JOC Article
pubs.acs.org/joc

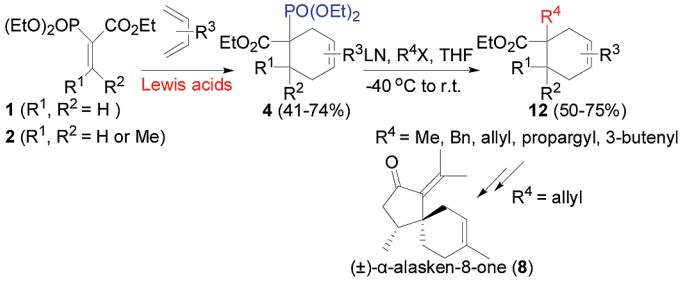
Investigation on Lewis Acid Mediated Diels−Alder Reactions of 2-Phosphono-2-alkenoates. Application to Total Synthesis of (±)-α-Alasken-8-one via Reductive Alkylation of Resulting Adduct

Chuan-Cheng Liao and Jia-Liang Zhu*

Department of Chemistry, National Dong Hwa University, Hualien 974, Taiwan, R.O.C.

jlzhu@mail.ndhu.edu.tw

Received August 11, 2009



The Lewis acid mediated Diels−Alder reactions of three 2-phosphono-2-alkenoates including triethyl 2-phosphonoacrylate (**1**), triethyl 2-phosphonobut-2-enoate (**2**), and ethyl 2-(diethoxyphosphono)-3-methylbut-2-enoate (**3**) have been investigated. Of several Lewis acids tested, tin(IV) chloride was shown to be the most effective at enhancing the regio- and stereoselectivity of the reactions of **1** with the electron-rich dienes to result in the formation of the single regio- and/or stereoisomers in good yields. Bearing the β methyl group(s), **2** displayed much less reactivity than **1** while **3** was completely unreactive under the study's conditions. Throughout the investigation, we found that the cycloadditions of **2**, especially of the *Z*-isomer, could be efficiently induced by using zinc chloride at elevated temperatures. Furthermore, a lithium naphthalenide (LN)-induced reductive alkylation process was applied to the resulting Diels−Alder adducts **4** to allow the phosphono group at the quaternary carbon centers to be replaced by various alkyl groups to afford the alkyl-substituted esters **12**, therefore practically turning **1** and **2** into the useful synthetic equivalents of the corresponding 2-alkyl 2-alkenoates that usually display poor Diels−Alder reactivity. Application of this combined operation has facilitated the total synthesis of the sesquiterpene natural product α-alasken-8-one (**8**) in racemic form.

Introduction

2-Phosphono-2-alkenoates are of considerable importance in synthetic chemistry where they are commonly used as the acceptors for 1,4-addition processes.[1,2] According to literature reports, the phosphonate modifications, such as the Horner−Wadsworth−Emmons olefination, were usually conducted after these addition reactions to ensure the formation of a variety of unsaturated acyclic,[1a,c,g] carbocyclic,[1b,k−m] and heterocyclic[1h,i] compounds. In addition, the applications of 2-phosphono-2-alkenoates into ene[3] and 1,3-cycloaddition reactions[4] have also been occasionally documented.

In view of their activated carbon−carbon double bond, one would expect that 2-phosphono-2-alkenoates may have

(1) For selected examples, see: (a) Kleschick, W. A.; Heathcock, C. H. *J. Org. Chem.* **1978**, *43*, 1256–1259. (b) Corbet, J. P.; Benezra, C. *J. Org. Chem.* **1981**, *46*, 1141–1147. (c) Minami, T.; Nishimura, K.; Hirao, I. *J. Org. Chem.* **1982**, *47*, 2360–2363. (d) Barton, D. H. R.; Géro, S. D.; Quiclet-Sire, B.; Samadi, M. *J. Chem. Soc., Chem. Commun.* **1989**, 1000–1001. (e) Junker, H.-D.; Phung, N.; Fessner, W. D. *Tetrahedron Lett.* **1999**, *40*, 7063–7066. (f) Yamazaki, S.; Yanase, Y.; Yamamoto, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1991–1996. (g) Shen, Y.; Jiang, G.-F.; Wang, G.; Zhang, Y. *J. Fluorine Chem.* **2001**, *109*, 141–144. (h) Martyres, D. H.; Baldwin, J. E.; Adlington, R. M.; Lee, V.; Probert, M. R.; Watkin, D. J. *Tetrahedron* **2001**, *57*, 4999–5007. (i) Bartoloméa, J. M.; Alcázar, J.; Andrés, I.; Bruyn, M. D.; Fernández, J.; Matesanz, E.; Emelen, K. V. *Tetrahedron Lett.* **2003**, *44*, 8545–8548. (k) Janecki, T.; Blaszczyk, E.; Studzian, K.; Janecka, A.; Krajewska, U.; Rózalski, M. *J. Med. Chem.* **2005**, *48*, 3516–3521. (l) Krawczyk, H; Albrecht, L. *Synthesis* **2008**, 3951–3956. (m) Albrecht, L.; Richter, B.; Kawczyk, H.; Jørgensen, K. A. *J. Org. Chem.* **2008**, *73*, 8337–8343.

(2) For a recent review, see: Janecki, T.; Kedzia, J.; Wasek, T. *Synthesis* **2009**, 1227–1254.

(3) For an example, see: Snider, B B.; Phillips, G. B. *J. Org. Chem.* **1983**, *48*, 3685–3689.

(4) For an example, see: Ye, Y.; Xu, G-Y; Zheng, Y.; Liu, L.-Z. *Heteroatom Chem.* **2003**, *14*, 309–311.

DOI: 10.1021/jo9017292 Published on Web 09/17/2009

also found wide application in Diels−Alder reactions as the dienophile for assembling phosphonate-containing cycles. However, in comparison with many other types of 2-substituted 2-alkenoates such as 2-halo,[5a,b] 2-carboxylate,[5c−e] and 2-keto-2-alkenoates,[5f,g] much less attention has been paid to 2-phosphono-2-alkenoates on their Diels−Alder cycloadditions with only a few examples being available in the literature.[6−8] Among these results, Marchand-Brynaert et al. reported several reactions of using trimethyl or triethyl 2-phosphonoacrylate as the dienophile to react with a few achiral or homochiral *N*-protected 1-aminobutadienes including *N*-buta-1,3-dienylsuccinimide,[6a] isopropyl *N*-dienyl-L-pyroglutamate,[6b] *N*-butadienyl-(*R*)-4-phenyloxazolidin-2-one, and *N*-butadienyl-(*R*)-4-phenyloxazolidine-2-thione.[6c−e] They found that in refluxing acetonitrile these reactions took place preferentially in an *endo*-to-phosphonate fashion to yield the major isomers[6] bearing the *cis* phosphono and amino groups. The observed stereoselectivity was explained on the basis of a special P−N stacking during the transition state. Apart from these, there are only two individual cases described, respectively, by McIntosh et al. and Siegel, which involve the Diels−Alder reaction between methyl 2-diethoxyphosphonoacrylate and isoprene in refluxing toluene to afford a mixture of two regioisomers (4:1) favoring the *para*-like one[7] and the reaction of triethyl 2-phosphonoacrylate with 6,6-diphenylfulvene at room temperature for 5 days to provide two stereoisomers in a ratio of 4.5:1 (major = *endo*-to-carboxylate).[8] In both cases, the authors did not provide any spectroscopic evidence to support the regio- or stereochemical assignments for the major isomers. As can be seen, the examples reported so far have been limited to the acrylate substrates, and in addition, the thermal reaction conditions[6,7] and/or the prolonged times (>2 d)[6a,8] were required presumably due to the inherent low reactivity of the dienophiles. Moreover, while exhibiting certain regio- and/or stereoselective bias, almost all of these reactions produced two[6a,c−e,7,8] or more[6b] regio- or stereoisomers, with the minor ones constituting at least 15% of the products. In regard to these limitations, development of more efficient and general procedures for the Diels−Alder reactions of 2-phosphono-2-alkenoates is therefore necessary.

The profound effect of Lewis acids on increasing the reactivity of various dienophiles toward electron-rich dienes, as well as the regio- and stereoselectivity of Diels−Alder reactions, has been well recognized.[9] For phosphonate-containing dienophiles, early reports by McClure and coworkers revealed that the stereoselectivity (*endo*-to-acetyl) of the Diels−Alder reactions between diethyl 3-oxo-1-butenyl phosphonate ester [$CH_3COCH{=}CHPO(OEt)_2$] and the electron-rich dienes could be enhanced with the assistance of the appropriate Lewis acids.[10] Drawing on the experience from these results, we then decided to evaluate the possibility of applying the Lewis acid strategy to the 2-phosphono-2-alkenoate system with the aim of increasing the efficiency and selectivity of the reaction and thereafter exploring the potential of utilizing the reaction to synthesize complex molecules. To the best of our knowledge, the attempt of Lewis acids on the Diels−Alder reactions of 2-phosphono-2-alkenoate has never been reported before. In our investigation, we primarily selected triethyl 2-phosphonoacrylate (**1**) (Figure 1) as the substrate to directly compare our results with those previously reported. In addition, we also chose ethyl 2-(diethoxyphosphono)but-2-enoate (**2**) and ethyl 2-(diethoxyphosphono)-3-methylbut-2-enoate (**3**) as the dienophiles of interest in order to survey the effect of β substitution on the cycloadditions.

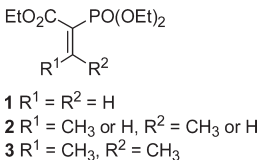


FIGURE 1. 2-Phosphono-2-alkenoates subjected to the study.

It was found that the regio- and stereoselectivities of the Diels−Alder reactions of **1** could be indeed enhanced by Lewis acids as compared with the corresponding reactions carried out without Lewis acids, and the extent of such enhancement was highly dependent on the choice of Lewis acid. Despite the fact that substrates **2** and **3** have been shown to be much less reactive than **1**, the selective Diels−Alder cycloadditions of **2** still could be induced with the concomitant use of the appropriate Lewis acid and the elevated temperature. From **1** and **2**, we were then able to prepare a range of phosphonate-containing cycloadducts as the single isomers. Furthermore, a lithium naphthalenide-mediated reductive alkylation operation facilitated by the phosphono group was applied to the resulting Diels−Alder adducts, thus tactically allowing for the installation of various alkyl groups to the quaternary carbon center of the unsaturated ring systems. In this paper, we report the results from these studies, as well as the application of the combined process into the first total synthesis of (±)-α-alasken-8-one, a natural product belonging to the acorane-type sesquiterpene family.

Results and Discussion

I. Investigation of the Diels−Alder Reactivity of 1−3. Dienophiles **1**−**3** were all readily prepared on a multigram scale from commercially available triethyl phosphonoacetate following the established procedures. Compound **1** was synthesized via the Knövenagel condensation between triethyl phosphonoacetate and formaldehyde with piperidine in refluxing methanol, followed by the dehydration of the resulting crude alcohol in refluxing toluene with catalytic

(5) For examples, see: (a) Lewis, J. W. *J. Chem. Soc. C* **1971**, 1158–1161. (b) Hartmut, P.; Gurdeep, S. S.; Stephan, K.; Gunadi, A.; Armin de, M. *Chem. Ber.* **1994**, *127*, 1051–1064. (c) Effio, A.; Griller, D.; Ingold, K. U.; Scaiano, J. C.; Sheng, S. J. *J. Am. Chem. Soc.* **1980**, *102*, 6063–6068. (d) Ireland, R. E.; Courtney, L.; Fitzsimmons, B. J. *J. Org. Chem.* **1983**, *48*, 5186–5198. (e) Herrerea, R.; Jimenez-Vazquez, H. A.; Modelli, A.; Jones, D.; Soederberg, B. C.; Tamariz, J. *Eur. J. Org. Chem.* **2001**, *24*, 4657–4669. (f) Hoye, T. R.; Caruso, A. J.; Magee, A. S. *J. Org. Chem.* **1982**, *47*, 4152–4156. (g) Inokuchi, T.; Okano, M.; Miyamoto, T. *J. Org. Chem.* **2001**, *66*, 8059–8063.

(6) (a) Defacqz, N.; Touillaux, R.; Tinant, B; Declercq, J-P; Peeters, D.; Marchand-Brynaert, J. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1965–1968. (b) Robiette, R.; Marchand-Brynaert, J. *J. Chem. Soc., Perkin Trans. 2* **2001**, 2155–2158. (c) Robiette, R.; Cheboub-Benchaba, K.; Peeters, D.; Marchand-Brynaert, J. *J. Org. Chem.* **2003**, *68*, 9809–9812. (d) Tinant, B.; Defacqz, N.; Robiette, R.; Touillaux, R.; Marchand-Brynaert, J. *Phosphorus, Sulfur, Silicon* **2004**, *179*, 389–402. (e) Monbaliu, J.-C.; Robiette, R.; Peeters, D.; Marchand-Brynaert, J. *Tetrahedron Lett.* **2009**, *50*, 1314–1317.

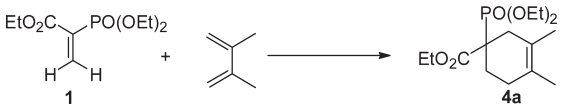
(7) McIntosh, L. M.; Pillon, L. Z. *Can. J. Chem.* **1984**, *62*, 2089–2093.

(8) Siegel, H. *Synthesis* **1985**, 798–801.

(9) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part B: Reaction and Synthesis*, 4th ed.; Kluwer Academic/Plenum Publishers: New York, 2001; pp 336−339.

(10) (a) McClure, C. K.; Hansen, K. B. *Tetrahedron Lett.* **1996**, *37*, 2149–2152. (b) McClure, C. K.; Herzog, K. J.; Bruch, M. D. *Tetrahedron Lett.* **1996**, *37*, 2153–2156.

TABLE 1. Diels–Alder Reactions between 1 and 2,3-Dimethyl-1,3-butadiene



entry	reaction conditions	time (h)	yield[a] (%)
1[b]	ether/25 °C	75	51
2[b]	$ZnCl_2$ (8 equiv)/ether/25 °C	15	63
3[b]	$ZnCl_2$ (2 equiv)/ether/25 °C	15	64
4[c]	$ZnCl_2$ (2 equiv)/ether/25 °C	15	51

[a]Isolated yield. [b]10 equiv of the diene was used. [c]5 equiv of the diene was used.

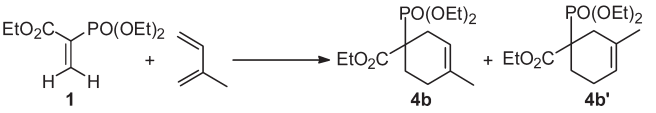
tosic acid under Dean–Stark conditions.[1h] Compounds **2** and **3** were similarly prepared in a three-step sequence, which involved the potassium *tert*-butoxide-induced alkylation of triethyl phosphonoacetate with iodoethane[11] or 2-iodopropane[12] in DMSO, followed by the selenylation of resulting triethyl 2-phosphonobutanoate or 2-phosphono-3-methylbutanoate with phenyl selenenyl chloride and sodium hydride in THF, and finally the hydrogen peroxide-promoted oxidative elimination of the selenylated intermediates in CH_2Cl_2 to give the formation of **2** or **3**.[12] Compound **2** thus obtained was a mixture of two isomers (E/Z = 49:51) which were difficult to separate by chromatographic purification. We thus directly used it as the mixture for the subsequent investigation without the separation.

With the required dienophiles in hand, we then directed our attention to investigate their Diels–Alder reactivity starting with **1**. We first examined the reactions between **1** and 2,3-dimethyl-1,3-butadiene performed with and without $ZnCl_2$ to clarify whether the reaction would be influenced by the Lewis acid (Table 1). It was found that the cycloaddition of **1** with an excess of the diene (10 equiv) could occur in diethyl ether solution at ambient temperature to afford adduct **4a** in moderate yield (51%) (entry 1). However, the reaction required extremely prolonged time (>3 d) to achieve completion. According to the previous protocol of using zinc chloride ($ZnCl_2$) (8 equiv) to facilitate the Diels–Alder reaction of ketovinylphosphonate in ether,[10b] we then applied the same conditions to our reaction. As compared with the reaction in entry 1, we observed that the cycloaddition process was indeed favored by the presence of $ZnCl_2$ as reflected by a much shorter reaction time (15 h) and a higher yield of **4a** (63%) (entry 2). Through a brief screen, we further discovered that the amount of $ZnCl_2$ could be reduced to 2 equiv as the minimum to maintain yield of the product (entry 3). It was also noticed that the above reactions were all accompanied by the formation of fair amounts of polymers resulting from the polymerization of the diene. The attempt to solve the problem by reducing the diene to 7 equiv or less resulted in more workable crude mixture and less polymers, but at the expense of the yields of **4a** (entry 4). Considering yield and ease of separating polar phosphonate-containing cycloadducts from less polar dienes and polymers through chromatography, we thus uniformly employed 10 equiv of dienes for the following investigation.

(11) Stritzke, K.; Schulz, S.; Nishida, R. *Eur. J. Org. Chem.* **2002**, 3884–3892.

(12) Ferguson, A. C.; Adlington, R. M.; Martyres, D. H.; Rutledge, P. J.; Cowley, A. *Tetrahedron* **2003**, *59*, 8233–8243.

TABLE 2. Diels–Alder Reactions between 1 and Isoprene



entry	reaction conditions[a]	time (h)	yield[b] (%)	ratio (**4b**/**4b′**)[d]
1	toluene/80 °C	24	71[c]	85:15
2	$ZnCl_2$ (2 equiv)/ether/25 °C	20	69[c]	95:5
3	$BF_3 \cdot OEt_2$ (1.2 equiv)/ether/0 °C	20	64[c]	95:5
4	$SnCl_4$ (1.2 equiv)/CH_2Cl_2/−30 °C	15	72	100:0

[a]10 equiv of isoprene was used in each case. [b]Isolated yield. [c]Combined yield of **4b** and **4b′**. [d]The ratio was determined on the basis of the integration of C-4 methyl signals on the ^{1}H NMR spectrum (**4b:** δ 1.59 ppm ; **4b′**: δ 1.66 ppm).

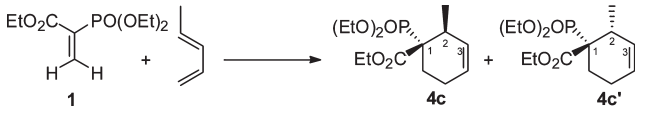
Having proven the positive influence of the Lewis acid on the cycloaddition, we subsequently explored a more important issue, that is, the effect of Lewis acids on the regio- and stereoselectivity of the Diels–Alder reactions. In addition to $ZnCl_2$, two Lewis acids traditionally used for the activation of dienophiles, i.e., tin(IV) chloride ($SnCl_4$) and trifluoride–diethyl etherate ($BF_3 \cdot OEt_2$), were screened by the reactions of **1** with isoprene, *trans*-piperylene, and cyclopentadiene, respectively. As a comparison, the corresponding thermal reaction conducted without Lewis acid was also examined for each diene.

The reaction between isoprene and **1** performed in ether was shown to be much slower than that of 2,3-dimethyl-1,3-butadiene. When carried out in toluene at 80 °C, the reaction could reach completion in 24 h to afford a pair of inseparable regioisomers **4b** and **4b′** in 71% yield. The NMR analysis indicated that the ratio between them was 85:15 in favor of **4b** (Table 2, entry 1). On the other hand, the reaction conducted with 2 equiv of $ZnCl_2$ in ether at room temperature (entry 2) provided the products in comparable yield (69%) as the thermal reaction but displayed noticeably enhanced regioselectivity in improving the **4b**/**4b′** ratio to 95:5. Also in an ethereal solution, the replacement of $ZnCl_2$ with $BF_3 \cdot OEt_2$ (1.2 equiv)[13] merely gave similar results in terms of the yield (64%) and isomeric ratio (**4b**/**4b′** = 95:5), except allowing for a lower temperature (0 °C) for the reaction to be completed (entry 3). After a few attempts, we found that with the use of 1.2 equiv[13] of $SnCl_4$ a completely regioselective reaction could be achieved in CH_2Cl_2 under extremely mild conditions (−30 °C) to give the formation of **4b** as a single isomer in good yield (72%) (entry 4). As a pure isomer, the predicted *para*-like assignment of **4b** could be easily confirmed by the correlation between the C-3 olefinic proton (δ 5.29) and one of the C-2 methylene protons (δ 2.69) on the 2D NOESY spectrum (see the Supporting Information).

When **1** was allowed to react with *trans*-piperylene, both regio- (*ortho*- or *meta*-orientation) and stereoselective (*endo*- or *exo*-to-carboxylate) issues arose with the possibility of yielding four regio- and/or stereoisomers. The conditions attested for isoprene were also attempted on the reaction, and the results are outlined in Table 3. When **1** and *trans*-piperylene were heated at 80 °C in toluene, the reaction was

(13) It was found that at least 1.2 equiv of Lewis acid was required to maintain the constant yield of the product(s).

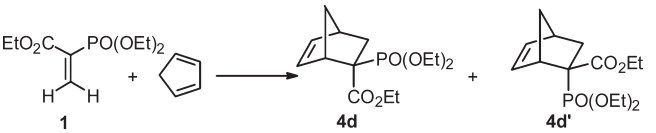
TABLE 3. Diels–Alder Reactions between 1 and *trans*-Piperylene



entry	reaction conditions[a]	time (h)	yield[b] (%)	ratio (**4c**/**4c′**)
1	toluene/80 °C	24	68[c]	87:13
2	$ZnCl_2$ (2 equiv)/ether/25 °C	20	63[c]	94:6
3	$BF_3 \cdot OEt_2$ (1.2 equiv)/ether/0 °C	20	69[c]	85:15
4	$SnCl_4$ (1.2 equiv)/CH_2Cl_2/−-30 °C	17	74	100:0

[a]10 equiv of isoprene was used in each case. [b]Isolated yield. [c]Combined yield of **4c** and **4c′**.

TABLE 4. Diels–Alder Reactions between 1 and Cyclopentadiene



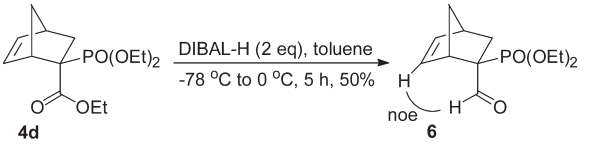
			yield[b] (%)	
entry	reaction conditions[a]	time (h)	**4d**	**4d′**
1	toluene/80 °C	24	64	9
2	$SnCl_4$ (1.2 equiv)/CH_2Cl_2/−30 °C	15	71	trace

[a]10 equiv of isoprene was used in each case. [b]Isolated yield.

completed in 24 h to furnish a mixture of two inseparable stereoisomers **4c** and **4c′** in 68% yield (entry 1). The ratio between them was identified as 87:13 on the basis of the integrations of C-2 methine signals (**4c**: δ 2.89; **4c′**: δ 3.06) on the ^{1}H NMR spectrum. Moreover, the splitting patterns of C-2 methyl signals on the ^{13}C NMR spectrum (**4c**: δ 18.0, J_{P-C} = 5.5 Hz; **4c′**: δ 18.4, J_{P-C} = 2.2 Hz) revealed that they were both *ortho*-orientated diastereoisomers. On this basis, we further observed that the **4c/4c′** ratio was increased by $ZnCl_2$ (**4c**/**4c′** = 94:6) (entry 2) and unexpectedly decreased by $BF_3 \cdot OEt_2$ (**4c**/′ = 85:15) (entry 3), which appeared to be inconsistent with the regiochemical outcomes obtained with isoprene. While the true reason is still not clear to us, we suspect that the different diastereoselectivities observed in two cases might be associated with the coordination states of the dienophile with the Lewis acids,[10a] which, to some extent, would direct the orientation of the dienophile to the diene during the transition state. Much to our interest, it was found that the use of $SnCl_4$ here was shown to be effective again to induce a completely stereocontrolled cycloaddition in affording **4c** exclusively in 74% yield (entry 4). The elucidation of the relative configuration of **4c** by spectroscopic methods (NOE or NOESY) turned out to be difficult due to extensive overlap of resonances and heteronuclear coupling to phosphorus. To address this problem, we managed to prepare its crystalline tosylhydrazone derivative (**5**) and used the X-ray crystallography analysis (see the Supporting Information) to establish the stereochemistry of **4c**. The *trans* steric relationship between the C-2 methyl and the phosphono substituents revealed that the reaction proceeded in an *endo* pathway directed by the carboxylate group.

The aforementioned experiments indicated that $SnCl_4$ used in dichloromethane was extremely effective for improving the regio- and stereoselectivity of the reactions of **1**. To further validate this, we investigated the reactions between **1** and cyclopentadiene under the thermal and $SnCl_4$-mediated conditions. As illustrated in Table 4, the thermal reaction produced diastereoisomers **4d** and **4d′** in 64% and 9% yield, respectively (entry 1), while the reaction performed with $SnCl_4$ led to the almost exclusive formation of **4d** in 71% yield with only a trace amount of **4d′** (< 2%) (entry 2), therefore once again demonstrating the remarkable efficiency of the established reaction conditions. Based on the configuration of **4c**, we judged that **4d** should also present as an *endo* diastereoisomer. However, the NOESY spectrum of **4d** failed to provide any diagnostic cross peaks between the olefinic protons (δ 6.19 and 5.96) and the ethyl protons

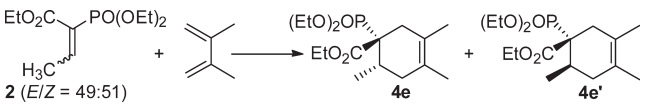
SCHEME 1



(δ 4.03–4.18, 1.15) of the ester group, most likely because of the *exo* orientation of the ethyl moiety. Therefore, **4d** was further converted into aldehyde **6** through the reduction with DIBHAL-H and whose 2D NOESY spectrum (see Supporting Information) helped us to unambiguously confirm the proposed structure of **4d** as evidenced by the correlation signal between the olefinic proton (δ 6.02) and the aldehyde proton (δ 9.51) (Scheme 1).

After establishing the optimal reaction conditions for **1**, we continued to investigate the Diels–Alder reactivity of **2** and **3**. Only differing from **1** by a methyl group at the β position, **2** (E/Z = 49:51), however, displayed much less reactivity than **1** toward 2,3-dimethyl-1,3-butadiene (Table 5). It was found that in the absence of Lewis acids, no reaction could happen in toluene at 80 °C or even under refluxing conditions (entry 1). Moreover, the reactions carried out with $BF_3 \cdot OEt_2$ in ether at 0 °C or $SnCl_4$ in CH_2Cl_2 at −30 °C also did not provide any desired adduct(s), and the effort to promote the cycloaddition by increasing the temperatures (rt to refluxing) only resulted in the formation of large amount of unidentified byproducts from the decomposition of **2** (entries 2 and 3). These results indicated the low reactivity of **2** and its incompatibility with the relatively strong Lewis acids. The application of $ZnCl_2$ to the reaction performed in ether also met with no success at room temperature, but could cause the desired cycloaddition to occur under the reflux conditions. By using TLC to monitor the progress of the reaction, we observed that the consumption of **2** was rapid at the beginning but became unusually slow after approximately 5 h. The reaction was allowed to proceed for 24 h to give rise to the formation of two isomeric adducts **4e** and **4e′** in 57% yield, coupled with 23% of recovered **2**. The NMR analysis indicated that the ratio between **4e** and **4e′** was 88:12 and the E/Z ratio of recovered **2** was 98:2 (entry 4). Therefore, given the concept that the stereochemistry of the dienophile was preserved in a concerted process, we were able to deduce the structures of **4e** and **4e′** from the ratio and the yield of the products and the E/Z ratios of the starting and recovered **2** combined with the percentage of the recovery. In this case, it was postulated that the prevailing

TABLE 5. Diels–Alder Reactions between 2 and 2,3-Dimethyl-1, 3-butadiene



entry	reaction conditions[a]	time (h)	yield[b] (%)	ratio (**4e**/**4e′**)[c]	recovered **2** (%) (*E*/*Z*)
1	toluene/80 °C to reflux	24			
2	$BF_3 \cdot OEt_2$ (1.2 equiv)/ether/0 °C to reflux	24			
3	$SnCl_4$ (1.2 equiv)/ CH_2Cl_2/−30 °C to reflux	24			
4	$ZnCl_2$ (2 equiv)/ ether/reflux	24	57	88:12	23 (98:2)
5	$ZnCl_2$ (2 equiv)/ toluene/ 90 °C	24	61	71:29	9 (90:10)

[a]10 equiv of isoprene was used in each case. [b]Isolated and combined yield of **4e** and **4e′**. [c]The ratio was determined by the integration of C-3 methyl signals (**4e**: δ 1.62; **4e′**: δ 1.60) on the ^{1}H NMR spectrum.

formation of **4e** from the *Z*-isomer should be attributed to the preference for an *endo*-to-carboxylate transition state by both isomers, during which an unfavorable steric interaction between the terminal methyl group of the *E*-form and the diene would hinder the approach of the two components to each other (Figure 2), thus suppressing the formation of **4e′**. We wondered if the higher temperature was required to circumvent the inherent low reactivity of the *E*-isomer and then subsequently performed a reaction at 90 °C in toluene. As shown in entry 5, such an attempt resulted in the increased 4e′/4e ratio (29:71) paralleling to the decreased *E*/*Z* ratio (90:10) of the recovered **2** (9%) but did not significantly improve the combined yield (61%) of the two isomers. Hence, it was proposed that the reaction of the *E*-isomer was promoted to some extent by employing the higher temperature, which, however, could in turn accelerate the decomposition of the starting material as reflected by the formation of more unidentified byproducts and less recovery of **2** as compared with the reaction in entry 4.

To confirm the *endo* pathway proposed for **2**, we further examined the reaction of **2** with *trans*-piperylene under the $ZnCl_2$-assisted reaction conditions (Table 6). It was interesting to find that the reaction conducted in refluxing ether only resulted in a single diastereoisomer **4f** in 41% yield, plus 33% of recovered **2** (*E*/Z = 93:7) (entry 1). As with **4c**, the direct elucidation of the structure of **4f** through the spectroscopic methods was shown to be difficult. Therefore, we again restored to the X-ray crystallographic analysis of its tosylhydrazone derivative (**7**) (see the Supporting Information).[14] The structure of **7** confirmed that **4f** was derived from the *Z*-isomer and generated through an *endo*-to-carboxylate transition state as we proposed for **4e** and **4e′**. Moreover, the reaction carried out in toluene at 90 °C produced a mixture of two inseparable isomers **4f** and **4f′** (**4f**/**4f′** = 70:30) in 59% yield, together with 19% of recovered **2** (*E*/*Z* = 90:10) (entry 2). For **4f′**, we were only able to prove its *ortho*

(14) Warmers, U.; König, W. A. *Phytochemistry* **1999**, *52*, 695–704.

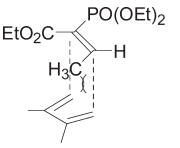
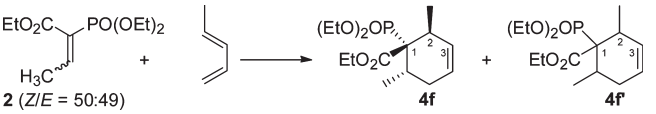


FIGURE 2. Proposed transition state for the reaction of the *E*-isomer of **2** with 2,3-dimethyl-1,3-butadiene.

TABLE 6. Diels–Alder Reactions between 2 and *trans*-Piperylene



entry	reaction conditions[a]	time (h)	yield (%)[b]	ratio (**4f**/**4f′**)[d]	recovered **2** (%) (*E*/*Z*)
1	$ZnCl_2$ (2 equiv)/ ether/reflux	24	41	100:0	33 (93:7)
2	$ZnCl_2$ (2 equiv)/ toluene/90 °C	24	59[c]	70:30	19 (90:10)

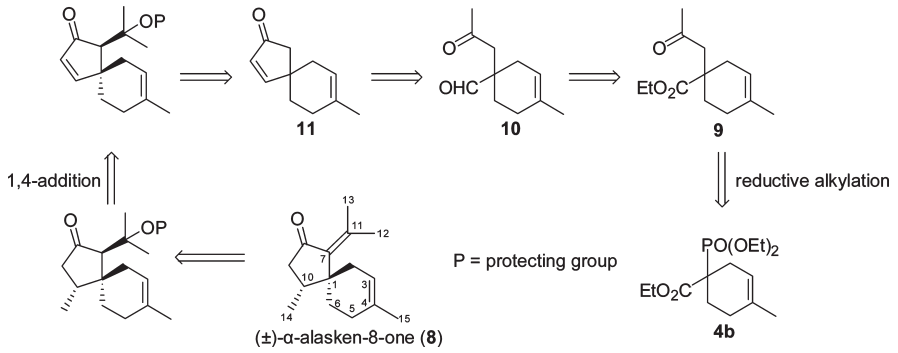
[a]10 equiv of isoprene was used in each case. [b]Isolated yield. [c]Combined yield of **4f** and **4f′**. [d]The ratio was determined by the integration of the signals of C-4 olefinic protons (**4f**: δ 5.45; **4f′**: δ 5.33) on the ^{1}H NMR spectrum.

regiochemical assignment by the fine coupling constant of C-2 methyl signals on the ^{13}C NMR spectrum (δ 18.1, J_{P-C} = 2.39 Hz) but still did not allow assignment of its stereochemistry due to the low content in the mixture and the difficulty of separating it from the major isomer. On the basis of the isomeric ratios of recovered **2** in both cases, we assume that **4f′** should be produced from the *E*-isomer following the same *endo* transition state as for **4f**. However, the possibility of forming **4f′** in an *exo* pathway still cannot be completely ruled out.

With the recognition of the relatively poor dienophilicity of **2**, we were not surprised to find that compound **3**, possessing an additional β methyl group, was even much less reactive than **2**. It completely did not react with 2,3-dimethyl-1,3-butadiene under all of the aforementioned conditions (Tables 1–6). Besides, the severe decomposition of **3** was observed throughout these cases. Furthermore, the reactions performed with two other reagent systems including $TiCl_4/CH_2Cl_2$ and $AlCl_3$/ether, or even under extreme conditions (toluene/130 °C, sealed tube), also failed to provide any desired product but rather complex mixtures. As we discussed above, the unfavorable steric hindrance exerted by the germinal methyl groups should be responsible for the nonreactive nature of **3**.

The investigation on the Diels–Alder reactivity of phosphonate substrates **1**–**3** was thus completed. In the investigation, **1** was shown to be most reactive toward the dienes. An intriguing feature was that it could undergo the highly regio- (*para* or *ortho*) and stereoselective (*endo*-to-carboxylate) cycloadditions with the assistance of $SnCl_4$, to afford the single isomeric adducts in good yields. We have also proved that the introduction of the methyl group(s) to the β position of **1** caused the dienophilicity to be dramatically decreased. Nevertheless, in accordance with the inherent preference for an *endo*-to-carboxylate transition mode, the β methyl group of **2** enabled the reactivity of the admixed *Z*, *E*-isomers to be efficiently differentiated, thus providing an

SCHEME 2. Retrosynthetic Strategy for the Synthesis of α-Alasken-8-one (8)



opportunity for us to selectively promote the cycloadditions of the *Z*-form while completely or partially suppressing the reactions of the *E*-form by choosing the appropriate Lewis acid and reaction conditions. In general, the protocol offered an efficient access into a range of phosphonate-containing cycles in a high degree of regio- and stereocontrol, which, as described below, practically facilitated the chemical manipulation of the resulting adduct into the sesquiterpene natural product α-alasken-8-one via a key reductive alkylation operation.

II. Reductive Alkylation of the Diels−Alder Adduct and the First Total Synthesis of (±)-α-Alasken-8-one. Having delineated the scope and efficiency of the Lewis acid-mediated Diels−Alder reaction of the 2-phosphono-2-alkenonates, we turned to its application to the first total synthesis of α-alasken-8-one (**8**), an acorane-type sesquiterpene natural product isolated by König's group from the essential oil of the liverwort *Calypogeia fissa* collected in the Harz mountains in Germany.[14] The structure and absolute stereochemistry of the naturally occurring (−)-α-alasken-8-one were established on the basis of the spectroscopic methods and the chemical correlation with (−)-α-alaskene, a known natural product isolated from the same source. To date, more than 50 members belonging to this sesquiterpene family have been isolated from natural sources,[15] which are characterized by a functionalized spiro[4,5]decane core containing two methyl groups at the C-4 and C-10 positions (acorane numbering) and an isopropyl or iospropylidene or isopropenyl moiety at the C-7 position. Toward the synthesis of these natural products, the stereocontrolled construction of the spirocyclic carbon skeleton presents the greatest obstacle, and therefore, a successful synthesis is essentially dependent on the efficient creation of a quaternary carbon center which is suitably substituted for the direct annulation into a spiro system.[16]

Our retrosynthetic strategy for the total synthesis of **8** is illustrated in Scheme 2. Benefiting from the regiocontrolled generation of **4b** in good yield, we envisioned that the phosphono group of **4b** could be replaced by 2-oxopropyl functionality via a newly attempted reductive alkylation reaction to result in keto ester **9**, which, after chemical modifications, could be further converted into keto aldehyde **10** as the precursor for the annulation. After the spiro skeleton was constructed, we planned to first introduce a protected 2-hydroxy-2-propyl group to the C-7 position of intermediate **11** as a latent substituent for the installation of iospropylidene moiety. This bulky group was thought to be added from the side of the Δ^3 double bond of the cyclohexene ring to avoid a skew butane-type interaction with C5−C6 methylene unites[16a] and also designed to direct the approach of the methyl transfer reagent during the later 1,4-addition step to ensure the correct stereochemical relationship between C-10 and C-1. Finally, sequential deprotection and dehydration would complete the total synthesis of **8**.

The reductive alkylation was intended to be induced by treating the Diels−Alder adducts with an electron-donating reagent to reductively cleave the phosphono group, followed by trapping the in situ generated enolates with an alkylating agent to allow for the installation of an alkyl group to the quaternary carbon centers. Liu et al. previously reported the application of a lithium naphthalenide (LN)-induced reductive alkylation process to the α-phosphono ketones for introducing an alkyl group to the angular position of the bicyclic ring systems.[17] In this context, we recently have also developed an efficient procedure to convert the α-cyano esters into the corresponding α, *β*-unsaturated esters using a LN-mediated reductive selenylation as a key operation.[18] In light of these experiences, we envisaged that the reductive alkylation operation should be applicable to α-phosphono esters. To confirm this, we first evaluated the reductive benzylation of **4a** by using LN[19] and di-*tert*-butylbiphenyl (LiDBB),[20] respectively, as the reducing reagent (Scheme 3). It was observed that upon the treatment with LN in a THF solution, **4a** could be readily reduced (∼30 min) under mild reaction conditions (−30 °C) to afford the enolate intermediate. The subsequent addition of benzyl bromide (6 equiv) to the reaction mixture resulted in the alkylated product **12a** in 70% yield. On the other hand, a relatively low

(15) (a) Sorm, F; Herout, V. *Collect. Czech. Chem. Commun.* **1948**, *13*, 177–206. (b) Vrkoc, J.; Jonas, J.; Herout, V.; Sorm, F. *Collect. Czech. Chem. Commun.* **1963**, *28*, 1084–1086. (c) McClure, R. J.; Schorno, K. S.; Bertrand, J A.; Zalkow, L. H. *J. Chem. Soc., Chem. Commun.* **1968**, 1135–1136. (d) Minato, H.; Fujita, R.; Takeda, K. *Chem. Pharm. Bull.* **1971**, *19*, 638–640. (e) Kaiser, R.; Naegeli, P. *Tetrahedron Lett.* **1972**, *13*, 2009–2012. (f) Kaiser, R.; Naegeli, P. *Tetrahedron Lett.* **1972**, *13*, 2013–2016. (g) Nawamaki, K.; Kuroyanagi, M. *Phytochemistry* **1996**, *43*, 1175–1182.

(16) For examples, see: (a) McCrae, D. A.; Dolby, L. *J. Org. Chem.* **1977**, *42*, 1607–1610. (b) Martin, S. F.; Chou, T. S. *J. Org. Chem.* **1978**, *43*, 1027–1031. (c) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. In *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley: New York, 1983; Vol. 5, pp 284−305. (b) Chen, Y.-J.; Lin, W. Y. *Tetrahedron* **1993**, *49*, 10263–10270. (c) Srikrishna, A.; Kumar, P. P. *Tetrahedron* **2000**, *56*, 8189–8195.

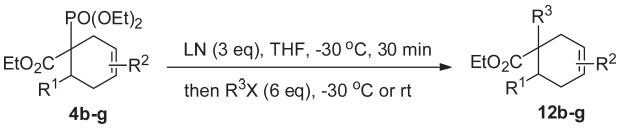
(17) Chien, C. F.; Wu, J-D; Ly, T. W.; Shia, K. S.; Liu, H. J. *Chem. Commun.* **2002**, 248–249.

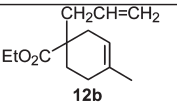
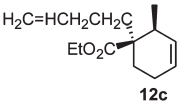
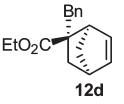
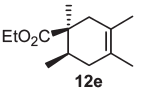
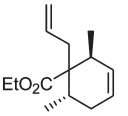
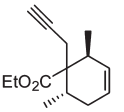
(18) Ko, Y. C.; Zhu, J. L. *Synthesis* **2007**, *23*, 3659–3665.

(19) For preparing a stock solution of LN, see: Liu, H. J.; Yip, J.; Shia, K. S. *Tetrahedron Lett.* **1997**, *38*, 2253–2256.

(20) For preparing a stock solution of LiDBB, see: Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924–1930.

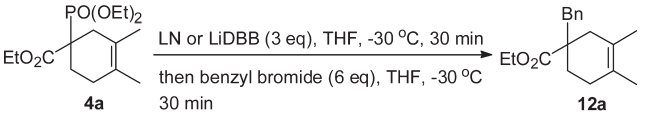
TABLE 7. LN-Mediated Reductive Alkylation Reactions of 4b−f



entry	substrate	R^3X	product	yield (%)[a]
1[b]	**4b**	allyl bromide	 **12b**	72
2[c,d]	**4c**	4-bromo-1-butene	 **12c**	60
3[b]	**4d**	benzyl bromide	 **12d**	51
4[b]	**4e**/**4e'** (88:12)	methyl iodide	 **12e**	75
5[d]	**4f**	allyl bromide	 **12f**	74[e]
6[d]	**4g**	propargyl bromide	 **12g**	50[f]

[a]Isolated. [b]After the addition of R^3X, the reaction was allowed to proceed at −30 °C for 30 min. [c]5 equiv of HMPA was introduced to the reaction mixture at −30 °C after the addition of R^3X. [d]After the addition of R^3X at −30 °C, the reaction was allowed to proceed at rt for 12 h. [e]The product was obtained as a mixture of two diastereomers in a ratio of 51:49, and the stereochemistry remains to be determined. [f]The product was obtained as a mixture of two diastereomers in a ratio of 60:40, and the stereochemistry remains to be determined.

SCHEME 3. LN-Mediated Reductive Benzylation of 4a



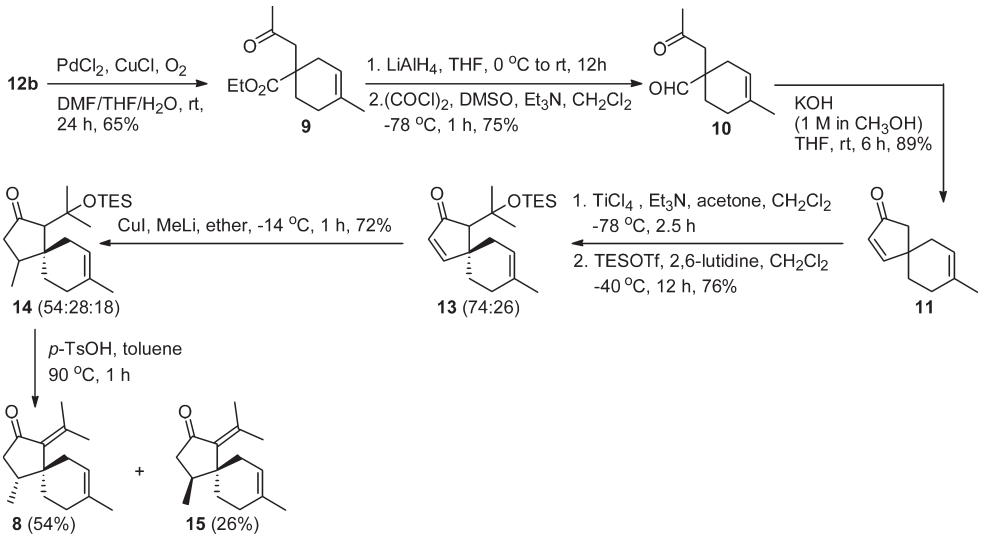
Reducing agent	Yield
LN	70%
LiDBB	63%

yield (63%) of **12a** was obtained with the employment of LiDBB, suggesting that LN was more effective than LiDBB for the reaction.

The LN-induced reductive alkylation process was proven to be general when applied into the remaining Diels−Alder adducts **4b**−**f** (Table 7). By treating with LN and various alkylating reagents including allyl bromide, 4-bromo-1-butene, benzyl bromide, methyl iodide, and propargyl bromide, these α-phosphono esters were all converted into the corresponding α-alkyl-substituted esters **12b**−**g** in synthetically useful yields (50−74%). Compounds **12c**−**e** were produced as single diastereomers (entries 2−4), whereas **12f** and **12g** were formed as mixtures of two isomers in a ratio of 51:49 and 60:40, respectively (entries 5 and 6). The relative configurations of **12c** and **12e**, which were established by the X-ray diffraction analysis of the tosylhydrazone or 3,5-dinitrobenzoate derivatives (see the Supporting Information), revealed that the introduction of the alkyl groups was sterically directed by the C-2 or C-6 methyl group of **4c** or **4e**/**4e'**. It is also noteworthy that for some reactions, the addition of hexamethylphosphoramide (HMPA) (entry 2) and/or the prolonged reaction time (12 h) as well as the higher temperature (rt) (entries 2, 5, and 6) were required after the LN treatment to circumvent the relative low reactivity of the alkylating reagent (entry 2) or the starting substrate (entries 5 and 6). We were thus able to efficiently introduce a variety of alkyl groups to the quaternary carbon centers of the unsaturated ring systems. The reductive alkylation operation, combined with the Diels−Alder reactions, has therefore practically turned **1** and **2** into the useful synthetic equivalents of the corresponding 2-alkyl 2-alkenoates that usually exhibit poor Diels−Alder reactivity.

The synthesis of the titled target **8** commenced with the oxidation of **12b** under the Wacker oxidative conditions to afford keto ester **9** in 65% yield (Scheme 4). To elaborate **9** into the key precursor **10**, we first reduced **9** into the corresponding diol by using lithium aluminum hydride in

SCHEME 4



THF. Not as we expected, the subsequent oxidation of the resulting crude diol with PCC or PDC in CH_2Cl_2 provided **10** only in 29% and 26% yield, respectively, together with large amounts of the six-membered hemiacetal byproducts resulting form the cyclization of the mono-oxidized intermediates. The employment of other oxidative conditions including Dess−Martin periodinane/CH_2Cl_2, RuO_4/CH_2Cl_2, or $(Ph_3P)_3RuCl_2/CH_2Cl_2$ also did not provide any reasonable yields of **10** (<25%). After considerable experimentation, it was discovered that a much more efficient oxidation could be affected under the Swern oxidative conditions [DMSO/$(CO)_2Cl_2/Et_3N/CH_2Cl_2$] to yield **10** in 75% yield over two steps. With **10** in hand, we then submitted it to the intramolecular condensation reaction for assembling the spiro skeleton, and this could be readily achieved by treating **10** with methanolic KOH solution in THF to result in the clean generation of the key intermediate **11** in 89% yield. Herein, the formation of **11** also represents the formal synthesis of two other sesquiterpene natural products, acorone and isoacorone, whose total syntheses through the intermediary of **11** were reported, respectively, by McCrae and Martin.[16a,b] As we designed, a protected hydroxyl propyl group would be next introduced to the C-7 position of **11**. To this end, **11** was sequentially treated with $TiCl_4$, Et_3N, and acetone to give the alcohol,[21] which, without purification, was further allowed to react with triethylsilyl trifluormethanesulfonate in the presence of 2,6-lutidine to provide silyl ether **13** in 76% yield as a 74:26 mixture of two diastereomers. The subsequent 1,4-addition reaction of **13** with lithium dimethylcuprate proceeded smoothly in affording compound **14** in 72% yield. Three of the seven possible diastereoisomers were detected for **14** in a ratio of 54:28:18. At the end, treatment of **14** with *p*-toluenesulfonic acid (*p*-TsOH·H_2O) in toluene at 90 °C for 1 h furnished R-alasken-8-one (**8**) and its 10-epimer **15** in 54% and 26% yield, respectively. The spectral data (IR, ^{1}H NMR, ^{13}C NMR, mass spectra) of **8** were found to agree well with those reported for the natural product.[14] In addition, the ratio between **8** and 15 indicated that the relative stereochemistry of the C-10 and C-1 positions of two major isomers of **14** should be identical with that of the natural product.

In conclusion, we have demonstrated that the highly selective Diels−Alder cycloadditions of **1** and **2** can be achieved under the appropriate Lewis acid-mediated reaction conditions. Moreover, the synthetic utility of the Diels−Alder reactions has been significantly expanded with the application of the resulting adducts into the LN-induced reductive alkylation process, thereby leading to the generation of a series of cyclic alkyl substituted esters with some of them being difficult to access by other synthetic methods. As we described herein, the concise total synthesis of (±)-α-alasken-8-one further underscore the value of this combined operation in natural product synthesis. Applications of Lewis acid-mediated reaction conditions into chiral 2-phosphono-2-alkenote molecules as well as the above reductive alkylation strategy into the synthesis of structurally related bicyclic spiro natural products such as phytoalexane- and vertispirane-type sesquiterpenes are currently underway in our laboratory.

Experimental Section

Ethyl 1-(Diethoxyphosphoryl)-3,4-dimethylcyclohex-3-enecarboxylate (4a). To a flame-dried 15 mL round-bottom flask were added anhydrous $ZnCl_2$ (0.41 g, 3.02 mmol) and ether (5 mL). The mixture was stirred under a nitrogen atmosphere for 20 min until $ZnCl_2$ was completely dissolved and then was added with a solution of **1** (0.36 g, 1.51 mmol) in ether (2 mL). The mixture was stirred at 25 °C for 30 min before 2,3-dimethyl-1,3-butadiene (1.75 mL, 15.1 mmol) was added. After being stirred at 25 °C for15 h, the reaction mixture was diluted with EtOAc (120 mL) and successively washed with water (2 × 20 mL) and brine (1 × 20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica gel, hexane−EtOAc, 5:1, 3:1, 1:1) afforded **4a** as a viscous oil: yield 0.31 g (64%); IR (neat) 1732, 1635, 1250, 1184, 1049, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21−4.09 (m, 6H), 2.60 (br d, J = 16.6 Hz), 2.46−2.34 (m, 2H), 2.11−2.02 (m, 1H), 1.90−1.81 (m, 2H), 1.62 (br s, 3H), 1.55 (br s, 3H), 1.31 (t, J = 7.0 Hz, 6H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (d, J_{C-P} = 3.1 Hz), 124.6, 123.3 (d, J_{C-P} = 13.4 Hz), 62.8 (d, J_{C-P} = 12.3 Hz), 62.7 (d, J_{C-P} = 11.7 Hz), 61.2,

(21) Nicolaou, K. C.; Zhang, H.; Ortiz, A.; Dagneau, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8605–8610.

48.5 (d, J_{C-P} = 132.5 Hz), 33.8 (d, J_{C-P} = 3.6 Hz), 28.3 (d, J_{C-P} = 13.0 Hz), 25.7 (d, J_{C-P} = 4.3 Hz), 19.1, 18.8, 16.4(d, J_{C-P} = 5.8 Hz), 14.1; HRMS-FAB *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{28}O_5P$ 319.1674, found 319.1669. Anal. Calcd for $C_{15}H_{27}O_5P$: C, 56.59; H, 8.55. Found: C, 56.72; H, 8.64.

1-(Diethoxyphosphoryl)-4-methylcyclohex-3-enecarboxylate (4b): Typical Procedure for the $SnCl_4$-Mediated Diels−Alder Reactions of 1. To a solution of **1** (0.11 g, 0.48 mmol) in DCM (2 mL) at −30 °C was added 0.57 mL of $SnCl_4$ (1 M in DCM, 0.57 mmol) under a N_2 atmosphere. The mixture was stirred at −30 °C for 30 min before isoprene (0.48 mL, 4.75 mmol) was added. The reaction mixture was stirred at −30 °C for 15 h and diluted with EtOAc (80 mL) and water (20 mL). The aqueous layer was separated and extracted with EtOAc (2 × 15 mL). The combined organic extracts were washed with water (2 × 15 mL) and brine (15 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (silica gel, hexane−EtOAc, 5:1, 3:1, 1:1) afforded **4b** as a viscous oil: yield 0.10 g (72%); IR (neat) 3047, 1726, 1680, 1644, 1252, 1184, 1022, 881 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (br s, 1H), 4.16−4.01 (m, 6H), 2.69 (br d, *J* = 17.1 Hz, 1H), 2.44−2.33 (m, 2H), 2.08−1.96 (m, 1H), 1.90−1.77 (m, 2H), 1.54 (br s, 3H), 1.25 (t, *J* = 7.1 Hz, 6H), 1.18 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (d, J_{C-P} = 3.5 Hz), 133.2, 118.2 (d, J_{C-P} = 13.8 Hz), 62.8 (d, J_{C-P} = 7.0 Hz), 61.2, 47.4 (d, J_{C-P} = 133.1 Hz), 28.1 (d, J_{C-P} = 3.5 Hz), 26.7 (d, J_{C-P} = 12.7 Hz), 25.3 (d, J_{C-P} = 3.9 Hz), 23.3, 16.4 (d, J_{C-P} = 5.8 Hz), 14.0; HRMS-FAB *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{26}O_5P$ 305.1518, found 305.1513. Anal. Calcd for $C_{14}H_{25}O_5P$: C, 55.25; H, 8.28. Found: C, 55.39; H, 8.31.

(1*S,2*S**)-Ethyl 1-(Diethoxyphosphoryl)-2-methylcyclohex-3-enecarboxylate (4c).** The typical procedure for the preparation of **4b** was followed by using **1** (1.76 g, 7.46 mmol) and *trans*-piperylene (7.82 mL, 74.60 mmol) as the starting substrates. Flash chromatography (silica gel, hexane−EtOAc, 5:1, 3:1, 1:1) afforded 1.69 g (74%) of **4c** as a yellowish oil: IR (neat) 3024, 1736, 1654, 1248, 1051, 1024, 682 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (dm, *J* = 10.8 Hz, 1H), 5.55 (dm, *J* = 10.8 Hz, 1H), 4.23−4.07 (m, 6H), 2.92 (br s, 1H), 2.37−2.18 (m, 2H), 2.14−1.98 (m, 2H), 1.31 (t, *J* = 7.2 Hz, 6H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.21 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2 (d, J_{C-P} = 2.6 Hz), 130.9 (d, J_{C-P} = 8.8 Hz), 125.0, 62.6 (d, J_{C-P} = 7.1 Hz), 62.3 (d, J_{C-P} = 7.3 Hz), 60.9, 51.4 (d, J_{C-P} = 135.4 Hz), 33.1 (d, J_{C-P} = 2.0 Hz), 25.5 (d, J_{C-P} = 4.2 Hz), 22.5 (d, J_{C-P} = 7.9 Hz), 18.0 (d, J_{C-P} = 5.4 Hz), 16.4 (d, J_{C-P} = 5.2 Hz), 16.3 (d, J_{C-P} = 5.2 Hz), 14.0; HRMS-FAB *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{26}O_5P$ 305.1518, found 305.1516. Anal. Calcd for $C_{14}H_{25}O_5P$: C, 55.25; H, 8.28, found: C, 55.37; H, 8.28.

(1*S,2*R**,4*S**)-2-(Diethoxyphosphoryl)bicyclo[2.2.1]hept-5-ene-2-carboxylic Acid Ethyl Ester (4d).** The typical procedure for the preparation of **4b** was followed by using **1** (0.33 g, 1.41 mmol) and cyclopentadiene (0.93 g, 14.13 mmol) (pregenerated by the thermolysis of dicyclopentadiene before the use) as the starting substrates. Flash chromatography (silica gel, hexane−EtOAc, 5:1, 3:1, 2:1 1:1) afforded 0.31 g of **4d** (71%) as a colorless oil and a trace amount of **4d′** (∼2 mg, < 2%). For **4d**: IR (neat) 3064, 1730, 1637, 1240, 1049, 1022 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (dd, *J* = 5.4, 3.0 Hz, 1H), 5.96 (dd, *J* = 5.4 Hz, 2.6 Hz), 4.19−4.03 (m, 6H), 3.44 (dm, *J* = 6.8 Hz, 1H), 2.92 (br s, 1H), 2.34 (ddd, *J* = 20.1, 12.1, 3.0 Hz,1H), 2.01−1.86 (m, 2H), 1.34−1.29 (m, 1H), 1.32 (t, *J* = 7.0 Hz, 4H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 139.3, 135.0 (d, J_{C-P} = 13.0 Hz), 62.8 (d, J_{C-P} = 7.1 Hz), 62.7 (d, J_{C-P} = 6.6 Hz), 61.1, 55.1 (d,, J_{C-P} = 130.4 Hz), 48.9, 47.6, 42.5 (d, J_{C-P} = 2.4 Hz), 33.0, 16.4 (d, J_{C-P} = 6.7 Hz), 16.3 (d, J_{C-P} = 7.4 Hz), 14.1; HRMS-FAB *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{24}O_5P$ 303.1361, found 303.1358.

(1*R,6*S**)-Ethyl 1-(Diethoxyphosphoryl)-3,4,6-trimethylcyclohex-3-enecarboxylate (4e) and (1*R**,6*R**)-Ethyl 1-(Diethoxyphosphoryl)-3,4,6-trimethylcyclohex-3-enecarboxylate (4e′): Typical Procedure for the $ZnCl_2$-Mediated Diels−Alder Reactions of 2 in Ether.** To anhydrous $ZnCl_2$ (0.33 g, 2.44 mmol) was added 1.5 mL of dry ether. The mixture was stirred under a nitrogen atmosphere for 20 min until $ZnCl_2$ was completely dissolved, and then a solution of **2** (*E*/*Z* = 49:51) (0.31 g, 1.24 mmol) in dry ether (3.0 mL) was added. Stirring was continued at 25 °C for 30 min before 2,3-dimethyl-1,3-butadiene (1.41 mL, 12.2 mmol) was added. The reaction mixture was then heated at reflux for 24 h, cooled to 25 °C, and diluted with EtOAc (130 mL). The solution was washed with water (2 × 15 mL) and brine (1 × 20 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography (silica gel, hexane−EtOAc, 3:1, 2:1, 1:2) afforded 0.071 g of recovered **2** (23%, *E*/*Z* = 98:2) and 0.26 g of a mixture of **4e** and **4e′** (57%) in a ratio of 88:12. For the mixture: IR (neat) 1734, 1639, 1236, 1052, 1025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$). For **4e**: δ 4.17−4.07 (m, 6H), 2.70 (br sextet, *J* = 7.1 Hz, 1H), 2.52−2.46 (dm, *J* = 5.3 Hz, 2H), 2.13 (br d, *J* = 17.8 Hz, 1H), 1.83−1.74 (m, 1H), 1.64 (s, 3H), 1.53 (s, 3H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.29 (t, *J* = 6.9 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H). For **4e′**: δ4.25−4.15 (m, 6H), 2.65−2.54 (m, 1H), 2.41 (br sextet, *J* = 6.7 Hz, 1H), 2.31 (br d, *J* = 16.1 Hz, 1H), 2.21−2.15 (m, 1H), 1.95−1.86 (m, 1H), 1.61 (s, 3H), 1.56 (s, 3H), 1.32 (t, *J* = 7.0 Hz, 3H), 1.28 (t, *J* = 7.0 Hz, 3H), 1.25 (t, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$). For **4e**: δ 171.3 (d, J_{C-P} = 3.2 Hz), 122.5 (d, J_{C-P} = 13.7 Hz), 121.7 (d, J_{C-P} = 1.7 Hz), 62.6 (d, J_{C-P} = 6.9 Hz), 62.5 (d, J_{C-P} = 7.6 Hz), 61.1, 53.1 (d, J_{C-P} = 131.4 Hz), 36.9 (d, J_{C-P} = 13.0 Hz), 30.5 (d, J_{C-P} = 3.8 Hz), 29.8 (d, J_{C-P} = 1.3 Hz), 19.1, 18.8, 16.9, 16.4 (d, J J_{C-P} = 5.9 Hz), 14.0. For **4e′**: 170.8 (d, J_{C-P} = 2.2 Hz), 124.1, 122.2 (d, J_{C-P} = 7.7 Hz), 62.5 (d, J_{C-P} = 7.6 Hz), 62.2 (d, J_{C-P} = 7.4 Hz), 61.0, 52.1 (d, J_{C-P} = 132.6 Hz), 37.8 (d, J_{C-P} = 7.7 Hz), 34.5 (d, J_{C-P} = 3.6 Hz), 32.3 (d, J_{C-P} = 3.6 Hz), 18.8, 18.7, 17.6 (d, J_{C-P} = 8.7 Hz), 16.3 (d, J_{C-P} = 3.7 Hz), 14.1. HRMS-FAB: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{30}O_5P$ 333.1831, found 333.1826.

(1*S,2*S**,6*S**)-1-(Diethoxyphosphoryl)-2,6-dimethylcyclohex-3-enecarboxylic Acid Ethyl Ester (4f).** The procedure for the preparation of **4e**/**4e′** (88:12) was followed by using **2** (*E*/*Z* = 49:51) (0.68 g, 2.70 mmol) and *trans*-piperylene (2.83 mL, 27.02 mmol) as the starting substrates. Flash chromatography (silica gel, hexane−EtOAc, 5:1, 3:1, 2:1, 1:2) afforded 0.22 g of recovered **2** (33%, *E*/*Z* = 93:7) plus 0.35 g (41%) of **4f** as a viscous oil: IR (neat) 1734, 1660, 1242, 1051, 126, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (dm, *J* = 12.3 Hz, 1H), 5.51 (dm, *J* = 12.3 Hz, 1H), 4.25−4.06 (m, 6H), 2.89 (m, 1H), 2.74−2.61 (m, 1H), 2.11 (br d, *J* = 17.0 Hz, 1H), 1.87 (br d, *J* = 17.0 Hz, 1H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.25 (d, *J* = 7.2 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (d, J_{C-P} = 2.9 Hz), 130.7 (d, J_{C-P} = 9.6 Hz), 123.5, 62.3 (d, J_{C-P} = 7.3 Hz), 62.0 (d, J_{C-P} = 7.2 Hz), 60.8, 55.9 (d, J_{C-P} = 134.4 Hz), 31.1, 31.0 (d, J_{C-P} = 8.3 Hz), 17.6, 17.5 (d, J_{C-P} = 5.3 Hz), 16.5 (d, J_{C-P} = 4.1 Hz), 16.4 (d, J_{C-P} = 4.1 Hz), 14.0; HRMS-FAB *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{28}O_5P$ 319.1674, found 319.1668. Anal. Calcd for $C_{15}H_{27}O_5P$: C, 56.59; H, 8.55. Found: C, 56.46; H, 8.54.

Ethyl 1-Benzyl-3,4-dimethylcyclohex-3-enecarboxylate (12a): Typical Procedure for the LN-Promoted Reductive Alkylation of 4. A 0.342 M solution of LN (4 mL, 1.37 mmol)[20] precooled to −35 °C was quickly added by syringe to a solution of **4a** (015 g, 0.46 mmol) in anhydrous THF (4 mL) at −35 °C under a nitrogen atmosphere. The resulting dark-green mixture was stirred at −35 °C for 30 min, benzyl bromide (0.34 mL, 2.77 mmol) was added, and stirrin was continued at −35 °C for 30 min. The mixture was then quenched with water (10 mL) and extracted with EtOAc (2 × 40 mL). The combined organic extracts were washed with water (10 mL) and brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography

(silica gel, hexane−EtOAc, 20:1, 5:1) afforded **12a** (0.087 g, 70%) as a viscous oil: IR (neat) 3062, 3030, 1722, 1604, 1495, 1447, 1180, 1093, 742, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27−7.18 (m, 3H), 7.07 (br d, J = 7.3 Hz, 2H), 4.06 (q, J = 7.1 Hz, 2H), 2.89 (d, J = 13.2 Hz, 1H), 2.81 (d, J = 13.2 Hz, 1H), 2.30 (br d, J = 16.7 Hz, 1H), 2.07−1.98 (m, 3H), 1.94 (br d, J = 16.7 Hz, 1H), 1.61 (s, 3H), 1.60−1.55 (m, 1H), 1.58 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2, 137.6, 130.0, 128.0, 126.4, 124.3, 123.8, 60.1, 47.1, 44.6, 38.6, 30.5, 29.3, 19.2, 18.7, 14.1; HRMS-FAB m/z $[M + H]^+$ calcd for $C_{18}H_{25}O_2$ 273.1855, found 273.1859.

Ethyl 1-Allyl-4-methylcyclohex-3-enecarboxylate (12b). The typical procedure for the preparation of **12a** was followed by using **4b** (0.14 g, 0.47 mmol) and allyl bromide (0.25 mL, 2.85 mmol). Flash chromatography (silica gel, hexane−EtOAc, 100:1, 80:1, 40:1) afforded **12b** as a colorless oil: yield 0.072 g (72%); IR (neat) 3078, 1732, 1461, 1207, 1034, 916 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.72 (dm, J = 18.0 Hz, 1H), 5.32 (br s, 1H), 5.06−5.03 (m, 1H), 5.02−4.99 (m, 1H), 4.12 (q, J = 7.2 Hz, 1H), 4.11 (q, J = 7.2 Hz, 1H), 2.45 (br d, J = 17.0 Hz, 1H), 2.32 (dd, J = 13.7, 7.7 Hz, 1H), 2.25 (dd, J = 13.7, 7.7 Hz, 1H), 2.01−1.87 (m, 4H), 1.67−1.58 (m, 1H), 1.62 (br d, J = 1.0 Hz, 3H), 1.23 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 133.9, 133.2, 119.0, 117.7, 60.2, 44.7, 42.3, 32.8, 29.7, 27.4, 23.3, 14.3; HRMS-EI m/z $[M]^+$ calcd for $C_{13}H_{20}O_2$ 208.1463, found 208.1459. Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.07; H, 9.71.

(1*R,2*S**)-Ethyl 1-(But-3-enyl)-2-methylcyclohex-3-enecarboxylate (12c).** By using **4c** (0.81 g, 2.66 mmol) and 4-bromo-1-butene (1.65 mL, 15.96 mmol) as the starting substrates, the preparation of **12c** was almost same as for preparing **12a** except for adding 2.34 mL of HMPA (13.31 mmol) to the reaction mixture right after the addition of 4-bromo-1-butene at −35 °C and allowing the reaction to proceed at 25 °C for 12 h after the addition of HMPA. Flash chromatography (silica gel, hexane−EtOAc, 160:1, 120:1) afforded **12c** as a yellowish oil: yield 0.36 g (60%); IR (neat) 3076, 3020, 1732, 1641, 1257, 1192 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (dm, J = 17.1 Hz, 1H), 5.59 (d, J = 12.0 Hz, 1H), 5.55 (d, J = 12.0 Hz, 1H), 4.98 (dm, J = 17.1 Hz, 1H), 4.92 (br d, J = 10.2 Hz, 1H), 4.15 (dq, J = 20.0, 7.1 Hz, 2H), 2.19−2.12 (m, 1H), 2.07−1.99 (m, 2H), 1.96−1.87 (m, 1H), 1.83−1.67 (m, 5H), 1.27 (t, J = 7.1 Hz, 3H), 0.89 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 138.5, 130.9, 124.7, 114.4, 60.0, 47.7, 38.2, 33.8, 29.4, 22.0, 20.4, 18.0, 14.3; HRMS-EI m/z $[M]^+$ calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1614.

(1*S,2*R**,4*S**)-Ethyl 2-Benzylbicyclo[2.2.1]hept-5-ene-2-carboxylate (12d).** The typical procedure for the preparation of **12a** was followed using **4d** (0.13 g, 0.43 mmol) and benzyl bromide (0.32 mL, 2.58 mmol). Flash chromatography (silica gel, hexane−EtOAc, 100:1, 80:1, 40:1) afforded **12d** as a viscous oil: yield 0.052 g (50%); IR (neat) 3062, 3033, 1732, 1604, 1496, 1454, 1182, 1115, 741, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28−7.19 (m, 3H), 7.10 (br d, J = 7.5 Hz, 2H), 6.18 (dd, J = 5.6, 3.0 Hz, 1H), 5.98 (dd, J = 5.6, 2.9 Hz, 1H), 4.07−3.91 (m, 2H), 3.23 (d, J = 13.5 Hz, 1H), 2.96 (br s, 1H), 2.94 (d, J = 13.5 Hz, 1H), 2.87 (br s, 1H), 1.83 (dd, J = 12.2, 2.6 Hz, 1H), 1.70 (d, J = 7.2 Hz, 1H), 1.69 (dd, J = 12.2, 3.6 Hz, 1H), 1.52 (dm, J = 6.7 Hz, 1H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 138.7, 138.4, 134.9, 129.5, 128.2 126.5, 60.1, 56.0, 50.3, 47.1, 46.0, 42.8, 36.0, 14.2; HRMS-FAB m/z $[M + H]^+$ calcd for $C_{17}H_{21}O_2$ 257.1542, found 257.1540. Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.84; H, 7.91.

(1*S,6*R**)-Ethyl 1,3,4,6-Tetramethylcyclohex-3-enecarboxylate (12e).** The typical procedure for the preparation of **12a** was followed using a mixture of **4e** and **4e′** (88:12) (0.46 g, 1.37 mmol) and iodomethane (0.51 mL, 8.22 mmol). Flash chromatography (silica gel, hexane−EtOAc, 100:1, 80:1, 40:1) afforded **12e** as a colorless oil: yield 0.23 g (75%); IR (neat) 1730, 1210, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.12 (q, J = 7.1 Hz, 2H), 2.43 (br d, J = 17.0 Hz, 1H), 2.21 (bd d, J = 17.0 Hz, 1H), 1.98−1.89 (m, 1H), 1.75 (br d, J = 17.7 Hz, 1H), 1.68 (br d, J = 17.7 Hz, 1H), 1.61 (br s, 3H), 1.58 (br s, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.14 (s, 3H), 0.84 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 122.6, 122.3, 60.0, 44.5, 37.1, 36.4, 34.5, 23.8, 19.1, 18.8, 16.9, 14.3; HRMS-EI m/z $[M]^+$ calcd for $C_{13}H_{22}O_2$ 210.1620, found 210.1612.

(2*S,6*S**)-Ethyl 1-Allyl-2,6-dimethylcyclohex-3-enecarboxylate (12f).** By using **4f** (0.32 g, 1.01 mmol) and allyl bromide (0.53 mL, 6.06 mmol) as the starting substrates, the preparation of **12f** was almost same as for preparing **12a** except for allowing the reaction to proceed at 25 °C for 12 h after the addition of allyl bromide. Flash chromatography (silica gel, hexane−EtOAc, 200:1, 150:1, 100:1) afforded **12f** as a mixture of two diastereomers (51:49): yield 0.17 g (74%); IR (neat) (for the mixture) 3076, 3019, 1726, 1654, 1637, 1203 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) major δ 6.15−6.05 (m, 1H), 5.10−4.99 (m, 4H), 4.02−3.86 (m, 2H), 2.99−2.90 (m, 1H), 2.52−1.97 (m, 3H), 1.68−1.56 (m, 2H), 1.07 (d, J = 7.3 Hz, 3H), 0.99 (d, J = 7.3 Hz, 3H), 0.93 (t, J = 7.0 Hz, 3H); minor δ 6.27−6.14 (m, 1H), 5.56−5.37 (m, 4H), 4.02−3.86 (m, 2H), 2.99−2.90 (m, 1H), 2.52−1.97 (m, 3H), 1.68−1.56 (m, 2H), 1.05 (d, J = 6.7 Hz, 3H), 0.99 (d, J = 7.3 Hz, 3H), 0.94 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) major δ 175.0, 136.1, 131.5, 123.3, 117.0, 59.7, 50.5, 37.0, 32.6, 32.0, 29.8, 16.9, 16.5, 14.1; minor δ 174.7, 137.3, 130.5, 124.8, 116.4, 59.5, 51.0, 37.5, 36.7, 31.8, 28.7, 18.2, 17.6, 14.0; HRMS-EI (for the mixture) m/z $[M]^+$ calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1612.

(2*S,6*S**)-Ethyl 2,6-Dimethyl-1-(prop-2-ynyl)cyclohex-3-enecarboxylate (12g).** By using **4f** (0.20 g, 0.64 mmol) and propargyl bromide (0.41 mL, 3.84 mmol) as the starting substrates, the preparation of **12g** was almost same as for preparing **12a** except for allowing the reaction to proceed at 25 °C for 12 h after the addition of propargyl bromide. Flash chromatography (silica gel, hexane−EtOAc, 200:1, 150:1, 80:1) afforded **12g** as a mixture of two diastereomers (60:40): yield 0.070 g (50%); IR (neat) (for the mixture) 3305, 3021, 2119, 1728, 1658, 1456, 1267, 640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) major δ 5.51 (dm, J = 10.1 Hz, 1H), 5.39 (dm, J = 10.1 Hz, 1H), 4.21−4.13 (m, 2H), 2.87−2.78 (m, 1H), 2.48−2.29 (m, 3H), 2.25−2.10 (m, 1H), 1.94 (t, J = 2.6, 1H), 1.73 (dm, J = 16.5 Hz, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.05 (d, J = 7.3 Hz, 3H), 0.91 (d, J = 7.0 Hz, 3H); minor δ 5.53 (m, 2H), 4.21−4.12 (m, 2H), 2.51−2.15 (m, 5H), 1.96 (t, J = 2.5 Hz, 1H), 1.73 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.09 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major δ 174.7, 130.9, 123.1, 82.1, 70.1, 60.4, 50.4, 33.2, 31.5, 29.8, 22.6, 16.7, 16.4, 14.3; minor δ 174.2, 130.1, 124.5, 82.9, 70.2, 60.2, 50.8, 38.1, 31.7, 28.6, 22.1, 18.1, 17.5, 14.2; HRMS-FAB (for the mixture) m/z $[M + H]^+$ calcd for $C_{14}H_{21}O_2$ 221.1542, found 221.1540.

Ethyl 4-Methyl-1-(2-oxopropyl)cyclohex-3-enecarboxylate (9). To a solution of **12b** (0.55 g, 2.65 mmol) in 38 mL of a 7:7:24 H_2O/THF/DMF mixture was added 0.12 g of $PdCl_2$ (0.65 mmol) and 0.38 g of CuCl (3.67 mmol). The mixture was flashed with oxygen gas for 15 min and then stirred under an oxygen atmosphere at 25 °C for 12 h. The reaction mixture was poured into water (20 mL) and extracted with EtOAc (2 × 60 mL). The combined organic extracts were successively washed with saturated NH_4Cl aqueous solution (20 mL), saturated $NaHCO_3$ aqueous solution (20 mL), water (20 mL), and brine (15 mL). After concentration, the crude mixture was subjected to the chromatography purification (silica gel, hexane−EtOAc, 20:1, 15:1, 8:1) to afford 0.39 g of **9** (65%): IR (neat) 3008, 1722, 1720, 1583, 1209, 1162, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.30 (br s, 1H), 4.12 (q, J = 7.2 Hz, 2H), 2.82 (d, J = 17.7 Hz, 1H), 2.73 (d, J = 17.7 Hz, 2H), 2.51 (br d, J = 17.3 Hz, 1H), 2.11

(s, 3H), 2.03−1.93 (m, 2H), 1.91−1.79 (m, 3H), 1.64 (br s, 3H), 1.21 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.9, 176.8, 132.5, 118.7, 60.5, 48.1, 41.9, 32.9, 30.6, 29.7, 27.0, 23.3, 14.1; HRMS-EI m/z $[M]^+$ calcd for $C_{13}H_{20}O_3$ 224.1412, found 224.1408. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.74; H, 8.87.

4-Methyl-1-(2-oxopropyl)cyclohex-3-enecarbaldehyde (10). To a suspension of LAH (0.61 g, 15.2 mmol) in anhydrous THF (13 mL) at 0 °C was slowly added a solution of **9** (0.49 g, 2.18 mmol) in 13 mL of dry THF under a nitrogen atmosphere. After being stirred at 0 °C for 2 h and 25 °C for 12 h, the reaction mixture was cooled to 0 °C, slowly quenched with 5 mL of aqueous NaOH solution (10%), and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated to furnish 0.36 g of crude diol, which was directly used for the next step.

To a solution of oxalyl chloride (0.75 mL, 8.58 mmol) in dry DCM (25 mL) at −78 °C under a N_2 atmosphere was added anhydrous DMSO (0.72 mL, 10.14 mmol). The resulting mixture was stirred at −78 °C for 10 min before the above diol in 2 mL of DCM was added. After being stirred for 1 h, the mixture was added with Et_3N (3.26 mL, 23.40 mmol), stirred for an additional 1 h at −78 °C, and then quenched with water (5 mL). The organic layer was separated, washed with water and brine, and concentrated under reduced pressure. The residue was purified using flash silica gel chromatography (hexane−EtOAc, 30:1, 20:1, 10:1) to give 0.29 g of **10** (75% over two steps): IR (neat) 3010, 2729, 1720, 1716, 1363 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 9.69 (s, 1H), 5.18 (br s, 1H), 2.38 (br d, J = 17.7 Hz, 1H), 2.27 (d, J = 17.9 Hz, 1H), 2.12 (d, J = 17.9 Hz, 1H), 1.78−1.65 (m, 2H), 1.64−1.55 (m, 2H), 1.51 (s, 3H), 1.46 (d, J = 1.0 Hz, 3H), 1.37−1.31 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 205.0, 204.9, 133.3, 118.8, 49.5, 45.0, 30.6, 29.4, 28.3, 26.5, 23.1.

8-Methylspiro[4.5]deca-3,7-dien-2-one (11). To a solution of **10** (0.26 g, 1.46 mmol) in THF (25 mL) was added an aqueous solution of KOH (1M, 2.5 mL, 2.46 mmol). The mixture was stirred at 25 °C for 7 h, diluted with EtOAc (120 mL), and washed with water (20 mL) and brine (20 mL). After concentration, the residue was subjected to the purification by flash chromatography (silica gel, hexane−EtOAc, 30:1, 20:1, 10:1) to afford 0.22 g of **11** (89%): IR (neat) 3012, 2964, 2913, 1716, 1675, 1587, 794 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 5.6 Hz, 1H), 6.07 (d, J = 5.6 Hz, 1H), 5.38 (br s, 1H), 2.23 (d, J = 18.7 Hz, 1H), 2.15 (d, J = 18.7 Hz, 1H), 2.14 (br d, J = 17.0 Hz, 1H), 2.05 (br s, 2H), 1.91 (d, J = 17.0 Hz, 1H), 1.69 (br s, 3H), 1.68−1.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.8, 172.2, 134.0, 132.0, 118.9, 47.5, 43.7, 36.5, 32.7, 28.0, 23.4; HRMS-EI m/z $[M]^+$ calcd for $C_{11}H_{14}O$ 162.1045, found 162.1053.

(5*R)-8-Methyl-1-[2-(triethylsilyloxy)prop-2-yl]spiro[4.5]deca-3,7-dien-2-one (13).** To a solution of **11** (0.21 g, 1.27 mmol) in dry CH_2Cl_2 (26 mL) at −78 °C was added $TiCl_4$ (1 M in CH_2Cl_2, 3.04 mL, 3.04 mmol) followed by Et_3N (1.04 mL, 7.48 mmol). After being stirred at −78 °C for 15 min and then −45 °C for 30 min, the mixture was cooled to −85 °C and mixed with 0.53 mL of reagent acetone (7.22 mmol). The reaction mixture was stirred at −85 °C for an additional 2.5 h before being mixed with 30 mL of saturated $NaHCO_3$ aqueous solution and Celite (3 g). The resulting suspension was filtered, and the filtrate was diluted with CH_2Cl_2 (120 mL), washed with water and brine, dried over $MgSO_4$, and concentrated to afford the crude alcohol. The resulting crude alcohol was subsequently dissolved by 26 mL of dry CH_2Cl_2, cooled to −78 °C, and mixed with 2,6-lutidine (1.79 mL, 15.21 mmol) followed by triethylsilyl trifluormethanesulfonate (1.45 mL, 6.34 mmol). The reaction mixture was stirred at −78 °C for 2 h and −40 °C for 12 h, quenched with 10 mL of saturated $NaHCO_3$ aqueous solution, and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with water and brine. After concentration, the residue was subjected to the purification by flash chromatography (silica gel, hexane−EtOAc, 150:1, 100:1) to afford 0.32 g of **13** (76%) as a 74:26 mixture of two isomers: IR (neat) (for the mixture) 3012, 2956, 2912, 1707, 1596, 1587, 1032, 742 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) major δ 7.28 (d, J = 5.9 Hz, 1H), 5.90 (d, J = 5.9 Hz, 1H), 5.32 (br s, 1H), 3.32 (br d, J = 16.9 Hz, 1H), 2.27−2.12 (m, 2H), 1.88−1.71 (m, 3H), 1.69 (s, 3H), 1.57 (br s, 3H), 1.34 (s, 3H), 1.28−1.21 (m, 1H), 0.95 (t, J = 7.9 Hz, 9H), 0.57 (q, J = 7.9 Hz, 6H); minor: δ 7.26 (d, J = 5.9 Hz, 1H), 5.88 (d, J = 5.9 Hz, 1H), 5.29 (br s, 1H), 2.84 (br d, J = 17.3 Hz, 1H), 2.57−2.48 (m, 2H), 1.88−1.71 (m, 3H), 1.67 (s, 3H), 1.58 (br s, 3H), 1.43 (s, 3H), 1.28−1.21 (m, 1H), 0.95 (t, J = 7.9 Hz, 9H), 0.57 (q, J = 7.9 Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6) major δ 206.6, 167.9, 131.4, 119.9, 76.0, 67.9, 48.2, 35.3, 33.2, 33.1, 28.3, 26.9, 23.1, 7.2, 7.0; minor δ 206.0 167.4, 132.1, 119.8, 76.2, 67.1, 48.6, 36.3, 33.7, 31.2, 28.3, 27.1, 23.2, 7.2, 7.0; HRMS-EI (for the mixture) m/z $[M]^+$ calcd for $C_{20}H_{34}O_2Si$ 334.2328, found 334.2324.

(5*R)-4,8-Dimethyl-1-[2-(triethylsilyloxy)prop-2-yl]spiro[4.5]dec-7-en-2-one (14).** To a suspension of purified CuI (636.5 mg, 3.28 mmol) in anhydrous ether (6.1 mL) at −14 °C was slowly added MeLi (1.6 M in ether, 3.51 mL, 5.61 mmol) within 6 min. The resulting pale yellow solution was stirred at −14 °C for an additional 20 min and then was slowly added with a solution of **13** (0.31 g, 0.94 mmol) in 6 mL of dry ether. After being stirred at −14 °C for 1 h, the reaction mixture was diluted with EtOAc (40 mL), washed with water and brine, dried over Na_2SO_4, and filtered. After concentration, the residue was subjected to purification by flash chromatography (silica gel, hexane−EtOAc, 200:1, 150:1) to afford 0.24 g of **14** (72%) as a 54:28:18 mixture of three isomers: IR (neat) (for the mixture) 1736, 1643, 1034, 1014, 744, 725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (for the mixture) δ 5.38 (br s, 0.46H), 5.33 (br s, 0.54H), 2.84 (br d, J = 17.7 Hz, 0.46H), 2.72 (br d, J = 16.9 Hz, 0.54H), 2.61−2.52 (m, 0.46H), 2.48 (dd, J = 18.1, 9.0 Hz, 0.54H), 2.44−2.32 (m, 0.46H), 2.26 (ddd, J = 18.1, 7.1, 0.5 Hz, 0.54H), 2.22−1.66 (m, 7H), 1.65 (br s, 1.38H), 1.62 (br s, 1.62H), 1.49 (d, J = 12.9 Hz, 2H), 1.40 (s, 1.12H), 1.34 (s, 2.16H), 1.32 (s, 0.72H), 1.00 (d, J = 6.6 Hz, 1.43H), 0.95−0.89 (m, 10H), 0.84 (d, J = 7.2 Hz, 0.57 Hz), 0.62−0.54 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) (for the mixture) δ 219.9, 219.0, 217.7, 132.9, 132.5, 132.4, 121.2, 120.4, 120.1, 76.1, 75.8, 70.8, 64.9, 64.1, 47.3, 45.9, 45.7, 45.4, 44.8, 44.5, 39.8, 37.9, 34.0, 33.6, 32.8, 32.7, 30.5, 30.4, 29.8, 29.5, 29.0, 28.4, 28.2, 28.0, 27.7, 27.3, 25.6, 23.4, 23.3, 17.8, 17.1, 15.3, 7.1, 7.0, 6.8, 6.7; MS (EI, 70 eV) m/z = 321.4 $[M - Et]^+$.

(4*R,5*S**)-4,8-Dimethyl-1-(prop-2-ylidene)spiro[4.5]dec-7-en-2-one [(±)-α-Alasken-8-one, 8] and (4*S**,5*S**)-4,8-Dimethyl-1-(prop-2-ylidene)spiro[4.5]dec-7-en-2-one (α-10-*epi*-Alasken-8-one, 15).** To a solution of **14** (36.5 mg, 0.10 mmol) in toluene (3.5 mL) was added *p*-toluenesulfonic acid monohydrate (40.2 mg, 0.21 mmol). The mixture was stirred at 90 °C for 1 h, cooled to 25 °C, diluted with EtOAc (40 mL), and successively washed with 5% $NaHCO_3$ aqueous solution (2 × 5 mL), water (10 mL), and brine (10 mL). Purification of the residue first by flash chromatography (silica gel, hexane−EtOAc, 150:1, 100:1, 60:1) and then by preparative TLC (silica gel, petroleum ether−THF, 120:1) afforded 12.3 mg of **8** (54%) and 5.9 mg of **15** (26%). **8**: IR (neat) 3156, 3014, 1633, 1630, 1442 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (br s, 1H), 2.53 (dd, J = 17.5, 7.6 Hz, 1H), 2.23 (s, 3H), 2.18−2.02 (m, 5H), 1.93 (s, 3H), 1.91 (dd, J = 17.5, 2.8 Hz, 1H), 1.88−1.78 (m, 1H), 1.77−1.70 (dm, J = 14.6 Hz,1H), 1.69 (s, 3H), 0.94 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.7, 149.5, 138.3, 134.7, 119.9, 46.3, 45.7, 34.3, 33.5, 28.0, 27.8, 23.9, 23.5, 23.4, 16.8; HRMS-EI m/z $[M]^+$ calcd for $C_{15}H_{22}O$ 218.1671, found 218.1676.

Compound **15**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (br s, 1H), 2.54 (dd, J = 17.3, 7.7 Hz, 1H), 2.46 (dm, J = 18.1 Hz, 1H), 2.21 (s, 3H), 2.16−1.96 (m, 6H), 1.93−1.91 (m, 1H), 1.92 (s, 3H), 1.67 (br s, 3H), 0.90 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 149.6, 138.1, 134.0, 120.6, 46.0, 45.7, 35.8, 32.6,

30.7, 28.0, 23.8, 23.7, 23.5, 18.1; HRMS-EI m/z $[M]^+$ calcd for $C_{15}H_{22}O$ 218.1671, found 218.1683.

Acknowledgment. We are grateful to the National Science Council of Republic of China (Taiwan) and National Dong Hwa University for financial support and the Department of Chemistry of National Chung Hsing University for the help with the HRMS and X-ray crystallography analyses.

Supporting Information Available: Synthesis and characterization of the mixtures of **4b**/**4b′** to **4d**/**4d′**, **4f**/**4f′**, and compounds **5**−**7**; 2D NOESY spectra of **4b** and **6**, synthesis and ORTEP drawings of the tosylhydrazone and 3,5-dinitrobenzoate derivatives of **12c** and **12e** (**16** and **17**), CIF files of **5**, **7**, **16**, and **17**, and copies of ^1H and ^{13}C NMR spectra of compounds **2**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.