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Lewis acid mediated asymmetric Diels–Alder reactions of chiral 2-phosphonoacrylates

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ABSTRACT

2-Phosphonoacrylates containing four chiral alcohol auxiliaries were efficiently prepared and evaluated in Lewis acid mediated Diels–Alder reactions. Under the activation of $SnCl_4$, all reactions performed in CH_2Cl_2 at −65 °C exclusively afforded the *endo* (*endo*-to-carboxylate) cycloadducts with dr's ranging from 50:50 to >99:1. The best facial selectivity was obtained from the substrate bearing a (−)-phenylmenthyl group, to give adducts as (dr >99:1) or almost as (dr = 99:1) single diastereomers. Detailed strategies for the structural elucidation of the cycloadducts as well as a rationalization of the observed stereoselectivity are described.

1. Introduction

2-Phosphono 2-alkenoates are valuable building blocks in organic synthesis where they are commonly employed as acceptors in Michael addition reactions for preparing many important acyclic, carbocyclic and in particular heterocyclic compounds.[1,2] In accordance with their activated C–C double bond, another interesting application is the use of 2-phosphono 2-alkenoates as dienophiles in Diels–Alder reactions. However, little attention has been paid to the Diels–Alder chemistry of 2-phosphono 2-alkenoates compared to their numerous applications in Michael additions. Among the few examples documented,[3–5] Marchand-Brynaert et al.[3] reported several reactions between 2-phosphonoacrylates and N-protected 1-aminobutadienes under thermal conditions. In addition, McIntosh[4] and Siegel et al.,[5] respectively, demonstrated two examples of the cycloaddition of phosphonoacrylates with isoprene and 6,6-diphenylfulvene. As described in these reports, the adducts were all formed as mixtures of regio- and/or stereoisomers. To address the limitations in stereo- and regiocontrol, we recently reported the application of a Lewis acid strategy to the Diels–Alder reaction of 2-phosphono 2-alkenoates.[6] Of the few Lewis acids examined, tin (IV) chloride ($SnCl_4$) was shown to be optimal in enhancing both the regio- and stereoselectivities of the reaction. For example, in the presence of $SnCl_4$ in CH_2Cl_2 at −30 °C, the cycloaddition between triethyl 2-phosphonoacrylate and *trans*-piperylene strictly followed the *endo*-to-carboxylate pathway and the *ortho*-rule to afford the adduct as the single isomer (Scheme 1). Our prior work also demonstrated that the β-methyl substituted analogues were far less reactive than phosphonoacrylate most likely due to steric effects.[6]

The asymmetric Diels–Alder reactions of chiral dienophiles[7,8] or dienes[9] have received a great deal of attention over the past few decades. The diastereo- or enantioselectivity of these reactions is generally achieved by the π-facial differentiation created by the chiral elements within dienophiles or dienes. Although the same goal can nowadays be attended by chiral ligand-based catalysts,[10] the rational design of easily accessible and recoverable chiral auxiliaries for the reagents is still an attractive research subject[8m,9b] for Diels–Alder chemistry. Our previous study established that the *endo*-to-carboxylate (*endo*) transition state is predominant for the Diels–Alder reaction of the 2-phosphonoacrylate under the activation of $SnCl_4$.[6] Based on this premise, we envisioned that the introduction of a chiral alcohol auxiliary to the carboxylate motif could offer the possibility of controlling the facial selectivity of the cycloaddition. So far, these types of chiral precursors have only been used in the 1,4-addition reactions with dimethyloxosulfonium methylide for preparing cyclopropane derivatives,[11] and not reported for the Diels–Alder reaction. As a result, we decided to extend our protocol to chiral 2-phosphonoacrylates and to explore the asymmetric synthesis of the cyclic adducts containing the phosphono and carboxylate functionalities suited for further elaborations.

2. Results and discussion

Four enantiomerically pure alcohols, (1*S*)-*endo*-(−)-borneol, (1*R*,2*S*)-*trans*-2-phenyl-1-cyclohexanol, (−)-phenylmenthol, and (−)-menthol were chosen as the chiral auxiliaries for our investigation. Previously these alcohols or analogues were all incorporated into other types of dienophiles as individual auxiliaries,[8c,g,f,h] but they have not been systematically investigated together for a

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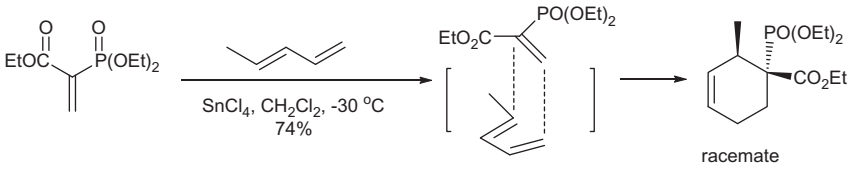
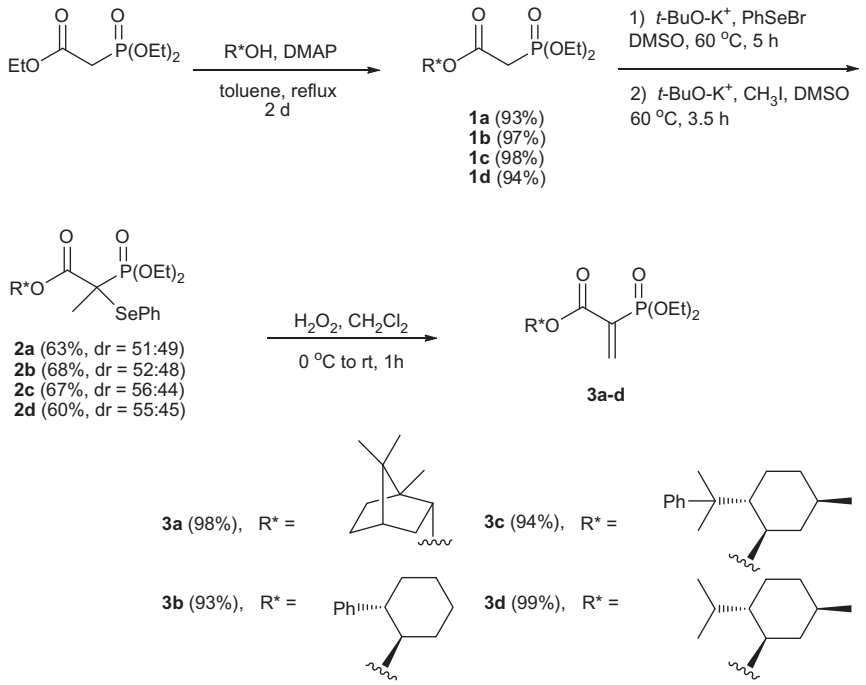
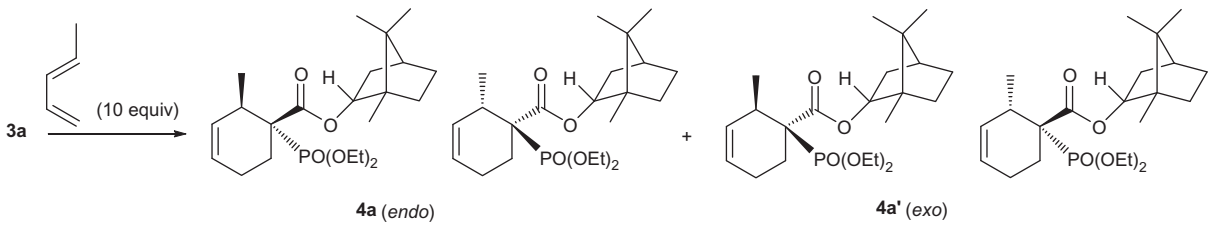


Scheme 1.



Scheme 2. Preparation of chiral 2-phosphonoacrylates.

Table 1
Cycloaddition between **3a** and *trans*-piperylene under various reaction conditions

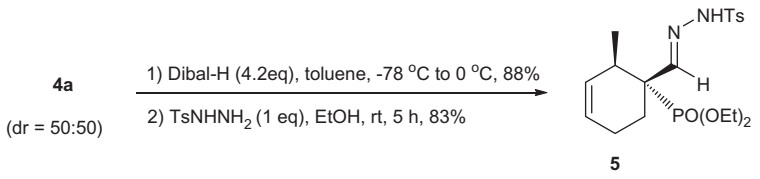


4a (*endo*) **4a'** (*exo*)

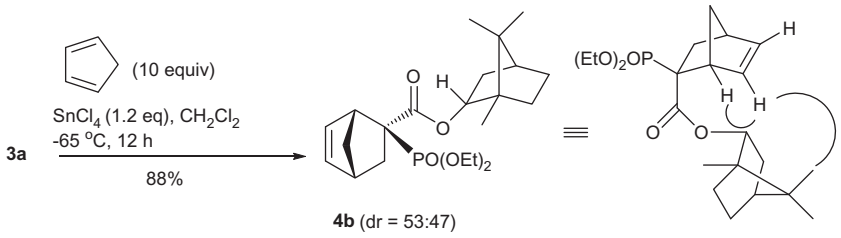
Entry	Reaction conditions	Time (h)	Yield[a] (%)	*endo*/*exo*[b]	dr[b]
1	Toluene/80 °C	8	77	82:18	41:41:9:9
2	$ZnCl_2$ (1.5 equiv)/toluene/80 °C	5	87	82:18	41:41:9:9
3	$ZnCl_2$ (1.5 equiv)/ether/rt	5	87	82:18	41:41:9:9
4	$TiCl_4$ (1.2 equiv)/CH_2Cl_2/−30 °C	6	52	54:46	27:27:23:23
5	BF_3OEt_2 (1.2 equiv)/ether/0 °C	7	79	84:16	42:42:8:8
6	$SnCl_4$ (1.2 equiv)/CH_2Cl_2/−30 °C	5	90	96:4	48:48:2:2
7	$SnCl_4$ (1.2 equiv)/CH_2Cl_2/−65 °C	12	84	100:0	50:50

[a] Isolated yield of mixture.
[b] Ratio was determined by integration of the 400 MHz proton NMR spectrum.

certain type of Diels–Alder reaction. The preparation of the chiral phosphonoacrylates began with the transesterification of triethyl phosphonoacetate with the corresponding chiral alcohols (R*OH) in the presence of 4-dimethyl aminopyridine (DMAP) to give the chiral phosphonoacetates **1a**–**d** in good yields (Scheme 2).[12] This was followed by sequential phenylselenylation[13] and methylation with phenylselenyl bromide and iodomethane to yield intermediates **2a**–**d**, which were then subjected to oxidative elimination with hydroperoxide in CH_2Cl_2 to yield the requisite substrates **3a**–**d** in almost quantitative yields.



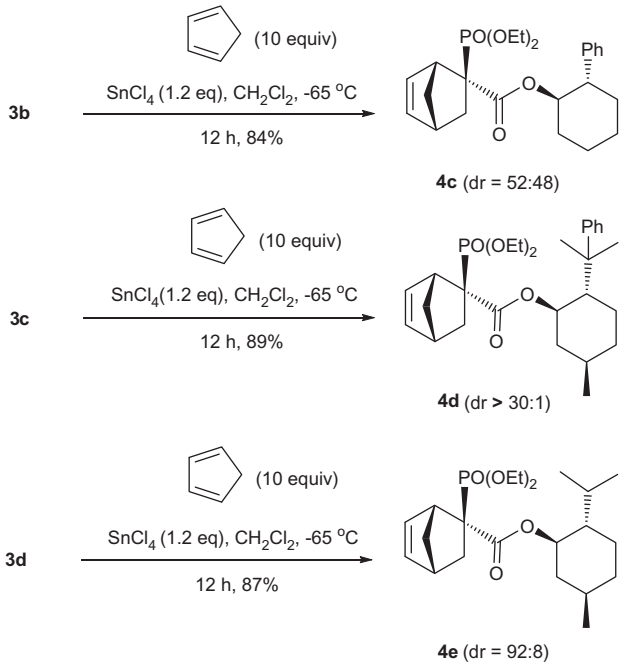
Scheme 3.



Scheme 4.

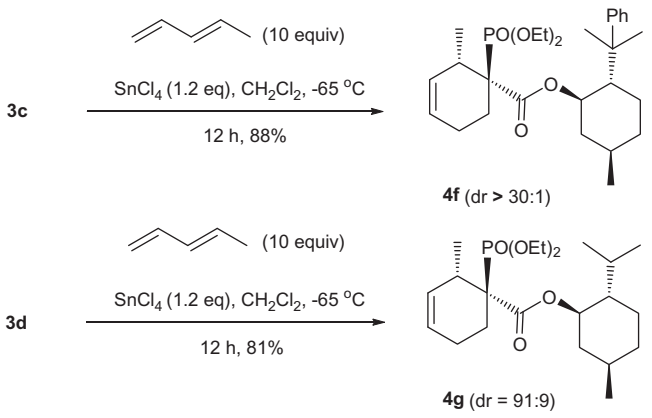
Compared with triethyl 2-phosphonoacrylate, substrates **3a**–**d** all carried bulkier ester groups that might cause a larger steric hindrance during the *endo*-like transition state. Therefore it was necessary to first clarify whether the previously observed *endo* pathway[6] was still applicable to these precursors. To this end, we initially examined the cycloaddition between **3a** with the largest auxiliary and *trans*-piperylene. As outlined in Table 1, the cycloaddition performed in toluene under thermal reaction conditions (80 °C) produced *endo* adduct **4a** and *exo* adduct **4a′**[14] as four mixed diastereomers (41:41:9:9) in an *endo*/*exo* ratio of 82:18 (entry 1). We also observed that the use of $ZnCl_2$ in toluene or in diethyl ether resulted in the same *endo*/*exo* ratio (entries 2 and 3). Subsequent attempts with $TiCl_4$ in CH_2Cl_2 or BF_3OEt_2 in ether to the reaction were also unsuccessful in improving the percentage of **4a** (entries 4 and 5), and with $TiCl_4$, the *endo*/*exo* ratio was even worse (54:46) than the uncatalyzed case (entry 1). As observed for triethyl 2-phosphonoacrylate,[6] $SnCl_4$ again demonstrated remarkable efficiency in improving the *endo* selectivity. When the reaction was carried out with $SnCl_4$ (1.2 equiv) in CH_2Cl_2 at −30 °C, the *endo*/*exo* ratio could be dramatically increased to 96:4 (entry 6). In an effort to further improve the ratio, we decreased the reaction temperature to −65 °C[15] and found that **4a**, albeit as a 50:50 diastereomeric mixture, could be formed exclusively (entry 7). To elucidate the structure of **4a**, we transformed it into the tosylhydrazone **5** in two steps (Scheme 3), and whose structure was previously conformed by X-ray analysis.[6] Under the same reaction conditions, the complete *endo* as well as the poor facial selectivity was similarly observed for the reaction of **3a** with cyclopentadiene to afford the *endo* adduct **4b** in 53:47 dr.[16] The *endo* structure of **4b** was assigned on the basis of 2D NOESY experiments as shown in Scheme 4. From these results it was apparent that the bornyl group was not an ideal choice for controlling the face selectivity of the cycloaddition, whereas the combination of $SnCl_4$ with CH_2Cl_2 could ensure an *endo*-like transition state.

Under the developed reaction conditions [$SnCl_4$ (1.2 equiv)/CH_2Cl_2/−65 °C], we continued to screen **3b**–**d** with cyclopentadiene (Scheme 5). The cycloaddition of **3b** produced the *endo* adduct **4c** in 84% yield and 52:48 dr,[16] indicating that the (1*R*)-*trans*-phenyl cyclohexyl group also exerted little effect on the facial control. The reaction of **3c** proceeded with a high diastereoselectivity to provide adduct **4d** as a single diastereomer (dr >30:1).[16] In comparison with this, a slightly low selectivity was obtained from the reaction of **3d** affording adduct **4e** in 92:8 dr.[16] These results suggest that both (1*R*)-phenylmenthyl and (1*R*)-menthyl auxiliaries should have the capability to control the diastereoselectivity of the cycloaddition with the former being more effective than the latter. To verify this, we carried out the reactions of **3c** and **3d** with *trans*-piperylene (Scheme 6), and found that adducts **4f** (dr >30:1)[16] and **4g** (dr = 91:9)[16,17] were formed in almost the same distereomeric ratios as **4d** and **4e**.



Scheme 5.

The overlapped proton signals of compounds **4c**–**e** made the direct elucidation of their *endo*/*exo* stereochemistry by NMR methods difficult. Moreover, our attempts at crystallizations of them and their derivatives were unsuccessful. We therefore turned to an indirect strategy by converting them into the known aldehyde **7**. Treatment of **4c**–**e** with diisobutylaluminum hydride in CH_2Cl_2 at −78 °C provided alcohol **6** and aldehyde **7**, in addition to a quantitative amount of the chiral alcohol (Scheme 7). After separation, the compound **6** was further oxidized into **7** with the structure being previously proven by NOESY experiment.[6] As for **4f** and **4g**,

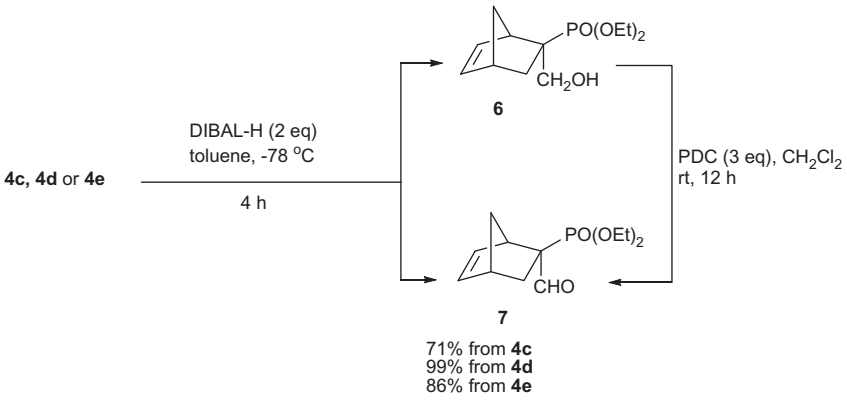


Scheme 6.

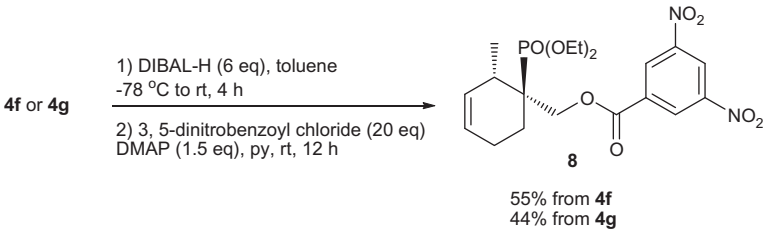
we, respectively, transformed them into 3,5-dinitrobenzoate derivative **8** via reduction followed by the esterification of the resulting alcohol (Scheme 8). The X-ray crystallography of **8** confirmed the *endo* stereochemistry of the major **4f** and **4g**. At this stage, it should be noted that the yields of **7** and **8** were not high enough to directly assign the stereochemistry (*endo*/*exo*) of the minor isomers of the corresponding adducts except for **4c** (dr = 52:48). Nevertheless the *endo* structures of the minor isomers could be proven by the HPLC experiments as depicted below.

With regard to the possible inaccuracy of using NMR inspection to identify the dr ratios, we also performed a chiral HPLC analysis[18] on the benzonate derivatives of **4d**–**g**. Accordingly, adducts **4d** and **4e** were converted into 3,5-dinitrobenzoate derivative **9** as for preparing **8** (Scheme 9). The HPLC analysis on **8** and **9**[19] allowed the precise determination of the diastereomeric ratios of **4d**–**g** (**4d**: dr >99:1; **4e**: dr = 92:8; **4f**: dr = 99:1; **4g**: dr = 91:9). In addition, the *endo* structure of the minor isomers of **4e**–**g** could be deduced by the same retention times of the minor components of **8** and **9** with those of one from the racemic mixtures.[20]

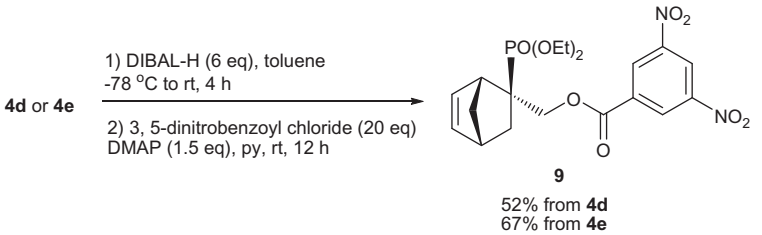
Finally we attempted to resolve the absolute stereochemistry of **4d**–**g** by converting them into the known alcohols. With **4d**, we first conducted the reductive methylation using lithium naphthalenide (LN) and iodomethane.[6] The reaction yielded two diastereomeric methylated esters **10a** and **10a**′, which were, respectively, subjected to the reduction with $LiAlH_4$ to yield the known chiral alcohols **11a** and **11a**′,[21] plus the recovered (−)-phenylmenthol (Scheme 10). In the same sequence, adducts **4e**–**g** were transformed into **11a** and **11b**. The comparison of the specific rotations



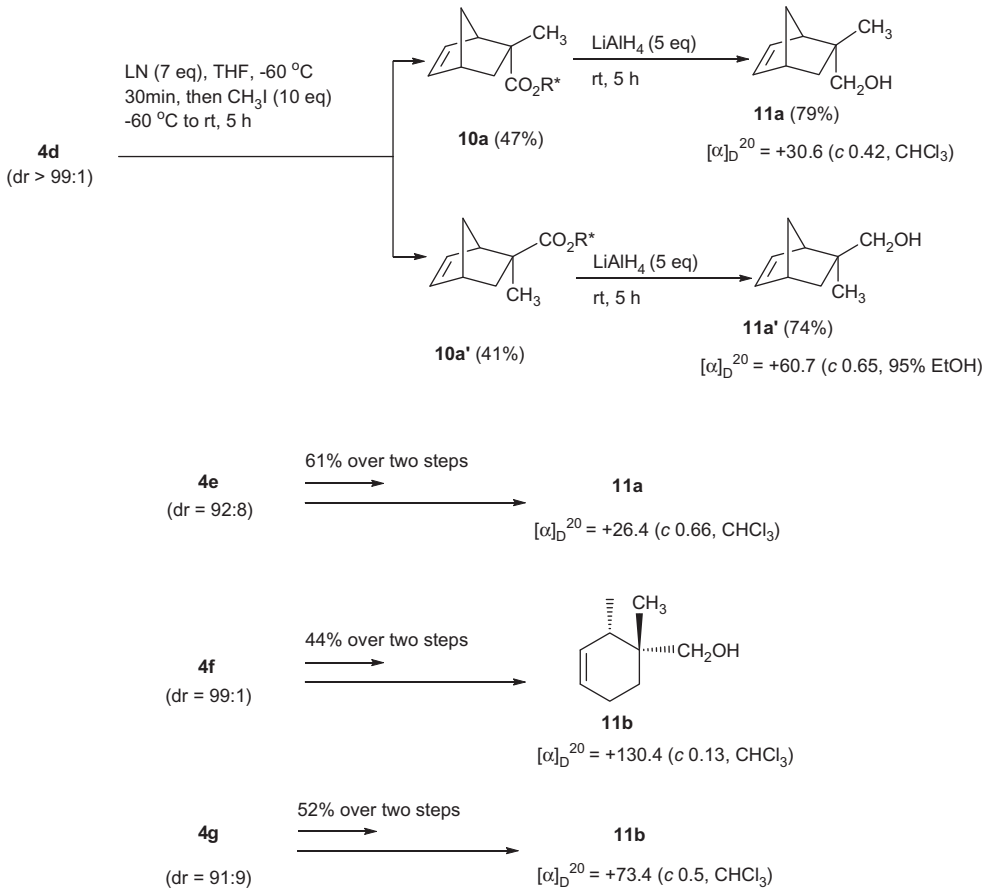
Scheme 7.



Scheme 8.



Scheme 9.



Scheme 10.

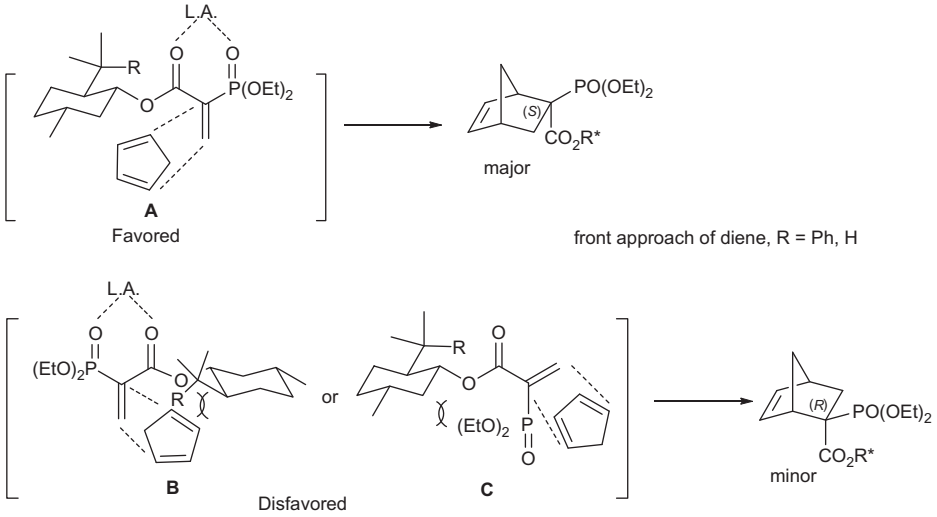
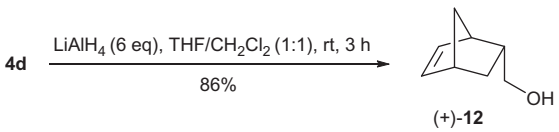


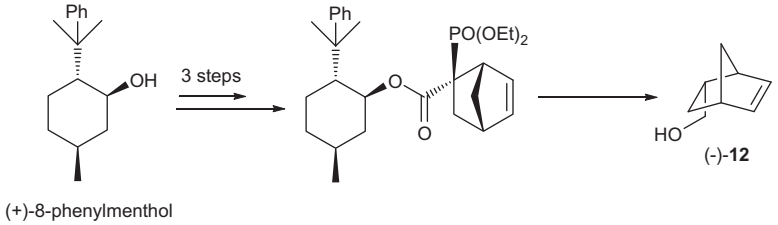
Figure 1. Proposed stereomodels for the cycloaddition of **3c** and **3d**.

of synthesized **11a**/**11a′** and **11b** with the reported ones[22,23] established the (*S*)-configuration of the newly created quaternary carbon centers of **4d** as well as the major isomers of **4e**–**g**.

As illustrated by the cycloaddition with cyclopentadiene, the preferential generation of the (*S*)-isomers from **3c** and **3d** should be attributed to the transition state **A** in Figure 1. In Figure 1, the diene approaches the dienophiles from the front side (*Si*-face) in an *endo*-to-carboxylate orientation. As such, the steric hindrance



Scheme 11.



Scheme 12.

imposed by the isopropyl and 1-methyl-1-phenyl-ethyl groups on the back side can be avoided. As for the formation of the minor (*R*)-isomers, one possible pathway involves the *endo* addition of the diene from the more hindered face (*Re*-face) of the dienophiles **B**. With respect to models **A** and **B**, it is reasonable to propose that the larger steric bias between the *Re*- and *Si*-faces of **3c** should be responsible for the better stereoselectivity of **3c** versus **3d**. Theoretically, the minor isomers can also be formed through the *endo* addition of the diene from the less hindered face, arranged in an *Re*-trigonal geometry[11] **C**. However, this model is considered to be less possible than **B** due to the impossibility of achieving double activation of the P═O and C═O bonds[24] by a Lewis acid and/or the unfavorable steric interaction between the phosphono and cyclohexyl moieties.

The high-yielding and enantio-controlled generation of the adducts allowed us to prepare some useful chiral norbornyl derivatives on large scales. In addition to replacing the phosphonyl group with an alkyl group as shown in Scheme 10, we also applied our recently developed $LiAlH_4$-mediated reductive dephosphonylation operation[25] to **4d** to produce 2-*endo*-hydroxymethyl-5-norbornene **12**, an useful synthetic intermediate,[26,27] in enantiopure form. Upon treatment with $LiAlH_4$ in CH_2Cl_2/THF, **4d** could be readily converted into (2*R*)-**12** in 86% yield with the quantitative recovery of the chiral alcohol (Scheme 11) {$[\alpha]_D^{20} = +70.6$ (*c* 0.6, 95% EtOH), lit.[28] $[\alpha]_D^{20} = +79.3$ (*c* 0.86, 95% EtOH)}. Moreover, (*2S*)-(−)-**12** was synthesized from (+)-phenylmenthol in the same sequence (Scheme 12). Thus, we were able to obtain both enantiomers of **12** in a common Diels–Alder strategy.

3. Conclusion

In conclusion, we have applied chiral 2-phosphonoacrylates to Diels–Alder reactions for the first time. Under the activation of $SnCl_4$, all precursors underwent facile cycloaddition to afford exclusively *endo* products. On this basis, the phenylmenthyl group was shown to be the most efficient auxiliary in controlling the facial selectivity of the reaction, in giving single diastereomers. Although the same chiral template has already been used for the asymmetric Diels–Alder reactions of several other 2-substituted acrylates (X = PhCO–, F–, Cl–, Me–, H–, etc.),[8f,29] none of these methods gave complete *endo*/*exo* and/or diastereofacial selectivity as observed in our case. The excellent stereoselectivity is presumably due to the activating capability of the phosphono group toward the C═C double bond. The recovery of the employed auxiliaries by simple reduction should also indicate the value of this protocol.

4. Experimental

4.1. General

All reagents were purchased from commercial suppliers and used without further purification. All reactions were performed under an atmosphere of nitrogen unless otherwise noted. Tetrahydrofuran and diethyl ether were freshly distilled from sodium–benzophenone, and dichloromethane, pyridine, dimethyl sulfoxide, and toluene were freshly distilled from calcium hydride before use. TLC analysis was carried out on glass-backed silica gel plates, and visualized by UV light, ethanolic solution of vanillin (5%), iodine, or aqueous $KMnO_4$ solution (10%). The products were purified by flash chromatography using silica gel (70–230 mesh). NMR spectra (^1H, ^{13}C NMR, DEPT, 2D-NOESY) were recorded on 400 or 600 MHz spectrometers using deuteriochloroform ($CDCl_3$) or deuteriobenzene (C_6D_6) as solvents. Chemical shift measurements are reported in delta (δ) units. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m). Coupling constants (*J*) are reported in Hertz (Hz). The resonances of infrared (IR) spectra are reported in wave numbers (cm^{-1}). High resolution mass spectra (HRMS) were determined in the electron impact (EI) mode and by a magnetic sector analyzer. Specific optical rotations were measured in a polarimeter with sodium light (589.6 nm). The enantiomeric purity *of the Diels–Alder* adducts was determined by HPLC analysis on their 3,5-dinitrobenzoate derivative using a Chiralcel OD-H column (diameter: 4.6 mm, length: 250 mm, particle size: 5 μm) and a UV detector (254 nm). Melting points were determined with a capillary melting point apparatus and are uncorrected.

4.2. Preparation of 1a–d

4.2.1. (1*S*,2*R*,4*S*)-1,7,7-Trimethylbicyclo[2.2.1]heptan-2-yl 2-(diethoxyphosphoryl)-acetate 1a. Typical procedure for the transesterification

To a solution of (−)-borneol (2.5 g, 16.2 mmol) in dry toluene (40 mL), triethyl phosphonoacetate (9.84 mL, 48.6 mmol) and 4-dimethyl aminopyridine (600 mg, 4.86 mmol) were added successively. The mixture was stirred in an oil bath at 115 °C for 2 days, then cooled to rt and concentrated under reduced pressure. The residue was subjected to chromatographic purification on silica gel (hexane–EtOAc: 10:1, 6:1, 3:1) to afford **1a** as a pale yellow oil (4.85 g, 93%) plus 91 mg of recovered phosphonoacetate. IR (neat) 2955, 1735, 1279, 1115, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.96–4.89 (m, 1H), 4.24–4.10 (m, 4H), 2.97 (d, J_{P-H} = 21.5 Hz, 2H), 2.34 (ddd, *J* = 18.7, 9.8, 3.9 Hz, 1H), 1.98 (ddd, *J* = 12.6, 9.0, 3.9 Hz, 1H), 1.80–1.70 (m, 2H), 1.67 (t, *J* = 4.5 Hz, 1H), 1.34 (t, *J* = 7.2 Hz, 6H), 1.26–1.21 (m, 1H), 1.01 (ddd, *J* = 23.5, 11.2, 4.0 Hz, 1H), 0.89 (s, 3H), 0.86 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9 (d, J_{c-p} = 6.5 Hz), 81.2, 62.4 (d, J_{c-p} = 6.1 Hz), 48.8, 47.8, 44.7, 36.4, 34.5 (d, J_{c-p} = 133.5 Hz), 27.9, 26.9, 19.6, 18.7 16.5 (d, J_{c-p} = 6.2 Hz), 13.3; HRMS-EI *m*/*z* $[M]^+$ Calcd for $C_{16}H_{29}O_5P$ 332.1753. Found: 332.1760. $[\alpha]_D^{20} = -18.1$ (*c* 0.62, 95% EtOH).

4.2.2. (1*R*,2*S*)-2-Phenylcyclohexyl 2-(diethoxyphosphoryl)-acetate 1b

The typical procedure for preparing **1a** was followed by using triethyl phosphonoacetate (3.27 mL, 16.17 mmol), (*1R,2S*)-*trans*-2-phenyl-1-cyclohexanol (950 mg, 5.39 mmol), and DMAP

(199.54 mg, 1.62 mmol) as the reagents. The chromatographic purification (silica gel, hexane–EtOAc, 8:1, 5:1, 3:1) yielded 1.76 g of **1b** (96.8%) and 47.3 mg of recovered phosphonoacetate. IR (neat) 3100, 1732, 1647, 1550, 1269, 1028, 968, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.21 (m, 2H), 7.21–7.10 (m, 3H), 5.02 (ddd, J = 10.1, 10.0, 5.1 Hz, 1H), 4.10–3.88 (m, 4H), 2.79–2.57 (m, 3H), 2.23–2.09 (m, 1H), 1.95–1.80 (m, 2H), 1.76 (m, 1H), 1.58–1.49 (m, 1H), 1.49–1.40 (m, 2H), 1.36–1.30 (m, 1H), 1.26 (t, J = 7.0 Hz, 3H), 1.22 (t, J = 7.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1 (d, J_{c-p} = 6.1 Hz), 142.9, 128.3, 127.4, 126.4, 77.1, 62.5 (d, J_{c-p} = 6.3 Hz), 62.4 (d, J_{c-p} = 6.2 Hz), 49.4, 34.2 (d, J_{c-p} = 134.1 Hz), 34.2, 32.0, 25.7, 24.7, 16.3 (d, J_{c-p} = 6.0 Hz); HRMS-EI m/z $[M]^+$ Calcd for $C_{18}H_{27}O_5P$ 354.1596. Found: 354.1587. $[\alpha]_D^{20} = -17.0$ (c 1.05, $CHCl_3$).

4.2.3. (1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-(diethoxyphosphoryl)-acetate 1c

The typical procedure for preparing **1a** was followed by using triethyl phosphonoacetate (2.48 mL, 12.3 mmol), (−)-phenylmenthol (950 mg, 4.09 mmol), and DMAP (151.4 mg, 1.23 mmol) as the reagents. The chromatographic purification (silica gel, hexane–EtOAc, 8:1, 5:1, 3:1) afforded 1.64 g of **1c** (98%) as a colorless oil. IR (neat) 3087, 3056, 2956, 1730, 1600, 1271, 1025, 972, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.24 (m, 4H), 7.18–7.07 (m, 1H), 4.83 (ddd, J = 10.7, 10.6, 4.4 Hz, 1H), 4.15–3.96 (m, 4H), 2.37 (dd, J = 21.2, 14.4 Hz, 1H), 2.08 (dd, J = 21.2, 14.4 Hz, 1H), 2.06–2.00 (m, 1H), 1.84 (tm, J = 15.2 Hz, 2H), 1.66–1.68 (m, 1H), 1.52–1.39 (m, 1H), 1.34–1.24 (m, 9H), 1.20 (s, 3H), 1.18–1.11 (m, 1H), 1.02–0.89 (m, 2H), 0.87 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (d, J_{c-p} = 5.9 Hz), 151.7, 127.9, 125.3, 125.1, 75.0, 62.3 (d, J_{c-p} = 5.9 Hz), 50.2, 41.3, 39.4, 34.4, 33.7 (d, J_{c-p} = 132.9 Hz), 31.2, 29.2, 26.2, 23.1, 21.7, 16.2 (d, J_{c-p} = 6.3 Hz); HRMS-EI m/z $[M]^+$ Calcd for $C_{22}H_{35}O_5P$ 410.2222. Found: 410.2230. $[\alpha]_D^{20} = +14.0$ (c 1.1, $CHCl_3$).

4.2.4. (1*R*,2*S*,5*R*)-(Diethoxy-phosphoryl)-acetic acid 2-isopropyl-5-methyl-cyclohexyl ester 1d

The typical procedure for preparing **1a** was followed by using triethyl phosphonoacetate (2.91 mL, 14.4 mmol), (1*R*,2*S*,5*R*)-(−)-menthol (750 mg, 4.8 mmol), and DMAP (177.7 mg, 1.44 mmol) as the reagents. The chromatographic purification (silica gel, hexane–EtOAc, 8:1, 5:1, 3:1) afforded 1.50 g of **1d** (94%) as a colorless oil, plus 28 mg of recovered phosphonoacetate. IR (neat) 2956, 1730, 1272, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.73 (ddd, J = 10.9, 10.9, 4.4 Hz, 1H), 4.24–4.10 (m, 4H), 2.94 (d, J = 21.7 Hz, 2H), 2.06–1.92 (m, 2H), 1.68 (br d, J = 12.8 Hz, 2H), 1.54–1.35 (m 2H), 1.35 (t, J = 7.08 Hz, 6H), 1.12–0.94 (m, 3H), 0.90 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1 (d, J_{c-p} = 6.1 Hz), 75.3, 62.3 (d, J_{c-p} = 4.7 Hz), 62.3 (d, J_{c-p} = 4.9 Hz), 46.7, 40.5, 34.4 (d, J_{c-p} = 133.4 Hz), 34.0, 31.2, 25.6, 23.0, 21.8, 20.6, 16.2 (d, J_{c-p} = 6.2 Hz), 15.8; HRMS-EI m/z $[M]^+$ Calcd for $C_{16}H_{31}O_5P$ 334.1909. Found: 334.1913. $[\alpha]_D^{20} = -47.3$ (c 1.1, $CHCl_3$).

4.3. Preparation of 2a–d

4.3.1. (1*S*,2*R*,4*S*)-2-(Diethoxy-phosphoryl)-2-phenylselanyl-propionic acid 1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl ester 2a

Potassium *tert*-butoxide (910.5 mg, 7.87 mmol) was added to a stirred solution of **1a** (2.2 g, 6.61 mmol) in dry DMSO (8.8 mL) pre-cooled at 0 °C in an ice bath. The ice bath was then removed and stirring was continued for 20 min followed by the addition of iodomethane (0.45 mL, 7.21 mmol). The mixture was heated at 60 °C for 3.5 h, cooled to rt and diluted with ethyl acetate (200 mL). The solution was successively washed with saturated aqueous NH_4Cl solution (45 mL), water (45 mL × 2), and brine (45 mL) and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, hexane–EtOAc, 8:1, 5:1, 3:1) to give 1.74 g of methyl phosphonate intermediate plus 507 mg of recovered **1a**. Potassium *tert*-butoxide (762.8 mg, 6.59 mmol) was added to a stirred solution of the freshly prepared methyl phosphonate (1.52 g, 4.40 mmol) in dry DMSO (14.3 mL) pre-cooled at 0 °C in an ice bath. The ice bath was then removed and stirring was continued for 15 min followed by the addition of phenylselenyl bromide (3.18 g, 13.18 mmol). The reaction mixture was heated at 60 °C for 5 h, then cooled to rt and diluted with ethyl acetate (220 mL). The solution was successively washed with aqueous acetic acid solution (10%, 45 mL), saturated aqueous $NaHCO_3$ solution (45 mL), water (45 mL × 2), and brine (45 mL). After concentration, the residue was purified by flash chromatography (silica gel, hexane–EtOAc, 8:1, 5:1, 4:1) to furnish 812.3 mg of **2a** as a mixture of two diastereomers (51/49) (63.4%, over two steps) followed by recovered methyl phosphonate (650 mg). IR (neat) 3057, 1718, 1577, 1253, 1049, 980, 830, 643, 545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) major isomer: δ 7.66–7.70 (m, 2H), 7.41–7.34 (m, 1H), 7.33–7.26 (m, 2H), 4.95–4.83 (m, 1H), 4.39–4.26 (m, 2H), 4.25–4.14 (m, 2H), 2.39–2.27 (m, 1H), 2.16–2.05 (m, 1H), 1.80–1.64 (m, 2H), 1.47 (d, J = 15.7 Hz, 3H), 1.41–1.29 (m, 7H), 1.27–1.15 (m, 1H), 1.07–0.98 (m, 1H), 0.89 (s, 3 H), 0.87 (s, 6 H); minor isomer: δ 7.66–7.70 (m, 2H), 7.41–7.34 (m, 1H), 7.33–7.26 (m, 2H), 4.95–4.83 (m, 1H), 4.39–4.26 (m, 2H), 4.25–4.14 (m, 2H), 2.39–2.27 (m, 1H), 2.16–2.05 (m, 1H), 1.80–1.64 (m, 2H), 1.46 (d, J = 15.7 Hz, 3H), 1.41–1.29 (m, 7H), 1.27–1.15 (m, 1H), 1.07–0.98 (m, 1H), 0.88 (s, 3 H), 0.87 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major: δ 170.3, 138.4, 129.7, 128.8, 126.0, 81.9, 63.3 (d, J_{c-p} = 7.3 Hz), 49.0, 47.9, 44.9, 44.8 (d, J_{c-p} = 145.2 Hz), 36.2, 28.0, 27.1, 19.8, 19.7, 18.9, 16.5 (d, J_{c-p} = 5.2 Hz), 13.4; minor: δ 170.5, 138.4, 129.7, 128.8, 126.0, 82.0, 64.3 (d, J_{c-p} = 4.5 Hz), 64.2 (d, J_{c-p} = 4.3 Hz), 48.9, 47.8, 44.8, 44.7 (d, J_{c-p} = 145.5 Hz), 36.2, 27.9, 27.0, 19.8, 19.7, 18.9, 16.6 (d, J_{c-p} = 6.1 Hz), 13.5; HRMS-EI m/z $[M]^+$ Calcd for $C_{23}H_{35}O_5PSe$ 502.1387. Found: 502.1394.

4.3.2. (1*R*,2*S*)-2-(Diethoxy-phosphoryl)-2-phenylselanyl-propionic acid 2-phenyl-cyclohexyl ester 2b

Potassium *tert*-butoxide (638.4 mg, 5.58 mmol) was added to a stirred solution of **1b** (1.66 g, 4.68 mmol) in dry DMSO (24 mL) pre-cooled at 0 °C in an ice bath. The ice bath was then removed and stirring was continued for 15 min followed by the addition of phenylselenyl bromide (1.0 g, 4.22 mmol). The mixture was heated at 60 °C for 4 h, cooled to rt and diluted with ethyl acetate (230 mL). The solution was successively washed with aqueous acetic acid solution (10%, 50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), water (50 mL × 2), and brine (50 mL). After concentration, the residue was purified by flash chromatography (silica gel, hexane–EtOAc, 8:1, 4:1, 2:1) to provide 1.87 g of the phenylselenyl phosphonate intermediate plus recovered **1b** (351.3 mg). Potassium *tert*-butoxide (1.1 g, 9.49 mmol) was added to a stirred solution of the freshly prepared phenylselenyl phosphonate (1.2 g, 2.37 mmol) in dry DMSO (4.5 mL) pre-cooled at 0 °C in an ice bath. The ice bath was then removed and stirring was continued for 25 min followed by the addition of iodomethane (0.6 mL, 9.49 mmol). The reaction mixture was heated at 60 °C for 5 h, then cooled to rt and diluted with ethyl acetate (210 mL). The solution was successively washed with a saturated aqueous NH_4Cl solution (40 mL), water (40 mL × 2), and brine (40 mL) and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, hexane–EtOAc, 10:1, 5:1, 3:1) to give 844.1 mg of **2b** (52/48) (67.8% over two steps). IR (neat) 3059, 1770, 1247, 1066, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) major: δ 7.44 (br d, J = 6.9 Hz, 1H), 7.32–7.07 (m, 9H), 5.08 (ddd, J = 10.4, 10.4, 4.3 Hz, 1H), 4.25–3.85 (m, 4H), 2.81–2.63 (m, 1H), 2.23–2.07 (m, 1H), 1.90 (br d, J = 13.4 Hz, 1H), 1.86–1.77 (m, 1H), 1.77–1.67 (m, 1H),

1.63–1.47 (m, 1H), 1.47–1.38 (m, 2H), 1.21 (t, J = 7.8 Hz, 6H), 1.16 (d, J = 6.6 Hz, 3H), 1.35–1.12 (m, 1H); minor: δ 7.44 (br d, J = 6.9 Hz, 1H), 7.32–7.07 (m, 9H), 4.98 (ddd, J = 10.5, 10.4, 4.4 Hz, 1H), 4.25–3.87 (m, 4H), 2.81–2.63 (m, 1H), 2.23–2.07 (m, 1H), 1.90 (br d, J = 13.4 Hz, 1H), 1.86–1.77 (m, 1H), 1.77–1.67 (m, 1H), 1.63–1.47 (m, 1H), 1.47–1.38 (m, 2H), 1.30 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.20 (d, J = 7.2 Hz, 3 H), 1.35–1.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major: δ 169.6, 143.2, 138.4, 129.4, 128.3, 127.5, 126.3, 126.2, 125.9, 77.5, 63.9 (d, J_{c-p} = 6.6 Hz), 63.8 (d, J_{c-p} = 5.9 Hz), 49.6, 44.9 (d, J_{c-p} = 145.5 Hz), 34.8, 34.0, 31.8, 31.7, 25.7, 24.6, 19.5 (d, J_{c-p} = 2.4 Hz), 16.5 (d, J_{c-p} = 5.5 Hz), 16.4 (d, J_{c-p} = 5.9 Hz); minor: δ 169.4, 143.0, 138.3, 129.4, 128.6, 127.8, 126.5, 126.2, 125.8, 78.0, 63.4 (d, J_{c-p} = 7.1 Hz),, 63.2 (d, J_{c-p} = 7.1 Hz), 49.2, 44.8 (d, J_{c-p} = 145.6 Hz), 34.8, 34.0, 31.8, 31.7, 25.7, 24.5, 19.8 (d, J_{c-p} = 2.0 Hz), 16.5 (d, J_{c-p} = 5.5 Hz), 16.4 (d, J_{c-p} = 5.9 Hz); HRMS-EI m/z [M]$^+$ Calcd for $C_{25}H_{33}O_5PSe$ 524.1231. Found: 524.1221.

4.3.3. (1*R*,2*S*,5*R*)-2-(Diethoxy-phosphoryl)-2-phenylselanyl-propionic acid 5-methyl-2-(1-methyl-1-phenyl-ethyl)-cyclohexyl ester 2c

The typical procedure for preparing **2b** was followed by using **1c** (1.6 g, 3.40 mmol) as the starting material. The phenylselenylation reaction produced 1.74 g of intermediate plus 359 mg of recovered **1c**. The subsequent methylation of phenylselenyl phosphonate (1.73 g) gave **2c** as mixture of two diastereomers (56/44) (1.20 g, 66.5% over two steps) after chromatographic purification (silica gel, hexane–EtOAc, 10:1, 6:1, 4:1). IR (neat) 3056, 1715, 1249, 1023, 971, 766, 546 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) major: δ 7.72 (br d, J = 7.6 Hz, 2H), 7.41–7.27 (m, 7H), 7.17–7.12 (m, 1H), 4.90 (ddd, J = 10.7, 10.8, 4.2 Hz, 1H), 4.39–4.10 (m, 4H), 2.03–1.86 (m, 2H), 1.46–1.35 (m, 10H), 1.35–1.23 (m, 8H), 1.05–0.88 (m, 2H), 0.84 (d, J = 6.4 Hz, 3H), 0.79–0.67 (m, 1H); minor: δ 7.76 (d, J = 7.6 Hz, 2H), 7.41 -7.27 (m, 7H), 7.17–7.12 (m, 1H), 4.98 (ddd, J = 10.6, 10.6, 4.4 Hz, 1H), 4.39–4.10 (m, 4H), 1.99–1.88 (m, 2H), 1.44–1.35 (m, 10H), 1.33–1.23 (m, 8H), 1.04–0.88 (m, 2H), 0.85 (d, J = 6.4 Hz, 3H), 0.77–0.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major: δ 169.6, 150.4, 138.6, 129.7, 128.8, 128.0, 125.8, 125.4, 77.3, 64.1 (d, J_{c-p} = 7.4 Hz), 63.6 (d, J_{c-p} = 7.1 Hz), 50.4, 44.8 (d, J_{c-p} = 147.4 Hz), 41.2, 40.5, 34.4, 31.3, 29.9, 27.5, 24.2, 23.6, 21.8, 19.7, 19.3, 16.6 (d, J_{c-p} = 5.1 Hz), 16.4 (d, J_{c-p} = 6.2 Hz); minor: δ 169.3, 150.7, 138.7, 129.6, 128.7, 128.1, 125.7, 125.3, 77.5, 64.6 (d, J_{c-p} = 7.4 Hz), 63.3 (d, J_{c-p} = 7.3 Hz), 50.2, 46.1 (d, J_{c-p} = 143.5 Hz), 41.4, 40.4, 34.3, 31.1, 29.9, 27.3, 24.2, 23.6, 21.8, 19.6, 19.2, 16.5 (d, J_{c-p} = 5.0 Hz), 16.4 (d, J_{c-p} = 6.2 Hz); HRMS-EI m/z [M]$^+$ Calcd for $C_{29}H_{41}O_5PSe$ 580.1857. Found: 580.1868.

4.3.4. (1*R*,2*S*,5*R*)-2-(Diethyl-phosphinoyl)-2-phenylselanyl-propionic acid 2-isopropyl-5-methyl-cyclohexyl ester 2d

The typical procedure for preparing **2b** was followed by using **1d** (1.45 g, 4.34 mmol) as the starting material. The phenylselenylation reaction produced 1.59 g of intermediate plus 347 mg of recovered **1d**. The subsequent methylation of phenylselenyl phosphonate (1.40 g) gave **2d** as a mixture of two diastereomers (55/45) (878.6 mg, 60% over two steps) after chromatographic purification (silica gel, hexane–EtOAc, 8:1, 5:1, 3:1). IR (neat) 3057, 1716, 1253, 1050, 989, 744, 647, 547 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) major: δ 7.72 (d, J = 7.6 Hz, 2H), 7.39 (br t, J = 7.4 Hz, 1H), 7.30 (br t, J = 7.6 Hz, 2H), 4.71 (ddd, J = 12.6, 10.8, 4.4 Hz, 1H), 4.37–4.15 (m, 4H), 2.23–1.88 (m, 2H), 1.69 (br d, J = 11.0 Hz, 2H), 1.47 (d, J = 15.7 Hz, 3H), 1.54–1.40 (m, 2H), 1.39–1.31 (m, 6H), 1.08–0.95 (m, 2H), 0.93–0.86 (m, 7H), 0.74 (d, J = 6.9 Hz, 3H); minor: δ 7.68 (d, J = 7.6 Hz, 2H), 7.39 (br t, J = 7.4 Hz, 1H), 7.30 (br t, J = 7.6 Hz, 2H), 4.74 (ddd, J = 10.8, 10.8, 4.4 Hz, 1H), 4.37–4.15 (m, 4H), 2.23–1.88 (m, 2H), 1.69 (br d, J = 11.0 Hz, 2H), 1.46 (d, J = 15.7, 3H), 1.54–1.40 (m, 2H), 1.39–1.31 (m, 6H), 1.08–0.95 (m, 2H), 0.93–0.86 (m, 7H), 0.81 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major: δ 169.6, 138.4, 129.6, 128.7, 126.1 (d, J_{c-p} = 3.1 Hz), 76.0, 64.0 (d, J_{c-p} = 7.4 Hz), 63.3 (d, J_{c-p} = 7.2 Hz), 46.8, 44.5 (d, J_{c-p} = 144.8 Hz), 40.2, 34.1, 31.3, 25.0, 22.7, 22.0, 21.0, 19.9 (d, J_{c-p} = 2.2 Hz), 16.4 (d, J_{c-p} = 5.9 Hz), 15.6; minor: δ 170.0, 138.3, 129.6, 128.7, 125.9 (d, J_{c-p} = 4.1 Hz), 76.1, 63.9 (d, J_{c-p} = 7.3 Hz), 63.5 (d, J_{c-p} = 7.0 Hz), 47.0, 44.7 (d, J_{c-p} = 145.0 Hz), 40.3, 34.2, 31.3, 25.6, 23.0, 22.0, 20.9, 19.9 (d, J_{c-p} = 2.3 Hz), 16.4 (d, J_{c-p} = 3.7 Hz), 15.9; HRMS-EI m/z [M]$^+$ Calcd for $C_{23}H_{37}O_5PSe$ 504.1544. Found: 504.1549.

4.4. Preparation of 3a–d

4.4.1. (1*S*,2*R*,4*S*)-2-(Diethoxy-phosphoryl)acrylic acid 1,7,7-trimethyl-bicyclo[2.2.1]hept-2-yl ester 3a. Typical procedure for the synthesis of 3

To a solution of **2a** (812 mg, 1.62 mmol) in CH_2Cl_2 (16 mL) precooled in an ice bath was added dropwise aqueous H_2O_2 (35%, 0.57 mL, 6.46 mmol) over 5 min. The resulting mixture was continued to stir at rt for an additional 1 h, then diluted with CH_2Cl_2 (230 mL) and successively washed with saturated aqueous $NaHCO_3$ solution (45 mL), water (45 mL × 2) and brine (45 mL). After separation, the organic layer was dried with Na_2SO_4, filtered and concentrated under reduced pressure to give crude **3a** (534.98 mg, 98%), which was found to decompose easily upon exposure to air within one day. The crude product with enough purity (>90%) was then used directly for the subsequent reaction without chromatographic purification. IR (neat) 1721, 1607, 1269, 1024, 973, 816 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (dd, J = 42.13, 1.9 Hz, 1H), 6.77 (dd, J = 20.3, 1.9 Hz, 1H), 5.00 (ddd, J = 9.9, 3.1, 2.4 Hz, 1H), 4.24–4.07 (m, 4H), 2.41 (dddd, J = 13.4, 9.1, 4.4, 1.8 Hz, 1H), 2.11 (ddd, J = 13.4, 9.2, 4.6 Hz, 1H), 1.82–1.73 (m, 1H), 1.71 (br t, J = 4.5 Hz, 1H), 1.38–1.32 (m, 1H), 1.34 (td, J = 7.2, 1.3 Hz, 6H), 1.28–1.21 (m, 1H), 1.08–0.97 (m, 1H), 0.92 (s, 3H), 0.89 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 (d, J_{c-p} = 15.1 Hz), 143.7 (d, J_{c-p} = 5.5 Hz), 133.2 (d, J_{c-p} = 183.8 Hz), 81.4, 62.3 (d, J_{c-p} = 3.1 Hz), 62.2 (d, J_{c-p} = 3.2 Hz), 48.8, 47.7, 44.7, 36.6, 27.9, 26.8, 19.5, 18.7, 16.2 (d, J_{c-p} = 6.0 Hz), 13.3.

4.4.2. (1*R*,2*S*)-2-(Diethoxy-phosphoryl)acrylic acid 2-phenyl-cyclohexyl ester 3b

The typical procedure for preparing **3a** was followed. From 593.8 mg of **2b** (1.13 mmol), 386.5 mg of crude **3b** was obtained (93%). IR (neat) 3097, 1720, 1647, 1261, 1027, 968, 802 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.12 (m, 5H), 6.70 (dd, J = 41.9, 1.8 Hz, 1H), 6.62 (dd, J = 22.4, 1.8 Hz, 1H), 5.15 (ddd, J = 10.3, 10.3, 4.4 Hz, 1H), 4.11–3.85 (m, 4H), 2.79 (ddd, J = 11.4, 11.8, 3.6 Hz, 1H), 2.32–2.02 (m, 1H), 2.03–1.75 (m, 3H), 1.66–1.47 (m, 3H), 1.45–1.36 (m, 1H), 1.25 (t, J = 7.0 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (d, J_{c-p} = 16.3 Hz), 143.0 (d, J_{c-p} = 4.7 Hz), 142.7, 133.0 (d, J_{c-p} = 183.6 Hz), 128.1, 127.3, 126.3, 77.0, 62.3 (d, J_{c-p} = 5.6 Hz), 62.2 (d, J_{c-p} = 5.6 Hz), 49.5, 33.9, 32.0, 25.6, 24.5, 16.1 (d, J_{c-p} = 6.0 Hz).

4.4.3. (1*R*,2*S*,5*R*)-2-(Diethoxy-phosphoryl)-acrylic acid 5-methyl-2-(1-methyl-1-phenyl-ethyl)-cyclohexyl ester 3c

The typical procedure for preparing **3a** was followed. From 755.4 mg of **2c** (1.30 mmol), 517.1 mg of crude **3c** was obtained (94%). IR (neat) 3088, 1714, 1632, 1297, 1094, 979, 796 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.20 (m, 4H), 7.14–7.03 (m, 1H), 6.42 (br d, J = 20.9 Hz, 1H), 6.05 (br d, J = 42.7 Hz, 1H), 4.71 (ddd, J = 10.7, 10.6, 4.3 Hz, 1H), 4.28–4.07 (m, 4H), 2.11 (ddd, J = 10.7, 10.7, 3.0 Hz, 1H), 1.90–1.94 (m, 1H), 1.76–1.60 (m, 2H), 1.56–1.41 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H), 1.33 (t, J = 7.3 Hz, 3H), 1.30 (s, 3H), 1.21 (s, 3H), 1.14–1.01 (m, 2H), 0.88 (d, J = 6.4 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (d, J_{c-p} = 17.9 Hz), 151.6, 142.9 (d, J_{c-p} = 4.4 Hz), 132.7 (d, J_{c-p} = 187.9 Hz), 128.1, 125.3, 125.0, 75.6, 62.7 (d, J_{c-p} = 5.9 Hz), 62.6 (d, J_{c-p} = 5.8 Hz), 50.3, 41.6, 39.6, 34.5, 31.3, 27.8, 26.6, 25.2, 21.7, 16.4 (d, J_{c-p} = 5.9 Hz).

4.4.4. (1*R*,2*S*,5*R*)-2-(Diethoxy-phosphoryl)-acrylic acid 2-isopropyl-5-methyl-cyclohexyl ester 3d

The typical procedure for preparing **3a** was followed. From 717 mg of **2d** (1.42 mmol), 489 mg of crude **3d** was obtained (99%). IR (neat) 1718, 1607, 1265, 1027, 927, 846 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (dd, J = 42.2, 1.6 Hz, 1H), 6.69 (dd, J = 20.4, 1.6 Hz, 1H), 4.75 (ddd, J = 10.9, 10.8, 4.4 Hz, 1H), 4.19–4.00 (m, 4H), 2.09 (br d, J = 12.0 Hz, 1H), 1.95–1.84 (m, 1H), 1.64 (br d, J = 11.4 Hz, 1H), 1.49–1.36 (m, 2H), 1.28 (t, J = 7.0 Hz, 6H), 1.06–0.94 (m, 2H), 0.86 (d, J = 6.1 Hz, 3H), 0.84 (d, J = 6.3 Hz, 3H), 0.87–0.82 (m, 1H), 0.70 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (d, J_{c-p} = 15.7 Hz), 134.4 (d, J_{c-p} = 5.1 Hz), 133.5 (d, J_{c-p} = 184.7 Hz), 75.7, 62.6 (d, J_{c-p} = 5.7 Hz), 62.5 (d, J_{c-p} = 5.7 Hz), 47.0, 40.6, 34.1, 31.4, 25.8, 23.1, 21.9, 20.8, 16.3 (d, J_{c-p} = 6.3 Hz), 16.0.

4.5. Diels–Alder reactions of 3

4.5.1. Formation of the mixture of (1*S*,2*R*,4*S*)-1,7,7-trimethyl bicyclo[2.2.1]heptan-2-yl (1*R**,2*R**)-1-(diethoxyphosphoryl)-2-methylcyclohex-3-ene carboxylate 4a and (1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl (1*R**,2*S**)-1-(diethoxy phosphoryl)-2-methylcyclohex-3-ene carboxylate 4a′

Dry toluene (4 mL) was added to $ZnCl_2$ (flame-dried, 213.8 mg, 1.57 mmol, 1.5 equiv) in a round-bottom flask under N_2. The resulting suspension was stirred for 30 min and then added to a solution of **3a** (360 mg, 1.05 mmol) in dry toluene (2 mL). After stirring for 20 min, *trans*-piperylene (1.1 mL, 10.46 mmol) was introduced and the reaction mixture was continued to stir at 80 °C for 5 h, cooled to rt and diluted with ethyl acetate (200 mL). The solution was washed with water (35 mL × 2) and brine (35 mL), and concentrated in vacuo. The residue was subjected to chromatographic purification (silica gel, hexane–EtOAc, 10:1, 5:1, 2:1) to give 376 mg (87.3%) of product as a mixture of four isomers (**4a** (*endo*)/**4a**′ (*exo*) = 82:18; dr = 41:41:9:9). IR (neat) 3054, 1727, 1242, 1028, 964, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) **4a** isomer one: δ 5.77–5.46 (m, 2H), 4.99–4.77 (m, 1H), 4.28–4.05 (m, 4H), 3.04–2.85 (m, 1H), 2.46–2.18 (m, 3H), 2.17–1.95 (m, 3H), 1.82–1.63 (m, 3H), 1.32 (t, J = 6.9 Hz, 6H), 1.29–1.19 (m, 1H), 1.27 (d, J = 7.3 Hz, 3H), 1.05–1.00 (m, 1H), 0.89 (s, 3H), 0.86(s, 3H), 0.87(s, 3H); **4a** isomer two: δ 5.77–5.46 (m, 2H), 4.99–4.77 (m, 1H), 4.28–4.05 (m, 4H), 3.04–2.85 (m, 1H), 2.46–2.18 (m, 3H), 2.17–1.95 (m, 3H), 1.82–1.63 (m, 3H), 1.32 (t, J = 6.9 Hz, 6H), 1.29–1.19 (m, 1H), 1.23 (d, J = 7.2 Hz, 3H), 1.05–1.00 (m, 1H), 0.89 (s, 3H), 0.86(s, 3H), 0.87(s, 3H); **4a**′ isomer one: δ 5.77–5.46 (m, 2H), 4.99–4.77 (m, 1H), 4.28–4.05 (m, 4H), 3.17–3.05 (m, 1H), 2.46–2.18 (m, 3H), 2.17–1.95 (m, 3H), 1.82–1.63 (m, 3H), 1.34 (t, J = 6.4 Hz, 6H), 1.29–1.19 (m, 1H), 1.22 (d, J = 6.8 Hz, 3H), 1.07–1.01 (m, 1H), 0.89 (s, 3H), 0.86(s, 3H), 0.83(s, 3H); **4a**′ isomer two: δ 5.77–5.46 (m, 2H), 4.99–4.77 (m, 1H), 4.28–4.05 (m, 4H), 3.17–3.05 (m, 1H), 2.46–2.18 (m, 3H), 2.17–1.95 (m, 3H), 1.82–1.63 (m, 3H), 1.34 (t, J = 6.4 Hz, 6H), 1.29–1.19 (m, 1H), 1.22 (d, J = 7.0 Hz, 3H), 1.07–1.01 (m, 1H), 0.89 (s, 3H), 0.86(s, 3H), 0.83(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) **4a** isomer one: δ 170.7 (d, J_{c-p} = 7.7 Hz), 131.3 (d, J_{C-P} = 9.6 Hz), 125.2, 81.3, 62.8 (d, J_{c-p} = 6.9 Hz), 62.1 (d, J_{c-p} = 6.3 Hz), 51.5 (d, J_{c-p} = 135.7 Hz), 48.8, 47.7, 44.8, 36.4, 33.2, 28.0, 27.2, 26.0 (d, J_{c-p} = 4.0 Hz), 22.6 (d, J_{c-p} = 5.5 Hz), 19.6, 18.9, 18.1 (d, J_{c-p} = 5.6 Hz), 16.5 (d, J_{c-p} = 6.2 Hz), 16.4 (d, J_{c-p} = 6.7 Hz), 13.6; **4a** isomer two: δ 170.6 (d, J_{c-p} = 7.8 Hz), 131.9 (d, J_{c-p} = 8.7 Hz), 124.9, 81.2, 62.8 (d, J_{c-p} = 6.9 Hz), 62.1 (d, J_{c-p} = 6.3 Hz), 51.3 (d, J_{c-p} = 135.7 Hz), 48.7, 47.7, 44.8, 36.3, 33.1, 28.0, 27.1, 25.2 (d, J_{c-p} = 3.9 Hz), 22.5 (d, J_{c-p} = 4.6 Hz), 19.6, 18.9, 18.0 (d, J_{c-p} = 5.0 Hz), 16.5 (d, J_{c-p} = 6.2 Hz), 16.4 (d, J_{c-p} = 6.7 Hz), 13.5; **4a**′ isomer one: δ 171.1 (d, J_{c-p} = 3.3 Hz), 131.5 (d, J_{c-p} = 13.6 Hz), 125.2, 81.1, 62.7 (d, J = 6.3 Hz), 51.9 (d, J = 132.3 Hz), 48.8, 47.8, 44.8, 36.1, 33.0, 27.9, 27.3, 26.0 (d, J = 4.0 Hz), 22.4 (d, J = 5.0 Hz), 20.6, 20.5, 18.5 (d, J = 3.1 Hz), 16.4 (d, J = 5.7 Hz), 13.5; **4a**′ isomer two: δ 171.0 (d, J_{c-p} = 4.4 Hz), 131.5 (d, J_{c-p} = 13.6 Hz), 125.2, 81.0, 62.7 (d, J = 6.3 Hz), 51.9 (d, J = 132.3 Hz), 48.8, 47.8, 44.8, 36.0, 33.0, 27.9, 27.3, 25.2 (d, J = 3.9 Hz), 22.3 (d, J = 6.1 Hz), 20.5, 20.4, 18.5 (d, J = 3.0 Hz), 16.4 (d, J = 5.7 Hz), 13.4; HRMS-EI m/z [M]$^+$ Calcd for $C_{22}H_{37}O_5P$ 412.2379. Found: 412.2387.

4.5.2. Formation of 4a. Typical procedure for the $SnCl_4$-mediated Diels–Alder reaction

To a solution of **3a** (151 mg, 0.44 mmol) in CH_2Cl_2 (2.3 mL) precooled at −65 °C was added $SnCl_4$ (1 M in CH_2Cl_2, 0.53 mL, 0.53 mmol, 1.2 equiv). After stirring for 45 min, *trans*-piperylene (0.46 mL, 4.39 mmol) was introduced and the reaction mixture was continued to stir at −65 °C for 12 h, and diluted with ethyl acetate (190 mL). The solution was washed with water (30 mL × 2) and brine (30 mL), and concentrated in vacuo. The crude residue was subjected to chromatographic purification (silica gel, hexane–EtOAc, 10:1, 5:1, 2:1) to give 156.6 mg (84.1%) of **4a** as a mixture of two *endo* diastereomers (dr = 50:50). IR (neat) 3054, 1727, 1242, 1028, 964, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) isomer one: δ 5.77–5.46 (m, 2H), 4.99–4.77 (m, 1H), 4.28–4.05 (m, 4H), 3.04–2.85 (m, 1H), 2.46–2.18 (m, 3H), 2.17–1.95 (m, 3H), 1.82–1.63 (m, 3H), 1.32 (t, J = 6.9 Hz, 6H), 1.29–1.19 (m, 1H), 1.27 (d, J = 7.3 Hz, 3H), 1.05–1.00 (m, 1H), 0.89 (s, 3H), 0.86(s, 3H), 0.87(s, 3H); isomer two: δ 5.77–5.46 (m, 2H), 4.99–4.77 (m, 1H), 4.28–4.05 (m, 4H), 3.04–2.85 (m, 1H), 2.46–2.18 (m, 3H), 2.17–1.95 (m, 3H), 1.82–1.63 (m, 3H), 1.32 (t, J = 6.9 Hz, 6H), 1.29–1.19 (m, 1H), 1.23 (d, J = 7.2 Hz, 3H), 1.05–1.00 (m, 1H), 0.89 (s, 3H), 0.86(s, 3H), 0.87(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) isomer one: δ 170.7 (d, J_{c-p} = 7.7 Hz), 131.3 (d, J_{C-P} = 9.6 Hz), 125.2, 81.3, 62.8 (d, J_{c-p} = 6.9 Hz), 62.1 (d, J_{c-p} = 6.3 Hz), 51.5 (d, J_{c-p} = 135.7 Hz), 48.8, 47.7, 44.8, 36.4, 33.2, 28.0, 27.2, 26.0 (d, J_{c-p} = 4.0 Hz), 22.6 (d, J_{c-p} = 5.5 Hz), 19.6, 18.9, 18.1 (d, J_{c-p} = 5.6 Hz), 16.5 (d, J_{c-p} = 6.2 Hz), 16.4 (d, J_{c-p} = 6.7 Hz), 13.6; isomer two: δ 170.6 (d, J_{c-p} = 7.8 Hz), 131.9 (d, J_{c-p} = 8.7 Hz), 124.9, 81.2, 62.8 (d, J_{c-p} = 6.9 Hz), 62.1 (d, J_{c-p} = 6.3 Hz), 51.3 (d, J_{c-p} = 135.7 Hz), 48.7, 47.7, 44.8, 36.3, 33.1, 28.0, 27.1, 25.2 (d, J_{c-p} = 3.9 Hz), 22.5 (d, J_{c-p} = 4.6 Hz), 19.6, 18.9, 18.0 (d, J_{c-p} = 5.0 Hz), 16.5 (d, J_{c-p} = 6.2 Hz), 16.4 (d, J_{c-p} = 6.7 Hz), 13.5; HRMS-EI m/z [M]$^+$ Calcd for $C_{22}H_{37}O_5P$ 412.2379. Found: 412.2381.

4.5.3. (1*R**,2*S**,4*R**)-2-(Diethoxy-phosphoryl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (1*S*,2*R*,4*S*)-1,7,7-trimethylbicyclo-[2.2.1]hept-2-yl ester 4b

The typical procedure for preparing **4a** was followed by using **3b** (189 mg, 0.55 mmol), cyclopentadiene (363 mg, 5.49 mmol) (pre-generated by the thermolysis of dicyclopentadiene), and $SnCl_4$ (1 M in CH_2Cl_2, 0.66 mL, 0.66 mmol). The chromatographic purification of the crude products (silica gel, hexane–EtOAc, 15:1, 8:1, 4:1) produced **4b** (198.6 mg, 88%) as a mixture of two *endo* diastereomers (dr = 53:47). IR (neat) 3107, 1728, 1245, 1025, 963, 884 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) major: δ 6.29–6.17 (m, 1H), 6.02 (m, 1H), 4.79 (ddd, J = 9.9, 2.8, 2.6 Hz, 1H), 4.26–4.03 (m, 4H), 3.52 (br s, 1H), 2.96 (br s, 1H), 2.42 (ddd, J = 12.1, 3.8, 3.7 Hz, 1H), 2.34–2.23 (m, 1H), 2.13–2.00 (m, 2H), 1.97–1.89 (m, 1H), 1.81–1.62 (m, 2H), 1.41–1.30 (m, 2H), 1.34 (t, J = 7.3 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.24–1.16 (m, 1H), 1.02–0.92 (m, 1H), 0.89–0.81 (m, 9H); minor: δ 6.29–6.17 (m, 1H), 5.97 (m, 1H), 4.69 (ddd, J = 9.7, 2.6, 2.6 Hz, 1H), 4.26–4.03 (m, 4H), 3.51 (br s, 1H), 2.96 (br s, 1H), 2.37 (ddd, J = 12.1, 3.7, 3.6 Hz, 1H), 2.34–2.23

(m, 1H), 2.13–2.00 (m, 2H), 1.97–1.89 (m, 1H), 1.81–1.62 (m, 2H), 1.41–1.30 (m, 2H), 1.34 (t, J = 7.3 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.24–1.16 (m, 1H), 1.02–0.92 (m, 1H), 0.89–0.81 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) major: δ 171.2, 139.3, 134.9 (d, J_{c-p} = 13.0 Hz), 80.8, 62.6 (d, J_{c-p} = 7.1 Hz), 55.0 (d, J_{c-p} = 130.8 Hz), 49.0, 48.9, 47.7, 47.5, 44.8, 42.6, 36.1, 32.8, 28.0, 27.1, 19.6, 18.8, 16.3 (d, J_{c-p} = 5.9 Hz), 13.6; minor: δ 171.1, 139.4, 134.6 (d, J_{c-p} = 13.1 Hz), 81.3, 62.4 (d, J_{c-p} = 6.5 Hz), 62.4 (d, J_{c-p} = 6.2 Hz), 54.9 (d, J_{c-p} = 130.8 Hz), 48.9, 48.5, 47.6, 47.4, 44.8, 42.6, 36.0, 32.3, 27.9, 27.1, 19.6, 18.8, 16.5 (d, J_{c-p} = 5.7 Hz), 16.4 (d, J_{c-p} = 5.7 Hz), 13.2; HRMS-EI m/z $[M]^+$ Calcd for $C_{22}H_{35}O_5P$ 410.2222. Found: 410.2223.

4.5.4. (1*R**,2*S**,4*R**)-2-(Diethoxy-phosphoryl)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (1*R*,2*S*)-2-phenyl-cyclohexyl ester 4c

The typical procedure for preparing **4a** was followed by using **3b** (322 mg, 0.76 mmol), cyclopentadiene (504 mg, 7.62 mmol) (pre-generated by the thermolysis of dicyclopentadiene), and $SnCl_4$ (1 M in CH_2Cl_2, 0.91 mL, 0.91 mmol). The chromatographic purification of the crude products (silica gel, hexane–EtOAc, 10:1, 6:1, 3:1) produced **4c** (277 mg, 84%) as a mixture of two diastereomers (dr = 52:48). IR (neat) 3193, 1725, 1647, 1550, 1242, 1028, 962, 706 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) major: δ 7.29–7.06 (m, 5H), 5.84–5.72 (m, 1H), 5.61–5.53 (m, 1H), 4.78 (ddd, J = 10.6, 10.5, 4.4 Hz, 1H), 4.23–3.84 (m, 4H), 3.01–3.09 (m, 1H), 2.78–2.58 (m, 2H), 2.34–1.61 (m, 5H), 1.61–1.16 (m, 11H), 1.06–1.10 (m, 2H); minor: δ 7.29–7.06 (m, 5H), 5.84–5.72 (m, 1H), 5.53–5.43 (m, 1H), 4.98 (ddd, J = 10.6, 10.5, 4.4 Hz, 1H), 4.23–3.84 (m, 4H), 3.33–3.24 (m, 1H), 2.78–2.58 (m, 2H), 2.34–1.61 (m, 5H), 1.61–1.16 (m, 11H), 1.12–1.15 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) major: δ 170.1, 143.6, 138.5, 134.2 (d, J_{c-p} = 12.9 Hz), 128.5, 127.6, 126.6, 77.6, 62.4 (d, J_{c-p} = 7.1 Hz), 62.3 (d, J_{c-p} = 7.0 Hz), 54.7 (d, J_{c-p} = 130.4 Hz), 49.7, 48.9, 47.3, 42.4, 34.2, 32.2, 31.6, 25.8, 24.5, 16.4 (d, J_{c-p} = 5.9 Hz), 16.3 (d, J_{c-p} = 5.9 Hz); minor: δ 170.1, 143.4, 138.7, 135.0 (d, J_{c-p} = 12.9 Hz), 128.2, 127.5, 126.2, 76.4, 62.6 (d, J_{c-p} = 7.4 Hz), 62.5 (d, J_{c-p} = 7.3 Hz), 55.3 (d, J_{c-p} = 130.4 Hz), 49.5, 48.8, 46.9, 42.3, 35.0, 32.3, 31.8, 25.7, 24.6, 16.6 (d, J_{c-p} = 6.2 Hz), 16.4 (d, J_{c-p} = 5.9 Hz); HRMS-EI m/z $[M]^+$ Calcd for $C_{24}H_{33}O_5P$ 432.2066. Found: 432.2061.

4.5.5. (1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl (1*R*,2*S*,4*R*)-2-(diethoxyphosphoryl)bicyclo[2.2.1]hept-5-ene-2-carboxylate 4d

The typical procedure for preparing **4a** was followed by using **3c** (360.7 mg, 0.85 mmol), cyclopentadiene (564.3 mg, 8.53 mmol) (pre-generated by the thermolysis of dicyclopentadiene), and $SnCl_4$ (1 M in CH_2Cl_2, 1.02 mL, 1.02 mmol). The chromatographic purification of the crude products (silica gel, hexane–EtOAc, 8:1, 4:1, 2:1) produced **4d** (370 mg, 89%) as a single diastereomer (dr >30:1) as revealed by NMR analysis. IR (neat) 3113, 1718, 1243, 1028, 963, 767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.29 (m, 4H), 7.20–7.13 (m, 1H), 6.26 (dd, J = 5.3, 3.0 Hz, 1H), 5.97 (dd, J = 5.3, 2.4 Hz, 1H), 4.68 (ddd, J = 10.5, 10.5, 3.8 Hz, 1H), 4.28–4.08 (m, 4H), 3.47 (br d, J = 5.72 Hz, 1H), 2.95 (br s, 1H), 2.28 (ddd, J = 19.0, 12.4, 3.5 Hz, 1H), 2.04 (m, 2H), 1.97–1.83 (m, 2H), 1.45 (s, 3H), 1.44–1.34 (m, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.32–1.28 (m, 1H), 1.30 (t, J = 7.0 Hz, 3H), 1.24 (s, 3H), 1.17–1.10 (m, 1H), 0.90–0.82 (m, 2H), 0.81 (d, J = 6.3 Hz, 3H), 0.74–0.64 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 150.8, 139.7, 134.0 (d, J_{C-P} = 13.1 Hz), 128.0, 125.7, 125.3, 77.9, 62.9 (d, J_{C-P} = 7.2 Hz), 62.4 (d, J_{C-P} = 6.8 Hz), 55.2 (d, J_{C-P} = 134.6 Hz), 50.7, 50.0, 47.7, 42.9, 41.0, 40.4, 34.6, 31.4, 31.3, 30.9, 27.7, 22.6, 21.8, 16.6 (d, J_{C-P} = 5.8 Hz), 16.4 (d, J_{C-P} = 5.6 Hz); HRMS-EI m/z $[M]^+$ Calcd for $C_{28}H_{41}O_5P$ 488.2692. Found: 488.2696. $[\alpha]_D^{20} = +48.5$ (c 0.63, $CHCl_3$).

4.5.6. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl (1*R*,2*S*,4*R*)-2-(diethoxyphosphoryl)bicyclo[2.2.1]hept-5-ene-2-carboxylate 4e

The typical procedure for preparing **4a** was followed by using **3d** (402.2 mg, 1.16 mmol), cyclopentadiene (767.5 mg, 11.61 mmol) (pre-generated by the thermolysis of dicyclopentadiene), and $SnCl_4$ (1 M in CH_2Cl_2, 1.39 mL, 1.39 mmol). The chromatographic purification of the crude products (silica gel, hexane–EtOAc, 10:1, 4:1, 2:1) produced **4e** (415 mg, 87%) as a mixture of two diastereomers (dr = 92:8) as indicated by NMR analysis. IR (neat) 3098, 1725, 1243, 1029, 963, 714 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) major: δ 6.22 (dd, J = 5.3, 3.0 Hz, 1H), 5.94 (dd, J = 5.3, 2.4 Hz, 1H), 4.52 (ddd, J = 10.9, 10.9, 4.2 Hz, 1H), 4.26–4.01 (m, 4H), 3.46 (br d, J = 4.8 Hz, 1H), 2.93 (br s, 1H), 2.33 (ddd, J = 19.5, 12.2, 3.6 Hz, 1H), 2.07–1.96 (m, 3H), 1.92 (ddd, J = 11.9, 9.0, 2.5 Hz, 1H), 1.65 (d, J = 11.3 Hz, 1H), 1.46–1.31 (m, 3H), 1.34 (t, J = 7.0 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.07–0.93 (m, 2H), 0.89 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H), 0.85–0.79 (m, 1H), 0.72 (d, J = 7.0 Hz, 3H); minor: δ 6.20 (m, 1H), 6.04–5.97 (m, 1H), 4.61 (ddd, J = 10.9, 10.8, 4.2 Hz, 1H), 4.26–4.01 (m, 4H), 3.46 (br d, J = 4.8 Hz, 1H), 2.93 (br s, 1H), 2.39 (ddd, J = 15.9, 12.1, 3.7 Hz, 1H), 2.07–1.96 (m, 3H), 1.92 (ddd, J = 11.9, 9.0, 2.5 Hz, 1H), 1.65 (d, J = 11.3 Hz, 1H), 1.46–1.31 (m, 3H), 1.34 (t, J = 7.0 Hz, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.07–0.93 (m, 2H), 0.89 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 6.7 Hz, 3H), 0.85–0.79 (m, 1H), 0.64 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major: δ 170.5, 139.4, 134.6 (d, J_{c-p} = 13.1 Hz), 75.7, 62.6 (d, J_{c-p} = 7.3 Hz), 62.5 (d, J_{c-p} = 6.8 Hz), 55.1 (d, J_{c-p} = 131.2 Hz), 49.1, 47.7, 46.9, 42.5, 40.2, 34.2, 32.3, 31.3, 25.6, 22.8, 22.0, 20.9, 16.5 (d, J_{c-p} = 6.2 Hz), 16.3 (d, J_{c-p} = 6.0 Hz), 15.7; minor: δ 170.5, 139.4, 134.8 (d, J_{c-p} = 13.1 Hz), 75.3, 62.6 (d, J_{c-p} = 7.3 Hz), 62.5 (d, J_{c-p} = 6.8 Hz), 55.2 (d, J_{c-p} = 131.2 Hz), 48.9, 47.7, 46.9, 42.5, 40.5, 34.2, 32.2, 31.4, 25.6, 22.6, 22.0, 20.9, 16.5 (d, J_{c-p} = 6.2 Hz), 16.3 (d, J_{c-p} = 6.0 Hz), 15.7; HRMS-EI m/z $[M]^+$ Calcd for $C_{22}H_{37}O_5P$ 412.2379. Found: 412.2375. $[\alpha]_D^{20} = +17.2$ (c 0.81, $CHCl_3$).

4.5.7. (1*R*,2*S*,5*R*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl (1*S*,2*S*)-1-(diethoxyphosphoryl)-2-methylcyclohex-3-ene carboxylate 4f

The typical procedure for preparing **4a** was followed by using **3c** (517.1 mg, 1.22 mmol), *trans*-piperylene (1.28 mL, 12.24 mmol), and $SnCl_4$ (1 M in CH_2Cl_2, 1.47 mL, 1.47 mmol). The chromatographic purification of the crude products (silica gel, hexane–EtOAc, 15:1, 5:1, 2:1) produced **4f** in 88% yield (530.2 mg) (dr >30:1). IR (neat) 3021, 1717, 1244, 1026, 962, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.23 (m, 4H), 7.19–7.05 (m, 1H), 5.61 (br d, J = 10.2 Hz, 1H), 5.55 (br d, J = 10.8 Hz, 1H), 4.91 (ddd, 10.5, 10.4, 3.9 Hz, 1H), 4.20–4.05 (m, 4H), 3.02–2.84 (m, 1H), 2.36–2.11 (m, 3H), 2.04–1.95 (m, 2H), 1.89 (ddd, J = 11.7 10.8, 3.1 Hz, 1H), 1.45–1.34 (m, 5H), 1.31 (t, J = 6.9 Hz, 6H), 1.26 (s, 3H), 1.20 (d, J = 7.1 Hz, 3H), 1.18–1.10 (m, 1H), 0.99–0.85 (m, 2H), 0.80 (d, J = 6.3 Hz, 3H), 0.76–0.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3 (d, J_{c-p} = 2.1 Hz), 150.6, 130.6 (d, J_{c-p} = 7.6 Hz), 128.0, 125.8, 125.7, 125.3, 77.0, 62.8 (d, J_{c-p} = 7.1 Hz), 62.2 (d, J_{c-p} = 7.4 Hz), 51.4 (d, J_{c-p} = 136.0 Hz), 50.5, 41.6, 40.5, 34.4, 33.2 (d, J_{c-p} = 2.1 Hz), 31.4, 27.7, 23.8 (d, J_{c-p} = 2.9 Hz), 22.7 (d, J_{c-p} = 6.9 Hz), 22.6, 21.8, 18.6 (d, J_{c-p} = 6.7 Hz), 16.5 (d, J_{c-p} = 6.3 Hz), 16.4 (d, J_{c-p} = 6.8 Hz); HRMS-EI m/z $[M]^+$ Calcd for $C_{28}H_{43}O_5P$ 490.2848. Found: 490.2857. $[\alpha]_D^{20} = +3.8$ (c 1.5, $CHCl_3$).

4.5.8. (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl) (1*S*,2*S*)-1-(diethoxyphosphoryl)-2-methylcyclohex-3-ene carboxylate 4g

The typical procedure for preparing **4a** was followed by using **3d** (355.6 mg, 1.03 mmol), *trans*-piperylene (1.08 mL, 10.27 mmol), and $SnCl_4$ (1 M in CH_2Cl_2, 1.23 mL, 1.23 mmol). The chromatographic purification of the crude products (silica gel, hexane–EtOAc, 10:1, 5:1, 2:1) produced 4 g (344.5 mg, 81%) as a mixture

of two diastereomers (dr = 91:9) as indicated by NMR spectra. IR (neat) 3085, 1730, 1247, 1027, 961, 789 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) major: δ 5.56 (br d, J = 10.5 Hz, 1H), 5.50 (br d, J = 10.1 Hz, 1H), 4.64 (ddd, J = 10.9, 10.8, 4.3 Hz, 1H), 4.27–3.87 (m, 4H), 3.10–2.80 (m, 1H), 2.41–2.26 (m, 1H), 2.20–2.11 (m, 1H), 2.09–1.86 (m, 4H), 1.64 (br d, J = 11.6 Hz, 2H), 1.49–1.35 (m, 2H), 1.28 (t, J = 7.0, 6H), 1.23 (d, J = 7.3 Hz, 3H), 1.09–0.87 (m, 3H), 0.85 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 7.1 Hz, 3H), 0.68 (d, J = 7.0 Hz, 3H); minor: δ 5.48–5.16 (m, 2H), 4.64 (ddd, J = 10.9, 10.8, 4.3 Hz, 1H), 4.27–3.87 (m, 4H), 3.10–2.80 (m, 1H), 2.41–2.26 (m, 1H), 2.20–2.11 (m, 1H), 2.09–1.86 (m, 4H), 1.64 (br d, J = 11.6 Hz, 2H), 1.49–1.35 (m, 2H), 1.35–1.25 (m, 6H), 1.19 (d, J = 7.2 Hz, 3H), 1.09–0.87 (m, 3H), 0.85 (d, J = 6.5 Hz, 3H), 0.84 (d, J = 7.1 Hz, 3H), 0.68 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major: δ 169.7 (d, J_{c-p} = 2.4 Hz), 131.4 (d, J_{c-p} = 10.3 Hz), 124.7, 75.1, 62.6 (d, J_{c-p} = 7.1 Hz), 62.0 (d, J_{c-p} = 7.3 Hz), 51.4 (d, J_{c-p} = 135.5 Hz), 46.9, 40.4, 34.1, 33.5, 31.3, 26.2 (d, J_{c-p} = 4.2 Hz), 25.1, 22.6, 22.5 (d, J_{c-p} = 9.1 Hz), 21.9, 20.9, 18.1 (d, J_{c-p} = 4.2 Hz), 16.4 (d, J_{c-p} = 6.0 Hz), 16.3 (d, J_{c-p} = 6.3 Hz), 15.5; minor: δ 169.7 (d, J_{c-p} = 2.4 Hz), 131.4 (d, J_{c-p} = 10.3 Hz), 124.8, 75.2, 62.6 (d, J_{c-p} = 7.1 Hz), 62.0 (d, J_{c-p} = 7.3 Hz), 51.4 (d, J_{c-p} = 135.5 Hz), 46.9, 40.5, 34.1, 33.5, 31.3, 26.2 (d, J_{c-p} = 4.2 Hz), 25.2, 22.6, 22.5 (d, J_{c-p} = 9.1 Hz), 21.9, 20.9, 18.1 (d, J_{c-p} = 4.2 Hz), 16.4 (d, J_{c-p} = 6.0 Hz), 16.3 (d, J_{c-p} = 6.3 Hz), 15.6; HRMS-EI m/z $[M]^+$ Calcd for $C_{22}H_{39}O_5P$ 414.2535. Found: 414.2549. $[\alpha]_D^{20} = +9.3$ (c 1.0, $CHCl_3$).

4.6. Conversion of 4a into tosylhydrazone 5

AT first, DIBAL-H (1 M in toluene, 1.0 mL, 1 mmol) was added to a solution of **4a** (98.9 mg, 0.24 mmol) in toluene (5 mL) pre-cooled to −78 °C in 2 min. The mixture was then stirred at 0 °C for 80 min, diluted with ethyl acetate (80 mL), and successively washed with aqueous HCl solution (10%, 10 mL × 2), water (10 mL × 2), and brine (15 mL). After concentration, the residue was subjected to chromatographic purification (silica gel, hexane–EtOAc, 8:1, 5:1, 2:1) to afford the aldehyde intermediate (55 mg, 88%) plus recovered (−)-borneol (40 mg). *p*-Toluenesulfonhydrazide (40.6 mg, 0.218 mmol) was then added to a solution of freshly prepared aldehyde (55 mg, 0.212 mmol) in absolute ethanol (5 mL). The mixture was continued to stir for 5 h and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, hexane–EtOAc, 5:1, 2:1) to give tosylhydrazone **5** (75 mg, 82%) with spectroscopic data (^1H and ^{13}C NMR) identical to previously reported ones.[6]

4.7. Conversion of 4c–e into the known aldehyde 7 via alcoholic intermediate 6

4.7.1. Conversion of 4c into 7

Under an N_2 atmosphere, diisobutylaluminum hydride (1 M in toluene, 1 mL, 1 mmol) was dropwise added to a solution of **4c** (dr = 52:48,[16] 215.8 mg, 0.50 mmol) in dry toluene (10 mL) pre-cooled at −78 °C. After stirring at −78 °C for 5 min, −25 °C for 1 h and 0 °C for an additional 2 h, the reaction mixture was slowly quenched with a 10% HCl aqueous solution (2.5 mL) and diluted with ethyl acetate (190 mL). The solution was washed with water (30 mL × 2) and brine (30 mL) and concentrated in vacuo. The residue was subjected to chromatographic purification on silica gel (hexane–EtOAc, 5:1, 3:1, 1:1) to give the known 2-formyl-bicyclo[2.2.1]hept-5-en-2-yl)-phosphonic acid diethyl ester **7** (19.8 mg, 20.6), (2-hydroxymethyl-bicyclo[2.2.1]hept-5-en-2-yl)-phosphonic acid diethyl ester **6** (48.4 mg, 93%), (1*R*,2*S*)-*trans*-2-phenyl-1-cyclohexanol (57 mg), and recovered **4c** (54.8 mg, dr = 52:48). Compound **6**: ^1H NMR (400 MHz, $CDCl_3$) δ 6.25–6.14 (m, 2H), 4.26–4.13 (m, 4H), 3.68 (dd, J = 15.8, 10.5 Hz, 3H), 3.36–3.27 (m, 3H), 2.89 (br s, 1H), 2.02 (ddd, J = 20.3, 12.4, 3.7 Hz, 1H), 1.92–1.96 (m, 1H), 1.42–1.44 (m, 1H), 1.36 (t, J = 6.9 Hz, 3H), 1.35 (t, J = 6.9 Hz, 3H), 0.78 (ddd, J = 12.4, 9.9, 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 135.6 (d, J_{c-p} = 13.2 Hz), 66.4 (d, J_{c-p} = 2.3 Hz), 62.3 (d, J_{c-p} = 7.2 Hz), 62.2 (d, J_{c-p} = 7.4 Hz), 47.7, 47.6 (d, J_{c-p} = 138.5 Hz), 45.9 (d, J_{c-p} = 2.5 Hz), 42.1, 31.1, 16.5 (d, J_{c-p} = 5.6 Hz); HRMS-EI m/z $[M]^+$ Calcd for $C_{12}H_{21}O_4P$ 260.1177. Found: 260.1183. To a solution of **6** (48.4 mg) in dry CH_2Cl_2 (4.6 mL) was added pyridium dichromate (214.2 mg, 0.56 mmol). The reaction mixture was continued to stir for 10 h, filtered through a Celite pad and concentrated. Chromatographic purification of the crude residue on silica gel (hexane–EtOAc, 6:1, 3:1, 1:1) afforded the known aldehyde **7** (45.1 mg, 71% over two steps based on recovered **4c**) as a single *endo* isomer. The spectroscopic data agree well with the previously reported ones.[6] Compound **7**: ^1H NMR (400 MHz, C_6D_6) δ 9.51 (br s, 1H), 5.89 (dd, J = 5.4, 3.2 Hz, 1H), 5.78 (dd, J = 5.4, 2.6 Hz, 1H), 3.98–3.83 (m, 4H), 3.44 (br d, J = 5.4 Hz, 1H), 2.63 (br s, 1H), 2.35 (d, J = 8.4 Hz, 1H), 2.24 (ddd, J = 19.0, 12.1, 3.4 Hz, 1H), 2.08 (ddd, J = 11.7, 8.9, 2.6 Hz, 1H), 1.29 (br d, J =8.4 Hz, 1H), 1.01 (t, J = 7.0 Hz, 3H), 0.96 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 196.0, 139.8, 133.3 (d, J_{c-p} = 13.6 Hz), 62.4 (d, J_{c-p} = 6.7 Hz), 62.2 (d, J_{c-p} = 7.0 Hz), 61.4 (d, J_{c-p} = 129.7 Hz), 47.3, 47.0, 43.4 (d, J_{c-p} = 2.8 Hz), 30.9, 16.2 (d, J_{c-p} = 6.1 Hz), 16.1 (d, J_{c-p} = 6.3).

4.7.2. Conversion of 4d into 7

Treatment of **4d** (dr >30:1,[16] 105 mg) with DIBAL-H (1 M in toluene, 0.43 mL) under the same reaction conditions as Section 4.7.1 produced **6** (11.4 mg), **7** (17 mg), (−)-phenylmenthol (30 mg), and recovered **4d** (50.4 mg, dr >30:1[16]). Subsequent oxidation of **6** (11.4 mg) by PDC furnished 10.9 mg of **7** (99.5%, over two steps based on recovered **4d**).

4.7.3. Conversion of 4e into 7

Treatment of **4e** (dr = 91:9,[16] 119.5 mg) with DIBAL-H (1 M in toluene, 0.58 mL) under the same reaction conditions as Section 4.7.1 produced **6** (36 mg), **7** (15 mg), (1*R*,2*S*,5*R*)-(−)-menthol (26.3 mg), and recovered **4e** (24.5 mg, dr = 91:9[16]). Subsequent oxidation of **6** (36 mg) by PDC furnished 31 mg of **7** (86%, over two steps based on recovered **4e**).

4.8. Conversion of 4f/4g into 8 and 4d/4e into 9

4.8.1. Conversion of 4f and 4g into 8

Under an N_2 atmosphere, diisobutylaluminum hydride (1 M in toluene, 1.31 mL, 1.31 mmol) was dropwise added to a solution of **4f** (dr >30:1,[16] 107 mg, 0.22 mmol) in dry toluene (4.4 mL) pre-cooled at −78 °C. After being stirred at −78 °C for 5 min and at rt for an additional 4 h, the reaction mixture was slowly quenched with 10% HCl aqueous solution (2 mL) and diluted with ethyl acetate (200 mL). The solution was washed with water (30 mL × 2) and brine (30 mL) and concentrated in vacuo. The residue was subjected to chromatographic purification on silica gel (hexane–EtOAc, 6:1, 3:1, 1:1) to give 40 mg of alcoholic intermediate together with 30 mg of recovered (−)-phenylmenthol. To a stirred solution of the freshly prepared alcohol (16.5 mg, 0.06 mmol) in dry pyridine (2.7 mL) was successively added 3,5-dinitrobenzoyl chloride (293 mg, 1.27 mmol) and 4-dimethyl aminopyridine (11.65 mg, 0.10 mmol). The reaction mixture was stirred for 12 h and diluted with ethyl acetate (95 mL). The solution was washed with 10% aqueous HCl solution (20 mL × 3), water (20 mL × 2), and brine (30 mL). After concentration, the crude residue was subjected to chromatographic purification on silica gel (hexane–EtOAc 3:1, 1:1) to produce 23 mg of 3,5-dinitro-benzoic acid 1-(diethoxy-phosphoryl)-2-methyl-cyclohex-3-enylmethyl ester **8** (78%, 55% over two steps). Crystallization in hexane/ethyl acetate/dichloromethane (3:1:1, v/v/v) furnished yellow crystals. Compound **8**: IR

(neat) 3101, 1736, 1548, 1027, 1274, 958, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 3H), 5.72 (br d, J = 9.7 Hz, 1H), 5.50–5.33 (m, 1H), 4.64 (dd, J = 55.3, 11.8 Hz, 1H), 4.59 (dd, J = 72.2, 12.1 Hz, 1H), 4.28–4.09 (m, 4H), 2.95 (br s, 1H), 2.28–1.87 (m, 4H), 1.33 (t, J = 7.0 Hz, 3H), 1.30 (t, J = 7.0 Hz, 3H), 1.17 (d, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 148.7, 134.0, 130.9 (d, J_{c-p} = 12.7 Hz), 129.6, 125.3, 122.4, 64.4 (d, J_{c-p} = 5.3 Hz), 63.0 (d, J_{c-p} = 7.3 Hz), 61.8 (d, J_{c-p} = 7.6 Hz), 40.8 (d, J_{c-p} = 143.0 Hz), 32.8 (d, J_{c-p} = 1.9 Hz), 24.8 (d, J_{c-p} = 2.5 Hz), 20.9 (d, J_{c-p} = 11.0 Hz), 17.0, 16.7 (d, J_{c-p} = 5.2 Hz), 16.5 (d, J_{c-p} = 5.6 Hz); HRMS-EI m/z $[M]^+$ Calcd for $C_{19}H_{25}N_2O_9P$ 456.1298. Found: 456.1301.

Compound **8** was similarly prepared from **4g** (dr = 91:9[16]) in 44% yield over two steps.

4.8.2. Conversion of 4d and 4e into 9

The typical procedure for preparing **8** was followed. 3,5-Dinitrobenzoic acid 2-(diethoxy-phosphoryl)-bicyclo[2.2.1]hept-5-en-2-ylmethyl ester (**9**) was obtained from **4d** and **4e** in 52% and 67% yields, respectively, over two steps. Compound **9**: IR (neat) 3101, 1734, 1546, 1275, 1023, 957, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 3H), 6.32 (dd, J = 4.9, 4.8 Hz, 1H), 6.14–5.98 (m, 1H), 4.33 (dd, J = 166.7, 11.7 Hz, 1H), 4.30–4.10 (m, 4H), 4.28 (dd, J = 184.0, 11.9 Hz, 1H), 3.34 (br s, 1H), 3.01 (br s, 1H), 2.36 (ddd, J = 20.2, 12.4, 3.5 Hz, 1H), 2.19 (br d, J = 8.6 Hz, 1H), 1.47–1.50 (m, 1H), 1.32 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 0.93–0.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 148.7, 139.2, 134.2 (d, J_{c-p} = 12.5 Hz), 134.1, 129.6, 122.4, 70.0 (d, J_{c-p} = 4.4 Hz), 62.7 (d, J_{c-p} = 7.2 Hz), 62.2 (d, J_{c-p} = 7.2 Hz), 48.0, 46.9, 45.5 (d, J_{c-p} = 144.2 Hz), 42.6, 31.6, 16.7 (d, J_{c-p} = 5.1 Hz), 16.6 (d, J_{c-p} = 5.4 Hz); HRMS-EI m/z $[M]^+$ Calcd for $C_{19}H_{23}N_2O_9P$ 454.1141. Found: 454.1139.

4.9. Conversion of 4d–g into compounds 11

4.9.1. Conversion of 4d into 11a/11a′ via 10a/10a′

Under a nitrogen atmosphere, a 0.34 M solution of lithium naphthalenide (LN) (7 mL, 2.38 mmol) in THF pre-cooled to −60 °C was quickly added by syringe to a solution of **4d** (166.1 mg, 0.34 mmol) in anhydrous THF (3 mL) at −60 °C. The resulting dark-green mixture was stirred at −60 °C for 30 min, then iodomethane (0.21 mL, 3.40 mmol) was added, and stirring was continued at −20 °C for 3 h and rt for 2 h. The mixture was then quenched with water (10 mL) and extracted with EtOAc (100 mL × 2). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered and concentrated. Flash chromatography (silica gel, hexane–EtOAc, 100:0, 250:1, 100:1) afforded methylated esters **10a** (43 mg, 47%) and **10a′** (37 mg, 41%). **10a**: IR (neat) 3058, 1714, 1646, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.22 (m, 4H), 7.16–7.09 (m, 1H), 6.08 (dd, J = 5.6, 3.0 Hz, 1H), 5.98 (dd, J = 5.6, 2.8 Hz, 1H), 4.70 (ddd, J = 10.6, 10.6, 4.2 Hz, 1H), 2.75 (br s, 1H), 2.70 (br s, 1H), 1.93 (ddd, J = 12.0, 10.6, 3.4 Hz, 1H), 1.87–1.80 (m, 1H), 1.69 (dd, J = 12.1, 2.6 Hz, 1H), 1.52–1.46 (m, 2H), 1.43–1.34 (m, 3H), 1.34 (s, 3H), 1.31 (s, 3H), 1.26–1.20 (m, 1H), 1.19 (s, 3H), 0.98–0.85 (m, 2H), 0.81 (d, J = 6.5 Hz, 3H), 0.77–0.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 151.2, 137.6, 135.0, 128.0, 125.6, 125.2, 75.5, 51.7, 50.2, 49.7, 47.0, 42.7, 41.7, 40.2, 36.8, 34.7, 31.3, 28.9, 27.3, 26.2, 24.9, 21.8; HRMS-EI m/z $[M]^+$ Calcd for $C_{25}H_{34}O_2$ 366.2559. Found: 366.2564. **10a′**: IR (neat) 3073, 1707, 1648, 1081 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.27 (m, 4H), 7.20–7.11 (m, 1H), 6.18 (dd, J = 5.6, 3.0 Hz, 1H), 6.01 (dd, J = 5.5, 3.1 Hz, 1H), 4.89 (ddd, J = 10.6, 10.6, 4.3 Hz, 1H), 2.83 (br s, 1H), 2.74 (br s, 1H), 2.12 (dd, J = 14.0, 3.9 Hz, 1H), 2.04 (ddd, J = 12.1, 10.7, 3.4 Hz, 1H), 1.94–1.83 (m, 1H), 1.60–1.54 (m, 1H), 1.50–1.41 (m, 3H), 1.37 (s, 3H), 1.31–1.28 (m, 1H), 1.25 (s, 3H), 1.09–0.99 (m, 2H), 0.98 (s, 3H), 0.86 (d, J = 6.5 Hz, 3H), 0.84–0.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 151.2, 138.6, 133.7, 128.1, 125.6, 125.2, 75.0, 50.0, 49.8, 49.6, 49.2, 42.8, 41.6, 40.2, 37.8, 34.6, 31.3, 28.4, 27.2, 25.7, 24.0, 21.8.; HRMS-EI m/z $[M]^+$ Calcd for $C_{25}H_{34}O_2$ 366.2559. Found: 366.2571.

To a stirred suspension of $LiAlH_4$ (95%, 21.8 mg, 0.55 mmol) in dry THF (0.6 mL) pre-cooled to 0 °C in an ice bath, a solution of **10a** (40 mg, 0.11 mmol) in 0.6 mL of THF was added dropwise via syringe under a nitrogen atmosphere. The ice bath was then removed and stirring was continued for 4 h at room temperature. The reaction mixture was re-cooled in an ice bath and 5% NaOH aqueous solution (1 mL) was added cautiously. The resulting pale gray suspension was diluted with ethyl acetate (60 mL) and successively washed with water (10 ml × 2) and brine (10 mL). After concentration, the crude residue was subjected to the chromatographic purification on silica gel (hexane–EtOAc: 15:1, 10:1, 5:1) to afford (1*R*,2*R*,4*R*)-2-methylbicyclo[2.2.1]hept-5-en-2-yl)methanol **11a** (11.9 mg, 79%). The NMR spectroscopic data were in agreement with those reported in the literature.[21] ^1H NMR (400 MHz, $CDCl_3$) δ 6.11 (dd, J = 5.8, 2.9 Hz, 1H), 6.09 (dd, J = 5.9, 2.8 Hz, 1H), 3.31 (d, J = 10.4 Hz, 1H), 3.24 (d, J = 10.4 Hz, 1H), 2.79 (br s, 1H), 2.54–2.46 (m, 1H), 1.60–1.62 (m, 1H), 1.46–1.41 (m, 1H), 1.38 (d, J = 3.7 Hz, 1H), 1.35 (d, J = 3.7 Hz, 1H), 1.25 (s, 3H), 0.86 (dd, J = 11.7, 2.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 135.2, 71.1, 49.6, 47.6, 43.7, 42.6, 37.0, 24.9; $[\alpha]_D^{20}$ = +30.6 (*c* 0.42, $CHCl_3$). {Lit. $[\alpha]_D^{20}$ = +33.9 ($CHCl_3$)}.[22]

The same treatment of **10a′** (53.7 mg, 0.15 mmol) with $LiAlH_4$ (95%, 29.3 mg, 0.73 mmol) afforded (1*R*,2*S*,4*R*)-2-methylbicyclo[2.2.1]hept-5-en-2-yl)methanol **11a′** (14.9 mg, 74%). The NMR spectroscopic data were in agreement with those reported in the literature.[21] ^1H NMR (400 MHz, $CDCl_3$) δ 6.14 (dd, J = 5.6, 2.9 Hz, 1H), 6.10 (dd, J = 5.4, 3.0 Hz, 1H), 2.78 (br s, 1H), 2.56 (br s, 1H), 1.55–1.57 (m, 1H), 1.45 (dd, J = 11.7, 3.7 Hz, 1H), 1.39–1.35 (m, 1H), 1.25 (br s, 1H), 0.93 (s, 3H), 0.79 (dd, J = 11.7, 2.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 135.4, 72.3, 47.8, 47.6, 43.7, 43.1, 37.3, 22.8; $[\alpha]_D^{20}$ = +60.7 (*c* 0.65, 95% EtOH). {Lit. $[\alpha]_D^{20}$ = +68.1 (95% EtOH)}.[22]

4.9.2. Conversion of 4e into 11a

An analogous procedure for the preparation of **11a**/**11a′** from **4d** was used. The reductive methylation of **4e** (226.4 mg, 0.55 mmol) afforded a methylated ester (127.2 mg, 80%) as a 91:9 mixture of two diastereomers after chromatographic purification. ^1H NMR (400 MHz, $CDCl_3$) major: δ 6.13 (dd, J = 5.6, 3.0 Hz, 1H), 6.00 (dd, J = 5.7, 2.8 Hz, 1H), 4.52 (ddd, J = 10.8, 10.8, 4.3 Hz, 1H), 2.81 (br s, 1H), 2.77 (br s, 1H), 2.01–1.83 (m, 3H), 1.72–1.60 (m, 2H), 1.54–1.56 (m, 1H), 1.48–1.32 (m, 4H), 1.40 (s, 3H), 1.09–0.96 (m, 1H), 0.93–0.82 (m, 2H), 0.91 (d, J = 7.1 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.74 (d, J = 7.0 Hz, 3H); minor: δ 6.21–5.86 (m, 1H), 4.62–4.53 (m, 1H), 2.77 (br s, 1H), 2.75 (br s, 1H), 2.01–1.83 (m, 3H), 1.72–1.60 (m, 2H), 1.54–1.56 (m, 1H), 1.48–1.32 (m, 4H), 1.40 (s, 3H), 1.09–0.96 (m, 1H), 0.93–0.82 (m, 2H), 0.91 (d, J = 7.1 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.71 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major: δ 177.0, 137.8, 135.1, 74.1, 51.0, 49.9, 47.0, 42.5, 40.6, 37.5, 34.3, 31.3, 26.5, 25.9, 23.0, 22.0, 20.9, 15.8; minor: δ 177.0, 137.6, 135.5, 73.8, 50.9, 50.3, 47.1, 46.7, 42.6, 40.7, 38.0, 34.3, 31.4, 26.4, 26.0, 23.1, 22.0, 20.9, 15.8.

The reduction of the methylated ester (44 mg, 0.15 mmol) with $LiAlH_4$ produced 16 mg of **11a** (61% over two steps) plus 17.5 mg of recovered (−)-menthol. The specific rotation of **11a** obtained was measured as $[\alpha]_D^{20}$ = +26.4 (*c* 0.66, $CHCl_3$).{Lit. $[\alpha]_D^{20}$ = +33.9 ($CHCl_3$)}.[22]

4.9.3. Conversion of 4f into 11b

An analogous procedure for the preparation of **11a**/**11a′** from **4d** was used. The reductive methylation of **4f** (159 mg, 0.32 mmol)

afforded 105 mg of methylated ester (80%) as a single diastereomer after chromatography (silica gel, hexane–EtOAc, 100:0, 300:1, 100:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.27 (m, 4H), 7.19–7.12 (m, 1H), 5.60–5.47 (m, 2H), 4.89 (ddd, J = 10.6, 10.6, 4.3 Hz, 1H), 2.09–1.99 (m, 2H), 1.98–1.83 (m, 3H), 1.71 (ddd, J = 13.6, 10.4, 6.5 Hz, 1H), 1.55–1.51 (m, 1H), 1.50–1.40 (m, 3H), 1.35 (s, 3H), 1.23 (s, 3H), 1.10 (s, 3H), 1.03–0.95 (m, 2H), 0.91 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H), 0.83–0.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8, 151.4, 130.9, 128.1, 125.5, 125.1, 124.3, 75.0, 50.0, 44.0, 41.9, 40.1, 37.9, 34.6, 31.3, 28.4, 27.2, 25.6, 24.5, 22.5, 22.0, 21.8, 18.2.

The reduction of the methylated intermediate (23 mg, 0.06 mmol) with $LiAlH_4$ produced 5.9 mg (44% over two steps) of (1*R*,2*S*)-1,2-dimethylcyclohex-3-enyl)methanol **11b** and 10.7 mg of (−)-phenylmenthol after chromatography (silica gel, hexane–EtOAc, 10:0, 3:1). 11b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66–5.57 (m, 1H), 5.54–5.44 (m, 1H), 3.46 (d, J = 10.6 Hz, 1H), 3.41 (d, J = 10.7 Hz, 1H), 2.06–1.97 (m, 3H), 1.54 (ddd, J = 13.1, 6.6, 6.6 Hz, 2H), 1.23–1.18 (m, 1H), 0.99 (s, 3H), 0.93 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.1, 125.3, 68.3, 37.5, 35.9, 27.9, 22.5, 22.3, 16.1; $[\alpha]_D^{20} = +130.4$ (*c* 0.13, $CHCl_3$).{Lit. *ent*-**11b**, $[\alpha]_D^{20} = -147$ ($CHCl_3$)}.[22]

4.9.4. Conversion of 4g into 11b

An analogous procedure for the preparation of **11a/11a′** from **4d** was used. The reductive methylation of **4g** (195 mg, 0.47 mmol) afforded 92 mg of a methylated ester (73%) as a 90:10 mixture of two diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) major: δ 5.62–5.48 (m, 2H), 4.62 (ddd, J = 10.8, 10.8, 4.2 Hz, 1H), 2.22–2.13 (m, 1H), 2.06–1.84 (m, 5H), 1.71–1.62 (m, 2H), 1.57–1.36 (m, 3H), 1.19 (s, 3H), 1.07–1.00 (m, 1H), 0.92 (d, J = 7.0 Hz, 3H), 0.91–0.85 (m, 2H), 0.89 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.73 (d, J = 7.0 Hz, 3H); minor: δ 5.62–5.48 (m, 2H), 4.69–4.62 (m, 1H), 2.22–2.13 (m, 1H), 2.06–1.84 (m, 5H), 1.71–1.62 (m, 2H), 1.57–1.36 (m, 3H), 1.19 (s, 3H), 1.07–1.00 (m, 1H), 0.92 (d, J = 6.8 Hz, 3H), 0.91–0.85 (m, 2H), 0.89 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major: δ 176.9, 130.9, 124.4, 74.0, 47.0, 44.2, 40.8, 37.7, 34.3, 31.4, 25.9, 25.2, 23.0, 22.5, 22.4, 22.1, 20.9, 18.1, 15.9; minor: δ 176.8, 130.7, 124.7, 74.0, 47.1, 44.0, 40.8, 37.7, 34.3, 31.4, 26.1, 25.6, 22.9, 22.5, 22.3, 22.2, 20.8, 18.0, 15.8.

The reduction of methylated ester (34 mg, 0.12 mmol) with $LiAlH_4$ produced 11.5 mg of **11b** (52% over two steps) and 13.4 mg of (−)-menthol. The specific rotation of **11b** obtained was determined as $[\alpha]_D^{20} = +73.4$ (*c* 0.5, $CHCl_3$). {Lit. *ent*-**11b**, $[\alpha]_D^{20} = -147$ ($CHCl_3$)}.[22]

4.10. Conversion of 4d into (2*R*)-2-*endo*-hydroxymethyl-5-norbornene (+)-12

To a stirred suspension of $LiAlH_4$ (95%, 435 mg, 10.9 mmol) in dry CH_2Cl_2 (9 mL) and THF (9 mL) pre-cooled at 0 °C in an ice bath, a solution of **4d** (666 mg, 1.364 mmol) in 18 mL of mixed CH_2Cl_2 and THF (v/v: 1/1) was added dropwise over 2 min via syringe under a nitrogen atmosphere. The ice bath was then removed and stirring was continued for an additional 3 h at room temperature. The reaction mixture was re-cooled in an ice bath and cautiously quenched with a 5% NaOH aqueous solution (20 mL). The resulting pale gray suspension was diluted with CH_2Cl_2 (150 mL) and successively washed with water (30 ml × 2) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (hexane–EtOAc: 15:1, 8:1) to afford 146 mg (86%) of (+)-**12** {$[\alpha]_D^{20} = +70.6$ (*c* 0.6, 95% EtOH), lit.[28] $[\alpha]_D^{20} = +79.3$ (*c* 0.86, 95% EtOH)} plus recovered (−)-phenylmenthol (285 mg). The ^{1}H NMR data were in agreement previously reported ones.[27] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (dd, J = 5.7, 3.0 Hz, 1H), 5.96 (dd, J = 5.7, 2.9 Hz, 1H), 3.40 (dd, J = 10.5, 6.4 Hz, 1H), 3.25 (dd, J = 10.5, 8.9 Hz, 1H), 2.93 (br s, 1H), 2.81(br s, 1H), 2.34–2.25 (m, 1H), 1.82 (ddd, J = 11.6, 9.2, 3.9 Hz, 1H), 1.45 (br d, J = 8.2 Hz, 1H), 1.26 (br d, J = 8.6 Hz, 2 H), 0.52 (ddd, J = 11.6, 4.4, 2.6 Hz, 1H); HRMS-EI *m*/*z* $[M]^+$ Calcd for $C_8H_{12}O$ 124.0888. Found: 124.0883.

4.11. Preparation of (−)-12

4.11.1. (1*S*,2*R*,5*S*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl-2-(diethoxyphosphoryl)-acetate

This compound was similarly prepared as for **1c**. From 250 mg of (+)-8-phenylmenthol, 411 mg of product was obtained (93%) after purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.26 (m, 4H), 7.16–7.10 (m, 1H), 4.83 (ddd, J = 10.7, 10.7, 4.4 Hz, 1H), 4.11–3.98 (m, 4H), 2.37 (dd, J = 21.2, 14.4 Hz, 1H), 2.07 (dd, J = 21.2, 14.4 Hz, 1H), 2.06–2.00 (m, 1H), 1.85 (brt, J = 15.4 Hz, 2H), 1.67 (br d, J = 13.0 Hz, 1H), 1.48–1.42 (m, 1H), 1.32–1.27 (m, 9H), 1.2 (s, 3H), 1.16–1.09 (m, 1H), 1.00–0.90 (m, 2H), 0.87 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1 (d, J_{c-p} = 6.1 Hz), 151.8, 127.9, 125.4, 125.1, 75.1, 62.4 (d, J_{c-p} = 5.7 Hz), 50.3, 41.3, 39.5, 34.5, 33.9 (d, J_{c-p} = 132.1 Hz), 31.3, 29.2, 26.3, 23.2, 21.8, 16.3 (d, J_{c-p} = 6.3 Hz).

4.11.2. (1*S*,2*R*,5*S*)-2-(Diethoxy-phosphoryl)-2-phenylselanyl-propionic acid 5-methyl-2-(1-methyl-1-phenyl-ethyl)-cyclohexyl ester

This compound was similarly prepared as for **2c**. From 411 mg of starting material, 174 mg of product (dr = 62:38)[16] was obtained in 30% yield over two steps. ^{1}H NMR (400 MHz, $CDCl_3$) major: δ 7.72 (br d, J = 7.0 Hz, 2H), 7.42–7.28 (m, 7H), 7.17–7.13 (m, 1H), 5.00–4.88 (m, 1H), 4.37–4.13 (m, 4H), 2.00–1.89 (m, 2H), 1.47–1.35 (m, 11H), 1.34–1.25 (m, 7H), 1.02–0.90 (m, 2H), 0.85 (d, J = 2.8 Hz, 3H), 0.81–0.66 (m, 1H); minor: δ 7.76 (br d, J = 7.0 Hz, 2H), 7.42–7.28 (m, 7H), 7.17–7.13 (m, 1H), 5.00–4.88 (m, 1H), 4.37–4.13 (m, 4H), 2.00–1.89 (m, 2H), 1.47–1.35 (m, 11H), 1.34–1.25 (m, 7H), 1.02–0.90 (m, 2H), 0.84 (d, J = 2.8 Hz, 3H), 0.81–0.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major: δ 169.6, 150.4, 138.5, 129.7, 128.8, 128.0, 125.8, 125.7, 125.3, 64.1 (d, J_{c-p} = 7.3 Hz), 63.6 (d, J_{c-p} = 7.3 Hz), 50.4, 44.9 (d, J_{c-p} = 146.6 Hz), 41.2, 40.5, 34.4, 31.3, 31.0, 27.5, 23.6, 21.6, 19.7 (d, J_{c-p} = 2.0 Hz), 16.6 (d, J_{c-p} = 5.1 Hz), 16.5 (d, J_{c-p} = 5.1 Hz); minor: 169.3, 150.6, 138.7, 129.6, 128.7, 128.1, 125.8, 125.7, 125.3, 64.6 (d, J_{c-p} = 7.3 Hz), 63.3 (d, J_{c-p} = 7.3 Hz), 50.2, 46.1 (d, J_{c-p} = 142.5 Hz), 41.3, 40.4, 34.4, 31.3, 29.9, 27.3, 24.2, 21.6, 19.3 (d, J_{c-p} = 2.0 Hz), 16.5 (d, J_{c-p} = 5.1 Hz), 16.4 (d, J_{c-p} = 5.1 Hz).

4.11.3. (1*S*,2*R*,5*S*)-2-(Diethoxy-phosphoryl)-acrylic acid 5-methyl-2-(1-methyl-1-phenyl-ethyl)-cyclohexyl ester

This compound was similarly prepared as for **3c**. From 141 mg of starting material, 95.2 mg of crude product was obtained (88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.22 (m, 4H), 7.11–7.06 (m, 1H), 6.42 (br d, J = 21.0 Hz, 1H), 6.05 (br d, J = 42.8 Hz, 1H), 4.94 (ddd, J = 10.7, 10.7, 4.3 Hz, 1H), 4.21–4.09 (m, 4H), 2.10 (ddd, J = 10.6, 10.8, 3.5 Hz, 1H), 1.93 (d, J = 12.0 Hz, 1H), 1.72–1.64 (m, 2H), 1.51–1.46 (m, 1H), 1.38–1.26 (m, 10H), 1.21 (s, 3H), 1.17–0.98 (m, 2H), 0.87 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (d, J_{c-p} = 18.1 Hz), 151.6, 142.9 (d, J_{c-p} = 4.4 Hz), 132.7 (d, J_{c-p} = 186.7 Hz), 128.1, 125.4, 125.1, 75.7, 62.7 (d, J_{c-p} = 5.9 Hz), 62.6 (d J_{c-p} = 5.8 Hz), 50.3, 41.6, 39.7, 34.5, 31.3, 27.8, 26.7, 25.3, 21.7, 16.4 (d, J_{c-p} = 5.9 Hz).

4.11.4. (1*S*,2*R*,5*S*)-5-Methyl-2-(2-phenylpropan-2-yl)cyclohexyl-(1*S*,2*R*,4*S*)-2(diethoxyphosphoryl)bicycle-[2.2.1]-hept-5-ene-2-carboxylate

This compound was similarly prepared as for **4d**. From 93 mg of starting dienophile, 98 mg of adduct was obtained in 91% yield as a

single diastereomer (dr >30:1).[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.27 (m, 4H), 7.18–7.14 (m, 1H), 6.28 (dd, J = 5.4, 3.0 Hz, 1H), 5.99 (dd, J = 5.3, 2.6 Hz, 1H), 4.70 (ddd, J = 10.5, 10.5, 3.9 Hz, 1H), 4.28–4.12 (m, 4H), 3.49 (br d, J = 5.8 Hz, 1H), 2.97 (br s, 1H), 2.30 (ddd, J = 19.1, 12.3, 3.6 Hz, 1H), 2.07–2.03 (m, 2H), 1.97–1.86 (m, 2H), 1.47 (s, 3H), 1.45–1.36 (m, 2H), 1.42 (t, J = 7.0 Hz, 3H), 1.36–1.30 (m, 1H), 1.32 (t, J = 7.0 Hz, 3H), 1.26 (s, 3H), 1.16–1.12 (m, 1H), 0.90–0.84 (m, 2H), 0.82 (d, J = 6.4 Hz, 3H), 0.75–0.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 150.8, 139.8, 134.0 (d, J_{c-p} = 13.0 Hz), 128.0, 125.8, 125.3, 77.9, 62.9 (d, J_{c-p} = 7.2 Hz), 62.4 (d, J_{c-p} = 7.0 Hz), 54.8 (d, J_{c-p} = 133.6 Hz), 50.7, 50.0, 47.7, 42.9, 41.0, 40.4, 34.6, 31.4, 31.3, 31.0, 27.7, 22.6, 21.8, 16.6 (d, J_{c-p} = 6.0 Hz), 16.4 (d, J_{c-p} = 5.6 Hz).

4.11.5. (2*S*)-2-*endo*-Hydroxymethyl-5-norbornene (−)-12

This compound was similarly prepared as for (+)-**12**. From 91 mg of the adduct, 19 mg (80%) of (−)-**12** was obtained after purification. The proton NMR data agreed with reported ones.[27] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.14 (dd, J = 5.7, 3.0 Hz, 1H), 5.96 (dd, J = 5.7, 2.9 Hz, 1H), 3.39 (dd, J = 10.4, 6.5 Hz, 1H), 3.25 (dd, J = 10.4, 8.9 Hz, 1H), 2.93 (br s, 1H), 2.81 (br s, 1H), 2.33–2.25 (m,1H), 1.82 (ddd, J = 11.6, 9.2, 3.8 Hz, 1H), 1.45 (br d, J = 8.2 Hz, 1H), 1.25 (br d, J = 8.5 Hz, 2H), 0.52 (ddd, J = 11.6, 4.5, 2.6 Hz, 1H); {$[\alpha]_D^{25} = -74.6$ (*c* 0.5, 95% EtOH), lit.[27] $[\alpha]_D^{25} = -93$ (*c* 0.5, 95% EtOH).

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14. The *ortho* regiochemistry of **4a**′ was confirmed by the ^{13}C–C–C–^{31}P coupling of C-2 methyl signals on the ^{13}C NMR spectrum [δ 18.5 ppm (d, J_{c-p} = 3.1 Hz) and 18.0 ppm (d, J_{c-p} = 5.0 Hz)].
15. A further decrease in temperatures, for example, −78 °C, did not change the diastereomeric ratio but rather led to poorer conversion of **4a**.
16. The diastereomeric ratio was determined by integration of the 400 MHZ proton NMR spectrum.
17. The *ortho* stereochemistry of the minor isomer of **4g** was confirmed by the ^{13}C–C–C–^{31}P coupling of the C-2 methyl signal on the ^{13}C NMR spectrum [δ 18.1 ppm (d, J_{c-p} = 4.2 Hz)].
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20. Racemic **8** and **9** were synthesized from our previously reported *endo* adducts[6] as the references for HPLC analysis.
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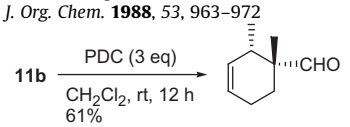
23. Since the NMR data of **11b** had not been reported, it was further oxidized into the known aldehyde to validate its *trans*-dimethyl steric relationship. The NMR data of the aldehyde were in agreement with the literature. See: Wu, P. L.; Chu, M.; Fowler, F. W. *J. Org. Chem.* **1988**, *53*, 963–972



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24. The double activation of the P=O and C=O by $SnCl_4$ is evidenced by the decreased C=O (1714 cm^{-1} → 1636 cm^{-1}) and P=O (1297 cm^{-1} → 1282 cm^{-1}) IR stretching frequencies of complexed **3c** relative to **3c**.
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