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# A dimethylsulfonium methylide mediated highly regioselective olefination of conjugated polyolefin 1,1-dioates to conjugated polyene-2-yl-malonates and their applications in Diels–Alder reactions

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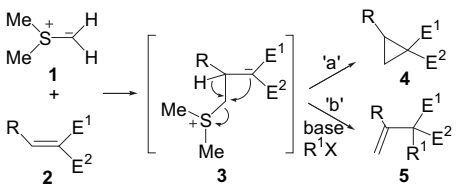
ABSTRACT

The reactions between dimethylsulfonium methylide and 1,3-diene- or 1,3,5-triene-1,1-dioates under specific conditions enable the highly regioselective tandem ylide addition–eliminative olefination to provide 1,3-butadien-2-yl- or 1,3,5-hexatriene-2-yl-malonates. Alkylation at malonate methine carbon of 1,3-butadien-2-ylmalonates with a suitable alkyl halide having in-built functionalities for a dienophile generation led to quick assembly of precursors for type 2 intramolecular Diels–Alder reaction. Syntheses of functionalized bicyclo[*n*.3.1] alkenes ($n$=5 or 6) with the double bond at the bridgehead position have been achieved via the IMDA. An asymmetric version of this reaction has been developed using a MacMillan's imidazolidinone catalyst, which provided a bicyclo[5.3.1] alkene with very high enantioselectivity. In situ methylation at malonate methine carbon of 1,3,5-hexatriene-2-yl-malonates followed by intermolecular Diels–Alder reaction with *N*-methylmaleimide provided the cycloadduct with complete regiocontrol and high diastereoselectivity.



## 1. Introduction

Carbon–carbon double bond forming reactions play important role in organic synthesis and a large number of methods have been developed over the past century. Amongst these, ylide mediated olefin synthesis from carbonyl compounds especially with phosphorus stabilized carbanions such as Wittig[1] and related reactions[2] are frequently used. In comparison, dimethylsulfonium methylide (popularly known as Corey–Chaykovsky reagent),[3] generated from a trimethylsulphonium salt and a base behaves differently. It is known to react with an aldehyde or a ketone to give an epoxide by an overall methylene insertion. Some interesting transformations are reported when excess reagent was used leading to the formation of allylic alcohol by further addition of the ylide on the epoxide.[4] In line with the carbonyl compounds, imines give aziridines and then further get transformed to allylic amines with excess of **1**.[5] The ylide also acts as a nucleophile and can be used for the conversion of halides and mesylates to one-carbon homologated terminal alkenes.[6] Although phosphorus ylides sometimes add in 1,4-fashion to suitably functionalized Michael acceptors,[7] dimethylsulfonium methylide has been widely used to add on Michael acceptors in 1,4-fashion to provide cyclopropanes.[3] Thus, the reaction of the ylide **1** with the Michael acceptor **2** gives a betaine intermediate **3**, which in principle can undergo various reactions (Scheme 1), the driving force in all cases being the elimination of $Me_2S$. The most well known amongst these is the formation of cyclopropane **4** (path 'a' Scheme 1). The other possible mode of reaction which could be envisioned from the intermediate **3** is the loss of a proton and $Me_2S$ in the presence of excess base resulting in the formation of an olefin **5** (path 'b'). While the formation of cyclopropane **4** following path 'a' has been well studied, olefination by path 'b' is not. We have recently reported[8] an interesting observation that **1** in combination with a base, like sodium dimsylate, undergoes a tandem ylide addition–eliminative olefination on various activated olefins thus favoring path 'b'. Thus, the combination also acted as an equivalent of carbene anion.[9] This strategy has been used in sequential tandem olefination–alkylation for the preparation of 1-substituted vinyl silanes, styrenes and products derived from them.[10] The methodology has been




**Scheme 1.** Two modes of reactions of dimethylsulfonium methylide with Michael acceptors.

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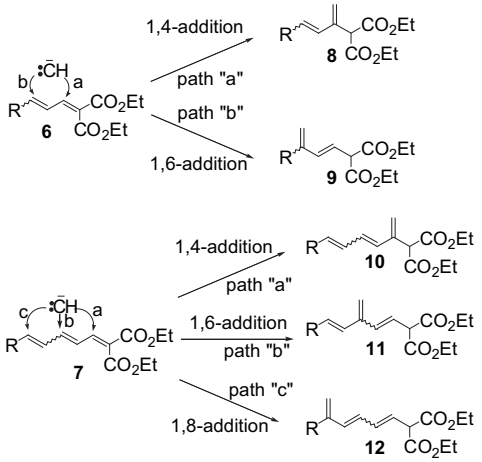
extended for sequential tandem double olefination of vinyl phosphonates and aldehydes to provide di and tri substituted 1,3-dienes with very high regio- and stereoselectivity.[11]

We were curious to know whether this novel olefination is applicable to extended conjugated system like 1,3-diendioates **6** or 1,3,5-triendioates **7** and if so formation of which regioisomer (Scheme 2) will dominate? Although, the conjugate addition[12] of carbon or heteroatomic nucleophilic reagents to activated olefins is a highly useful reaction in organic synthesis, the regioselectivity issue viz. 1,4-addition versus 1,6-addition[13–16] sometimes becomes challenging to extended conjugate systems. This report is the full version of our preliminary communication[17] relating to the first example of tandem 1,4-addition–elimination of ylide **1** to 4-aryl/alkyl substituted 1,3-diendioates **6** to give 1,3-butadien-2-yl-malonates **8**, a novel class of dienes with a functionality at 2-position amenable for further maneuvering and/or quick lodging of a dienophile fragment. We also report that this technique can be extended for regioselective olefination of 1,3,5-trienedioates **7** under specific conditions to provide 1,3,5-hexatriene-2-yl-malonates **10**. Intramolecular type 2 DA (T2IMDA) reaction with former class of products and intermolecular DA with latter class of products also provided interesting bridged bicyclo[*n*.3.1] and fused ring systems, respectively.

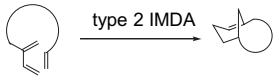



**Scheme 2.** Probable olefination pathways of 1,3-diendioates or 1,3,5-triendioates with ylide **1**.

## 2. Results and discussion

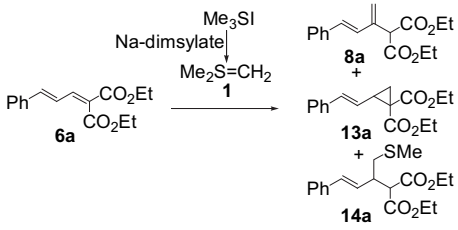
Bicyclo[*n*.3.1] alkenes with multiple functionalities and a bridgehead double bond are found in a number of biologically important natural products including paclitaxel (taxol),[18] phomoidrides (CP molecules),[19] esperamicin,[20] and other classes of natural products.[21] Amongst the few available direct methods,[22] the T2IMDA reaction[23] (Scheme 3) is the most efficient one to assemble a bridged bicyclic framework, incorporating a bridgehead double bond[24] (*anti*-Bredt olefin). The syntheses of these ring systems via T2IMDA proceed with predictable regio- and stereoselectivity.

For T2IMDA, the dienophile component is attached to 2-position of the 1,3-diene with an appropriate tether. For this, 1,3-butadienes substituted with suitable functionality at 2-position is a prerequisite, which would enable the attachment of the dienophile fragment. A number of methods have been developed for their preparation.[25–28] Many of these methodologies involve organometallic species such as 1,3-butadienyl-2-metal[26] or 2,3-butadienyl-1-metal,[27] which often suffer from poor regioselectivity or low yield and, in some cases, require starting materials that are not readily accessible. More recently, attractive alternative methods such as Barbier-type coupling[25,28c] and ethylene–alkyne cross-metathesis[28b,d] have been reported for their preparation. However, although efficient, few methods are applicable to the synthesis of 2-substituted 1,3-butadienes where a quick assembly of a dienophile fragment can be made to perform T2IMDA. We have found out conditions for a regioselective nucleophilic addition (1,4-addition) of dimethylsulfonium methylide in combination with a base or excess of itself (a carbene anion equivalent[9]) to 1,3-diene 1,1-dioates **6** (Scheme 2) providing 1,3-diene-2-yl-malonates.




**Scheme 3.** Schematic representation of T2IMDA.

When 4-phenyl dienedioate **6a** was added to ylide **1**, generated using 1.2 equiv of $Me_3SI$ and 2.5 equiv sodium dimsylate in DMSO/THF (3:7) under the reported conditions,[8] we obtained a mixture of diene **8a**, vinylcyclopropane **13a**, and the thiomethyl product **14a** (**8a**/**13a**/**14a**=50:20:30) (Scheme 4; Table 1, entry 1). The diene **8a** and the vinylcyclopropane **13a** were also inseparable. Although, the formation of the cyclopropane **13a** could be curbed (Table 1) by increasing the quantities of the base (3–4 equiv) and the salt (1.5–2.5 equiv) (Table 1, entries 2 and 3), the formation of the thiomethyl product **14a**[29] could not be minimized. Besides, sodium dimsylate is known for its explosive nature. Therefore, we modified[10b] the procedure for the generation of the ylide **1** by using *n*-BuLi in THF instead of sodium dimsylate. As *n*-BuLi is reactive, it cannot be used in excess. Instead, excess ylide was generated using 3 equiv each of *n*-BuLi and trimethylsulfonium iodide in THF at −10 °C. When 4-phenyl dienedioate **6a** was added to excess ylide (3 equiv), generated by the modified procedure, the dienic product **8a** was formed in very good yield (96%) (Scheme 5). The reaction was highly regioselective and the dienic product **9** could not be detected as 1,6-addition of ylide **1** did not take place. Moreover, if the reaction was quenched with MeI (5 equiv) before work up, methylated product **15a** was obtained in 87% yield.

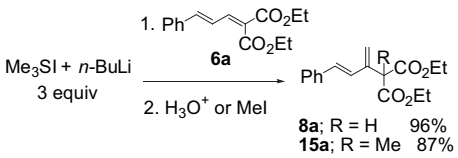



**Scheme 4.** Reaction of diendioate **6a** with ylide **1** generated from $Me_3SI$ and Na-dimsylate.

**Table 1**
Tandem addition–eliminative olefination on **6a** mediated by $Me_3SI$ and Na-dimsylate

| Entry | Na-dimsylate (equiv) | $Me_3SI$ (equiv) | **8a**/**13a**/**14a**[a] |
|---|---|---|---|
| 1 | 2.5 | 1.2 | 50:20:30 |
| 2 | 3 | 1.5 | 74:—[b]:26 |
| 3 | 4 | 2.5 | 78:—[b]:22 |
| 4 | 3 | 3 | 45:30:25 |

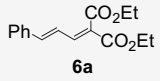
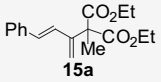
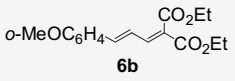
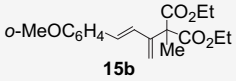
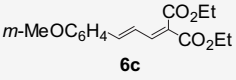
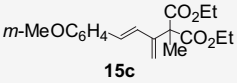
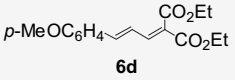
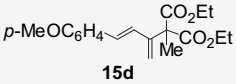
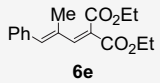
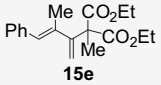
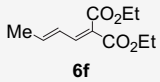
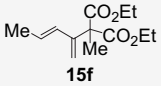
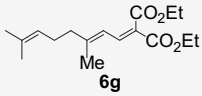
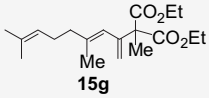
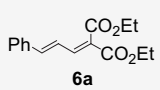
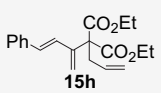
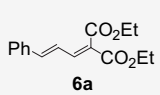
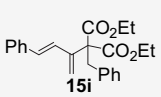
[a] Determined from crude product by $^1H$ NMR.
[b] Peaks for **13a** could not be seen in the $^1H$ NMR spectrum of the crude reaction mixture.




**Scheme 5.** Reaction of diendioate **6a** with ylide **1** generated from $Me_3SI$ and *n*-BuLi.

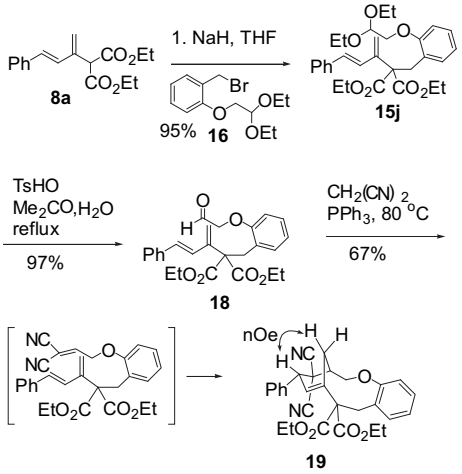
To find the generality of the olefination–alkylation process, a few diendioates **6b–e** (Table 2) were prepared from the commercially available substituted cinnamaldehydes by Knoevenagel condensation with diethyl malonate. When these substrates were reacted with dimethylsulfonium methylide **1**, generated using *n*-BuLi and trimethylsulfonium iodide, the desired products **15b–e** were isolated in good yields after methylation (Table 2). Methoxy substituent in the aryl ring and methyl substituent at position-3 of the diendioates did not retard the reaction (Table 2, entries 2–5). The substituent at position-4 of the diene **6** may not necessarily to be an aryl group, e.g., Me in diene **6f** (Table 2, entry 6), and Me and an alkyl group in **6g** (Table 2, entry 7) also gave the desired methylated products **15f** and **15g**, respectively. The stereochemistry of the double bond at γ,δ position remained unaffected during the process. The (*E*)-stereochemistry of this double bond in products **15a–d** was assigned from the $^1$H coupling constants ($J \approx 16$ Hz). The starting dienes **6e** and **6g** were contaminated with 18% and 35% of (*Z*)-isomer, respectively. Thus the products **15e** and **15g** were also contaminated with the isomeric product in the same proportions. When the reaction between **6a** and ylide **1** was quenched with 3 equiv of allyl and benzyl bromides, the corresponding alkylated products **15h** (74%) and **15i** (53%) were isolated. The lower yields are probably due to protonation of the malonate carbanion by the byproducts formed due to decomposition of the excess ylide used in the reaction. The yields were therefore improved (Table 2; entries 8 and 9) by adding anhydrous $K_2CO_3$ into the reaction mixture prior to addition of bromides.

**Table 2**
Sequential tandem sulfonium ylide addition–eliminative olefination–alkylation of diendioates **6**

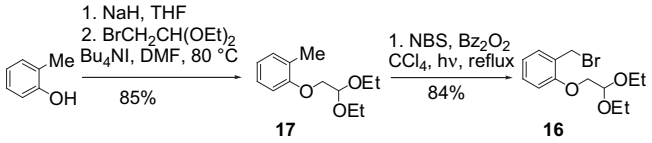
| Entry | Substrate | Product | Yield[a] (%) |
|---|---|---|---|
| 1 |  **6a** |  **15a** | 87 |
| 2 |  **6b** |  **15b** | 81 |
| 3 |  **6c** |  **15c** | 88 |
| 4 |  **6d** |  **15d** | 85 |
| 5 |  **6e** |  **15e** | 78 |
| 6 |  **6f** |  **15f** | 68 |
| 7 |  **6g** |  **15g** | 65 |
| 8 |  **6a** |  **15h** | 83[b] |
| 9 |  **6a** |  **15i** | 81[c] |

[a] Isolated yield.
[b] 3 equiv each of $K_2CO_3$ and allyl bromide used.
[c] 3 equiv each of $K_2CO_3$ and benzyl bromide used.

By quenching the reaction with a suitable alkyl halide, which has desired tether length and an in-built dienophile, or has the capability to provide one, the system would be ideally suited for T2IMDA. The cycloadduct from T2IMDA reaction would be the bicyclo[*n*.3.1] alkene with a bridgehead double bond and the size of the bridge would depend upon the tether length. As a model study, the olefination product **8a** was deprotonated using sodium hydride and reacted with the substituted benzyl bromide **16**,[30] which provided the alkylated diene **15j** in excellent yield (Scheme 6). The benzyl bromide in turn was prepared from *o*-cresol as shown in Scheme 7. For this, sodium phenolate of *o*-cresol was alkylated with bromoacetaldehyde diethyl acetal in the presence of catalytic amount of tetrabutylammonium iodide to give the acetal **17**, which in turn underwent benzylic bromination to bromide **16** by *N*-bromosuccinimide initiated by dibenzoyl peroxide in $CCl_4$. The acetal group in **15j** was hydrolyzed (Scheme 6) and the resulting aldehyde **18** was subjected to Knoevenagel condensation with malononitrile catalyzed by triphenylphosphine[31] under solvent-free condition at 80 °C. Interestingly, a domino[32] Knoevenagel–T2IMDA sequence




**Scheme 6.** Synthesis of a bicyclo[6.3.1] alkene by T2IMDA.




**Scheme 7.** Synthesis of substituted benzyl bromide **16**.

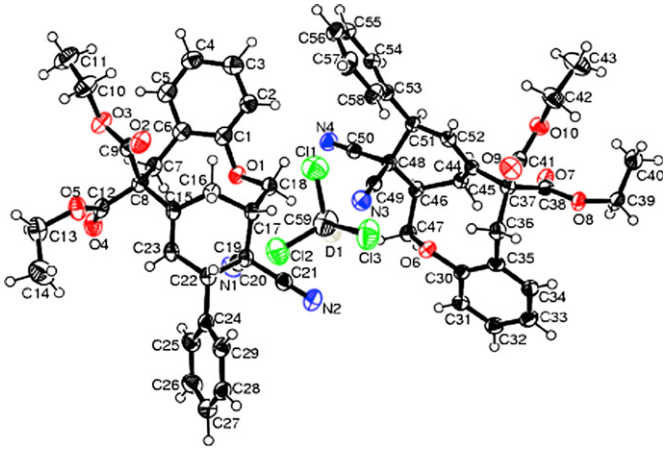
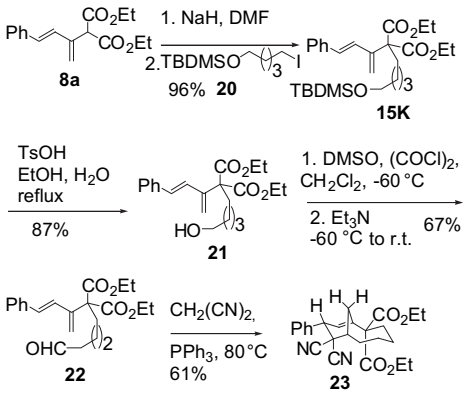


**Figure 1.** ORTEP plot of two molecules of **19**+$CDCl_3$.

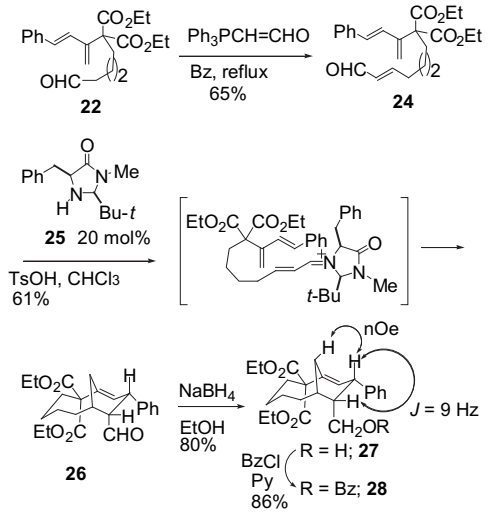
provided the bridged bicyclic product **19** with a bicyclo[6.3.1] alkene in good yield. The stereochemical feature of **19** was determined by COSY and ROESY analysis and was further confirmed by X-ray crystallography[33] as shown in Figure 1.

Inspired by this, we next aimed to make the lower homologue, bicyclo[5.3.1] alkene system. For this, diene-2-yl malonate **8a** was reacted with sodium hydride in DMF and the resulting anion was alkylated with 5-*tert*-butyldimethylsilyloxypentyl iodide **20**,[34] which provided the desired alkylated product **15k** in excellent yield (96%) (Scheme 8). Silyl deprotection with *p*-toluenesulfonic acid in aqueous ethanol gave the alcohol **21**, which on Swern oxidation provided the corresponding aldehyde **22** in very good yield. Following the domino[32] Knoevenagel–T2IMDA procedure developed for aldehyde **18** to bridged bicyclic product **19**, when aldehyde **22** was treated with malononitrile in the presence of catalytic amount of triphenylphosphine[31] under solvent-free conditions at 80 °C, the bridged bicyclo[5.3.1] alkene **23** was produced in moderate yield.



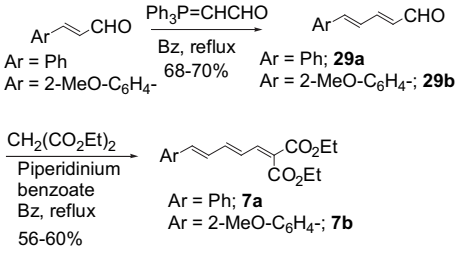

**Scheme 8.** Synthesis of a bicyclo[5.3.1] alkene by T2IMDA.

Bicyclo[5.3.1] alkenes are the key structural feature in many natural and biologically important molecules. They also possess a number of chiral centers depending upon the substituents. At this stage it was therefore imperative to induce asymmetry during the build up of the bicyclo skeleton. MacMillan and co-workers[35] have shown that their imidazolidine derived catalysts can activate α,β-unsaturated carbonyl compounds as dienophiles as well as impart enantioselectivity in type 1 and 2 IMDA reactions. Shea and co-workers[36] have also used similar strategy to introduce asymmetry while building bicyclo[*n*.3.1] alkenes by T2IMDA reactions. We, therefore, converted aldehyde **22** to α,β-unsaturated aldehyde **24** by reacting with formylmethylenetriphenylphosphorane[37] and then subjected under T2IMDA in the presence of 20 mol% of MacMillan's imidazolidinone catalyst **25** (Scheme 9). We were delighted to find that a facile cycloaddition took place to provide the corresponding bicyclo[5.3.1] aldehyde **26** in good yield and as a single diastereoisomer with excellent enantioselectivity. The enantiomeric purity (92% ee) of the product **26** was ascertained by chiral HPLC analysis of the corresponding benzoate **28**, obtained by borohydride reduction of the aldehyde to alcohol **27** followed by benzoylation with benzoyl chloride. The stereochemical feature of **28** was also determined by ROESY analysis and $^1$H coupling constant values (Scheme 9). The absolute stereochemistry of the product **26** was not determined but tentatively assigned to be 6*R*,7*S* following MacMillan's T2IMDA outcome.[35]

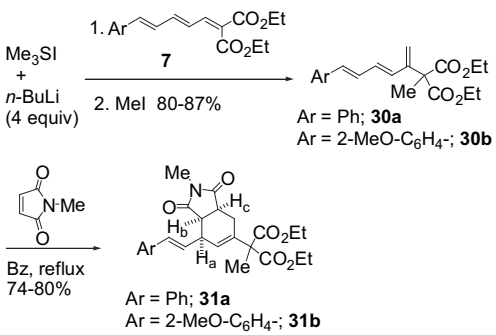



**Scheme 9.** Chiral synthesis of a bicyclo[5.3.1] alkene by T2IMDA.

Subsequent to our studies on the olefination of dienedioates, similar reactions between the trienedioates **7a**,**b** and dimethylsulfonium methylide **1** were attempted. The trienedioates were prepared by Knoevenagel condensation of diethyl malonate with dienic aldehydes **29a**,**b** (Scheme 10), which in turn were prepared by Wittig reaction of formylmethylenetriphenylphosphorane[37] with cinnamaldehyde and 3-(2-methoxyphenyl)-propenal, respectively. When trienedioate **7a** was added to dimethylsulfonium methylide, generated using 4 equiv each of $Me_3SI$ and *n*-BuLi in THF under the established conditions for dien-1,1-dioates **6**, we were gratified to obtain only one regioisomeric olefin product **30a** formed by exclusive addition of the ylide in 1,4-fashion followed by eliminative olefination and methylation, as the reaction was quenched by adding methyl iodide (Scheme 11). Similarly, the trien-1,1-dioate **7b** also provided the olfination product **30b** in good yield after methylation. Formation of 1,6 and 1,8 addition products viz. **11** and **12**, respectively, could not be detected in both the cases. These trienic products **30a**,**b** were not very stable and decompose on storing even at lower temperature. So for their characterization, these trienes were individually reacted with *N*-methylmalemide to give the Diels–Alder adducts **31a**,**b** in excellent regioselectivity and yield. The stereochemistry of the major diastereoisomer **31a** was assigned to be all cis on the basis of ROESY interactions between $H_a$ and $H_c$ protons (Scheme 11). These adducts were contaminated




**Scheme 10.** Synthesis of triene-1,1-dioates.




**Scheme 11.** Reaction of trien-1,1-dioates with ylide **1**.

with small amounts (~25%) of the 1,2-trans diastereoisomer since the trienedioates were contaminated with the 3,4-cis isomer in the same proportion.

## 3. Conclusions

The reactivities of alkylidene malonates with extended conjugation for dimethylsulfonium methylide mediated olefination have been thoroughly investigated. The studies have shown that in all cases the sulfonium ylide adds to the alkylidene malonates exclusively in 1,4-fashion leading to 1,3-butadien-2-yl- or 1,3,5-hexatriene-2-yl-malonates. No other regioisomer formation was observed. This study led to the synthetically valuable intermediates suitable for quick assembly of dienophiles thus ready for a T2IMDA. The ability of this methodology has been demonstrated by synthesizing a bicyclo[6.3.1] dodecene and bicyclo[5.3.1] undecene skeletons efficiently in a domino Knoevenagel–T2IMDA sequence with excellent stereocontrol. An asymmetric version of the T2IMDA using a chiral organocatalyst has been achieved with very high enantio- and diastereocontrol. 1,3,5-Hexatriene-2-yl-malonates also underwent DA cycloaddition with *N*-methylmalimide with very high regio- and stereoselectivity.

## 4. Experimental

### 4.1. General details

*n*-BuLi (1.6 M in hexane) solution was purchased from Aldrich. All reactions were carried out in flame-dried glasswares under an atmosphere of high purity nitrogen/argon. THF was dried over Na/benzophenone ketyl. Trimethylsulfonium iodide was purchased from Spectrochem, India. Solvent removal was carried out using a rotary evaporator connected to a dry ice condenser. TLC (0.5 mm) was carried out using home made silica plates with fluorescence indicator. Column chromatography was performed on silca gel (230–400 mesh).

$^1$H and $^{13}$C NMR spectra were recorded in either a 200 MHz ($^1$H: 200 MHz, $^{13}$C: 50 MHz) or 500 MHz ($^1$H: 500 MHz, $^{13}$C: 125 MHz) Bruker spectrometers. $^1$H and $^{13}$C shifts are given in parts per million, $\delta$ scale and are measured relative to internal $CHCl_3$ and $CDCl_3$ as standards, respectively. High resolution mass spectra were recorded at 60–70 eV on a Waters Micromass Q-TOF spectrometer (ESI, Ar) or on a Bruker Daltonics Micro TOF-Q spectrometer (ESI, $N_2$). Optical rotations were recorded on a JASCO DIP-370 Polarimeter. Enantiomeric excess (ee) determinations were carried out by HPLC using a JASCO (JASCO PU-2080) instrument fitted with a Daicel chiralpak AD-H column and UV-2075 detector with $\lambda$ fixed at 254 nm. Elemental analyses were performed at the Hydrometallurgy Division, Bhabha Atomic Research Centre, Mumbai. The IR spectra were recorded with a JASCO FT IR spectrophotometer in NaCl cells or in KBr discs. Peaks are reported in $cm^{-1}$. Melting points (mp) were determined on a Fischer John's melting point apparatus and were uncorrected. Imidazolidinone catalyst **25**[35] and formylmethylenetriphenylphosphorane[37] were prepared following the literature procedures.

Suitable X-ray quality crystals of **19** were grown in $CDCl_3$ and X-ray diffraction studies were undertaken. Relevant crystallographic data has been submitted to the Cambridge Crystallographic Data Centre (CCDC 671605). X-ray crystallographic data were collected at the Department of Chemistry, IIT, Mumbai from single crystal samples of volume $0.42\times0.38\times0.33$ mm$^3$ at 150(2) K mounted on a OXFORD DIFFRACTION XCALIBUR-S CCD system equipped with graphite monochromated Mo K$\alpha$ radiation (0.71073 Å). The data were collected by $\omega$–$2\theta$ scan mode, and absorption correction was applied by using multi-Scan. The structure was solved by direct methods SHELX-97 and refined by full-matrix least squares against $F^2$ using SHELX-97[38] software. Non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were geometrically fixed and allowed to refine using a riding model.

### 4.2. General procedures

*4.2.1. General procedure I. Preparation of dienals **29a**,**b**.* A mixture of α,β-unsaturated aldehyde (10 mmol, 2 equiv) and formylmethylenetriphenylphosphorane[37] (1.52 g, 5 mmol, 1 equiv) in benzene (15 mL) was heated at 80 °C argon atmosphere. After 17 h, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica-gel using hexane/ethyl acetate as eluent to give dienals **29a**,**b**[39] (68–70%).

*4.2.2. General procedure II. Preparation of dienoates **6a**–**g**.* A mixture of α,β-unsaturated aldehyde (7 mmol, 1 equiv), diethyl malonate (1.06 mL, 7 mmol, 1 equiv), piperidine (0.14 mL, 1.4 mmol, 0.2 equiv), and benzoic acid (171 mg, 1.4 mmol, 0.2 equiv) in benzene (16 ml) was refluxed for 3 h under a Dean-Strake apparatus. The reaction mixture was brought to room temperature, washed with water, and evaporated under vacuum. The residue was purified by column chromatography on silica-gel using hexane/ethyl acetate as eluent to give the dienoates **6a**–**g** (60–90%).

*4.2.3. General procedure III. Preparation of trienoates **7a**,**b**.* A solution of the appropriate dienal **29** (2.08 mmol, 1 equiv), diethyl malonate (0.32 mL, 2.08 mmol, 1 equiv), piperidine (42 μL, 0.42 mmol, 0.2 equiv), benzoic acid (51 mg, 0.42 mmol, 0.2 equiv) in benzene (10 mL) was refluxed in a Dean-Starke apparatus for 3 h. The reaction mixture was concentrated on rotary evaporator and the residue was purified by chromatography on silica-gel using hexane/ethyl acetate as eluent to give trienoates **7a**,**b**[40] (56–60%).

*4.2.4. General procedure IV. Preparation of 1,3-dienes **15a**–**i**.* To a −10 °C suspension of $Me_3SI$ (612 mg, 3 mmol) in THF (3 ml) was added *n*-BuLi (3 mmol, 1.9 mL of 1.6 M hexane solution). After 15 min, appropriate diendioate **6** (1.0 mmol) in THF (3 mL) was introduced and the reaction mixture was slowly allowed to warm to room temperature. After 1 h, the reaction mixture was cooled on an ice-water bath and methyl iodide (0.32 mL, 5 mmol) or allyl bromide/benzyl bromide (3 mmol) was added and stirred at ambient temperature for 15 h. The reaction mixture was diluted with water and extracted with diethyl ether. The combined extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residues were purified by column chromatography on silica-gel using hexane/ethyl acetate as eluent to give the dienes **15a**–**i**.

*4.2.5. General procedure V. Preparation of 1,3,5-trienes **30a**,**b**.* To a −10 °C suspension of $Me_3SI$ (470 mg, 2.3 mmol) in THF (5 mL) was added *n*-BuLi (2.3 mmol, 1.43 mL of 1.6 M hexane solution). After 15 min, a solution of the appropriate trienoate **7** (0.57 mmol) in THF (2 mL) was added to the reaction mixture at −10 °C and was allowed slowly to rise to room temperature in a period of 1.5 h. The reaction mixture was cooled to 0 °C and methyl iodide (180 μL, 2.85 mmol) was added into the reaction mixture and stirred overnight. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was washed with water, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica-gel using hexane/ethyl acetate as eluent to give the methylated trienes **30a**,**b** (80–87%).

*4.2.6. General procedure VI. Reaction of **6a** with $Me_3SI$ and sodium dimsylate. 4.2.6.1. (I) Protonation.* A solution of sodium dimsylate (2.5–4 mmol) in DMSO (2.5 mL) was prepared. The solution was

diluted with THF (3 mL) and cooled on an ice-salt bath (−8 °C). Solid trimethylsulfonium iodide (1.2–3 mmol) was introduced into the flask and the reaction mixture was stirred under same conditions for 15 min. A solution of **6a** (274 mg, 1 mmol) in dry THF (3 mL) was rapidly added to the reaction mixture. It was slowly brought to room temperature (about 1 h) and stirred for 1 h. The reaction mixture was diluted with water and extracted with ether. The organic extract was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography on silica-gel using hexane/EtOAc (95:5) as eluent to give **8a** (37–60 mg, 13–21%) and an inseparable mixture of **13a** and **14a**.

*4.2.6.2. (II) Methylation.* A solution of sodium dimsylate (3 mmol) in DMSO (2.5 mL) was prepared. The solution was diluted with THF (3 mL) and cooled on an ice-salt bath (−8 °C). Solid trimethylsulfonium iodide (1.5 mmol) was introduced into the flask and the reaction mixture was stirred under same conditions for 15 min. A solution of **6a** (274 mg, 1 mmol) in dry THF (3 mL) was rapidly added to the reaction mixture. After 1 h, the reaction mixture was cooled on an ice-water bath and methyl iodide (0.32 mL, 5 mmol) was added and stirred at ambient temperature for 15 h. The reaction mixture was diluted with water and extracted with diethyl ether. The combined extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residues were purified by column chromatography on silica-gel using hexane/ethyl acetate as eluent to give the diene methylated product **15a** (205 mg, 68%) and the methylated product of thiomethyl derivative **14a** (53 mg, 15%).

*4.2.7. (4E)-Ethyl 2-[2-(2′,2′-diethoxyethyloxy)phenyl]methyl-2-ethoxycarbonyl-3-methylene-5-phenyl-4-pentenoate (**15j**).* A solution of **8a** (251 mg, 0.87 mmol) in THF (5 mL) was added to an oil-free suspension of sodium hydride (42 mg, 0.96 mmol, ~55% in oil) in THF (1 mL) at 0 °C. The reaction mixture was stirred at room temperature for 15 min, cooled on an ice-bath, and a solution of bromide **16** (300 mg, 1 mmol) in THF (2 mL) was added. The reaction mixture was brought to room temperature and stirred for 15 h. The reaction mixture was diluted with water and extracted with ether. The combined extract was washed with brine and concentrated under vacuum. The residue was purified by silica-gel chromatography using hexane/ethyl acetate as eluent to provide **15j** (410 mg, 95%). $R_f$ (90% hexane/EtOAc) 0.59; $\nu_{max}$ (liquid film) 3020, 2983, 1722 and 963 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 7.31–7.15 (7H, m, Ph, Ar), 6.86 (1H, t, *J*=7.4 Hz, Ar), 6.78–6.70 (2H, m, PhC*H*=CH, Ar), 6.60 (1H, d, *J*=16 Hz, PhCH=C*H*), 5.58 (1H, s, PhCH=CHC=$CH_aH_b$), 5.19 (1H, s, PhCH=CHC=$CH_aH_b$), 4.75 (1H, t, *J*=5.2 Hz, C*H*O($CH_2CH_3$)$_2$), 4.23–4.11 (4H, m, 2×$CO_2CH_2CH_3$), 3.89 (2H, d, *J*=5.2 Hz, ArO$CH_2$), 3.75–3.53 (6H, m, CHO($CH_2CH_3$)$_2$, Ar$CH_2$), 1.22 (6H, t, *J*=7 Hz, 2×$CO_2CH_2CH_3$), 1.19 (6H, t, *J*=7 Hz, 2×$OCH_2CH_3$); $\delta_C$ (50 MHz, $CDCl_3$) 169.8 (2C), 157.0, 142.9, 137.1, 130.9, 129.3, 128.3 (2C), 128.2, 127.8, 127.3, 126.4 (2C), 125.4, 120.3, 114.5, 111.0, 100.7, 69.0, 63.5, 62.7 (2C), 61.2 (2C), 33.2, 15.2 (2C), 13.7 (2C); *m*/*z* (ESI) 533 ($M^+$+Na, 10%), 397 (100), 221 (14), 120 (7); HRMS (ESI): $MNa^+$, found 533.2504. $C_{30}H_{38}O_7Na$ requires 533.2515.

*4.2.8. (8E)-1-tert-Butyldimethylsilyoxy-6,6-diethoxycarbonyl-7-methylene-9-phenyl-8-nonene (**15k**).* A solution of the dien-2-yl-malonate **8a** (1.8 g, 6.25 mmol) in DMF (10 mL) was added to a stirred oil-free suspension of NaH (300 mg, 55% in oil, 6.9 mmol) in DMF (10 mL). After 0.5 h at room temperature, a solution of 5-*tert*-butyldimethylsilyloxy-1-iodopentane (3 g, 9.4 mmol) in DMF (5 mL) was added to the reaction mixture and stirred for 18 h. The reaction mixture was diluted with water and extracted with benzene. The organic extract was washed with water, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography to give the alkylated malonate **15k** (2.9 g, 96%). $R_f$ (95% hexane/EtOAc) 0.29; $\nu_{max}$ (liquid film) 3026, 2954, 2931, 2857, 1732, 1495, 1463, 1448, 1247, 1177, 1096, 1038, 963, 836, 775, 754 and 693 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 7.40–7.22 (5H, m, Ph), 6.77 (1H, d, *J*=16.2 Hz, PhC*H*=CH), 6.66 (1H, d, *J*=16.2 Hz, PhC*H*=C*H*), 5.60 (1H, s, C=$CH_aH_b$), 5.25 (1H, s, C=$CH_aH_b$), 4.22 (4H, q, *J*=7.2 Hz, 2×$CO_2CH_2CH_3$), 3.57 (2H, t, *J*=6.4 Hz, SiO$CH_2$), 2.09 (2H,br t, *J*=7.2 Hz, $CH_2CCO_2Et$), 1.51 (2H, t, *J*=6.4 Hz, $CH_2$), 1.40–1.30 (4H, m, 2×$CH_2$), 1.25 (6H, t, *J*=7.2 Hz, 2×$CO_2CH_2CH_3$), 0.03 (6H, s, $SiMe_2$), 0.88 (9H, s, SiBu-*t*); $\delta_C$ (50 MHz, $CDCl_3$) 169.8 (2C), 142.9, 136.8, 129.9, 128.3 (2C), 127.8, 127.4, 126.3 (2C), 114.5, 62.6, 62.2, 61.0 (2C), 34.1, 32.3, 25.9, 25.7 (3C), 24.2, 18.0, 13.8 (2C), −5.6 (2C).

*4.2.9. (4E)-Ethyl 2-ethoxycarbonyl-2-[2-(2′-ethanaloxy)phenyl]methyl-3-methylene-5-phenyl-4-pentenoate (**18**).* A solution of acetal **15j** (510 mg, 1 mmol), *p*-toluene sulfonic acid (48 mg, 0.25 mmol) in 2% aqueous acetone (50 mL) was heated under reflux for 15 h in argon atmosphere. The reaction mixture was neutralized with solid sodium bicarbonate and the solvent was evaporated. The residue was purified by silica-gel column chromatography using hexane/ethyl acetate as eluent to give the aldehyde **18** (421 mg, 97%). $R_f$ (80% hexane/EtOAc) 0.24; $\nu_{max}$ (liquid film) 3090, 3070, 3035, 2980, 2936, 1733, 1601, 1494, 1479, 1454, 1367, 1247, 1118, 1036 and 754 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 9.80 (1H, s, CHO), 7.28–7.14 (7H, m, Ph, Ar), 6.94 (1H, t, *J*=7.4 Hz, Ar), 6.72 (1H, d, *J*=16 Hz, PhC*H*=CH), 6.60 (1H, d, *J*=7.6 Hz, Ar), 6.54 (1H, d, *J*=15.8 Hz, PhC*H*=CH), 5.58 (1H, s, PhC*H*=CHC=$CH_aH_b$), 5.24 (1H, s, PhC*H*=CHC=$CH_aH_b$), 4.41 (2H, d, *J*=0.8 Hz, ArO$CH_2$CHO), 4.27–4.13 (4H, m, 2×$CO_2CH_2CH_3$), 3.70 (2H, s, Ar$CH_2$), 1.22 (6H, t, *J*=7.2 Hz, 2×$CO_2CH_2CH_3$); $\delta_C$ (50 MHz, $CDCl_3$) 199.6, 169.7 (2C), 156.2, 142.6, 136.9, 131.7, 129.4, 128.5 (2C), 128.2 (2C), 127.5, 126.4 (2C), 125.6, 121.3, 114.8, 110.9, 72.6, 63.4, 61.4 (2C), 33.6, 13.8 (2C).

*4.2.10. (1RS,14SR)-15,15-Dicyano-14-phenyl-3-oxa-tricyclo[10.3.1.0*4,9*]hexadeca-4(9),5,7,12-tetraene-11,11-dicarboxylic acid diethyl ester (**19**).* A mixture of aldehyde **18** (180 mg, 0.41 mmol), triphenylphosphine (22 mg, 0.08 mmol), and malononitrile (0.15 mL, 2.4 mmol) was heated (75 °C, bath) under argon for 4 h. The reaction mixture was brought to room temperature, excess malononitrile was removed under high vacuum and the residue was purified by silica-gel column chromatography using hexane/ethyl acetate as eluent to give **19** (132 mg, 67%) as a colorless solid. Mp 175–176 °C. $R_f$ (80% hexane/EtOAc) 0.35; $\nu_{max}$ ($CHCl_3$) 3063, 3024, 2982, 2959, 2248, 1731, 1637, 1601, 1585, 1494, 1453, 1392, 1368, 1276, 1222, 1183, 1122, 1061, 1036, 860 and 756 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 7.45–7.42 (5H, m, Ph), 7.28 (1H, dt, *J*=8, 1.5 Hz, Ar), 7.24 (1H, dd, *J*=7.5, 1.5 Hz, Ar), 6.98 (1H, t, *J*=7.5 Hz, Ar), 6.92 (1H, d, *J*=8 Hz, Ar), 5.96 (1H, t, *J*=3 Hz, C=CH), 4.73 (1H, d, *J*=12.5 Hz, O$CH_aH_b$), 4.46 (1H, dd, *J*=13, 6 Hz, O$CH_aH_b$), 4.32 (1H, m, $CO_2CH_aH_bCH_3$), 4.29–4.22 (1H, m, $CO_2CH_aH_bCH_3$), 4.20–4.14 (2H, m, $CO_2CH_2CH_3$), 3.73 (1H, d, *J*=13.5 Hz, Ar$CH_aH_b$), 3.72 (1H, d, *J*=3 Hz, PhC*H*), 3.50 (1H, d, *J*=13.5 Hz, Ar$CH_aH_b$), 3.12 (1H, dd, *J*=7.5, 6 Hz, CNCCH), 2.69 (1H, ddt, *J*=16, 8, 2 Hz, C=C–$CH_aH_b$), 2.61 (1H, d, *J*=16 Hz, C=C–$CH_aH_b$), 1.32 (3H, t, *J*=7 Hz, $CO_2CH_2CH_3$), 1.26 (3H, t, *J*=7.5 Hz, $CO_2CH_2CH_3$); $\delta_C$ (50 MHz, $CDCl_3$) 169.7, 168.8, 161.6, 142.7, 136.2, 133.1, 129.4, 129.3 (2C), 129.1, 129.0 (2C), 127.3, 125.0, 122.5, 117.9, 116.4, 114.1, 73.4, 64.2, 62.0, 61.6, 48.1, 46.2, 44.3, 38.1, 27.4, 14.0, 13.9; *m*/*z* (ESI) 486 (3%), 485 ($M^+$+H, 100), 439 (3). HRMS (ESI): $MH^+$, found 485.2059. $C_{29}H_{29}N_2O_5$ requires 485.2076.

*4.2.11. (8E)-6,6-Diethoxycarbonyl-7-methylene-9-phenyl-nona-8-ene-1-ol (**21**).* *p*-Toluenesulfonic acid (17 mg, 0.09 mmol) was added to a stirred solution of silyl ether **15k** (440 mg, 0.9 mmol) in EtOH/THF/water (80:15:5) (10 mL). After 2 h at room temperature, the reaction mixture was concentrated on rotary evaporator. The residue was diluted with water and extracted with ethyl acetate.

The organic extract was washed with water, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography using hexane/ethyl acetate as eluent to give the alcohol **21** (292 mg, 87%). $R_f$ (70% hexane/EtOAc) 0.3; $\nu_{max}$ (liquid film) 3435 (br), 2979, 2934, 2869, 1733, 1637, 1600, 1464, 1448, 1369, 1242, 1094, 1037, 961, 912, 862, 752 and 695 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 7.41–7.18 (5H, m, Ph), 6.77 (1H, d, $J$=16 Hz, PhC*H*), 6.65 (1H, d, $J$=16 Hz, PhC*H*=C*H*), 5.60 (1H, s, C=$CH_aH_b$), 5.23 (1H, s, C=C$H_aH_b$), 4.22 (4H, q, $J$=7.2 Hz, 2×$CO_2CH_2CH_3$), 3.61 (2H, t, $J$=6.6 Hz, C$H_2$OH), 2.14–2.05 (2H, m, C$H_2CCO_2Et$), 1.63–1.50 (3H, m, OH and $CH_2$), 1.42–1.31 (4H, m, 2×$CH_2$), 1.25 (6H, t, $J$=7.2 Hz, 2×$CO_2CH_2CH_3$); $\delta_C$ (50 MHz, $CDCl_3$) 170.0 (2C), 142.7, 136.8, 129.9, 128.3 (2C), 127.7, 127.4, 126.2 (2C), 114.6, 62.2, 62.1, 61.1 (2C), 34.0, 32.0, 25.8, 24.2, 13.7 (2C); $m/z$ (ESI) 397 ($M^+$+Na, 31%), 375 ($M^+$+H, 52), 329 (40), 283 (23), 201 (8), 155 (13); HRMS (ESI): $MH^+$, found 375.2172. $C_{22}H_{31}O_5$ requires 375.2171.

*4.2.12. (8E)-6,6-Diethoxycarbonyl-7-methylene-9-phenyl-nona-8-eneal (**22**).* Oxalyl chloride (80 μL, 0.91 mmol, 1.1 equiv) was added to a solution of DMSO (130 μL, 1.83 mmol, 2.2 equiv) in $CH_2Cl_2$ (2 mL) at −60 °C. After stirring for 5 min, a solution of alcohol **21** (310 mg, 0.83 mmol, 1 equiv) in $CH_2Cl_2$ (3 mL) was added and the reaction mixture was stirred at −60 °C for 15 min. Triethylamine (578 μL, 4.15 mmol, 5 equiv) was added and the reaction mixture was stirred for 5 min at −60 °C. The reaction mixture was allowed to attain room temperature and was diluted with water. The reaction mixture was extracted with $CH_2Cl_2$ and the organic extract was washed with water, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography using hexane/ethyl acetate as eluent to give the aldehyde **22** (208 mg, 67%). The material was unstable and used directly in the next step. $R_f$ (90% hexane/EtOAc) 0.19; $\nu_{max}$ (liquid film) 3082, 3025, 2980, 2938, 2872, 2722, 2255, 1728, 1636, 1600, 1494, 1448, 1389, 1366, 1246, 1096, 1034, 963, 912, 858, 754, 731 and 695 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) (200 MHz, $CDCl_3$) 9.73 (1H, br s, CHO), 7.46–7.19 (5H, m, Ph), 6.76 (1H, d, $J$=16 Hz, PhC*H*=CH), 6.64 (1H, d, $J$=16 Hz, PhC*H*=C*H*), 5.59 (1H, s, C=$CH_aH_b$), 5.21 (1H, s, C=C$H_aH_b$), 4.22 (4H, q, $J$=7.2 Hz, 2×$CO_2CH_2CH_3$), 2.42 (2H, t, $J$=7.2 Hz, C$H_2$CHO), 2.14–2.05 (2H, m, C$H_2CCO_2Et$), 1.73–1.52 (2H, m, $CH_2$), 1.50–1.31 (2H, m, $CH_2$), 1.25 (6H, t, $J$=7.2 Hz, 2×$CO_2CH_2CH_3$); $\delta_C$ (50 MHz, $CDCl_3$) 202.1, 169.9 (2C), 142.9, 136.9, 130.3, 128.5 (2C), 127.8, 127.6, 126.4 (2C), 114.8, 62.4, 61.3 (2C), 43.3, 33.9, 24.2, 22.2, 13.9 (2C).

*4.2.13. (9RS)-2,2-Diethoxycarbonyl-8,8-dicyano-9-phenyl-bicyclo[5.3.1]undec-1-(10)-ene (**23**).* A mixture of aldehyde **22** (46 mg, 0.12 mmol), triphenylphosphine (32 mg, 0.12 mmol), and malononitrile (8 μL, 0.12 mmol) was heated (75 °C, bath) under argon for 4 h. The reaction mixture was brought to room temperature and the residue was purified by silica-gel column chromatography using hexane/ethyl acetate as eluent to give **23** (31 mg, 61%) as colorless solid. Mp 113–115 °C. $R_f$ (80% hexane/EtOAc) 0.47; $\nu_{max}$ ($CHCl_3$) 3031, 2935, 2835, 2244, 1728, 1663, 1602, 1410, 1440, 1367, 1297, 1236, 1120, 1099, 1033, 826, 733 and 703 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 7.51–7.36 (5H, m, Ph), 5.97 (1H, br s, C=CH), 4.15–4.13 (4H, m, 2×$CO_2CH_2CH_3$), 3.96 (1H, br s, PhC*H*), 2.80–2.56 (2H, m, $CH_2$), 2.55–2.35 (2H, m, $CH_2$), 2.33–2.20 (1H, m, CH), 2.05–1.67 (4H, m, 2×$CH_2$), 1.62–1.40 (2H, m, $CH_2$), 1.27 (3H, t, $J$=7.2 Hz, $CO_2CH_2CH_3$), 1.23 (3H, t, $J$=7.2 Hz, $CO_2CH_2CH_3$); $\delta_C$ (50 MHz, $CDCl_3$) 170.2, 169.7, 139.4, 137.5, 129.4 (2C), 129.2 (2C), 128.9, 125.1, 117.8, 113.3, 62.8, 61.8, 61.7, 48.8, 43.2, 40.6, 35.4, 30.7, 27.8, 25.1, 24.5, 14.0 (2C); $m/z$ (ESI) 421 ($M^+$+H, 39%), 348 (8), 347 (100); HRMS (ESI): $MH^+$, found 421.2124. $C_{25}H_{29}N_2O_4$ requires 421.2127.

*4.2.14. (2E,10E)-8,8-Diethoxycarbonyl-9-methylene-11-phenyl-undec-2,10-dieneal (**24**).* A mixture of aldehyde **22** (225 mg, 0.6 mmol) and formylmethylenetriphenylphosphorane[36] (365 mg, 1.2 mmol, 2 equiv) in dry benzene (5 mL) was heated under argon atmosphere at 80 °C for 3 days. The reaction mixture was concentrated on rotary evaporator and the residue was purified by column chromatography using hexane/ethyl acetate as eluent to provide the α,β unsaturated aldehyde **24** (155 mg, 65%). This product is contaminated with ~10% of 2*Z*,10*E*-isomer. $R_f$ (90% hexane/EtOAc) 0.19; $\nu_{max}$ (liquid film) 3023, 2981, 2934, 2858, 1730, 1687, 1638, 1448, 1243, 1097, 1029, 971, 910, 756, 734 and 694 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 9.40 (1H, d, $J$=8 Hz, CHO from 2*Z*-isomer), 9.36 (1H, d, $J$=8 Hz, CHO), 7.31–7.10 (5H, m, Ph), 6.78–6.62 (1H, m, C*H*=CHCHO), 6.67 (1H, d, $J$=16 Hz, PhC*H*=C*H*), 6.54 (1H, d, $J$=16 Hz, PhC*H*=CH), 5.99 (1H, ddt, $J$=15.6, 8, 1.2 Hz, C*H*=C*H*CHO), 5.50 (1H, s, C=$CH_aH_b$), 5.11 (1H, s, C=C$H_aH_b$), 4.13 (4H, q, $J$=7.2 Hz, 2×$CO_2CH_2CH_3$), 2.30–2.18 (2H, m, C$H_2$C*H*=CHCHO), 2.04–1.96 (2H, m, C$H_2CCO_2Et$), 1.50–1.25 (4H, m, 2×$CH_2$), 1.15 (6H, t, $J$=7.2 Hz, 2×$CO_2CH_2CH_3$); $\delta_C$ (50 MHz, $CDCl_3$) 193.7, 170.4 (minor), 169.8 (2C), 158.2, 152.5 (minor), 146.5 (minor), 142.6, 136.7, 134.0 (minor), 132.7, 130.1, 128.3 (2C), 127.5 (2C), 126.3 (2C), 114.7, 62.2, 61.2 (2C), 33.7, 32.0, 27.8, 24.0, 13.8 (2C).

*4.2.15. (8R,9S)-2,2-Diethoxycarbonyl-9-phenylbicyclo[5.3.1]undec-1-(10)-ene-8-carbaldehyde (**26**).* Water (33 μL) was added to a stirred solution of unsaturated aldehyde **24** (125 mg, 0.31 mmol), imidazolidinone catalyst **25** (15 mg, 0.062 mmol, 20 mol%), and *p*-toluenesulfonic acid (12 mg, 0.062 mmol, 20 mol%) in chloroform (1.6 mL). After 4 days at room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The organic extract was washed with water, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography using hexane/ethyl acetate as eluent to give the bicyclic product **26** (56 mg, 61%) and recovered aldehyde **26** (32 mg). $R_f$ (90% hexane/EtOAc) 0.29; $[\alpha]_D^{26}$ +86.7 (*c* 1.2, $CHCl_3$); $\nu_{max}$ (liquid film) 3062, 3028, 2981, 2934, 2925, 2854, 1725, 1464, 1367, 1038, 910, 731 and 635 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 9.57 (1H, s, CHO), 7.26–7.08 (5H, m, Ph), 5.68 (1H, br s, PhCHC*H*=C), 4.23–3.90 (4H, m, 2×$CO_2CH_2CH_3$), 3.74 (1H, dt, $J$=3.3, 2 Hz, PhC*H*), 2.45–1.85 (6H, m), 1.80–1.30 (6H, m), 1.15 (3H, t, $J$=7 Hz, $CO_2CH_2CH_3$), 1.10 (3H, t, $J$=7.2 Hz, $CO_2CH_2CH_3$); $\delta_C$ (50 MHz, $CDCl_3$) 201.8, 171.0, 170.4, 145.1, 135.3, 128.8 (3C), 128.1 (2C), 126.4, 62.9, 61.4 (2C), 61.3, 39.2, 35.9, 34.7, 31.7, 28.5, 25.5, 24.9, 14.0 (2C).

*4.2.16. (8R,9S)-2,2-Diethoxycarbonyl-8-hydroxymethyl-9-phenyl-bicyclo[5.3.1]undec-1-(10)-ene (**27**).* Sodium borohydride (5 mg, 0.13 mmol) was added to a stirred solution of the bicyclic aldehyde **26** (20 mg, 0.05 mmol) in ethanol (0.5 mL) at 0 °C and stirred for 1 h. The reaction mixture was concentrated on rotary evaporator, diluted with water, and extracted with ethyl acetate. The organic extract was washed with water, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography using hexane/ethyl acetate as eluent to give the alcohol **27** (16 mg, 80%). $R_f$ (80% hexane/EtOAc) 0.22; $[\alpha]_D^{25}$ +81.5 (*c* 1.08, $CHCl_3$); $\nu_{max}$ (liquid film) 3607–3400 (br), 3026, 2979, 2922, 2854, 1729, 1451, 1366, 1300, 1239, 1157, 1040 and 703 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 7.23–7.09 (5H, m, Ph), 5.63 (1H, s, C=C*H*), 4.18–3.91 (4H, m, 2×$CO_2CH_2CH_3$), 3.52 (1H, dd, $J$=10.6, 4.6 Hz, $CH_aH_bOH$), 3.38 (1H, dd, $J$=10.6, 7.4 Hz, $CH_aH_bOH$), 2.84 (1H, dd, $J$=8.2, 1.8 Hz, PhC*H*), 2.16–2.14 (4H, m, C=C$CH_2$ and C$H_2CCO_2Et$), 2.11–2.00 (1H, m, $HOCH_2CH$), 1.80–1.30 (8H, m, 3×$CH_2$, OH and C=C$CH_2CH$), 1.16 (3H, t, $J$=8 Hz, $CO_2CH_2CH_3$), 1.08 (3H, t, $J$=8 Hz, $CO_2CH_2CH_3$); $\delta_C$ (50 MHz, $CDCl_3$) 171.2, 170.4, 146.0, 136.1, 130.1, 128.5 (2C), 128.4 (2C), 126.2, 64.4, 63.0, 61.3, 61.2, 51.0, 43.8, 36.0, 35.2, 34.4, 29.3, 25.4, 24.7, 14.0, 13.9.

*4.2.17. (8R,9S)-8-Benzyloxymethyl-2,2-diethoxycarbonyl-9-phenyl-bicyclo[5.3.1]undec-1-(10)-ene (**28**).* Benzoyl chloride (15 μL, 0.1 mmol) was added to a stirred solution of the alcohol **27** (12 mg, 0.03 mmol) and 4-dimethylaminopyridine (3.5 mg, 0.03 mmol) in $CH_2Cl_2$ (0.5 mL) at 0 °C. The reaction mixture was stirred overnight at room temperature, diluted with water, and extracted with

chloroform. The organic extract was washed with water, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography using hexane/ethyl acetate as eluent to give the benzoate **28** (13 mg, 86%). $R_f$ (85% hexane/EtOAc) 0.26; $[\alpha]_D^{25}$ +26.08 (*c* 0.23, $CHCl_3$); $\nu_{max}$ (liquid film) 3026, 2979, 2925, 2853, 1722, 1451, 1385, 1274, 1245, 1217, 1112, 1069 and 1025 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 7.95 (2H, d, *J*=7 Hz, Ph), 7.55 (1H, t, *J*=7 Hz, Ph), 7.41 (2H, t, *J*=8 Hz, Ph), 7.34–7.28 (2H, m, Ph), 7.25–7.20 (3H, m, Ph), 5.80 (1H, d, *J*=2.5 Hz, C=C*H*), 4.26–4.16 (4H, m, $CO_2CH_2CH_3$, $CO_2CH_aH_bCH_3$, $PhCO_2CH_2$), 4.13–4.04 (1H, m, $CO_2CH_aH_bCH_3$), 3.16 (1H, dd, *J*=9, 2.5 Hz, PhC*H*), 2.40–2.30 (3H, m), 2.23–2.16 (1H, m), 1.96–1.83 (1H, m), 1.82–1.49 (6H, m), 1.48–1.38 (1H, m), 1.28 (3H, t, *J*=7 Hz, $CO_2CH_2CH_3$), 1.19 (3H, t, *J*=7 Hz, $CO_2CH_2CH_3$); $\delta_C$ (125 MHz, $CDCl_3$) 171.1, 170.4, 166.6, 146.3, 136.6, 132.87, 130.1 (2C), 129.5 (2C), 128.6 (2C), 128.4 (2C), 128.3 (2C), 126.4, 66.6, 63.1, 61.4, 61.3, 47.6, 44.1, 35.9, 35.2 (2C), 29.9, 29.3, 24.4, 14.0, 13.9; *m*/*z* (ESI) 527 ($M^+$+Na, 33), 522 (18), 383 (67), 337 (15), 279 (100); HPLC (5% isopropanol in hexane; 1 mL/min) $t_R$ (8*R*,9*S*)-**28** 16.7 min (95.8%), $t_R$ (8*S*,9*R*)-**28** 38.6 min (4.2%); HRMS (ESI): $MNa^+$, found 527.2384. $C_{31}H_{36}O_6Na$ requires 527.2404.

*4.2.18. (4E,6E)-Ethyl 2-ethoxycarbonyl-2-methyl-3-methylene-7-phenyl-4,6-heptadienoate (**30a**).* Yield: 149 mg, 80%. The product decomposes on standing. $R_f$ (95% hexane/EtOAc) 0.5; $\nu_{max}$ (liquid film) 3058, 3024, 2983, 2938, 2872, 1731, 1631, 1600, 1464, 1448, 1376, 1260, 1107, 1020, 990, 911, 861, 750, 732 and 693 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 7.46–7.25 (5H, m, Ph), 6.92–6.43 (3H, m), 6.31 (1H, d, *J*=15.5 Hz, PhC*H*), 5.53 (1H, s, $C=CH_aH_b$), 5.11 (1H, s, $C=CH_aH_b$), 4.28 (4H, q, *J*=7 Hz, $2\times CO_2CH_2CH_3$), 1.72 (3H, s, $CCH_3$), 1.31 (6H, t, *J*=7 Hz, $2\times CO_2CH_2CH_3$); $\delta_C$ (125 MHz, $CDCl_3$) 170.8 (2C), 144.1, 137.0, 132.9, 131.6, 130.8, 128.8, 128.4 (2C), 127.4, 126.2 (2C), 113.6, 61.5 (2C), 58.8, 21.1, 13.8 (2C).

*4.2.19. (4E,6E)-Ethyl 2-ethoxycarbonyl-2-methyl-3-methylene-7-(2-methoxyphenyl)-4,6-heptadienoate (**30b**).* Yield: 87%. $R_f$ (95% hexane/EtOAc) 0.41; $\nu_{max}$ (liquid film) 2982, 2939, 2837, 1731, 1629, 1593, 1488, 1464, 1375, 1295, 1246, 1106, 1025, 993, 902, 861 and 752 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 7.47 (1H, d, *J*=7.3 Hz), 7.21 (1H, t, *J*=7.5 Hz), 7.05–6.73 (4H, m), 6.60 (1H, dd, *J*=15, 8.8 Hz, ArC*H*=C*H*), 6.24 (1H, d, *J*=15 Hz, ArCH), 5.54 (1H, s, $CH_3CCH=CH_aH_b$, minor), 5.47 (1H, s, $CH_3CCH=CH_aH_b$), 5.04 (1H, s, $CH_3CCH=CH_aH_b$), 4.23 (4H, q, *J*=7.1 Hz, $2\times CO_2CH_2CH_3$), 3.86 (3H, s, $OCH_3$ major), 3.83 (3H, s, $OCH_3$ minor), 1.68 (3H, s, $CCH_3$), 0.92 (6H, t, *J*=7.2 Hz, $2\times CO_2CH_2CH_3$); $\delta_C$ (125 MHz, $CDCl_3$) 171.0 (2C), 156.7, 144.4, 131.8, 131.0, 129.5, 128.6, 127.8, 126.3, 126.1, 120.6, 113.4, 110.8, 61.6 (2C), 59.0, 55.4, 21.3, 13.9 (2C).

*4.2.20. (1RS,2SR,6SR)-8-Azamethyl-7,9-dicarbonyl-4-(1,1-diethoxyxarbonyl-1-ethyl)-2-(2-phenylethenyl)-bicyclo[4.3.0]nona-3-ene (**31a**).* A solution of triene **30a** (69 mg, 0.21 mmol), *N*-methylmalimide (23 mg, 0.21 mmol) in benzene (2 mL) was heated under reflux for 3 h. The reaction mixture was concentrated and the residue was purified by column chromatography to give bicyclic product **31a** (68 mg, 74%). This product is contaminated with ~25% of another diastereoisomer. The diastereomeric products were separated by preparative TLC.

*4.2.20.1. Data for the (1RS,2SR,6SR) diastereoisomer (major).* $R_f$ (80% hexane/EtOAc) 0.36; $\nu_{max}$ (liquid film) 3024, 2984, 1776, 1727, 1699, 1440, 1384, 1285, 1261, 1217, 1108, 1018, 910, 759 and 735 $cm^{-1}$; $\delta_H$ (500 MHz, $CDCl_3$) 7.39–7.26 (5H, m, Ph), 6.51 (1H, d, *J*=16 Hz, PhC*H*), 6.23 (1H, dd, *J*=16, 5 Hz, PhC*H*=C*H*), 5.91 (1H, d, *J*=6.5 Hz, $CH_3CC=CH$), 4.28–4.20 (4H, m, $2\times CO_2CH_2CH_3$), 3.72 (1H, br t, *J*=7 Hz, C=CHC*H*), 3.20 (1H, dt, *J*=8.5, 3 Hz), 3.11 (1H, dd, *J*=9, 2.5 Hz), 3.01 (3H, s, $NCH_3$), 2.65 (1H, dd, *J*=16, 8 Hz), 2.56 (1H, dd, *J*=16, 3 Hz), 1.60 (3H, s, $CH_3C$), 1.29 (3H, t, *J*=7 Hz, $CO_2CH_2CH_3$), 1.28 (3H, t, *J*=7 Hz, $CO_2CH_2CH_3$); $\delta_C$ (50 MHz, $CDCl_3$) 179.3, 178.8, 170.5, 170.4, 138.1, 136.7, 130.5, 128.5 (2C), 127.9, 127.5, 126.2 (2C), 125.8, 61.7, 61.6, 59.7, 44.6, 39.5, 38.5, 26.5, 25.0, 20.0, 13.9 (2C); *m*/*z* (ESI) 462 ($M^+$+Na, 100%), 440 (55), 438 (44), 436 (25); HRMS (ESI): $MH^+$, found 440.2042. $C_{25}H_{30}NO_6$ requires 440.2068.

*4.2.20.2. Data for the (1RS,2RS,6SR) diastereoisomer (minor).* $R_f$ (80% hexane/EtOAc) 0.36; $\nu_{max}$ (liquid film) 3023, 2983, 1775, 1729, 1699, 1438, 1384, 1285, 1261, 1109, 1021, 994, 967 and 751 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 7.46–7.26 (5H, m, Ph), 6.72 (1H, dd, *J*=15.8, 7.9 Hz, PhC*H*=C*H*), 6.54 (1H, d, *J*=15.9 Hz, PhC*H*), 5.85 (1H, br s, $CH_3CC=CH$), 4.25 (4H, q, *J*=7 Hz, $2\times CO_2CH_2CH_3$), 3.35–3.10 (3H, m, 3×CH), 2.96 (3H, s, *N*Me), 2.79 (1H, d, *J*=15.6 Hz, $CH_aH_b$), 2.54 (1H, dd, *J*=14.8, 5.6 Hz, $CH_aH_b$), 1.57 (3H, s, MeC), 1.30 (6H, t, *J*=7 Hz, $2\times CO_2CH_2CH_3$); $\delta_C$ (125 MHz, $CDCl_3$) 179.1, 177.6, 170.5, 170.4, 137.5, 136.9, 131.9, 128.5 (2C), 128.3, 128.0, 127.5, 126.4 (2C), 61.8, 61.7, 59.4, 45.2, 40.2, 40.0, 27.3, 24.7, 20.1, 14.0 (2C); *m*/*z* (ESI) 462 ($M^+$+Na, 21%), 440 (25), 439 (19), 438 (64).

*4.2.21. (1RS,2SR,6SR)-8-Azamethyl-7,9-dicarbonyl-4-(1,1-diethoxyxarbonyl-1-ethyl)-2-[2(2-methoxyphenyl)ethenyl]-bicyclo[4.3.0]nona-3-ene (**31b**).* A solution of triene **30b** (53 mg, 0.15 mmol), *N*-methylmalimide (17 mg, 0.15 mmol) in benzene (2 mL) was heated under reflux for 3 h. The reaction mixture was concentrated and the residue was purified by column chromatography to give bicyclic product **31b** (56 mg, 80%). This product is contaminated with ~25% of another diastereoisomer. The diastereomeric products were separated by preparative TLC.

*4.2.21.1. Data for the (1RS,2SR,6SR) diastereoisomer (major).* $R_f$ (80% hexane/EtOAc) 0.24; $\nu_{max}$ (liquid film) 2982, 2932, 1776, 1729, 1699, 1597, 1489, 1438, 1383, 1286, 1244, 1107, 1024 and 754 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 7.39 (1H, d, *J*=7.6 Hz, Ar), 7.20 (1H, d, *J*=7.8 Hz, Ar), 6.95–6.84 (2H, m, Ar), 6.80 (1H, d, *J*=16 Hz, ArC*H*), 6.20 (1H, dd, *J*=16, 6.3 Hz, ArC*H*=C*H*), 5.85 (1H, dd, *J*=7.9, 1.4 Hz), 3.83 (3H, s, $OCH_3$), 3.75–3.60 (1H, m), 3.18 (1H, m), 3.11 (1H, dd, *J*=9.2, 2.4 Hz), 2.98 (3H, s, $OCH_3$), 2.65 (1H, dd, *J*=17, 7.2 Hz), 2.51 (1H, dd, *J*=15.6, 3 Hz), 1.56 (3H, s, $CCH_3$), 1.25 (6H, t, *J*=7 Hz, $2\times CO_2CH_2CH_3$); $\delta_C$ (125 MHz, $CDCl_3$) 179.4, 179.0, 170.5 (2C), 156.5, 137.8, 128.6, 128.4, 126.8, 126.0, 125.8, 125.4, 120.6, 110.8, 61.7, 61.5, 59.8, 55.4, 44.6, 39.6, 38.9, 26.5, 25.0, 20.0, 14.0 (2C); *m*/*z* (ESI) 492 ($M^+$+Na, 100%), 470 (15), 466 (24); HRMS (ESI): $MH^+$, found 470.2151. $C_{26}H_{32}NO_7$ requires 470.2173.

*4.2.21.2. Data for the (1RS,2RS,6SR) diastereoisomer (minor).* $R_f$ (80% hexane/EtOAc) 0.24; $\nu_{max}$ (liquid film) 2923, 2851, 1727, 1699, 1599, 1489, 1439, 1381, 1285, 1244, 1108, 1024 and 753 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 7.50 (1H, d, *J*=6.7 Hz, Ar), 7.20 (1H, d, *J*=7.4 Hz, Ar), 6.96–6.81 (3H, m), 6.64 (1H, dd, *J*=16, 8.3 Hz, ArC*H*=C*H*), 5.83 (1H, br s), 4.20 (4H, q, *J*=7 Hz), 3.84 (3H, s, $OCH_3$), 3.37–3.10 (3H, m), 2.92 (3H, s, $OCH_3$), 2.75 (1H, d, *J*=14.9 Hz), 2.61–2.40 (1H, m), 1.53 (3H, s, $CCH_3$), 1.26 (6H, t, *J*=6.9 Hz, $2\times CO_2CH_2CH_3$); $\delta_C$ (125 MHz, $CDCl_3$) 179.2, 177.7, 170.5, 170.4, 156.5, 137.2, 128.8, 128.6, 128.4, 127.0, 126.6, 126.0, 120.7, 110.7, 61.8, 61.6, 59.4, 55.4, 45.4, 40.4, 40.2, 27.2, 24.7, 20.1, 14.0 (2C); *m*/*z* (ESI) 492 ($M^+$+Na, 40%), 470 (12), 469 (15), 468 (100).

## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.02.013.

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