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A New Method for Construction of Cyclic Enones via Phosphonate Anions

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ABSTRACT

The reaction of 2,2-disubstituted 1,3-cyclohexanediones (**1**) with dimethyl methylphosphonate anion in the presence of trimethylsilyl chloride produces 3-substituted 2-cyclohexenones (**2**) in moderate to very good yields. This new overall reaction is accounted for by (1) attack of the phosphonate anion on a carbonyl group, (2) retro-aldol cleavage, (3) reorganization of the acidic proton, and (4) an intramolecular Wadsworth-Emmonds condensation. The new rearrangement is applied to a short synthesis of (±)-α-acoradiene. The synthesis of 3-substituted 2-cyclopentenones (10) is accomplished via two-step processes.

INTRODUCTION

3-Substituted 2-cyclohexenones are versatile building blocks for the synthesis of complex cyclic natural products such as spirocyclic and fused ring sesquiterpenes. The synthetic method most commonly used is based either on the 1,4-addition of organocopper reagents to 3-halo(or acetoxy)-2-cyclohexenones [1] or on the 1,2-addition of organolithium or magnesium reagents to 3-alkoxy-2-cyclohexenones [2]. These organometallic-based procedures are subject to inherent drawbacks involved in the use of organometallic reagents; introduction of secondary alkyl groups or of functional groups often causes difficulties.

Another method, which involves the intramolecular aldol condensation of 1,4- or 1,5-diketones [3], requires often drastic reaction conditions and therefore is applicable only to simple substrates. Furthermore, the aldol method is not suitable to the selective synthesis of either a kinetically or a thermodynamically controlled product from nonsymmetrical diketones.

We report herein a new approach for the synthesis of 3-substituted 2-cyclohexenones via phosphonate anions. The reaction of 2,2-disubstituted 1,3-cyclohexanediones (**1**) with methyl dimethylphosphonate anion produces **2** in moderate to very good yields (Scheme 1) [4].

RESULTS AND DISCUSSION

Synthesis of 3-Substituted Cyclohex-2-en-1-ones

We first examined the effect of the phosphonate structure on the conversion of **1a** to **2a**. Treatment of **1a** with the phosphonate anion prepared from $MeP(O)(OMe)_2$ and *n*-BuLi in THF gave **2a** in 47% yield. The use of $MeP(O)(OiPr)_2$ produced **2a** in 18% yield. Instead of these phosphonates, cyclic phosphonates **6** and **7** were used; **6** gave **2a** in 49% yield under the same condition as in the case of $MeP(O)(OMe)_2$, although **7** did not afford **2a**. Next, we examined the effect of the bases and additives on the conversion of **1a** to **2a** using $MeP(O)(OMe)_2$. The yield of **2a** increased by the use of LDA instead of *n*-BuLi; the use of LDA (1.2 equiv) in THF gave a 65% yield of **2a**. The use of ether as a solvent decreased the yield of **2a**. Finally, we found that the yield increased dramatically by the use of TMSCl as an additive; the reaction of **1a** with the phosphonate anion prepared from 1.2 equiv of $MeP(O)(OMe)_2$ and 1.2 equiv of LDA in THF at −70°C followed by the addition of 1.2 equiv of TMSCl and subsequent stirring for 36 hours at room

Dedicated to Professor Yao-Zeng Huang on the occasion of his eightieth birthday.

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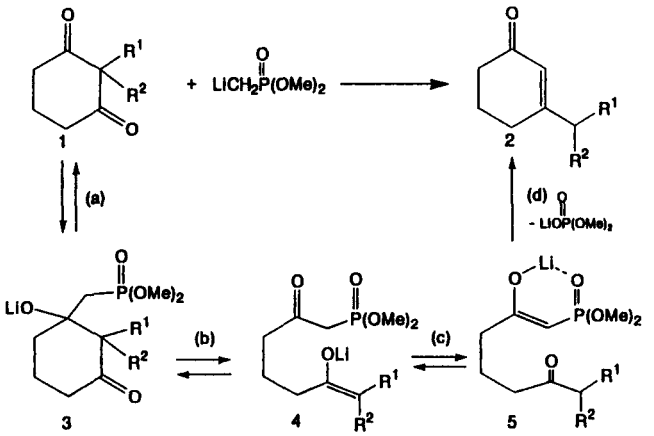
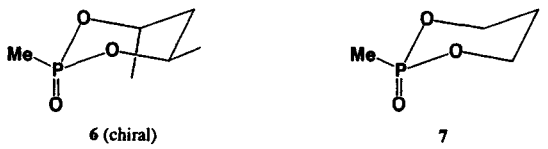


1 a; R^1 = Me, R^2 = $PhCH_2$
b; R^1 = Me, R^2 = CH_2=$CHCH_2$
c; R^1 = Me, R^2 = Me
d; R^1 = Me, R^2 = Me_2C=$CHCH_2CH_2$
e; R^1 = Me, R^2 = n-Bu
f; R^1 = Me, R^2 = $MeO_2CCH_2CH_2$
g; R^1 = Me, R^2 = Et



6 (chiral) 7

SCHEME 1

temperature, gave **2a** in 93% isolated yield. The use of BF_3·OEt_2 as an additive did not give the desired product.

The results are summarized in Table 1. The use of *n*-BuLi as a base resulted in low yields (entries 3, 5, and 9). Phosphonate-containing compounds were detected when the desired cyclohexenones were obtained in low yields (entries 9 and 10). Presumably, the sequential enolizations are arrested on the way to the final product (see Scheme 1 and Reaction Pathways).

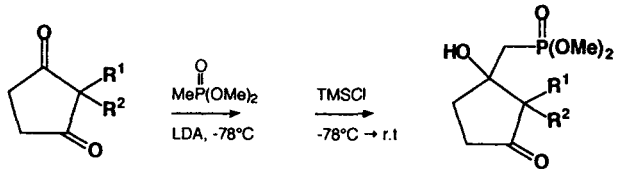
Reaction Pathways

The observed rearrangement can be explained by the sequence shown in Scheme 1: (1) the phosphonate anion attacks one of the two carbonyl groups of **1** to give **3**; (2) retro-aldol cleavage of **3** produces the keto phosphonate anion **4**; (3) reorganization of the acidic protons affords **5**; (4) an intramolecular Wadsworth-Emmonds reaction of **5** gives the final product **2**. TMSCl may shift the equilibrium in the forward direction. When the reaction was quenched after a short period, the protonated product of **5** was isolated along with **2**. Furthermore, the following observations in regard to related systems support the above mechanism. A similar retro-aldol cleavage was observed in the reaction of 2,2-disubstituted 1,3-cyclohexanedione (**1**) with alcoholic sodium hydroxide [5], and the bond reorganization in enol lactones has been reported previously [6].

TABLE 1 Synthesis of **2** from **1**

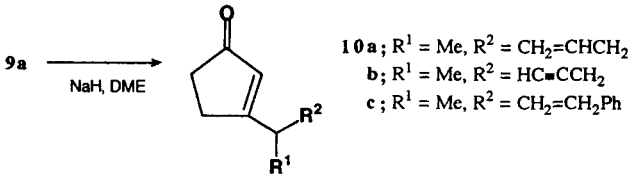
Entry	*Substrate*	*Method*[a]	*Product (**2a–g**) Isolated Yield, %*
1	**1a**	A	93 (**2a**)
2	**1a**	B	65 (**2a**)
3	**1a**	C	47 (**2a**)
4	**1b**	A	89 (**2b**)
5	**1c**	C[b]	58 (**2c**)
6	**1d**	A	61 (**2d**)
7	**1e**	A	65 (**2e**)
8	**1e**	B	61 (**2e**)
9	**1f**	C[b]	33 (**2f**)[c]
10	**1g**	A	22 (**2g**)[c]

[a]Method A: see Experimental section (standard procedure). Method B: same as method A except for absence of TMSCl. Method C: same as method B except for use of *n*-BuLi instead of LDA.
[b]Instead of methyl dimethylphosphonate, 2,4,6-trimethyl-2-oxo-1,3,2-dioxaphosphorinane was used as a phosphonate.
[c]Unidentified polar products, presumably phosphonate-containing compounds, were produced along with the desired product.



8 a; R^1 = Me, R^2 = CH_2=$CHCH_2$
b; R^1 = Me, R^2 = HC≡CCH_2
c; R^1 = Me, R^2 = CH_2=CH_2Ph

9 a; R^1 = Me, R^2 = CH_2=$CHCH_2$
b; R^1 = Me, R^2 = HC≡CCH_2
c; R^1 = Me, R^2 = CH_2=CH_2Ph



10 a; R^1 = Me, R^2 = CH_2=$CHCH_2$
b; R^1 = Me, R^2 = HC≡CCH_2
c; R^1 = Me, R^2 = CH_2=CH_2Ph

Synthesis of 3-Substituted Cyclopent-2-en-1-ones

Being stimulated by the success of the cyclohexenone synthesis, we extended the present phosphonate method to five membered analogues. The reaction of **8a** with dimethyl lithiomethylphosphonate under similar conditions as above proceeded in a different way: the phosphonate addition product **9a** was obtained in 23% yield, and the starting material was recovered in 31% yield. When

the reaction was quenched at −78°C prior to the addition of TMSCl, **9a** was obtained in 53% yield along with 43% yield of recovered **8a**. Treatment of **9a** with NaH in dimethoxyethane at room temperature gave the desired cyclopentenone **10a** in 56% yield. The use of *t*-BuOK as a base in *t*-BuOH gave **10a** in 36% yield, and no rearrangement took place with KH-DME even under refluxing for 10 hours. Accordingly, it is clear that the sequential rearrangement observed in the case of 1,3-cyclohexanediones does not occur in the five membered analogue; instead, the two-step procedure is required to accomplish the synthesis of cyclopentenones. In fact, the same two-step process as above was required in the case of **8b** and **8c**; **8b** gave **9b**, which was converted to **10b** in 34% yield upon treatment with *t*-BuOK/*t*-BuOH-THF, and similarly, **8c** produced **10c** in 78% yield through **9c**.

Difference between the Six- and Five-Membered Diketones

The multistep rearrangement proceeded well with the six-membered cyclic diketones, whereas the reaction of the five-membered analogue stopped at the first step to give the 1,2-adduct of the phosphonate anion. Perhaps the difference arises from a different reactivity in the retro-aldol cleavage of the intermediates (**3** and its five-membered analogue). In the six-membered system, the C_2—C_3 δ-bond of **11** is parallel to the π-orbital of the carbonyl group. Therefore, the C=O π-system assists the bond cleavage, which is a stereoelectronically allowed process, [7] to give **12** in good yield. In contrast, the C_2—C_3 bond of the five-membered system **13** is nearly perpendicular to the π-orbital of the carbonyl group. The assistance of the π-system to the bond cleavage is negligible. In addition to this, the Li—O bond has a covalent character. Therefore, the bond cleavage of **13** (M=Li) must be very sluggish. When M=Na or K, an increased ionic character of the C—O bond helps the retro-aldol reaction to occur to give **14**.

Application to Formal Total Synthesis of (±)-α-Acoradiene

The present method was applied to a short formal synthesis of (±)-α-acoradiene **18**. Selective ozonolysis [8] of **2d** followed by reductive workup with Zn/AcOH gave the enone-aldehyde **15** in quantitative yield. Allylsilane **16** was prepared in 50% yield using the Seyferth-Fleming method [9]. The intramolecular Sakurai-Hosomi type of condensation in the presence of $EtAlCl_2$ [10] gave the corresponding spiroketones **17** as a mixture of three diastereomers in 53% yield (**17a**:**17b**:**17c** = 2:2:1). The desired diastereomer **17a** [11] results from the *synclinal-1* transition state, while the other two diastereomers **17b** and **17c** are produced via the antiperiplanar transition states (Scheme 2). Accordingly, the ratio of the synclinal vs. antiperiplanar products is 2:3. Schinzer has reported that a synclinal transition state is involved in a related system [10]. However, the cyclization of **16** proceeds predominantly through the antiperiplanar transition state, indicating that the transition-state geometry of the intramolecular cyclization is highly dependent on the substrate structures. Synthesis of **18** from **17a** can be performed according to the procedure reported by Oppolzer and co-workers [11] (Scheme 3).

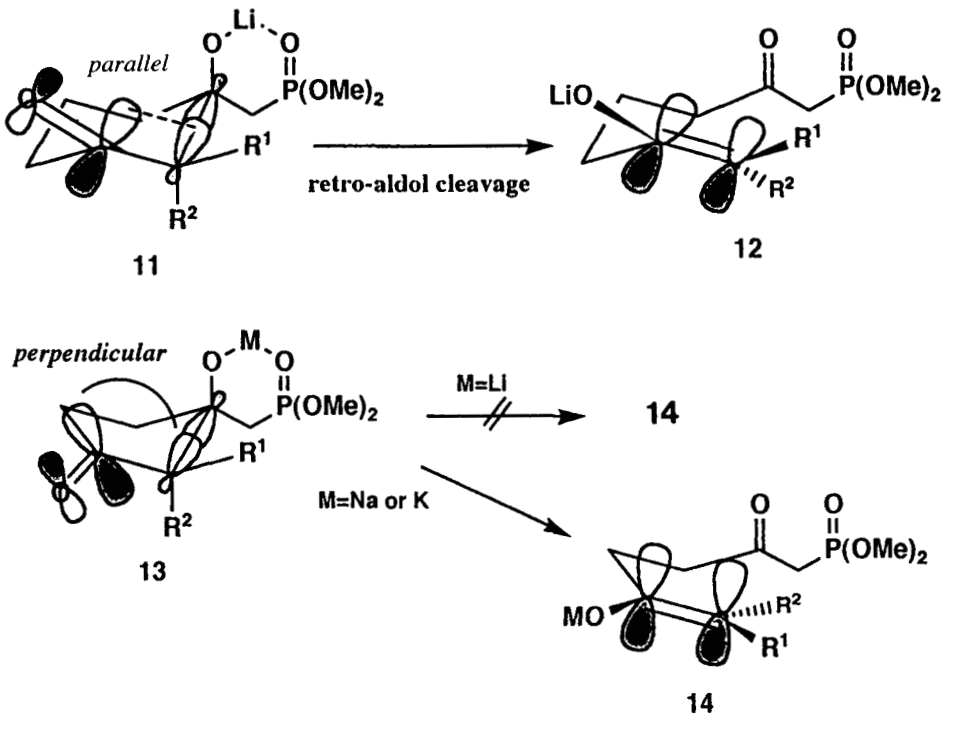
An Attempt at the Asymmetric Synthesis of **2**

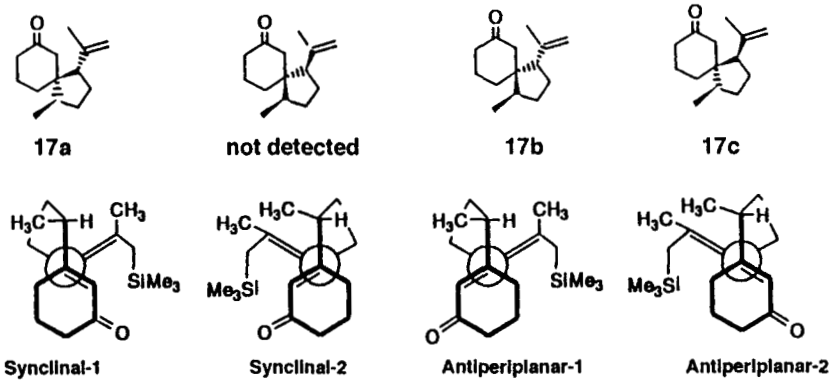
The asymmetric synthesis of **2a** was attempted by using chiral phosphonates in which chiral anxiliaries were introduced in the phosphonate ester group. The reaction of **1a** with **6** under the standard condition gave **2a** with a specific rotation of −3.4°. The homochiral phosphonate **19** was synthesized according to a modified method of the known procedure [12]. The reaction of **1a** with **19** produced **2a** in 47% yield with $[\alpha]_D^{28}$ + 12.2° (c 1.1, $CHCl_3$). The ee of **2a** was determined by HPLC using a chiral column (CHIRAL CELL OC, 20 mm ϕ × 500 mm, 9% IPA/*n*-hexane, flow rate 4.0 mL/min). After recycling 15 times, two enantiomers were separated, and the ratio of (+)-**2a**:(−)-**2a** was 62:38 (24% ee). Although an asymmetric induction was observed via **19**, the extent of the enantiomer excess was not high. Further work should be carried out on the asymmetric synthesis.

EXPERIMENTAL SECTION

Synthesis of **2** *from* **1**

Seventy-six milligrams (0.61 mmol) of dimethyl methylphosphonate were placed in an oven-dried, 30 mL, two-necked, round-bottom flask containing a magnetic stirring bar. The flask was flushed with argon, then sealed with a rubber septum. Dry tetrahydrofuran (6 mL) was added with a syringe, and the flask was placed in a Dry Ice-isopropyl alcohol bath. After 5 minutes, 0.30 mL (0.63 mmol) of 2.1 M lithium diisopropylamide in cyclohexane was added with a syringe and the stirring was continued for 40 minutes. Eighty-three milligrams (0.50 mmol) of **1b** were placed in an oven-dried, 20 mL, two-necked, round-bottom flask. The flask was flushed with argon, then sealed with a rubber septum. Dry tetrahydrofuran (2 mL) was added with a syringe. The solution was transferred dropwise, via a cannula, into the methyl dimethylphosphonate anion solution as prepared previously and the stirring was continued for 9.5 hours at −70°C. Sixty-five milligrams (0.60 mmol) of chlorotrimethylsilane (TMSCl) were placed in an oven-dried, 20 mL, two-necked, round-bottom flask. The flask was





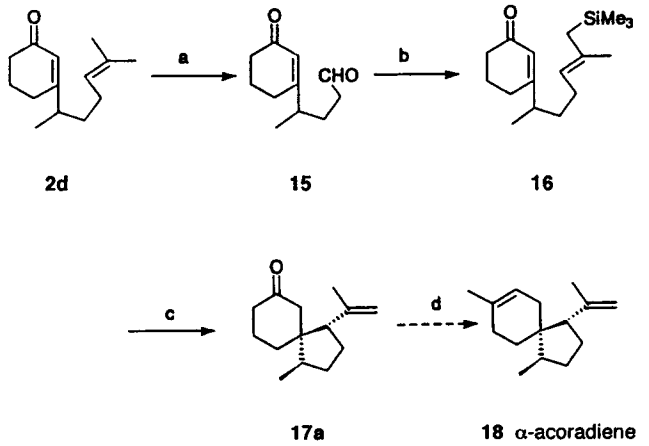
Synclinal : Antiperiplanar = 17a : (17b + 17c) = 2 : 3

SCHEME 2

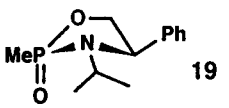
flushed with argon, then sealed with a rubber septum. Dry tetrahydrofuran (2 mL) was added with a syringe. The solution was transferred dropwise, via a cannula, into the reaction mixture. After the addition of TMSCl, the reaction mixture was allowed to warm to room temperature and stirred for an additional 36 hours. The reaction mixture was treated with saturated aqueous ammonium chloride solution, and diluted with ether. The separated aqueous layer was extracted with ether. The combined organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. Concentration under vacuum gave 113.9 mg of crude product as an oil. Purification with column chromatography (5 g of SiO_2 60 E. Merck No. 5554, 4.8% ethyl acetate/*n*-hexane) gave 72.8 mg (0.443 mmol, 89% yield) of **2b** as a colorless oil.

1b: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 5.58 (1H, dddd, J = 17, 9.5, 7.0, and 7.0 Hz) 5.09 (1H, m) 5.04 (1H, m) 2.66 (2H, dd, J = 6.0, and 2.0 Hz) 2.64 (2H, d, J = 6.0 Hz) 2.53 (2H, ddd, J = 7.0, 1.0, and 1.0 Hz) 2.05–1.85 (2H, m) 1.25 (3H, s); IR $\nu_{CCl_4/cm^{-1}}$ 2960, 1730, 1700, 1320, 1020, 930.

2b: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 5.87 (1H, brs) 5.69 (1H, dddd, J = 17, 10, 7.0, and 7.0 Hz) 5.02 (1H, dddd, J = 17, 1.5, 1.5, and 1.5 Hz) 5.01 (1H, dddd,



[a](a) O_3, CH_2Cl_2, then Zn, AcOH; (b) $Ph_3P{=}C(CH_3)CH_2SiMe_3$, THF; (c) $EtAlCl_2$, toluene, -75°C; (d) Reference 11.



SCHEME 3

J = 10, 2.0, 1.0, and 1.0 Hz) 2.36–1.95 (9H, m) 1.11 (3H, d, J = 6.5 Hz); IR $\nu_{CCl_4/cm^{-1}}$ 2980, 2950, 1675, 1625, 1330, 1260, 1250, 1220, 1200, 1000, 920, 900; MS (EI, 25eV, 80°C) *m/e* (rel int/%) 164 (M^+, 13.7), 149 (2.9), 135 (3.5), 131 (6.3), 122 (1.2), 121 (28.2), 108 (12.0), 107 (4.9), 96 (8.3), 95 (100), 94 (14.1), 93 (44.5), 91 (8.1), 81 (6.3), 80 (5.6), 79 (40.7), 68 (7.1), 67 (37.6), 55 (24.8), 53 (2.3); HR-MS (EI) calcd for $C_{11}H_{16}O$ 164.1202. Found 164.1201. The synthesis of **2a** was carried out without aqueous workup. This reaction was performed as described in the general procedure except that 115 mg (0.532 mmol) of **1a** and 73 mg (0.67 mmol) of TMSCl were used. The reaction mixture was concentrated under vacuum without aqueous workup and subjected to column chromatography (5 g of SiO_2 60 E. Merck No. 5554, 4.8% ethyl acetate/*n*-hexane) directly. Cyclohexenone **2a** (106.1 mg, 0.495 mmol, 93% yield) was obtained as a colorless oil.

2a: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 7.30–7.10 (5H, m) 5.86 (1H, brs) 2.80 (1H, m) 2.64–2.58 (2H, m) 2.35–2.25 (4H, m) 1.98–1.90 (2H, m) 1.09 (3H, d, J = 6.6 Hz); IR $\nu_{CCl_4/cm^{-1}}$ 2980, 2950, 2890, 1675, 1620, 1460, 895, 700; MS (EI, 25eV, 80°C) *m/e* (rel int/%) 214 (M^+, 4.5), 182 (6.2), 139 (39.7), 126 (56.9), 124 (20.3), 112 (4.3), 111 (85.7), 109 (3.1), 100 (59.7), 98 (12.7), 97 (22.0), 96 (39.5), 95 (10.6), 93 (5.1), 92 (9.3), 91 (100), 84 (4.7), 81 (5.3), 72 (17.9), 69 (21.0), 68 (1.1), 67 (6.4), 56 (2.6), 55 (10.8); HR-MS (EI) calcd for $C_{15}H_{18}O$ 214.1358. Found 214.1356.

2c: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 5.89 (1H, m) 2.44–2.30 (5H, m) 1.99 (2H, m) 1.11 (6H, d, J = 7.0 Hz).

1e: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 2.72–2.62 (4H, m) 2.04 (1H, m) 1.87–1.74 (3H, m) 1.26 (2H, m) 1.22 (3H, s) 1.10 (2H, m) 0.87 (3H, t, J = 7.0 Hz); IR $\nu_{CCl_4/cm^{-1}}$ 2960, 2870, 1725, 1700, 1460, 1420, 1380, 1320, 1280, 1130, 1020, MS (EI, 25eV, 80°C) *m/e* (rel int/%) 182 (M^+, 7.9), 139 (39.7), 126 (65.9), 124 (19.2), 112 (2.2), 111 (100), 100 (39.5), 98 (25.2), 97 (21.5), 96 (21.5), 93 (2.5), 84 (3.2), 81 (3.6), 72 (21.0), 70 (4.3), 69 (33.5), 67 (7.3), 55 (22.2); HR-MS (EI) calcd for $C_{11}H_{18}O_2$ 182.1307. Found 182.1304

2e: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 5.87 (1H, brs) 2.4–2.2 (5H, m) 2.05–1.95 (2H, m) 1.55–1.20 (6H, m) 1.08 (3H, d, J = 7.0 Hz) 0.88 (3H, t, J = 7.0 Hz); IR $\nu_{CCl_4/cm^{-1}}$ 2970, 2950, 2880, 1675, 1625, 1460, 1430, 1390, 1360, 1330, 1260, 1200, 900; MS (EI, 25eV, 80°C) *m/e* (rel int/%) 180 (M^+, 4.0), 137 (13.8), 125 (3.5), 124 (82.0), 110 (2.8), 109 (16.2), 100 (67.2), 97 (27.6), 96 (100), 95 (31.2), 84 (11.7), 82 (3.0), 81 (23.0), 72 (42.7), 68 (3.5), 67 (15.6), 55 (6.9); HR-MS (EI) calcd for $C_{12}H_{20}O$ (M^+) 180.1515. Found 180.1496.; calcd for $C_{11}H_{17}O$ (M^+-CH_3) 165.1280. Found for $C_{11}H_{17}O$ (M^+-CH_3) 165.1291.

1f: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 3.64 (3H, s) 2.71 (2H, dd, J = 2.0, and 6.5 Hz) 2.68 (2H, d, J = 6.5 Hz) 2.22 (2H, m) 2.14 (2H, m) 1.98 (2H, m) 1.27 (3H, s); IR $\nu_{CCl_4/cm^{-1}}$ 2960, 1740, 1735, 1700, 1440, 1380, 1320, 1300, 1270, 1220, 1200, 1180, 1030, 905; HR-MS (EI) calcd for $C_{11}H_{16}O_4$ 212.1048. Found for $C_{11}H_{16}O_4$ 212.1048.

2f: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 5.87 (1H, brs) 3.67 (3H, s) 2.4–2.22 (7H, m) 2.02–1.7 (4H, m) 1.12 (3H, d, J = 7.0 Hz); IR $\nu_{CCl_4/cm^{-1}}$ 2950, 1740, 1670, 1620, 1460, 1440, 1370, 1320, 1260, 1190, 1170, 895; HR-MS (EI) calcd for $C_{12}H_{18}O_3$ 210.1265. Found for $C_{12}H_{18}O_3$ 210.1257.

1g: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 2.61 (4H, t, J = 6.5 Hz) 2.39 (2H, t, J = 7.0 Hz) 1.79 (4H, q, J = 7.3 Hz) 0.76 (6H, t, J = 7.3 Hz); IR $\nu_{CCl_4/cm^{-1}}$ 2960, 2880, 1730, 1695, 1460, 1435, 1380, 1320, 1220, 1020, 905; HR-MS (EI) calcd for $C_{10}H_{16}O_2$ (M^+) 168.1151. Found for $C_{10}H_{16}O_2$ (M^+) 168.1139. Calcd for $C_8H_{11}O_2$ (M^+-C_2H_5) 139.0759. Found for $C_8H_{11}O_2$ (M^+-C_2H_5) 139.0759.

2g: ^{1}H-NMR (60 MHz) δ_{CDCl_3} 5.87 (1H, brs) 2.5–1.2 (11H, m) 0.83 (6H, t, J = 7.0 Hz); IR $\nu_{CCl_4/cm^{-1}}$ 2960, 2870, 1670; MS (EI, 25eV, 80°C) *m/e* (rel int/%) 166 (M^+, 18.4), 151 (1.6), 137 (3.1), 129 (33.0), 128 (3.6), 123 (2.3), 110 (85.5), 109 (8.9), 101 (38.9), 100 (40.5), 96 (8.2), 95 (46.7), 87 (2.7), 84 (40.9), 83 (4.6), 82 (16.4), 81 (14.3), 79 (2.7), 71 (19.5), 67 (19.5), 59 (100), 58 (2.4), 55 (65.6); HR-MS (EI) calcd for $C_{11}H_{18}O$ 166.1358. Found for $C_{11}H_{18}O$ 166.1358.

Synthesis of **9** *from* **8**

Dimethyl methylphosphate (541 mg, 4.36 mmol) was placed in an oven-dried, 50 mL, two-necked,

round-bottomed flask equipped with a magnetic stirring bar. The flask was flushed with argon, then sealed with a rubber septum. Dry tetrahydrofuran (THF) (30 mL) was added with a syringe, and the flask was placed in a Dry Ice-IPA bath. After 5 minutes, 2.1 M lithium diisopropylamide (LDA) in cyclohexane (1.9 mL, 4.0 mmol) was added dropwise with a syringe and the stirring was continued for 1 hour. In an oven-dried, 20 mL, two-necked, round-bottom flask equipped with a rubber septum was placed **8a** (553 mg, 3.63 mmol). The flask was evacuated under vacuum, then flushed with argon. Dry THF (6 mL) was added with a syringe. The solution was transferred dropwise, via a cannula, into the dimethyl methylphosphonate anion solution prepared above over 10 minutes. After 4 hours, the reaction was quenched by adding dilute ammonium chloride solution and the cooling bath was removed immediately. Extraction with methylene chloride, washing with saturated brine, drying over anhydrous magnesium sulfate, and concentration under vacuum gave crude product (1.065 g) as a yellow oil. The crude product was purified by column chromatography (45 g of SiO_2 60 E. Merck No. 5554, 1% methanol/methylene chloride) to give **9a** (520 mg, 1.88 mmol, 52% yield) as a yellow oil and recovered **8a** (231 mg, 1.52 mmol, 42%).

9a: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 6.00 (1H, dddd, J = 17, 10, 8.0, and 7.0 Hz) 5.14 (1H, dddd, J = 17, 1.5, 1.5, and 1.5 Hz) 5.10 (1H, dddd, J = 10, 1.5, 1.5, and 1.5 Hz) 4.00 (1H, s) 3.81 (3H, d, J = 6 Hz) 3.77 (3H, d, J = 6.0 Hz) 2.50–2.25 (6H, m) 2.05 (1H, ddd, J = 13, 10.5, and 9.0 Hz) 1.96 (1H, dd, J = 20, and 15 Hz) 0.90 (3H, s); IR $\nu_{CCl_4/cm^{-1}}$ 3450, 2850, 1740, 1640, 1460, 1405, 1240, 1180, 1060, 1040, 920, 850. Anal calcd for $C_{12}H_{21}O_5P$: C, 52.17%; H, 7.66%. Found: C, 52.35%; H, 7.58%.

Similarly, the reaction of **8b** (150 mg, 1.00 mmol) with methyl dimethylphosphonate gave **9b** (47.5 mg, 0.17 mmol, 17% yield) along with recovered **8b** (81 mg, 0.54 mmol, 54%).

9b: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 4.10 (1H, s) 3.82 (3H, d, J = 5.0 Hz) 3.78 (3H, d, J = 5.0 Hz) 2.86 (1H, dd, J = 17, and 15.5 Hz) 2.68 (1H, ddd, J = 17, 2.5, and 0.5 Hz) 2.50–2.20 (4H, m) 2.12–2.04 (3H, m) 1.08 (3H, s); IR $\nu_{CCl_4/cm^{-1}}$ 3550–3200, 3300 (s), 3000, 1740, 1220, 1040, 980, 920, 860, 830; HR-MS (EI) calcd for $C_{12}H_{19}O_5P$ 274.0970 (M^+). Found 274.0971 (M^+).

The reaction of **8c** (104 mg, 0.51 mmol) with methyl dimethylphosphonate gave **9c** (49 mg, 0.15 mmol, 29% yield) along with recovered **8c** (61 mg, 0.30 mmol, 59%).

9c: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 7.40–7.15 (5H, m) 4.30 (1H, s) 3.85 (3H, d, J = 11 Hz) 3.73 (3H, d, J = 11 Hz) 3.30 (1H, d, J = 13.5 Hz) 2.88 (1H, d, J = 13.5 Hz) 2.70 (1H, ddd, J = 19, 10.5, and 9.0 Hz) 2.48 (1H, ddd, J = 14, 9.0, and 1.0 Hz) 2.37 (1H, brdd, J = 13, and 9.0 Hz) 2.12 (1H, ddd, J = 13, 10.5, and 9.0 Hz) 1.80–1.65 (2H, m) 0.90 (3H, s); IR $\nu_{CCl_4/cm^{-1}}$ 3550–3300, 3000, 1740, 1495, 1465, 1460, 1400, 1370, 1220, 1070, 1040, 990, 960, 930, 860, 710; HR-MS (EI) calcd for $C_{16}H_{23}O_5P$ 326.1283 (M^+). Found 326.1283 (M^+).

Base-Promoted Rearrangement of **9a** *to* **10a**

Sodium hydride (60% disp in mineral oil, 25 mg, 0.63 mmol) was placed in an oven-dried, 20 mL, two-necked, round-bottom flask equipped with a magnetic stirring bar and a rubber septum. The flask was evacuated under vacuum, then flushed with argon. Sodium hydride was washed with three portions of dry dimethoxyethane (DME), then 3 mL of dry DME was added with a syringe. The flask was placed in an ice-water bath. **9a** (59 mg, 0.214 mmol) was placed in an oven-dried, 20 mL, two-necked, round-bottom flask equipped with a rubber septum. Dry DME (2 mL) was added with a syringe, and the solution was transferred dropwise, via a cannula, into the suspension of sodium hydride prepared above over 10 minutes. The mixture was stirred at O°C for 1.5 hours, and then at room temperature for 18 hours. The reaction was quenched by adding dilute ammonium chloride solution. Extraction with methylene chloride, washing with saturated brine, drying over anhydrous magnesium sulfate, and concentration under vacuum gave pure **10a** (18 mg, 0.12 mmol, 56% yield) as a colorless oil.

10a: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 5.95 (1H, m) 5.72 (1H, dddd, J = 16.5, 10.5, 7.0, and 7.0 Hz) 5.06 (1H, dddd, J = 16.5, 1.5, 1.5, and 1.5 Hz) 5.04 (1H, dddd, J = 10.5 1.5, 1.5, and 1.5 Hz) 2.65–2.58 (3H, m) 2.42–2.23 (4H, m) 1.17 (3H, d, J = 7.0 Hz); IR $\nu_{CCl_4/cm^{-1}}$ 3100, 2970, 2920, 1710, 1640, 1610, 1440, 1180, 1170, 990, 920, 860; HR-MS (EI) calcd for $C_{10}H_{14}O$ 150.1045 (M^+). Found 150.1046 (M^+).

Base Promoted Rearrangement of **9b** *and* **9c**

In an oven-dried, 20 mL, two-necked, round-bottom flask equipped with a magnetic stirring bar and a rubber septum was placed potassium tert-butoxide (KOt-Bu) (21 mg, 0.19 mmol). The flask was evacuated under vacuum, then flushed with argon. Dry THF (3 mL) and tert-butyl alcohol (0.03 mL) were added with syringes. The mixture was placed in an ice-water bath. **9b** (34 mg, 0.12 mmol) was placed in an oven-dried, 20 mL, two-necked, round-bottom flask equipped with a rubber septum. The flask was evacuated under vacuum, then flushed with argon. Dry THF (2 mL) was added with a syringe, and the solution was transferred dropwise, via a cannula, into the KOt-Bu solution prepared above over 5 minutes. The mixture was stirred at room temperature for 19 hours, then treated with dilute ammonium chloride solution.

Extraction with methylene chloride, washing with saturated brine, drying over anhydrous magnesium sulfate, and concentration under vacuum gave crude products (22 mg). The crude products were purified by column chromatography to give pure **10b** (6 mg, 0.04 mmol, 34% yield) along with recovered **9b** (5 mg, 0.02 mmol, 17%).

10b: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 6.03 (1H, dd, J = 2.5, and 1.5 Hz) 2.77 (1H, brdq, J = 6.5, and 6.5 Hz) 2.66–2.63 (2H, m) 2.44–2.41 (4H, m) 2.01 (1H, t, J = 2.5 Hz) 1.28 (3H, d, J = 7.0 Hz); IR $\nu_{CCl_4/cm^{-1}}$ 3300 (s), 2970, 2920, 1715, 1615, 1460, 1440, 1250, 1180, 980; MS (EI, 25eV, 80°C) *m/e* (rel int/%) 149 (13.6), 148 (M+, 100), 147 (13.2), 133 (31.8), 120 (34.1), 119 (12.5), 109 (28.4), 106 (33.0), 105 (79.5), 94 (18.2), 92 (18.5), 91 (68.2), 81 (37.5), 79 (26.1), 78 (9.1), 77 (14.8), 67 (13.6), 65 (9.1), 53 (29.5).

The KOt-Bu promoted rearrangement of **9c** (69 mg, 0.21 mmol) was performed as described above except that tert-butyl alcohol was used as solvent. After column chromatography (2.5 g of SiO_2 60 E. Merck No. 5554, 9% ethyl acetate/*n*-hexane), 33 mg (0.16 mmol, 78% yield) of **10c** were isolated as a colorless oil.

10c: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 7.35–7.10 (5H, m) 5.94 (1H, m) 2.90–2.85 (2H, m) 2.68 (1H, m) 2.59–2.55 (2H, m) 2.38 (2H, dd, J = 4.5, and 4.5 Hz) 1.15 (3H, d, J = 6.5 Hz); IR $\nu_{CCl_4/cm^{-1}}$ 3020, 2970, 2920, 1715, 1610, 1490, 1450, 1440, 1180, 700; HR-MS (EI) calcd for $C_{14}H_{16}O$ 200.1202 (M^+). Found 200.1215 (M^+).

Formal Synthesis of (±)-α-Acoradiene. Synthesis of **2d**

This reaction was performed as described in the general procedure except that 109 mg (0.499 mmol) of **1d** were used, and the reaction mixture was stirred for 12.5 hours at 40°C after warming to room temperature. Column chromatography (7 g of SiO_2 60 E. Merck No. 5554, 4.8% ethyl acetate/*n*-hexane) gave 62.6 mg (0.303 mmol, 61% yield) of **2d** and 5.4 mg (0.026 mmol, 5.2% recovery) of **1d** in the fraction eluted with *n*-hexane-EtOAc along with 15.4 mg of unidentified polar materials in the fraction eluted with CH_2Cl_2.

1d: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 5.00 (1H, m) 2.75–2.58 (4H, m) 2.03–1.80 (6H, m) 1.65 (3H, s) 1.56 (3H, s) 1.24 (3H, s); IR $\nu_{CCl_4/cm^{-1}}$ 2980, 2945, 1730, 1700, 1460, 1425, 1380, 1025; MS (EI, 25eV, 80°C) *m/e* (rel int/%) 206 (M^+-2, 13.1), 150 (14.3), 148 (2.0), 137 (70.2), 128 (30.3), 127 (100), 124 (66.0), 111 (11.7), 110 (19.3), 109 (22.5), 98 (27.6), 97 (7.1), 96 (12.2), 95 (37.4), 93 (2.1), 84 (3.9), 83 (51.6), 82 (99), 81 (40.6); HR-MS (EI) Calcd for $C_{13}H_{20}O_2$ (M^+-H) 207.1385. Found 207.1370.

2d: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 5.87 (1H, brs) 5.06 (1H, m) 2.38–2.25 (5H, m) 2.02–1.90 (4H, m) 1.68 (3H, brs) 1.58 (3H, brs) 1.54–1.36 (2H, m) 1.09 (3H, d, J = 7.0 Hz); IR $\nu_{CCl_4/cm^{-1}}$ 2960, 2930, 2670, 1620, 1455, 1380, 1350, 1320, 1260, 1190, 890; MS (EI, 25eV, 80°C) *m/e* (rel int/%) 206 (M^+, 8.4), 166 (12.6), 150 (9.1), 148 (7.0), 137 (66.7), 129 (4.4), 124 (66.1), 123 (9.2), 110 (50.6), 109 (32.5), 97 (15.3), 96 (36.1), 95 (51.1), 93 (16.0), 84 (23.5), 83 (6.8), 82 (100), 81 (33.3), 79 (5.3), 71 (24.8), 69 (13.7), 68 (2.2), 67 (43.9), 55 (41.5); HR-MS (EI) Calcd for $C_{14}H_{22}O$ 206.1671. Found 206.1670.

A 200 mL, round-bottom flask equipped with a magnetic stirring bar and a Claisen adapter with a gas inlet and a drying tube ($CaCl_2$) was charged with 1.031 g (4.997 mmol) of **2d** and 100 mL of dry methylene chloride containing 0.45 mL (5.6 mmol) of pyridine. A small amount of Sudan III was added as an indicater. The flask was placed in a Dry Ice-isopropyl alcohol bath, and a stream of ozone was bubbled through the light-red solution. After 30 minutes, the light-red color of the solution disappeared. After this point, TLC showed that the reaction was essentially complete, then a stream of oxygen was passed in for 5 minutes to displace the ozone. The cold (−75°C) reaction mixture was immediately poured into a 200 mL Erlenmeyer flask containing 2.55 g (39.0 mmol) of powdered zinc and a magnetic stirring bar. Acetic acid (5 mL) was added, and the mixture was vigorously stirred in a water bath for 2 hours. The reaction mixture was filtered through Celite pad and the filtrate was washed with water (10 mL × 2), 5% sodium hydroxide solution (10 mL × 2), water (10 mL × 3), and saturated brine, then dried over anhydrous magnesium sulfate. Concentration under vacuum gave 1.2 g of crude aldehyde. ^{1}H-NMR (60 MHz) showed that the crude product contained enone-aldehyde **15** and a small amount of solvents. Unpurified **15** was used for a next reaction to avoid decomposition through the purification steps.

416 mg (1.12 mmol) of ethyl triphenylphosphonium bromide was placed in an oven-dried, 50 mL, two-necked, round-bottom flask equipped with a magnetic stirring bar and a rubber septum. The flask was evacuated under vacuum, then flushed with argon. Dry THF (10 mL) was added with a syringe, and the flask was placed in an ice-water bath. *n*-Butyllithium in *n*-hexane (1.62 M, 0.80 mL, 1.30 mmol) was added dropwise with a syringe to the stirred white suspension, and the stirring was continued for 55 minutes at room temperature. The reaction mixture became a red solution with the formation of ethylidenetriphenylphosphorane. The flask was placed in an ice-water bath, 240 mg (1.12 mmol) of (iodomethyl)trimethylsilane was placed in an oven-dried, 20 mL, two-necked, round-bottomed flask. The flask was flushed with argon, then sealed with a rubber septum. Dry THF (2 mL) was added with a syringe. The solution was transferred, via a cannula, into the ethylidenetriphen-

ylphosphorane solution prepared above, and the stirring was continued for 4 hours at room temperature. The reaction mixture became a yellow suspension. The flask was placed in a Dry Ice-isopropyl alcohol bath. After 5 minutes, *n*-butyllithium in *n*-hexane (1.62 M, 0.08 mL, 1.30 mmol) was added dropwise, with a syringe, and the stirring was continued for 1.5 hours at −75°C. The reaction mixture became a deep-red solution. 178 mg (0.988 mmol) of **15** was placed in an oven-dried, 20 mL, two-necked, round-bottomed flask equipped with a rubber septum. The flask was evacuated under vacuum, then flushed with argon. Dry THF (3 mL) was added with a syringe. The solution was transferred dropwise, via a cannula, into the deep-red solution of the Wittig reagent prepared above, and the stirring was continued for 0.5 hour at −75°C. The light-red reaction mixture was allowed to warm to room temperature and stirred for an additional 3 hours. The reaction was quenched by adding saturated ammonium chloride solution, and the mixture was diluted with ether. The separated aqueous layer was extracted with ether. The combined organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, then concentrated under vacuum to give 694.9 mg of crude product. Purification by column chromatography (30 g of SiO_2 60 E. Merck No. 5554, 4.8% ethyl acetate/*n*-hexane) gave 135.4 mg (0.486 mmol, 49% yield) of **16** as a colorless oil. ^{1}H-NMR (270 MHz) examination indicated that the geometric isomer of **16** was not produced. After storage for 1 year in a refrigerator, the E/Z isomerization occurred.

16: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 5.87 (1H, brs) 4.90 (1H, m) 2.37–2.27 (5H, m) 2.00–1.85 (4H, m) 1.66–1.40 (4H, m) 1.45 (3H, brd, J = 3.5 Hz) 1.08 (3H, d, J = 7.0 Hz) 0.01 (9H, s); HR-MS (EI) calcd for $C_{17}H_{30}OSi$ 278.2066. Found 278.2065.

26.6 mg (0.0955 mmol) of **16** was placed in an oven-dried, 20 mL, two-necked, round-bottom flask equipped with a magnetic stirring bar and a rubber septum. The flask was evacuated under vacuum, then flushed with argon. Dry toluene (10 mL) was added with a syringe, and the flask was placed in a Dry Ice-isopropyl alcohol bath. After 5 minutes, ethylaluminum dichloride in *n*-hexane (1 M, 0.14 mL, 0.14 mmol) was added dropwise, with a syringe, and the stirring was continued for 25 minutes. The reaction was quenched by adding 10 mL of water, and the mixture was diluted with ether. The separated aqueous layer was extracted with ether, and the combined organic layer was dried over anhydrous magnesium sulfate. Concentration and purification by column chromatography (3.5 g of SiO_2 60 E. Merck No. 5554, 4.8% ethyl acetate/*n*-hexane) gave 10.4 mg (0.0504 mmol, 53% yield) of spirocyclic ketones as a mixture of three diastereomers. The diastereomeric ratio was determined to be **17a/17b/17c** = 2/2/1 by ^{1}H-NMR spectroscopy (270 MHz). These diastereomers were further separated by preparative HPLC (YMC SIL-5-06 S-5 60A SIL, 3.2% ethyl acetate/*n*-hexane, flow rate 18 mL/min, retention time **17a**: 22 minutes **17b**: 20 minutes **17c**: 24 minutes)

17a: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 4.96 (1H, m) 4.72 (1H, m) 2.51 (1H, t, J = 9.0 Hz) 2.30–2.26 (2H, m) 2.16 (1H, d, J = 13 Hz) 2.12 (1H, d, J = 13 Hz) 2.06–1.60 (7H, m) 1.76 (3H, brs) 1.34–1.23 (2H, m) 0.89 (3H, d, J = 7.0 Hz); HR-MS (EI) calcd for $C_{14}H_{22}O$ 206.1671. Found 206.1670.

17b: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 4.88 (1H, m) 4.68 (1H, m) 2.35–2.16 (5H, m) 2.0–1.44 (7H, m) 1.76 (3H, dd, J = 0.6, and 0.6 Hz) 1.30–1.16 (2H, m) 0.91 (3H, d, J = 6.5 Hz); HR-MS (EI) calcd for $C_{14}H_{22}O$ 206.1671. Found 206.1670.

17c: ^{1}H-NMR (270 MHz) δ_{CDCl_3} 4.94 (1H, m) 4.77 (1H, m) 2.41 (1H, d, J = 14 Hz) 2.26–2.17 (4H, m) 1.92–1.52 (7H, m) 1.77 (3H, brs) 1.41–1.26 (2H, m) 0.94 (3H, d, J = 7.0 Hz); HR-MS (EI) calcd for $C_{14}H_{22}O$ 206.1671 (M^+). Found 206.1670 (M^+).

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