system. ^{13}C NMR spectra are referenced to the central peak of the signal from $CDCl_3$ at 77.16 ppm. Multiplicity was assigned from DEPT135 and DEPT90 experiments. Structure elucidation was made according to literature precedents or using 2D NMR techniques such as COSY, HSQC, edited HSQC and/or HMBC. IR spectra were recorded neat on a FT-ATR IR system, and the data are given in reciprocal centimeters (cm^{-1}). Mass spectra were obtained by electronic impact (EI-TOF) or electrospray ionization (ESI-TOF) with ionization potential of 70 eV. Elemental analyses were performed with a CHNS "TruSpec Micro" LECO analyzer.

2.2. General procedure for epoxidations

To a solution of the alkene in dry DCM (0.1 M) were added, under Ar atmosphere at 0 °C, $NaHCO_3$ (1.1 eq) and MCPBA (1.1 eq) sequentially. The reaction was monitored by TLC and, once completed, was diluted with Et_2O and KF (4 eq) was added. The mixture was stirred for 10 min, then was filtered through a celite pad and the solvent was removed under reduced pressure.

2.3. General procedure for oxidative cleavage

H_5IO_6 (1.3 eq) was added to a solution of the epoxide in THF: H_2O (1:1, 0.1 M). Once TLC analysis revealed the reaction was completed, it was diluted with EtOAc and saturated with NaCl (powder). The mixture was poured into a separatory funnel and was extracted three times with EtOAc. The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated.

2.4. General procedure A for HWE reactions (with phosphonates bearing MeO groups)

To an ice-cooled suspension of *t*-BuOK (1 eq) in dry THF (0.2 M) was added a solution of the phosphonate in THF (0.4 M) under Ar atmosphere. After stirring for 15 min, the mixture was cooled to −78 °C, a solution of the aldehyde (1 eq) in dry THF (0.4 M) was incorporated dropwise and the reaction was allowed to warm to rt. After 45 min, it was

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stopped with NH_4Cl aqueous saturated solution and was extracted three times with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated.

2.5. General procedure B for HWE reactions (with phosphonates bearing ArO groups)

To an ice-cooled suspension of NaH (1 eq) in dry THF (0.2 M) was added a solution of the phosphonate in THF (0.4 M) under Ar atmosphere. After stirring for 15 min, the mixture was cooled to −78 °C, a solution of the aldehyde (1 eq) in dry THF (0.4 M) was incorporated dropwise and the reaction was allowed to warm to rt. After 45 min, it was stopped with a NH_4Cl aqueous saturated solution and was extracted three times with EtOAc. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated.

2.6. General procedure for hydrolysis

To a solution of the diester in THF:MeOH:H_2O (1:1:1, 0.1 M) was added $LiOH{\cdot}H_2O$ (25 eq), and the mixture was heated at 70 °C for 15 h. After that, it was cooled to 0 °C and the pH was adjusted to pH = 1 by adding a 3 M HCl solution. Then, the mixture was diluted with Et_2O, saturated with NaCl (powder), poured into a separatory funnel and extracted three times with Et_2O. The organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated.

2.7. Procedure for the synthesis of each product

The compounds described below are organized according to the synthetic order in which they were prepared.

2.7.1. Methyl 2-(dimethoxyphosphoryl)-6-methylhept-5-enoate (**12**)

t-BuOK (6.90 g, 61.50 mmol, 1.7 eq) was added to a solution of methyl 2-(dimethoxyphosphoryl)acetate (**14**) (9 mL, 54.49 mmol) in dry DMF (25 mL) at 0 °C and under Ar atmosphere. The mixture was stirred for 10 min, then 5-bromo-2-methyl-2-pentene (5 mL, 36.47 mmol) was added slowly and the reaction was allowed to warm to rt. After 18 h, the reaction was quenched with 1 M HCl (44 mL), Et_2O (50 mL) was added and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (150 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. Purification by flash chromatography (*n*-hexane:EtOAc 60:40) gave **12** (7.71 g, 80%) as a yellowish oil: ^{1}H NMR (400 MHz, δ, $CDCl_3$) 1.57 (s, 3H, H_8), 1.68 (s, 3H, H_7), 1.79–1.90 (m, 1H, H_3), 1.95–2.11 (m, 3H, H_3, 2×H_4), 2.95–3.05 (m, 1H, H_2), 3.76 (s, 3H, CO_2Me), 3.77 (d, J = 5.5 Hz, 3H, MeOP), 3.80 (d, J = 5.4 Hz, 3H, MeOP), 5.04 (t, J = 6.8 Hz, 1H, H_5); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 17.8 (CH_3, C_8), 25.9 (CH_3, C_7), 26.8 (CH_2, d, J_{C-P} = 15.6 Hz, C_3), 27.1 (CH_2, d, J_{C-P} = 5.1 Hz, C_4), 44.5 (CH, d, J_{C-P} = 131.8 Hz, C_2), 52.6 (CH_3, CO_2Me), 53.4 (CH_3, d, J_{C-P} = 7.7 Hz, MeOP), 53.5 (CH_3, d, J_{C-P} = 7.2 Hz, MeOP), 122.5 (CH, C_5), 133.8 (C, C_6), 169.8 (C, C_1); MS (EI) *m*/*z* (relative intensity) 264 $(M)^+$ (10), 233 (11), 182 (100), 124 (27); HRMS (EI) calcd for $C_{11}H_{21}O_5P$ [$(M)^+$] 264.1127, found 264.1127.

2.7.2. Methyl 2-(bis(o-tolyloxy)phosphoryl)-6-methylhept-5-enoate (**13**)

NaH (326 mg, 8.14 mmol, 1 eq) was added, under Ar atmosphere, to a solution of methyl 2-(bis(*o*-tolyloxy)phosphoryl) acetate (**15**) (2.72 g, 8.14 mmol) in dry DMSO (5 mL). After stirring over 30 min, 5-bromo-2-methyl-2-pentene (1.4 mL, 9.76 mmol, 1.2 eq) was added slowly and the mixture was stirred for 1 h. Then, it was heated at 40 °C for 16 h. After that, it was allowed to reach rt and a NH_4Cl saturated aqueous solution (5 mL) and EtOAc (5 mL) were added. The layers were separated and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by flash chromatography (*n*-hexane:EtOAc 90:10) affording **13** (2.30 g, 68%) as a yellow oil: ^{1}H NMR (500 MHz, δ, $CDCl_3$) 1.59 (s, 3H, H_8), 1.69 (s, 3H, H_7), 2.07–2.18 (m, 3H, H_3, 2×H_4), 2.20 (s, 3H, MeAr), 2.24 (s, 3H, MeAr), 2.29–2.37 (m, 1H, H_3), 3.32–3.40 (m, 1H, H_2), 3.76 (s, 3H, CO_2Me), 5.07 (t, J = 6.0 Hz, 1H, H_5), 7.05 (dd, J = 7.2, 7.2 Hz, 2H, $H_{4'}$, $H_{4''}$), 7.10 (dd, J = 7.5, 7.5 Hz, 2H, $H_{5'}$, $H_{5''}$), 7.15–7.17 (m, 2H, $H_{3'}$, $H_{3''}$), 7.25 (d, J = 8.1 Hz, 1H, $H_{6'}$), 7.29 (d, J = 8.0 Hz, 1H, $H_{6''}$); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 16.4 (CH_3, 2C, 2×MeAr), 17.8 (CH_3, C_8), 25.8 (CH_3, C_7), 26.7 (CH_2, d, J_{C-P} = 16.2 Hz, C_3), 27.2 (CH_2, d, J_{C-P} = 4.3 Hz, C_4), 45.5 (CH, d, J_{C-P} = 135.0 Hz, C_2), 52.7 (CH_3, CO_2Me), 120.3 (CH, 2C, $C_{6'}$, $C_{6''}$), 122.2 (CH, C_5), 125.2 (CH, 2C, $C_{4'}$, $C_{4''}$), 127.1 (CH, 2C, $C_{5'}$, $C_{5''}$), 129.3 (C, d, J_{C-P} = 3.6 Hz, $C_{2''}$), 129.4 (C, d, J_{C-P} = 3.6 Hz, $C_{2'}$), 131.5 (CH, 2C, $C_{3'}$, $C_{3''}$), 134.1 (C, C_6), 149.1 (C, $C_{1''}$), 149.2 (C, $C_{1'}$), 168.8 (C, d, J_{C-P} = 5.3 Hz, C_1); MS (EI) *m*/*z* (relative intensity) 416 $(M)^+$ (56), 334 (100), 302 (46), 274 (15); HRMS (EI) calcd for $C_{23}H_{29}O_5$ [$(M)^+$] 416.1753, found 416.1765; Elem. Anal. calcd for $C_{23}H_{29}O_5$ C 66.33, H 7.02, found C 66.58, H 7.1.

2.7.3. Methyl 2-(dimethoxyphosphoryl)-4-(3,3-dimethyloxiran-2-yl)butanoate (**16**)

According to the general procedure for epoxidations, alkene **12** (380 mg, 1.44 mmol) yielded, after flash chromatography (*n*-hexane:EtOAc 20:80), the epoxide **16** (325 mg, 80%) as a yellowish oil: ^{1}H NMR (400 MHz, δ, $CDCl_3$) 1.18 (s, 3H, Me), 1.23 (s, 3H, Me), 1.40–1.62 (m, 2H, H_4), 1.87–2.17 (m, 2H, H_3), 2.62–2.66 (m, 1H, H_5), 2.93–3.07 (m, 1H, H_2), 3.70 (s, 3H, CO_2Me), 3.73 (d, J = 7.3 Hz, 3H, MeOP), 3.75 (d, J = 7.6 Hz, 3H, MeOP); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 18.6 (CH_3, d, J_{C-P} = 3.5 Hz, Me), 24.1 (CH_2, dd, J_{C-P} = 16.6, 4.2 Hz, C_3), 24.7 (CH_3, Me), 27.6 (CH_2, dd, J_{C-P} = 14.6, 14.6 Hz, C_4), 44.6 (CH, d, J_{C-P} = 131.7 Hz, C_2), 52.6 (CH_3, CO_2Me), 53.4 (CH_3, d, J_{C-P} = 6.3 Hz, MeOP), 53.5 (CH_3, J_{C-P} = 6.3 Hz, MeOP), 58.2 (C, d, J_{C-P} = 26.1 Hz, C_6), 63.3 (CH, d, J_{C-P} = 29.0 Hz, C_5), 169.2 (C, d, J_{C-P} = 4.3 Hz, C_1); HRMS (ESI) calcd for $C_{11}H_{21}O_6$NaP [$(M+Na)^+$] 303.0973, found 303.0966; Elem. Anal. calcd for $C_{11}H_{21}O_6$NaP C 47.14, H 7.55, found C 47.19, H 7.51.

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*2.7.4. Methyl 2-(bis(o-tolyloxy)phosphoryl)-4-(3,3-dimethyloxiran-2-yl)butanoate (**17**)*

According to the general procedure for epoxidations, alkene **13** (835 mg, 2.00 mmol) yielded, after flash chromatography (*n*-hexane:EtOAc 70:30), the epoxide **17** (627 mg, 73%) as a yellowish oil: ^{1}H NMR (500 MHz, δ, $CDCl_3$) 1.26 (s, 3H, Me), 1.30 (s, 3H, Me), 1.57–1.79 (m, 2H, H_4), 2.20 (s, 3H, MeAr), 2.25 (s, 3H, MeAr), 2.27–2.48 (m, 2H, H_3), 2.71–2.76 (m, 1H, H_5), 3.35–3.49 (m, 1H, H_2), 3.77 (d, J = 4.0 Hz, 3H, CO_2-Me), 7.03–7.07 (m, 2H, $H_{4'}$, $H_{4''}$), 7.08–7.12 (m, 2H, $H_{5'}$, $H_{5''}$), 7.15–7.18 (m, 2H, $H_{3'}$, $H_{3''}$), 7.25 (d, J = 6.7 Hz, 1H, $H_{6'}$), 7.30 (d, J = 8.0 Hz, 1H, $H_{6''}$); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 16.3 (CH_3, 2C, 2×MeAr), 18.6 (CH_3, d, J_{C-P} = 2.8 Hz, Me), 24.2 (CH_2, dd, J_{C-P} = 23.4, 4.2 Hz, C_3), 24.7 (CH_3, Me), 27.6 (CH_2, d, J_{C-P} = 14.5 Hz, C_4), 45.6 (CH, dd, J_{C-P} = 134.2, 3.7 Hz, C_2), 52.7 (CH_3, CO_2Me), 58.2 (C, d, J_{C-P} = 31.1 Hz, C_6), 63.2 (CH, d, J_{C-P} = 23.3 Hz, C_5), 120.1 (CH, $C_{6'}$), 120.2 (CH, $C_{6''}$), 125.2 (CH, 2C, $C_{4'}$, $C_{4''}$), 127.1 (CH, 2C, $C_{5'}$, $C_{5''}$), 129.2 (C, d, J_{C-P} = 4.5 Hz, $C_{2''}$), 129.3 (C, d, J_{C-P} = 4.5 Hz, $C_{2'}$), 131.4 (CH, 2C, $C_{3'}$, $C_{3''}$), 148.9 (C, $C_{1''}$), 149.0 (C, $C_{1'}$), 168.4 (C, d, J_{C-P} = 5.6 Hz, C_1); HRMS (ESI) calcd for $C_{23}H_{29}O_6PNa$ [$(M+Na)^+$] 455.1599, found 455.1594; Elem. Anal. calcd for $C_{23}H_{29}O_6PNa$ C 63.88, H 6.76, found C 63.79, H 6.90.

*2.7.5. Methyl 2-(dimethoxyphosphoryl)-5-oxopentanoate (**10**)*

According to the general procedure for oxidative cleavage, epoxide **16** (300 mg, 1.07 mmol) allowed us to obtain the phosphonate-aldehyde **10** (253 mg, 99%) as a yellowish oil. Purity of **10** was checked by NMR analysis and then was immediately submitted to the next reaction. ^{1}H NMR (400 MHz, δ, $CDCl_3$) 2.17–2.25 (m, 2H, H_4), 2.50–2.66 (m, 2H, H_3), 3.40 (dt, J = 23.2, 7.3 Hz, 1H, H_2), 3.75 (s, 3H, CO_2-Me), 3.77 (d, J = 3.6 Hz, 3H, MeOP), 3.80 (d, J = 3.6 Hz, 3H, MeOP), 9.73 (s, 1H, H_5); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 19.5 (CH_2, d, J_{C-P} = 4.3 Hz, C_3), 41.7 (CH_2, d, J_{C-P} = 12.5 -Hz, C_4), 43.6 (CH, d, J_{C-P} = 132.0 Hz, C_2), 52.6 (CH_3, CO_2-Me), 53.36 (CH_3, d, J_{C-P} = 6.6 Hz, MeOP), 53.44 (CH_3, J_{C-P} = 6.6 Hz, MeOP), 169.2 (C, d, J_{C-P} = 4.9 Hz, C_1), 200.4 (CH, C_5); HRMS (ESI) calcd for $C_8H_{15}O_6PNa$ [$(M+Na)^+$] 261.0504, found 261.0509.

*2.7.6. Methyl 2-(bis(o-tolyloxy)phosphoryl)-5-oxopentanoate (**11**)*

According to the general procedure for oxidative cleavage, epoxide **17** (563 mg, 1.30 mmol) allowed us to obtain the phosphonate-aldehyde **11** (433 mg, 85%) as a yellowish oil. Purity of **11** was checked by NMR analysis and then was immediately submitted to the next reaction. ^{1}H NMR (600 MHz, δ, $CDCl_3$) 2.20 (s, 3H, MeAr), 2.24 (s, 3H, MeAr), 2.45–2.54 (m, 2H, H_3), 2.67 (dt, J = 19.0, 7.1 Hz, 1H, H_4), 2.76 (dt, J = 19.0, 7.0 Hz, 1H, H_4), 3.44 (ddd, J = 23.9, 8.3, 6.4 Hz, 1H, H_2), 3.76 (s, 3H, CO_2Me), 7.04–7.08 (m, 2H, $H_{4'}$, $H_{4''}$), 7.09–7.13 (m, 2H, $H_{5'}$, $H_{5''}$), 7.16–7.18 (m, 2H, $H_{3'}$, $H_{3''}$), 7.23 (d, J = 8.1 Hz, 1H, $H_{6'}$ or $H_{6''}$), 7.30 (d, J = 7.9 Hz, 1H, $H_{6''}$ or $H_{6'}$), 9.77 (s, 1H, CHO); ^{13}C NMR (150 MHz, δ, $CDCl_3$) 16.5 (CH_3, 2C, 2×MeAr), 19.9 (CH_2, d, J_{C-P} = 4.2 Hz, C_3), 41.9 (CH_2, d, J_{C-P} = 13.4 Hz, C_4), 44.9 (CH, d, J_{C-P} = 134.9 Hz, C_2), 52.9 (CH_3, CO_2Me), 120.2 (CH, d, J_{C-P} = 2.7 Hz, $C_{6'}$), 120.3 (CH, d, J_{C-P} = 2.7 -Hz, $C_{6''}$), 125.4 (CH, 2C, $C_{4'}$, $C_{4''}$), 127.2 (CH, 2C, $C_{5'}$, $C_{5''}$), 129.3 (C, d, J_{C-P} = 2.8 Hz, $C_{2'}$), 129.4 (C, d, J_{C-P} = 2.8 Hz, $C_{2''}$), 131.6 (CH, 2C, $C_{3'}$, $C_{3''}$), 148.97 (C, d, J_{C-P} = 2.2 Hz, $C_{1'}$), 149.03 (C, d, J_{C-P} = 1.7 Hz, $C_{1''}$), 168.5 (C, d, J_{C-P} = 5.6 Hz, C_1), 200.5 (CH, C_5); HRMS (ESI) calcd for $C_{20}H_{23}O_6PNa$ [$(M+Na)^+$] 413.1130, found 413.1135.

*2.7.7. (Z)-dimethyl 6-(dimethoxyphosphoryl)-2-(4-methylpent-3-en-1-yl)hept-2-enedioate (**19**)*

Phosphonate **13** (38.5 mg, 0.09 mmol) and phosphonate-aldehyde **10** (22 mg, 0.09 mmol) were submitted to the general procedure B for the HWE reactions, with the following modifications: addition of the reagents was performed at rt and then the reaction was refluxed for 1 h. Phosphonates **19** and **18** were obtained as an inseparable mixture (11.5 mg, 33%, 1.6/1). Description of the major product is given as follows: ^{1}H NMR (400 MHz, δ, $CDCl_3$) 1.57 (s, 3H, $H_{6'}$), 1.67 (s, 3H, $H_{5'}$), 2.04–2.10 (m, 2H, $H_{2'}$), 2.22–2.40 (m, 4H, 2×H_5, 2×$H_{1'}$), 2.43–2.57 (m, 2H, H_4), 2.96–3.05 (m, 1H, H_6), 3.72 (s, 3H, CO_2Me), 3.76 (s, 3H, CO_2Me), 3.77 (d, J = 6.1 Hz, 3H, MeOP), 3.80 (d, J = 6.1 Hz, 3H, MeOP), 5.04–5.13 (m, 1H, $H_{3'}$), 5.75–5.88 (m, 1H, H_3); ^{13}C NMR (125 MHz, δ, $CDCl_3$) 17.8 (CH_3, $C_{6'}$), 25.8 (CH_3, $C_{5'}$), 26.7 (CH_2, d, J_{C-P} = 4.6 Hz, C_5), 27.8 (CH_2, $C_{2'}$), 28.3 (CH_2, d, J_{C-P} = 15.6 Hz, C_4), 34.9 (CH_2, $C_{1'}$), 44.6 (CH, d, J_{C-P} = 132.6 Hz, C_6), 51.4 (CH_3, C_1(O)OMe), 52.7 (CH_3, C_7(O)OMe), 53.5 (CH_3, d, J_{C-P} = 6.5 Hz, MeOP), 53.6 (CH_3, d, J_{C-P} = 6.5 Hz, MeOP), 123.4 (CH, $C_{3'}$), 132.5 (C, C_2 or $C_{4'}$), 133.5 (C, $C_{4'}$ or C_2), 139.5 (CH, C_3), 168.3 (C, C_1), 169.5 (C, d, J_{C-P} = 4.6 Hz, C_7); HRMS (ESI) calcd for $C_{17}H_{29}O_7PNa$ [$(M+Na)^+$] 399.1549, found 399.1556; Elem. Anal. calcd for $C_{17}H_{29}O_7$-PNa C 54.25, H 7.77, found C 54.19, H 8.12.

*2.7.8. (E)-dimethyl 6-(bis(o-tolyloxy)phosphoryl)-2-(4-methylpent-3-en-1-yl)hept-2-enedioate (**20**)*

Phosphonate **12** (58.8 mg, 0.22 mmol) and phosphonate-aldehyde **11** (86.8 mg, 0.22 mmol) were submitted to the general procedure A for the HWE reactions, with the following modifications: addition of the reagents was performed at rt and then the reaction was refluxed for 4 h. Phosphonates **20** and **21** were obtained as an inseparable mixture (12.9 mg, 11%, 1.5/1 respectively). Description of the major product is given as follows: ^{1}H NMR (500 MHz, δ, $CDCl_3$) 1.56 (s, 3H, $H_{6'}$), 1.66 (s, 3H, $H_{5'}$), 2.03–2.12 (m, 2H, $H_{2'}$), 2.19 (s, 3H, MeAr), 2.23 (s, 3H, MeAr), 2.25–2.42 (m, 5H, 1xH_4, 2×H_5, 2×$H_{1'}$), 2.51–2.65 (m, 1H, H_4), 3.29–3.41 (m, 1H, H_6), 3.74 (s, 3H, C_1(O)OMe), 3.76 (s, 3H, C_7(O)OMe), 5.04–5.13 (m, 1H, $H_{3'}$), 6.68 (t, J = 6.8 Hz, 1H, $H_{3'}$), 7.03–7.07 (m, 2H, $H_{4''}$, $H_{4'''}$), 7.08–7.12 (m, 2H, $H_{5''}$, $H_{5'''}$), 7.14–7.19 (m, 2H, $H_{3''}$, $H_{3'''}$), 7.21–7.24 (m, 1H, $H_{6''}$), 7.27–7.30 (m, 1H, $H_{6'''}$); ^{13}C NMR (125 MHz, δ, $CDCl_3$) 16.46 (CH_3, MeAr), 16.49 (CH_3, MeAr), 17.8 (CH_3, $C_{6'}$), 25.8 (CH_3, $C_{5'}$), 26.4 (CH_2, d, J_{C-P} = 4.6 Hz, C_5), 27.2 (CH_2, $C_{1'}$), 27.3 (CH_2, d, J_{C-P} = 15.5 Hz, C_4), 27.8 (CH_2, $C_{2'}$), 45.8 (CH, d, J_{C-P} = 134.9 Hz, C_6), 51.9 (CH_3, C_1(O)OMe), 52.9 (CH_3, C_7(O) OMe), 120.4 (CH, d, J_{C-P} = 2.1 Hz, 2C, $C_{6''}$, $C_{6'''}$), 123.5 (CH, $C_{3'}$), 125.4 (CH, 2C, $C_{4''}$, $C_{4'''}$), 127.2 (CH, 2C, $C_{5''}$, $C_{5'''}$), 129.4 (C, d, J_{C-P} = 5.5 Hz, $C_{2''}$ or $C_{2'''}$), 129.5 (C, d, J_{C-P} = 5.5 Hz, $C_{2'''}$ or $C_{2''}$), 131.6 (CH, 2C, $C_{3''}$, $C_{3'''}$), 132.6 (C, $C_{4'}$), 133.9 (C, C_2), 139.9 (CH, C_3), 149.07 (C, $C_{1''}$ or $C_{1'''}$), 149.14 (C, $C_{1'''}$ or $C_{1''}$), 168.2 (C, C_1), 168.7 (C, d, J_{C-P} = 5.5 Hz, C_7); HRMS

(ESI) calcd for $C_{29}H_{37}O_7PNa$ [$(M+Na)^+$] 551.2170, found 551.2163.

2.7.9. (*Z*)-dimethyl 6-(bis(o-tolyloxy)phosphoryl)-2-(4-methylpent-3-en-1-yl)hept-2-enedioate (**21**)

Phosphonate **13** (104 mg, 0.25 mmol) and phosphonate-aldehyde **11** (97 mg, 0.25 mmol) were submitted to the general procedure B for the HWE reactions, with the following modifications: addition of the reagents was performed at rt and then the reaction was refluxed for 4 h. Phosphonates **21** and **20** were obtained as an inseparable mixture (46 mg, 35%, 2.5/1 respectively). Description of the major product is given as follows: ^{1}H NMR (400 MHz, δ, $CDCl_3$) 1.57 (s, 3H, $H_{6'}$), 1.67 (s, 3H, $H_{5'}$), 2.07 (dt, J = 7.8, 7.8 Hz, 2H, $H_{2'}$), 2.19 (s, 3H, MeAr), 2.24 (s, 3H, MeAr), 2.26–2.32 (m, 2H, $H_{1'}$), 2.33–2.43 (m, 2H, H_5), 2.46–2.64 (m, 2H, H_4), 3.36 (ddd, J = 23.6, 11.1, 3.1 Hz, 1H, H_6), 3.72 (s, 3H, C_1(O)OMe), 3.76 (s, 3H, C_7(O)OMe), 5.07 (t, J = 7.2 Hz, 1H, $H_{3'}$), 5.80 (t, J = 7.5 Hz, 1H, H_3), 7.03–7.06 (m, 2H, $H_{4''}$, $H_{4'''}$), 7.08–7.11 (m, 2H, $H_{5''}$, $H_{5'''}$), 7.15–7.17 (m, 2H, $H_{3''}$, $H_{3'''}$), 7.23 (d, J = 7.9 Hz, 1H, $H_{6''}$), 7.28 (d, J = 7.9 Hz, 1H, $H_{6'''}$); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 16.4 (CH_3, 2C, 2×MeAr), 17.8 (CH_3, $C_{6'}$), 25.8 (CH_3, $C_{5'}$), 26.7 (CH_2, d, J_{C-P} = 4.1 Hz, C_5), 27.8 (CH_2, $C_{2'}$), 28.3 (CH_2, d, J_{C-P} = 16.8 Hz, C_4), 34.8 (CH_2, $C_{1'}$), 45.6 (CH, d, J_{C-P} = 133.9 Hz, C_6), 51.4 (CH_3, C_1(O)OMe), 52.7 (CH_3, C_7(O)OMe), 120.3 (CH, 2C, $C_{6''}$, $C_{6'''}$), 123.4 (CH, $C_{3'}$), 125.3 (CH, 2C, $C_{4''}$, $C_{4'''}$), 127.2 (CH, 2C, $C_{5''}$, $C_{5'''}$), 129.4 (C, d, J_{C-P} = 5.5 Hz, $C_{2''}$ or $C_{2'''}$), 129.5 (C, d, J_{C-P} = 5.5 Hz, $C_{2'''}$ or $C_{2''}$), 131.6 (CH, 2C, $C_{3''}$, $C_{3'''}$), 132.6 (C, $C_{4'}$), 133.7 (C, C_2), 139.2 (CH, C_3), 149.1 (C, $C_{1''}$ or $C_{1'''}$), 149.2 (C, $C_{1'''}$ or $C_{1''}$), 168.2 (C, C_1), 168.6 (C, d, J_{C-P} = 5.2 Hz, C_7); HRMS (ESI) calcd for $C_{29}H_{37}O_7PNa$ [$(M+Na)^+$] 551.2170, found 551.2175.

2.7.10. (*E*)-methyl 2-(3-(furan-3-yl)propylidene)-6-methylhept-5-enoate (**22**)

According to the general procedure A for HWE reactions, phosphonate **12** (1.1 g, 4.17 mmol) yielded a mixture of alkenes **22** and **23** in a 5.3/1 ratio. After flash chromatography (*n*-hexane:EtOAc 98:2), the alkene **22** (688 mg, 63%) was obtained as a colorless oil: ^{1}H NMR (400 MHz, δ, $CDCl_3$) 1.58 (s, 3H, H_8), 1.67 (s, 3H, H_7), 2.05 (dt, J = 7.5, 7.5 Hz, 2H, H_4), 2.31 (t, J = 7.7 Hz, 2H, H_3), 2.43 (dt, J = 7.3, 7.3 Hz, 2H, $H_{2'}$), 2.56 (t, J = 7.5 Hz, 2H, $H_{3'}$), 3.73 (s, 3H, CO_2Me), 5.12 (t, J = 7.2 Hz, 1H, H_5), 6.27 (s, 1H, $H_{4''}$), 6.76 (t, J = 7.3 Hz, 1H, $H_{1'}$), 7.23 (s, 1H, $H_{2''}$), 7.35 (s, 1H, $H_{5''}$); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 17.7 (CH_3, C_8), 24.3 (CH_2, $C_{3'}$), 25.8 (CH_3, C_7), 27.2 (CH_2, C_3), 27.7 (CH_2, C_4), 29.2 (CH_2, $C_{2'}$), 51.8 (CH_3, CO_2Me), 111.0 (CH, $C_{4''}$), 123.7 (CH, C_5), 124.2 (C, $C_{3''}$), 132.4 (C, C_6), 132.7 (C, C_2), 139.1 (CH, $C_{2''}$), 141.8 (CH, $C_{1'}$), 143.1 (CH, $C_{5''}$), 168.4 (C, C_1); ATR-FTIR (neat) ν_{max} (cm^{-1}) 2925, 2859, 1712, 1437, 1272, 1161, 630; MS (EI) m/z (relative intensity) 262 $(M)^+$ (8), 247 (2), 203 (100), 81 (97); HRMS (EI) calcd for $C_{16}H_{22}O_3$ [$(M)^+$] 262.1569, found 262.1557.

2.7.11. (*Z*)-methyl 2-(3-(furan-3-yl)propylidene)-6-methylhept-5-enoate (**23**)

According to the general procedure B for HWE reactions, phosphonate **13** (1.00 g, 2.41 mmol) yielded a mixture of alkenes **23** and **22** in a 4/1 ratio. After flash chromatography (*n*-hexane: EtOAc 98:2), the alkene **23** (378 mg, 60%) was obtained as a colorless oil: ^{1}H NMR (400 MHz, δ, $CDCl_3$) 1.57 (s, 3H, H_8), 1.68 (s, 3H, H_7), 2.08 (dt, J = 7.3, 7.3 Hz, 2H, H_4), 2.26 (t, J = 7.4 Hz, 2H, H_3), 2.53 (t, J = 7.4 Hz, 2H, $H_{3'}$), 2.68 (dt, J = 7.3, 7.3 Hz, 2H, $H_{2'}$), 3.73 (s, 3H, CO_2Me), 5.07 (t, J = 7.1 Hz, 1H, H_5), 5.88 (t, J = 7.2 Hz, 1H, $H_{1'}$), 6.28 (s, 1H, $H_{4''}$), 7.22 (s, 1H, $H_{2''}$), 7.34 (s, 1H, $H_{5''}$); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 17.8 (CH_3, C_8), 24.8 (CH_2, $C_{3'}$), 25.8 (CH_3, C_7), 27.9 (CH_2, C_4), 29.9 (CH_2, $C_{2'}$), 34.8 (CH_2, C_3), 51.3 (CH_3, CO_2Me), 111.1 (CH, $C_{4''}$), 123.6 (CH, C_5), 124.4 (C, $C_{3''}$), 132.3 (C, C_2 or C_6), 132.4 (C, C_6 or C_2), 139.1 (CH, $C_{2''}$), 141.4 (CH, $C_{1'}$), 142.9 (CH, $C_{5''}$), 168.5 (C, C_1); ATR-FTIR (neat) ν_{max} (cm^{-1}) 2924, 2858, 1713, 1439, 1202, 1160, 630; MS (EI) m/z (relative intensity) 262 $(M)^+$ (8), 247 (5), 203 (48), 81 (100); HRMS (EI) calcd for $C_{16}H_{22}O_3$ [$(M)^+$] 262.1569, found 262.1564.

2.7.12. (*E*)-methyl 2-(2-(3,3-dimethyloxiran-2-yl)ethyl)-5-(furan-3-yl)pent-2-enoate (**24**)

According to the general procedure for epoxidations, alkene **22** (682 mg, 2.60 mmol) yielded, after flash chromatography (*n*-hexane:EtOAc 90:10), the epoxide **24** (579 mg, 80%) as a colorless oil: ^{1}H NMR (400 MHz, δ, $CDCl_3$) 1.21 (s, 3H, Me), 1.26 (s, 3H, Me), 1.59 (dt, J = 7.0, 7.0 Hz, 2H, $H_{2'}$), 2.35–2.49 (m, 4H, 2×H_4, 2×$H_{1'}$), 2.56 (t, J = 7.2 Hz, 2H, H_5), 2.68 (t, J = 6.3 Hz, 1H, $H_{2''}$), 3.71 (s, 3H, CO_2Me), 6.25 (s, 1H, $H_{4'''}$), 6.80 (t, J = 7.3 Hz, 1H, H_3), 7.21 (s, 1H, $H_{2'''}$), 7.33 (s, 1H, $H_{5'''}$); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 18.7 (CH_3, Me), 23.8 (CH_2, $C_{1'}$), 24.1 (CH_2, C_5), 24.9 (CH_3, Me), 28.5 (CH_2, $C_{2'}$), 29.2 (CH_2, C_4), 51.8 (CH_3, CO_2Me), 58.5 (C, $C_{3''}$), 63.7 (CH, $C_{2''}$), 110.9 (CH, $C_{4'''}$), 123.9 (C, $C_{3'''}$), 131.9 (C, C_2), 139.1 (CH, $C_{2'''}$), 142.4 (CH, C_3), 143.0 (CH, $C_{5'''}$), 168.0 (C, C_1); MS (EI) m/z (relative intensity) 278 $(M)^+$ (1), 264 (44), 218 (10), 81 (100); HRMS (EI) calcd for $C_{16}H_{22}O_4$ [$(M)^+$] 278.1518, found 278.1527.

2.7.13. (*Z*)-methyl 2-(2-(3,3-dimethyloxiran-2-yl)ethyl)-5-(furan-3-yl)pent-2-enoate (**25**)

According to the general procedure for epoxidations, alkene **23** (351 mg, 1.34 mmol) yielded, after flash chromatography (*n*-hexane:EtOAc 90:10), the epoxide **25** (299 mg, 80%) as a colorless oil: ^{1}H NMR (400 MHz, δ, $CDCl_3$) 1.22 (s, 3H, Me), 1.27 (s, 3H, Me), 1.64 (dt, J = 7.1, 7.1 Hz, 2H, $H_{2'}$), 2.31–2.47 (m, 2H, $H_{1'}$), 2.53 (t, J = 7.4 Hz, 2H, H_5), 2.67 (t, J = 6.3 Hz, 1H, $H_{2''}$), 2.71 (dt, J = 7.3, 7.3 Hz, 2H, H_4), 3.73 (s, 3H, CO_2Me), 5.97 (t, J = 7.2 Hz, 1H, H_3), 6.26 (s, 1H, $H_{4''}$), 7.21 (s, 1H, $H_{2''}$), 7.33 (s, 1H, $H_{5''}$); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 18.8 (CH_3, Me), 24.7 (CH_2, C_5), 24.9 (CH_3, Me), 28.7 (CH_2, $C_{2'}$), 29.9 (CH_2, C_4), 31.6 (CH_2, $C_{1'}$), 51.4 (CH_3, CO_2Me), 58.5 (C, $C_{3''}$), 63.7 (CH, $C_{2''}$), 111.0 (CH, $C_{4'''}$), 124.3 (C, $C_{3'''}$), 131.6 (C, C_2), 139.1 (CH, $C_{2'''}$), 142.5 (CH, C_3), 142.9 (CH, $C_{5'''}$), 168.1 (C, C_1); ATR-FTIR (neat) ν_{max} (cm^{-1}) 2954, 2922, 2853, 1712, 1195, 1120, 630; MS (EI) m/z (relative intensity) 278 $(M)^+$ (1), 246 (23), 218 (11), 81 (100); HRMS (EI) calcd for $C_{16}H_{22}O_4$ [$(M)^+$] 278.1518, found 278.1530; Elem. Anal. calcd for $C_{16}H_{22}O_4$ C 69.04, H 7.97, found C 68.73, H 7.99.

2.7.14. (*E*)-methyl 5-(furan-3-yl)-2-(3-oxopropyl)pent-2-enoate (**26**)

According to the general procedure for oxidative cleavage, epoxide **24** (320 mg, 1.15 mmol) allowed us to obtain the

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aldehyde **26** (192 mg, 70%) as a yellowish oil. Purity of **26** was checked by NMR analysis and then was immediately submitted to the next reaction. ^{1}H NMR (400 MHz, δ, $CDCl_3$) 2.44–2.52 (m, 4H, 2×H_4, 2×$H_{2'}$), 2.56–2.59 (m, 4H, 2×H_5, 2×$H_{1'}$), 3.73 (s, 3H, CO_2Me), 6.26 (s, 1H, $H_{4''}$), 6.82 (t, J = 7.3 Hz, 1H, H_3), 7.23 (s, 1H, $H_{2''}$), 7.35 (s, 1H, $H_{5''}$), 9.74 (s, 1H, $H_{3'}$); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 19.7 (CH_2, $C_{2'}$), 24.0 (CH_2, C_5), 29.3 (CH_2, C_4), 43.3 (CH_2, $C_{1'}$), 51.9 (CH_3, $CO_2\underline{Me}$), 110.9 (CH, $C_{4''}$), 123.9 (C, $C_{3''}$), 131.0 (C, C_2), 139.2 (CH, $C_{2''}$), 143.1 (CH, C_3 or $C_{5''}$), 143.1 (CH, $C_{5''}$ or C_3), 167.8 (C, C_1), 201.5 (CH, $C_{3'}$); HRMS (EI) calcd for $C_{13}H_{16}O_4Na$ [$(M+Na)^+$] 259.0946, found 259.0949.

2.7.15. (Z)-methyl 5-(furan-3-yl)-2-(3-oxopropyl)pent-2-enoate (27)

According to the general procedure for oxidative cleavage, epoxide **25** (281 mg, 1.01 mmol) allowed us to obtain the aldehyde **27** (214 mg, 90%) as a yellowish oil. Purity of **27** was checked by NMR analysis and then was immediately submitted to the next reaction. ^{1}H NMR (400 MHz, δ, $CDCl_3$) 2.52–2.60 (m, 6H, 2×H_5, 2×$H_{1'}$, 2×$H_{2'}$), 2.72 (dt, J = 7.3, 7.3 Hz, 2H, H_4), 3.74 (s, 3H, CO_2Me), 6.01 (t, J = 7.2 Hz, 1H, H_3), 6.26 (s, 1H, $H_{4''}$), 7.22 (s, 1H, $H_{2''}$), 7.35 (s, 1H, $H_{5''}$), 9.74 (s, 1H, $H_{3'}$); the product decomposed in the NMR tube before we could obtain a well-resolved ^{13}C NMR spectra; MS (EI) m/z (relative intensity) 236 $(M)^+$ (8), 192 (9), 177 (10), 81 (100); HRMS (EI) calcd for $C_{13}H_{16}O_4$ [$(M)^+$] 236.1049, found 236.1053.

2.7.16. (2E,6E)-dimethyl 6-(3-(furan-3-yl)propylidene)-2-(4-methylpent-3-en-1-yl)hept-2-enedioate (5)

According to the general procedure A for HWE reactions, phosphonate **12** (76 mg, 0.29 mmol) and aldehyde **26** (68 mg, 0.29 mmol) yielded a mixture of diesters **5** and **6** in a 3.8/1 ratio. After flash chromatography (*n*-hexane:EtOAc 95:5), the diester **5** (51 mg, 48%) was obtained as a colorless oil: ^{1}H NMR (500 MHz, δ, $CDCl_3$) 1.57 (s, 3H, $H_{6'}$), 1.66 (s, 3H, $H_{5'}$), 2.05 (dt, J = 7.5, 7.5 Hz, 2H, $H_{2'}$), 2.26 (dt, J = 7.4, 7.4 Hz, 2H, H_4), 2.29 (t, J = 7.4 Hz, 2H, $H_{1'}$), 2.41 (t, J = 7.6 Hz, 2H, H_5), 2.44 (dt, J = 7.6, 7.6 Hz, 2H, $H_{2''}$), 2.57 (t, J = 7.5 Hz, 2H, $H_{3''}$), 3.72 (s, 3H, C_1(O)OMe), 3.74 (s, 3H, C_7(O)OMe), 5.10 (tt, J = 7.3, 1.3 Hz, 1H, $H_{3'}$), 6.26 (s, 1H, $H_{4'''}$), 6.72 (t, J = 7.5 Hz, 1H, H_3), 6.82 (t, J = 7.4 Hz, 1H, $H_{1''}$), 7.23 (s, 1H, $H_{2'''}$), 7.35 (s, 1H, $H_{5'''}$); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 17.7 (CH_3, $C_{6'}$), 24.1 (CH_2, $C_{3''}$), 25.7 (CH_3, $C_{5'}$), 26.2 (CH_2, C_5), 27.0 (CH_2, $C_{1'}$), 27.8 (CH_2, $C_{2'}$), 28.1 (CH_2, C_4), 29.3 (CH_2, $C_{2''}$), 51.6 (CH_3, C_1(O)O$\underline{Me}$), 51.8 (CH_3, C_7(O)O$\underline{Me}$), 110.8 (CH, $C_{4'''}$), 123.7 (CH, $C_{3'}$), 123.9 (C, $C_{3'''}$), 131.6 (C, C_6), 132.3 (C, $C_{4'}$), 132.6 (C, C_2), 139.1 (CH, $C_{2'''}$), 141.5 (CH, C_3), 142.7 (CH, $C_{1''}$), 143.0 (CH, $C_{5'''}$), 167.9 (C, C_7), 168.3 (C, C_1); ATR-FTIR (neat) ν_{max} (cm^{-1}) 2954, 2863, 1714, 1440, 1271, 1199, 634; MS (EI) m/z (relative intensity) 374 $(M)^+$ (1), 342 (18), 315 (3), 81 (100); HRMS (EI) calcd for $C_{22}H_{30}O_5$ [$(M)^+$] 374.2093, found 374.2101.

2.7.17. (2Z,6E)-dimethyl 6-(3-(furan-3-yl)propylidene)-2-(4-methylpent-3-en-1-yl)hept-2-enedioate (6)

According to the general procedure B for HWE reactions, phosphonate **13** (120 mg, 0.29 mmol) and aldehyde **26** (68 mg, 0.29 mmol) gave a mixture of diesters **6** and **5** in a 2/1 ratio. After flash chromatography (*n*-hexane:EtOAc 95:5), the diester **6** (49 mg, 45%) was obtained as a yellowish oil: ^{1}H NMR (500 MHz, δ, $CDCl_3$) 1.57 (s, 3H, $H_{6'}$), 1.67 (s, 3H, $H_{5'}$), 2.07 (dt, J = 7.5, 7.5 Hz, 2H, $H_{2'}$), 2.24 (t, J = 7.7 Hz, 2H, $H_{1'}$), 2.39 (t, J = 7.6 Hz, 2H, H_5), 2.46 (dt, J = 7.4, 7.4 Hz, 2H, $H_{2''}$), 2.48 (dt, J = 7.6, 7.6 Hz, 2H, H_4), 2.57 (t, J = 7.6 Hz, 2H, $H_{3''}$), 3.70 (s, 3H, C_1(O)OMe), 3.73 (s, 3H, C_7(O)OMe), 5.08 (tt, J = 7.2, 1.3 Hz, 1H, $H_{3'}$), 5.85 (t, J = 7.5 Hz, 1H, H_3), 6.28 (s, 1H, $H_{4'''}$), 6.80 (t, J = 7.3 Hz, 1H, $H_{1''}$), 7.24 (s, 1H, $H_{2'''}$), 7.35 (s, 1H, $H_{5'''}$); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 17.8 (CH_3, $C_{6'}$), 24.2 (CH_2, $C_{3''}$), 25.8 (CH_3, $C_{5'}$), 26.7 (CH_2, C_5), 27.9 (CH_2, $C_{2'}$), 29.17 (CH_2, C_4 or $C_{2''}$), 29.23 (CH_2, $C_{2''}$ or C_4), 34.9 (CH_2, $C_{1'}$), 51.3 (CH_3, C_1(O)O$\underline{Me}$), 51.8 (CH_3, C_7(O)O$\underline{Me}$), 111.0 (CH, $C_{4'''}$), 123.6 (CH, $C_{3'}$), 124.1 (C, $C_{3'''}$), 132.0 (C, C_6), 132.38 (C, C_2 or $C_{4'}$), 132.43 (C, $C_{4'}$ or C_2), 139.2 (CH, $C_{2'''}$), 140.6 (CH, C_3), 142.5 (CH, $C_{1''}$), 143.1 (CH, $C_{5'''}$), 168.2 (C, C_7), 168.5 (C, C_1); ATR-FTIR (neat) ν_{max} (cm^{-1}): 2922, 2854, 1713, 1437, 1196, 1158, 631; HRMS (ESI) calcd for $C_{22}H_{30}O_5$-Na [$(M+Na)^+$] 397.1991, found 397.1993.

2.7.18. (7E,6Z)-dimethyl 6-(3-(furan-3-yl)propylidene)-2-(4-methylpent-3-en-1-yl)hept-2-enedioate (7)

According to the general procedure A for HWE reactions, phosphonate **12** (99 mg, 0.38 mmol) and aldehyde **27** (89 mg, 0.38 mmol) were combined. After flash chromatography (*n*-hexane:EtOAc 95:5), an inseparable mixture of diesters **7** and **8** (92 mg, 65%, 4/1 respectively) was obtained. Description of the title compound (major product) is given as follows: ^{1}H NMR (400 MHz, δ, $CDCl_3$) 1.56 (s, 3H, $H_{6'}$), 1.65 (s, 3H, $H_{5'}$), 2.04 (dt, J = 7.0, 7.0 Hz, 2H, $H_{2'}$), 2.21–2.31 (m, 4H, 2×H_4, 2×$H_{1'}$), 2.33–2.37 (m, 2H, H_5), 2.52 (t, J = 7.1 Hz, 2H, $H_{3''}$), 2.70 (dt, J = 7.1, 7.1 Hz, 2H, $H_{2''}$), 3.71 (s, 3H, C_1(O)OMe), 3.72 (s, 3H, C_7(O)OMe), 5.10 (t, J = 7.0 Hz, 1H, $H_{3'}$), 5.92 (t, J = 7.3 Hz, 1H, $H_{1''}$), 6.25 (s, 1H, $H_{4'''}$), 6.68 (t, J = 7.1 Hz, 1H, H_3), 7.20 (s, 1H, $H_{2'''}$), 7.32 (s, 1H, $H_{5'''}$); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 17.7 (CH_3, $C_{6'}$), 24.6 (CH_2, $C_{3''}$), 25.7 (CH_3, $C_{5'}$), 27.1 (CH_2, $C_{1'}$), 27.7 (CH_2, $C_{2'}$), 28.4 (CH_2, C_4), 29.9 (CH_2, $C_{2''}$), 33.8 (CH_2, C_5), 51.3 (CH_3, $CO_2\underline{Me}$), 51.6 (CH_3, $CO_2\underline{Me}$), 111.0 (CH, $C_{4'''}$), 123.7 (CH, $C_{3'}$), 124.2 (C, $C_{3'''}$), 131.3 (C, C_6), 132.3 (C, $C_{4'}$), 132.5 (C, C_2), 139.1 (CH, $C_{2'''}$), 141.5 (CH, C_3), 142.7 (CH, $C_{5'''}$), 142.9 (CH, $C_{1''}$), 167.9 (C, C_7), 168.3 (C, C_1); ATR-FTIR (neat) ν_{max} (cm^{-1}): 2919, 2851, 1712, 1269, 1199, 1123, 630; MS (EI) m/z (relative intensity) 374 $(M)^+$ (3), 342 (31), 315 (8), 81 (100); HRMS (EI) calcd for $C_{22}H_{30}O_5$ [$(M)^+$] 374.2093, found 374.2086.

2.7.19. (2Z,6Z)-dimethyl 6-(3-(furan-3-yl)propylidene)-2-(4-methylpent-3-en-1-yl)hept-2-enedioate (8)

The general procedure B for HWE reactions was applied to phosphonate **13** (156 mg, 0.38 mmol) and aldehyde **27** (89 mg, 0.38 mmol). After flash chromatography (*n*-hexane:EtOAc 95:5), an inseparable colorless mixture of diesters **8** and **7** (113 mg, 80%, 2.3/1 respectively) was obtained. Description of the title compound (major product) is given as follows: ^{1}H NMR (400 MHz, δ, $CDCl_3$) 1.55 (s, 3H, $H_{6'}$), 1.64 (s, 3H, $H_{5'}$), 2.05 (dt, J = 7.1, 7.1 Hz, 2H, $H_{2'}$), 2.21 (t, J = 7.6 Hz, 2H, $H_{1'}$), 2.32 (t, J = 7.5 Hz, 2H, H_5), 2.48–2.54 (m, 4H, 2×H_4, 2×$H_{3''}$), 2.68 (dt, J = 7.3, 7.3 Hz, 2H, $H_{2''}$), 3.68 (s, 3H, C_1(O)OMe), 3.70 (s, 3H, C_7(O)OMe), 5.05 (t, J = 6.9 Hz, 1H, $H_{3'}$), 5.78 (t, J = 7.3 Hz, 1H, H_3), 5.89 (t,

J = 7.1 Hz, 1H, $H_{1''}$), 6.23 (s, 1H, $H_{4'''}$), 7.19 (s, 1H, $H_{2'''}$), 7.30 (s, 1H, $H_{5'''}$); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 17.6 (CH_3, $C_{6'}$), 24.6 (CH_2, C_4), 25.7 (CH_3, $C_{5'}$), 27.8 (CH_2, $C_{2'}$), 29.0 (CH_2, $C_{3''}$), 29.8 (CH_2, $C_{2''}$), 34.1 (CH_2, C_5), 34.7 (CH_2, $C_{1'}$), 51.1 (CH_3, $CO_2\underline{Me}$), 51.2 (CH_3, $CO_2\underline{Me}$), 110.9 (CH, $C_{4'''}$), 123.5 (CH, $C_{3'}$), 124.2 (C, $C_{3'''}$), 131.5 (C, C_6), 132.1 (C, $C_{4'}$), 132.3 (C, C_2), 139.0 (CH, $C_{2'''}$), 140.7 (CH, C_3), 142.1 (CH, $C_{1''}$), 142.8 (CH, $C_{5'''}$), 168.0 (C, C_7), 168.3 (C, C_1); ATR-FTIR (neat) ν_{max} (cm^{-1}) 2923, 2857, 1714, 1438, 1199, 1124, 1024; (EI) m/z (relative intensity) 374 $(M)^+$ (3), 315 (11), 246 (27), 81 (100); HRMS (EI) calcd for $C_{22}H_{30}O_5$ [$(M)^+$] 374.2093, found 374.2094.

2.7.20. (2E,6E)-6-(3-(furan-3-yl)propylidene)-2-(4-methylpent-3-en-1-yl)hept-2-enedioic acid (1)

Diester **5** (32 mg, 0.09 mmol) was subjected to the general procedure for hydrolysis. After flash chromatography (*n*-hexane:EtOAc 70:30), the diacid **1** (20 mg, 68%) was obtained as a yellowish oil: ^{1}H NMR (400 MHz, δ, $CDCl_3$) 1.58 (s, 3H, $H_{6'}$), 1.66 (s, 3H, $H_{5'}$), 2.07 (dt, J = 7.2, 7.2 Hz, 2H, $H_{2'}$), 2.27 (t, J = 7.3 Hz, 2H, $H_{1'}$), 2.32 (dt, J = 7.5, 7.5 Hz, 2H, H_4), 2.47 (t, J = 7.2 Hz, 2H, H_5), 2.49 (dt, J = 7.5, 7.5 Hz, 2H, $H_{2''}$), 2.60 (t, J = 7.1 Hz, 2H, $H_{3''}$), 5.10 (t, J = 6.5 Hz, 1H, $H_{3'}$), 6.27 (s, 1H, $H_{4'''}$), 6.90 (t, J = 7.5 Hz, 1H, H_3), 6.96 (t, J = 7.2 Hz, 1H, $H_{1''}$), 7.24 (s, 1H, $H_{2'''}$), 7.35 (s, 1H, $H_{5'''}$); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 17.8 (CH_3, $C_{6'}$), 24.1 (CH_2, $C_{3''}$), 25.5 (CH_2, C_5), 25.8 (CH_3, $C_{5'}$), 26.7 (CH_2, $C_{1'}$), 27.9 (CH_2, $C_{2'}$), 28.5 (CH_2, C_4), 29.6 (CH_2, $C_{2''}$), 110.9 (CH, $C_{4'''}$), 123.6 (CH, $C_{3'}$), 123.8 (C, $C_{3'''}$), 131.4 (C, C_6), 132.0 (C, C_2), 132.6 (C, $C_{4'}$), 139.2 (CH, $C_{2'''}$), 143.2 (CH, $C_{5'''}$), 144.3 (CH, C_3), 145.2 (CH, $C_{1''}$), 173.0 (C, C_7), 173.3 (C, C_1); ATR-FTIR (neat) ν_{max} (cm^{-1}) 2923, 2856, 2559, 1678, 1422, 1275, 874; HRMS (ESI) calcd for $C_{20}H_{26}O_5Na$ [$(M+Na)^+$] 369.1678, found 369.1679.

2.7.21. (2Z,6E)-6-(3-(furan-3-yl)propylidene)-2-(4-methylpent-3-en-1-yl)hept-2-enedioic acid (2)

The general procedure for hydrolysis was applied to diester **6** (14 mg, 0.04 mmol). After flash chromatography (*n*-hexane:EtOAc 70:30), the diacid **2** (6.9 mg, 53%) was obtained as a yellowish oil: ^{1}H NMR (400 MHz, δ, $CDCl_3$) 1.57 (s, 3H, $H_{6'}$), 1.67 (s, 3H, $H_{5'}$), 2.10 (dt, J = 7.3, 7.3 Hz, 2H, $H_{2'}$), 2.24 (t, J = 7.4 Hz, 2H, $H_{1'}$), 2.42 (dt, J = 7.5, 7.5 Hz, 2H, $H_{2''}$), 2.43 (t, J = 7.6 Hz, 2H, H_5), 2.56 (t, J = 7.5 Hz, 2H, $H_{3''}$), 2.64 (dt, J = 7.6, 7.6 Hz, 2H, H_4), 5.08 (t, J = 7.3 Hz, 1H, $H_{3'}$), 5.90 (t, J = 8.5 Hz, 1H, H_3), 6.27 (s, 1H, $H_{4'''}$), 6.93 (t, J = 7.2 Hz, 1H, $H_{1''}$), 7.23 (s, 1H, $H_{2'''}$), 7.35 (s, 1H, $H_{5'''}$); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 17.8 (CH_3, $C_{6'}$), 24.2 (CH_2, $C_{3''}$), 25.8 (CH_3, $C_{5'}$), 26.1 (CH_2, C_5), 27.9 (CH_2, $C_{2'}$), 28.7 (CH_2, C_4), 29.6 (CH_2, $C_{2''}$), 34.7 (CH_2, $C_{1'}$), 110.9 (CH, $C_{4'''}$), 123.4 (CH, $C_{3'}$), 124.0 (C, $C_{3'''}$), 131.2 (C, C_6), 132.6 (C, $C_{4'}$), 133.1 (C, C_2), 139.2 (CH, $C_{2'''}$), 141.5 (CH, C_3), 143.1 (CH, $C_{5'''}$), 144.3 (CH, $C_{1''}$), 173.5 (C, C_7), 174.4 (C, C_1); ATR-FTIR (neat) ν_{max} (cm^{-1}) 2922, 2854, 2653, 1684, 1441, 1274, 874; HRMS (ESI) calcd for $C_{20}H_{26}O_5Na$ [$(M+Na)^+$] 369.1673, found 369.1678.

2.7.22. (2E,6Z)-6-(3-(furan-3-yl)propylidene)-2-(4-methylpent-3-en-1-yl)hept-2-enedioic acid (3)

A mixture of diesters **7**/**8** (13.0 mg, 0.04 mmol, 4/1) was subjected to the general procedure for hydrolysis. After flash chromatography (*n*-hexane:EtOAc 70:30), the minority diacid **4** was retained in the column, and the diacid **3** (6.6 mg, 69%) was obtained as a colorless oil: ^{1}H NMR (500 MHz, δ, $CDCl_3$) 1.58 (s, 3H, $H_{6'}$), 1.67 (s, 3H, $H_{5'}$), 2.06 (dt, J = 7.5, 7.5 Hz, 2H, $H_{2'}$), 2.27 (t, J = 7.8 Hz, 2H, $H_{1'}$), 2.37 (dt, J = 7.0, 7.0 Hz, 2H, H_4), 2.50 (t, J = 6.8 Hz, 2H, H_5), 2.55 (t, J = 7.5 Hz, 2H, $H_{3''}$), 2.73 (dt, J = 7.4, 7.4 Hz, 2H, $H_{2''}$), 5.10 (tt, J = 7.3, 1.3 Hz, 1H, $H_{3'}$), 6.06 (t, J = 7.3 Hz, 1H, $H_{1''}$), 6.28 (s, 1H, $H_{4'''}$), 6.93 (t, J = 7.9 Hz, 1H, H_3), 7.23 (s, 1H, $H_{2'''}$), 7.35 (s, 1H, $H_{5'''}$); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 17.8 (CH_3, $C_{6'}$), 24.6 (CH_2, $C_{3''}$), 25.8 (CH_3, $C_{5'}$), 26.6 (CH_2, $C_{1'}$), 27.8 (CH_2, $C_{2'}$), 30.0 (CH_2, $C_{2''}$), 30.1 (CH_2, C_4), 33.5 (CH_2, C_5), 111.0 (CH, $C_{4'''}$), 123.7 (CH, $C_{3'}$), 124.2 (C, $C_{3'''}$), 131.8 (C, C_6), 132.2 (C, C_2), 132.4 (C, $C_{4'}$), 139.2 (CH, $C_{2'''}$), 143.0 (CH, $C_{5'''}$), 144.3 (CH, C_3), 144.6 (CH, $C_{1''}$), 173.3 (C, C_1), 173.6 (C, C_7); ATR-FTIR (neat) ν_{max} (cm^{-1}) 2921, 2852, 1686, 1448, 1276, 1103, 630; HRMS (ESI) calcd for $C_{20}H_{26}O_5Na$ [$(M+Na)^+$]: 369.1678, found 369.1679.

2.7.23. (2Z,6Z)-6-(3-(furan-3-yl)propylidene)-2-(4-methylpent-3-en-1-yl)hept-2-enedioic acid (4)

A mixture of diesters **8**/**7** (21.8 mg, 0.06 mmol, 2.3/1) was submitted to the general procedure for hydrolysis, but the saturation with NaCl in the work-up was suppressed. Once concentrated, the crude was redissolved in Et_2O and washed with an EDTA saturated aqueous solution (2 × 1 mL) and then with H_2O (2 × 2 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (*n*-hexane:EtOAc 80:20) yielded the corresponding mixture of **4** and **3** (14 mg, 70%, 2.3/1 respectively). Description of the title compound (major product) is given as follows: ^{1}H NMR (400 MHz, δ, $CDCl_3$) 1.59 (s, 3H, $H_{6'}$), 1.68 (s, 3H, $H_{5'}$), 2.10 (dt, J = 7.7, 7.7 Hz, 2H, $H_{2'}$), 2.26 (t, J = 7.7 Hz, 2H, $H_{1'}$), 2.40 (t, J = 7.3 Hz, 2H, H_5), 2.53 (t, J = 7.7 Hz, 2H, $H_{3''}$), 2.69 (dt, J = 7.8, 7.8 Hz, 2H, H_4), 2.77 (dt, J = 7.4, 7.4 Hz, 2H, $H_{2''}$), 5.09 (t, J = 6.1 Hz, 1H, $H_{3'}$), 5.87 (t, J = 8.2 Hz, 1H, H_3), 5.97 (t, J = 6.9 Hz, 1H, $H_{1''}$), 6.27 (s, 1H, $H_{4'''}$), 7.22 (s, 1H, $H_{2'''}$), 7.34 (s, 1H, $H_{5'''}$); ^{13}C NMR (100 MHz, δ, $CDCl_3$) 17.8 (CH_3, $C_{6'}$), 24.7 (CH_2, $C_{3''}$), 25.8 (CH_3, $C_{5'}$), 28.0 (CH_2, $C_{2'}$), 28.9 (CH_2, C_4), 30.0 (CH_2, $C_{2''}$), 34.5 (CH_2, $C_{1'}$), 34.6 (CH_2, C_5), 111.0 (CH, $C_{4'''}$), 123.5 (CH, $C_{3'}$), 124.3 (C, $C_{3'''}$), 130.7 (C, C_6), 132.5 (C, $C_{4'}$), 132.7 (C, C_2), 139.1 (CH, $C_{2'''}$), 142.7 (CH, C_3), 142.9 (CH, $C_{5'''}$), 145.6 (CH, $C_{1''}$), 173.7 (C, C_7), 174.4 (C, C_1); ATR-FTIR (neat) ν_{max} (cm^{-1}) 2920, 2853, 2579, 1680, 1533, 1439, 1260; HRMS (ESI) calcd for $C_{20}H_{26}O_5Na$ [$(M+Na)^+$] 369.1678, found 369.1677.

3. Results and discussion

Initially, we proposed the synthesis of the thymifodioic/incanic acids **1**–**4** through hydrolysis of their methyl esters **5**–**8**, which could be accessed from the building blocks shown in Scheme 1.

Aldehyde **9** is commercially available or easily synthesized from 3-furaldehyde, following the 3-steps procedure described in the literature (Davis et al., 2005). Phosphonates **12** and **13** are synthetic equivalents of **10** and **11** respectively, considering that the trisubstituted double bond is susceptible to turning into an aldehyde. Stereoisomerism of the internal double bonds could be controlled by means of the substitution pattern of the phosphonate group: methoxy groups should lead to an

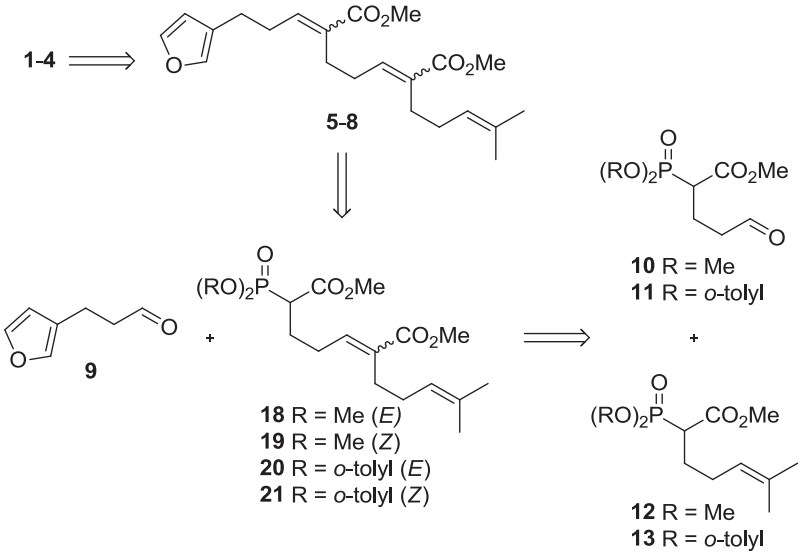
E geometry whereas *o*-tolyloxy groups must induce a *Z* geometry (Ando, 1997). Other groups, such as trifluoroethoxy (Still and Gennari, 1983) or *o*-*t*-butylphenoxy (Touchard et al., 2005), are also valid for achieving a *Z* geometry in the HWE reaction, though we selected Ando reagent because of the availability in our laboratory. Phosphonate-aldehydes (PAs) **10** and **11** were selected to build the central core of the desired compounds. These molecules have two functional groups available to be submitted to a chemoselective Horner–Wadsworth–Emmons (HWE) reaction (Horner et al., 1959; Wadsworth and Emmons, 1961) or even two sequential HWE reactions. Precisely due to this bi-functionality, these ambivalent molecules show a promising potential as building blocks for iterative synthesis, especially when the desired target molecule contains internal double bonds. To the best of our knowledge, there are few examples of reactions involving this kind of ambivalent molecules in the bibliography, which are mainly used in intramolecular condensations (Snider and Phillips, 1983; Kodama et al., 1986; Krawczyk and Albrecht, 2008; Napolitano et al., 2010; Ando and Sato, 2011), whereas intermolecular examples are rare (Krawczyk et al., 2008; Gastl and Laschat, 2010). The modularity found in compounds **1**–**8** and the absence of information in the literature about ambivalent PAs encouraged us to analyze their reactivity in HWE reactions through their two functional groups, and to apply the conclusions of this study in the development of a unified synthetic strategy for the first total synthesis of all four stereoisomers of thymifodioic/incanic acids (**1**–**4**).

As shown in Scheme 2, phosphonate **12** was synthesized in 80% yield by treatment of commercially available trimethyl phosphonoacetate (**14**) with *t*-BuOK and the corresponding alkyl bromide (Odejinmi and Wiemer, 2005). Phosphonate **15**, which was also obtained from commercially available **14** following the procedure described by Ando (Ando, 1997), underwent the same α-alkylation conditions. Unfortunately, the yield fell to 13%, probably due to the higher steric hindrance of the *o*-tolyloxy groups attached to the phosphorus in compound **15**. In order to improve this result, we employed NaH, a less bulky base than *t*-BuOK, achieving a better result in the synthesis of phosphonate **13**.

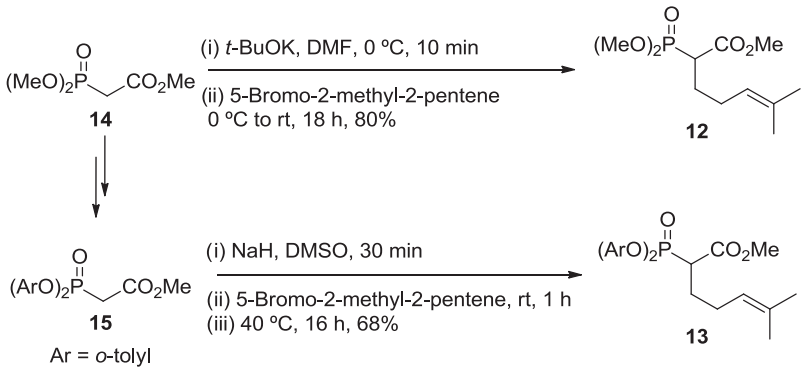
In order to obtain PAs **10** and **11** from phosphonates **12** and **13** respectively, we tried firstly an ozonolysis reaction, but it did not work properly. Fortunately, the epoxidation of the double bonds and a subsequent oxidative cleavage of epoxides **16** and **17** using H_5IO_6 provided the desired PAs in good yields (Scheme 3).

With these building blocks in hand, we carried out a HWE reaction between PAs **10** and **11** and their precursors **12** and **13** in order to build the phosphonates **18**–**21**, with controlled stereochemistry in the double bond and bearing a phosphonate group suitable for a subsequent HWE reaction with aldehyde **9** to access diesters **5**–**8** (Table 1).

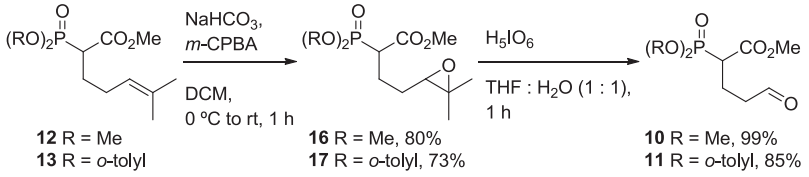
Phosphonate **12** was treated with *t*-BuOK at 0 °C, and 15 min later was cooled to −78 °C, treated with PA **10** and allowed to warm to rt. As this typical HWE reaction procedure did not show any product, the mixture was heated during 20 h, after which the ^{1}H NMR analysis of the crude revealed that an inseparable mixture of the desired phosphonate **18**, the *Z*-isomer **19** and the remaining phosphonate **12** was obtained (entry 1, Table 1). This mixture was immediately submitted to a HWE with aldehyde **9** to get a mixture of diesters **5**–**8**, where **5** was the majority compound, with an overall yield of 8% from **14** after 5 reaction steps (Scheme 4). As the low overall yield and low stereoselectivity are limited by the HWE reaction between **12** and **10**, we decided to test the different combinations between phosphonates and PAs. As high temperatures appeared to be necessary for the reaction, we planned to perform the treatment of **12** with *t*-BuOK and the addition of the PA **11** at rt, with immediate reflux of the reaction mixture. However, with this modification we obtained only 11% yield of a mixture of isomers *E*/*Z* (**20**/**21**, 1.5/1) (entry 2, Table 1). In order to continue with this systematic study, we tried the HWE reaction between PA **11** and phosphonate **13**, employing high temperatures and NaH as base, and obtaining a mixture of *E*-**20** and the major isomer *Z*-**21** (1/2.5) with a 35% yield (entry 3). This yield dropped when



Scheme 1 Retrosynthesis of thymifodioic/incanic acids **1**–**4**.



Scheme 2 Synthesis of phosphonates **12** and **13**.

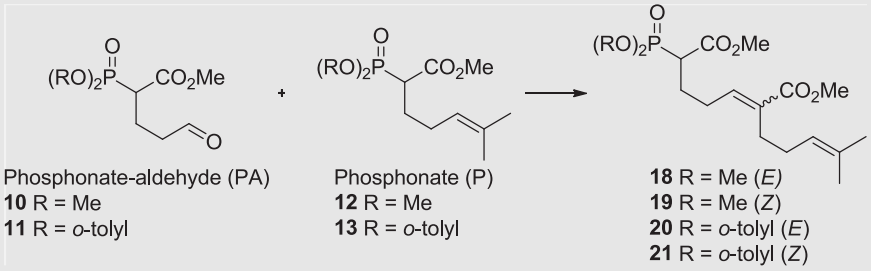


Scheme 3 Synthesis of phosphonate-aldehydes **10** and **11**.

the temperature of the reaction was reduced to 40 °C (entry 4) or when another solvent system was used (entry 5). Recovering the best conditions of entry 3, we tried the last combination between phosphonate **13** and PA **10**, achieving similar yield (33%) of a mixture of isomers *Z*-**19**/*E*-**18** (1.6/1) (entry 6).

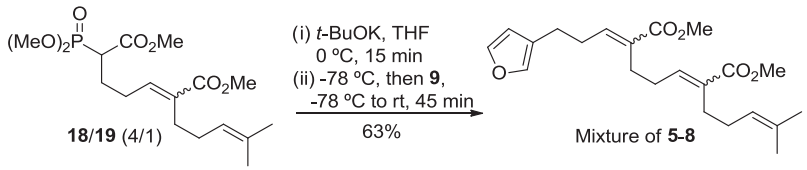
Once we concluded that the aldehyde group of the PAs did not react properly with phosphonates and the yields achieved in the synthesis of phosphonates **18**–**21** were unsatisfactorily low to achieve our goal of an efficient and general protocol for the synthesis of thymifodioic/incanic acids **1**–**4**, we decided to plan an alternative route to the target compounds. At first, we unsuccessfully tried another pathway to obtain phosphonate **18** (a peripheral discussion about this pathway can be found in Electronic Supplementary Material), but finally we proposed a different order in the formation of the double bonds, starting with the same materials **9**, **12** and **13**

Table 1 Study of the reactivity of the phosphonate-aldehyde acting as aldehydes facing phosphonates.[a]

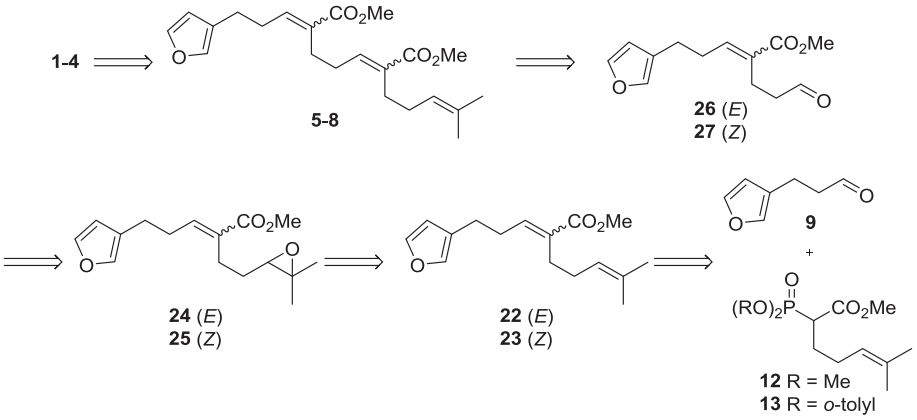


Entry	PA	P	Base	Conditions	Products[b]	Yield (%)
1	**10**	**12**	*t*-BuOK	−78 °C to rt, 2 h; then reflux, 20 h	**18**/**19** (4/1)	20[c]
2	**11**	**12**	*t*-BuOK	rt, then reflux, 4 h	**20**/**21** (1.5/1)	11
3	**11**	**13**	NaH	rt, then reflux, 4 h	**20**/**21** (1/2.5)	35
4	**11**	**13**	NaH	rt, then 40 °C, 4 h	**20**/**21** (1/1.2)	15
5[d]	**11**	**13**	NaH	rt, then reflux, 4 h	**20**/**21** (1/1)	9
6	**10**	**13**	NaH	rt, then reflux, 1 h	**18**/**19** (1/1.6)	33

[a] THF was used as solvent, unless another solvent is indicated.
[b] Relation between products based on ^{1}H NMR analysis.
[c] Not isolated yield.
[d] Benzene:toluene (3:1) mixture was used as solvent.



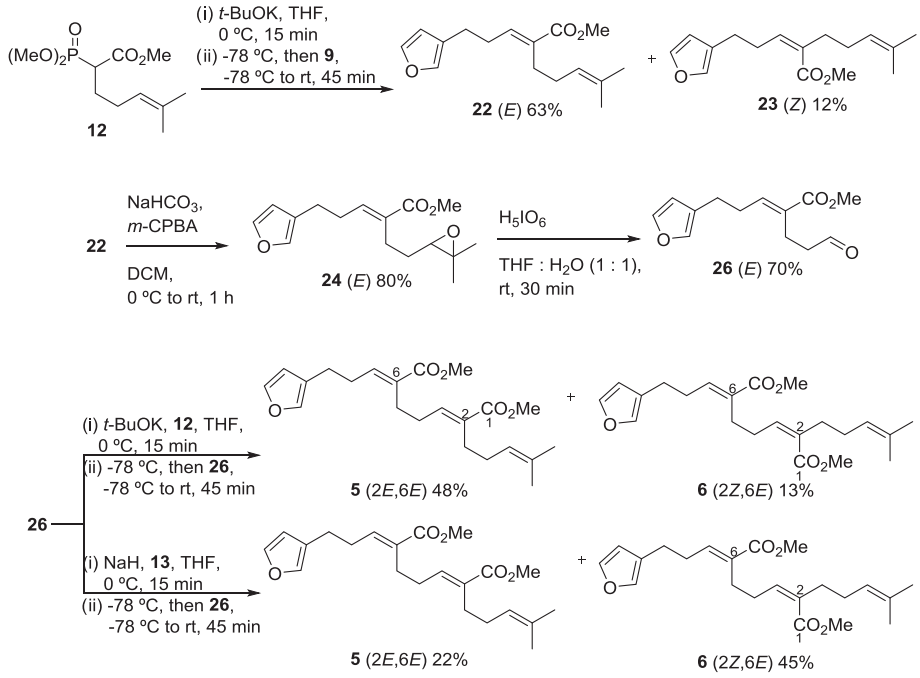
Scheme 4 HWE reaction between aldehyde 9 and an elaborated phosphonate.



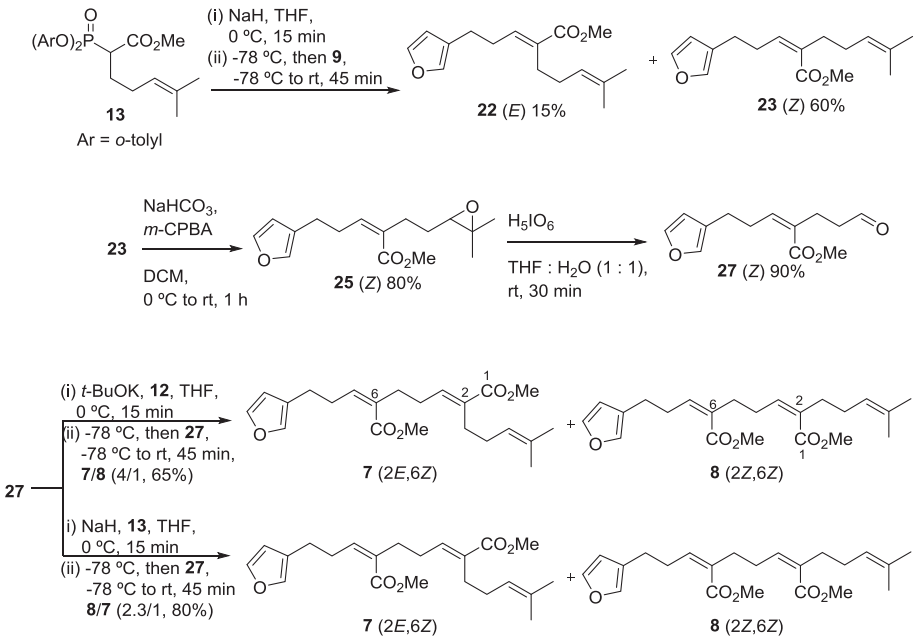
Scheme 5 Alternative retrosynthesis of thymifodioic/incanic acids **1**–**4**.

(Scheme 5). The HWE reaction of **9** with phosphonates **12** and **13** should allow the synthesis of the alkenes **22** and **23** respectively, whose successive epoxidations and oxidative cleavages would yield epoxides **24** and **25**, and then aldehydes **26** and **27**. Combination of these aldehydes again with phosphonates **12** and **13** should lead us to desired diesters **5**–**8**. This approach makes use of **12** and **13** as synthetic equivalents of PAs, with the aldehyde group easily available from the trisubstituted alkene, once phosphonate group has reacted in the HWE reaction with aldehyde **9** (Davis et al., 2005).

In order to prove the efficacy of this new strategy, we decided to apply it to the synthesis of the dimethyl diesters **5** and **6**. As can be seen in Scheme 6, the synthesis of these products started with the HWE reaction between freshly prepared aldehyde **9** and the previously obtained bench-stable phosphonate **12** to obtain the required *E*-alkene **22**. However, a 5.3/1



Scheme 6 Syntheses of thymifodioic/incanic dimethyl diesters **5** and **6**.

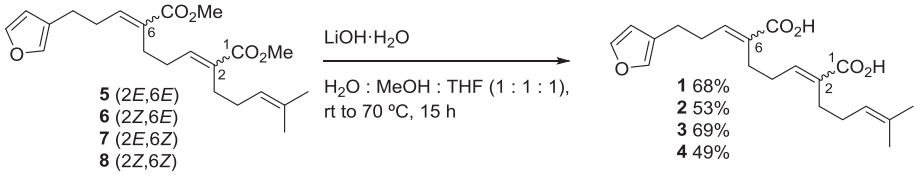


Scheme 7 Syntheses of thymifodioic/incanic dimethyl diesters **7** and **8**.

mixture of alkenes **22** and **23** was obtained with a global yield of 75%. Flash chromatography allowed us to separate both isomers, which were obtained with yields of 63% and 12%, respectively. Thus, the isomeric ratio (i.r.) obtained during the HWE reaction was 84:16, meaning a stereoselectivity of 68%. Both isomers were easily identified by ^{1}H NMR analysis, since they differ clearly in the chemical shift shown by the proton in beta position with respect to the carbonyl group (δ = 6.76 ppm in *E*-alkene **22** versus δ = 5.88 ppm in *Z*-alkene **23**). The bigger deshielding shown by the beta proton in the *E*-isomer arises from the magnetic anisotropy caused by the carbonyl group, which is closer to that proton in the space than in the *Z*-isomer. Desired major compound **22** was then treated with *m*-CPBA to yield epoxide **24**, which was submitted to an oxidative cleavage to afford aldehyde **26**. This aldehyde was combined with phosphonate **12** to yield a 3.7/1 mixture of the desired (2*E*,6*E*)-diester **5** and its (2*Z*,6*E*)-isomer **6** with a yield of 61% (79:21 i.r.). Although both isomers were separated by column chromatography, we aspired to prepare diester **6** as the major product. To our delight, when the same precursor aldehyde **26** was submitted to a HWE reaction with phosphonate **13**, target diester **6** was obtained with a yield of 45% after being separated from minority (2*E*,6*E*)-isomer **5** (67:33 i.r.).

Once we checked that the methodology shown in Scheme 5 was more efficient than that originally proposed in Scheme 1, we focused on the synthesis of the diesters **7** and **8** (Scheme 7). To install the *Z* geometry in the position 2 of the target compounds, phosphonate **13** was chosen as starting material. The HWE reaction between **13** and the aldehyde **9** allowed us to obtain a 4/1 mixture of alkenes **23** and **22** with a yield of 75% and a stereoselectivity of 60%. These values were similar to those obtained in the HWE of phosphonate **12** with aldehyde **9** (Scheme 6). Once separated from its *E*-isomer by column chromatography, alkene **23** was epoxidated and then transformed in the aldehyde **27** in a 72% yield after two steps. Aldehyde **27** was submitted to a HWE reaction with phosphonate **12** to yield an inseparable 4/1 mixture of diesters **7** and **8** (65%, 80:20 i.r.). By contrast, when aldehyde **27** was combined with phosphonate **13**, the (2*Z*,6*Z*)-diester **8** was obtained as the major isomer (80% of an inseparable mixture of **8** and **7**, 70:30 i.r.). These results, together with those regarding the HWE reaction between aldehyde **26** and phosphonates **12** and **13** shown in Scheme 6, indicate that Ando phosphonate **13** leads to better yields than the less bulkier phosphonate **12**, although the stereoselectivity is lower.

Once synthesized the four stereoisomers of the dimethyl diesters of thymifodioic/incanic acids, we expected that their hydrolysis would afford the corresponding acids. At first, we tried a mild method employing trimethyltin hydroxide (Nicolaou et al., 2005), but it did not work properly, probably due to molecules **5**–**8** containing two α,β-unsaturated esters with trisubstituted double bonds, and this kind of compounds usually needs more drastic conditions, such as a long reaction



Scheme 8 Conversion of dimethyl diesters **5**–**8** into thymifodioic/incanic acids **1**–**4**.

times, high temperatures and a large excess of some alkali hydroxides (Morris et al., 2009). Fortunately, with these conditions, thymifodioic/incanic acids were successfully obtained, with yields between 49% and 69% (Scheme 8). Additionally, the inseparable mixture of the diesters **7** and **8** resulted in the corresponding mixture of diacids **3** and **4**, and to our pleasure, it could be separated by flash chromatography.

4. Conclusion

We have achieved the first total syntheses of the natural products 2,6-(*Z*,*E*)-thymifodioic/incanic acid and bioactive 2,6-(*E*,*E*)-thymifodioic/incanic acid, as well as their stereoisomers, in only five steps from commercial common precursor **9** with overall yields ranging from 8% to 16%. Our methodology is based on a conceptually simple but efficient strategy in which the same molecule provides latent ylides and carbonyl groups, being considered as a synthetic equivalent of a stimulating ambivalent phosphonate-aldehyde synthon. The key step is the use of an iterative Horner–Wadsworth–Emmons condensation, a well-known, non-expensive and widely accessible reaction that allows the access to the target molecules through two different strategies by changing the addition order of the same building blocks. With products **1**–**8** in hand, and armed with this methodology that permit the rapid access to a panoply of synthetic derivatives or other linear terpenoids, a deeper structure–activity study can be now developed to evaluate their application as insecticides against *T. molitor* larvae.

Acknowledgments

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.arabjc.2016.01.008.

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