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Synthesis of 1,3-Dienes of (*E*,*Z*) Configuration by a Three-Component Coupling Strategy

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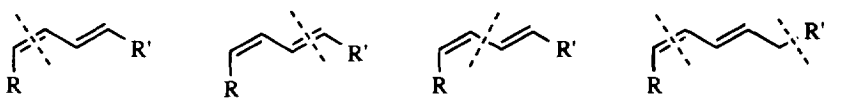
Abstract: Three-component coupling of an anionic nucleophile, butadienyltriphenylphosphonium bromide, and an aldehyde gave conjugated dienes of predominantly (*E*,*Z*) configuration. Dianions of β-dicarbonyl systems and dicarboxylic acids, and monoanions of sulfones were employed as nucleophiles. Stereoselectivity in favor of an (*E*,*Z*)-1,3-diene was highest when a β-dicarbonyl dianion was used in conjunction with an α-branched aldehyde.

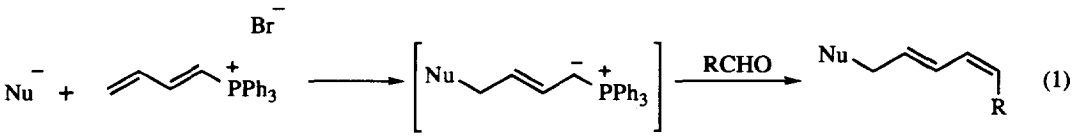
The stereospecific construction of conjugated dienes of (*E*,*Z*) configuration is an important synthetic process for which a large number of practical solutions have been devised.[1] In general, this construction falls into one of three categories (methods A – C) in which the diene is assembled across the (*Z*) double bond (method A), at the (*E*) olefin (method B), or by linking two alkenes of specified configuration at the single bond (method C). Methods A and B frequently invoke a second process following initial bond construction, such as semihydrogenation of a conjugated enyne,[2] or elimination of an allylic function as in the Julia[3] and Peterson[4] syntheses or Trost's palladium(0) catalyzed decarboxylative elimination.[5] Wittig reactions have also played a valuable role in the synthesis of (*E*,*Z*)-1,3-dienes,[6] the combination of a trans α,β-unsaturated aldehyde and an unstablized ylide being stereochemically more reliable than addition of an (*E*)-allylic ylide to an aldehyde for this purpose.[7] Undoubtedly the most versatile method for elaborating 1,3-dienes of known configuration involves transition metal-catalyzed cross-coupling of vinyl partners (method C). The Suzuki,[8] Stille,[9] and Heck[10] reactions exemplify this approach, and if the coupling partners are available in geometrically pure form a very high level of stereocontrol is achieved in these processes.



A B C D

In spite of the considerable progress made in stereoselective diene synthesis in recent years,[11] there remains a need for methodology which fabricates this subunit in the complex milieu found in natural products.[12] A protocol which inserts a 1,3-diene unit in regiocontrolled fashion between two reactive termini would be the ideal objective. To this end, strategies were considered which interposed the four carbons of a 2-butene synthon between nucleophilic and electrophilic carbon centers. This approach is represented schematically as method D in the options for diene synthesis shown above. It differs from method A, B, and C in requiring that *two* carbon–carbon connections be made concurrently, one through a σ linkage and the other via olefination.

In practical terms, the concept embraced by the symbolization D is best realized via addition of a nucleophile to a butadienylphosphonium salt (**1**), thereby generating an ylide **2** that can undergo Wittig reaction with an aldehyde (eq. 1). The expectation that *s*-trans diene **1** would initially produce an allylphosphorane of (*E*) configuration and that subsequent Wittig reaction of the ylide **2** would yield a (*Z*) olefin is supported by Fuchs' observations with **1**.[13] In Fuchs' work, however, an alternative process involving the *s*-cis isomer of **1** was postulated that was assumed to lead to the *cis* isomer of **2**. While this would accommodate the intramolecular pathway leading to cyclohexa-1,3-dienes described by Fuchs, it was pointed out that the possibility of isomerization of **2** must also be considered. For our purpose, it was clearly necessary to suppress this isomerization if good diene stereoselectivity was to be achieved.[14] Our plan was therefore to offer **2** a reactive aldehyde so that rapid Wittig olefination would ensue.



1 **2** **3** (1)

Initially, enolate dianions of β-dicarbonyl systems were employed as the nucleophilic partner in the three-component coupling shown in eq 1.[15] This was later extended to dianions of carboxylic acids and α-sulfonyl anions.[16] The fear that intramolecular olefination might supervene with dianions of β-dicarbonyl systems proved to be unfounded, and addition of these dianions to geometrically pure (*E*)-**1** at low temperature proceeded smoothly to give the persistent red color characteristic of **2**. The color faded as **2** underwent Wittig reaction with an aldehyde at 0 °C, and the (*E*,*Z*) diene **3** accompanied by varying amounts of the (*E*,*E*) isomer was isolated after an acidic work up. Subsequently, it was discovered that **1** can be generated in situ from (*E*)-4-bromo-2-butenyltriphenylphosphonium bromide (**5**)[17] with no loss of stereoselectivity or diminution of yield if an additional equivalent of base is incorporated into the medium. The optimized sequence beginning with (*E*)-1,4-dibromo-2-butene (**4**) is shown in scheme 1.

Relatively stable enolates such as the monoanions of malonate and acetoacetate were ineffective in the three-component diene synthesis, affording principally the products of direct (Knoevenagel) condensation with the aldehyde and only *ca* 5% of a diene. Dianions of β-dicarbonyl compounds, on the other hand, afforded (*E*,*Z*) dienes accompanied by lesser amounts of the (*E*,*E*) isomer. The ratio of (*E*,*Z*) to (*E*,*E*) diene was determined in each case by ^{13}C NMR spectroscopy using the ratio of averaged signal intensities of the four olefinic carbon signals for each isomer. The ratio was confirmed in several cases by high pressure liquid chromatography. Assignment of configuration to diene isomers was made by ^{1}H NMR spectroscopy using either COSY or single frequency decoupling experiments. The measured chemical shifts and coupling constants of olefinic protons of (*E*,*Z*) dienes were uniform throughout the series, with J_{ab} = 11 Hz, J_{bc} = 11 Hz, and J_{cd} = 15 Hz. These values are in close agreement with data reported for (*E*,*Z*)- 1,3-dienes.[18] The results of coupling reactions employing enolate dianions with **1** and various aldehydes are summarized in Table 1. In all cases, alkylation occurred at the γ site of the dianion[19] and in a conjugate mode with **1**.

Scheme 1

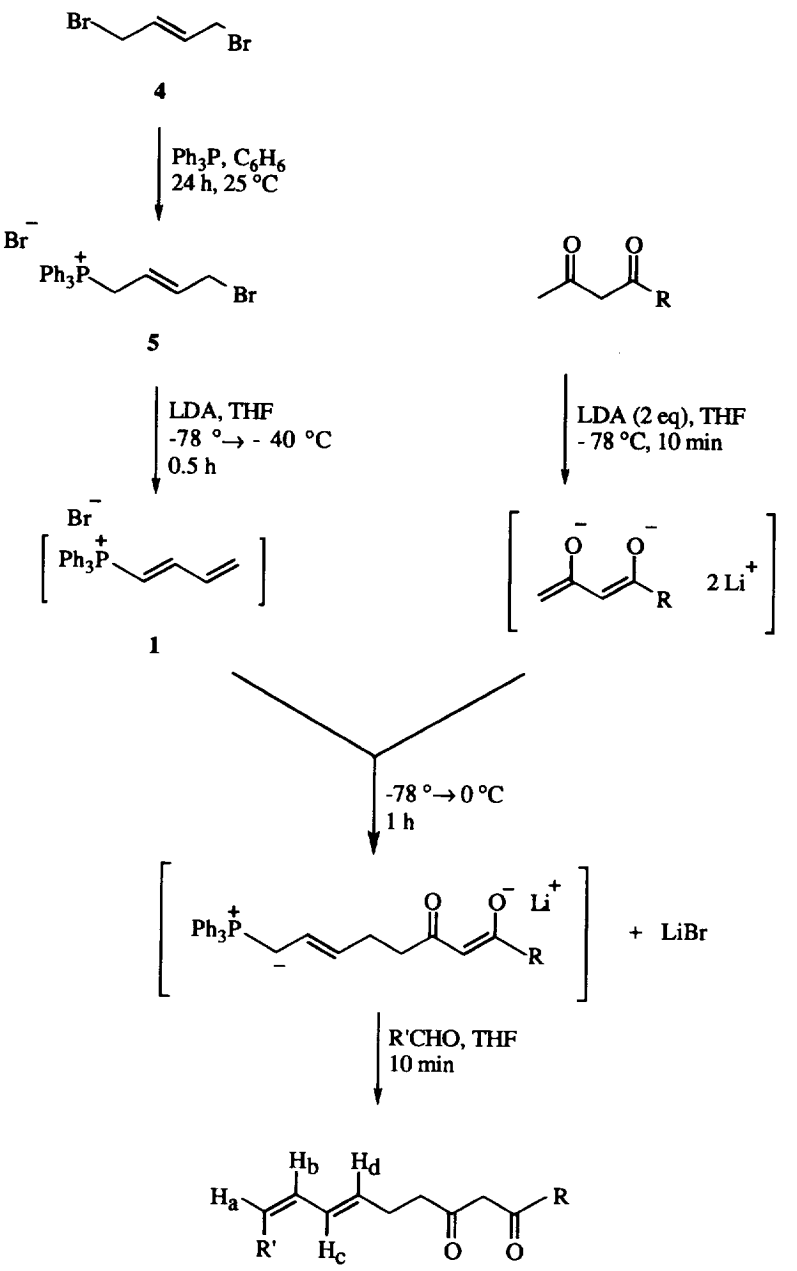
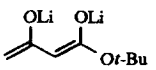
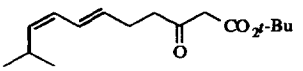
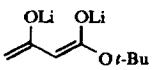
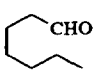
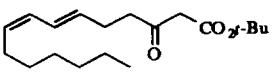
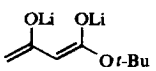
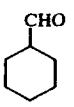
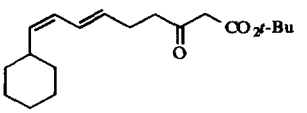
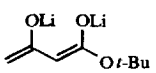
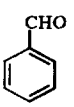
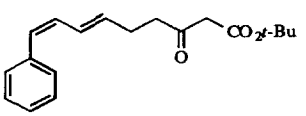
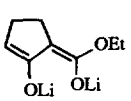
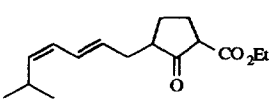
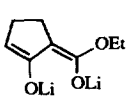
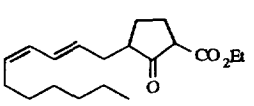
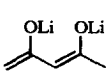
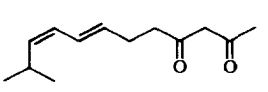
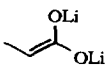
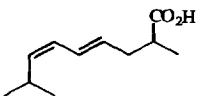
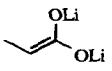
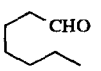
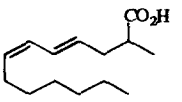
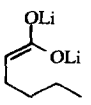
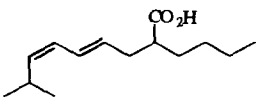
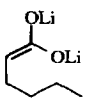
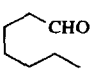
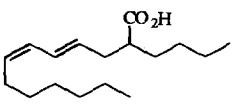
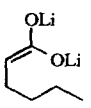
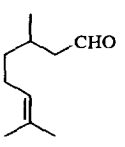
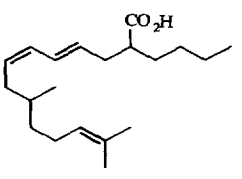

Br
Br
4
Ph3P, C6H6
24 h, 25 °C
Br
Ph3P
Br
5
LDA, THF
-78 °→ - 40 °C
0.5 h
Br
Ph3P
1
O
O
R
LDA (2 eq), THF
- 78 °C, 10 min
O
O
R
2 Li+
-78 °→ 0 °C
1 h
Ph3P
O
O
Li+
R
+ LiBr
R'CHO, THF
10 min
Ha
Hb
Hd
Hc
R'
R
O
O

Table 1. Dienes Prepared by Three-Component Coupling with 1 Using the Dianion of a β-Dicarbonyl System as the Nucleophile.

Entry	Nucleophile	Aldehyde	Major Product		Yield (%)	(*E,Z*:*E,E*) Ratio
1				(6)	62	16:1
2				(7)	62	6:1
3				(8)	53	11:1
4				(9)	40	2:1
5				(11)	48	12:1
6				(12)	54	5:1
7				(13)	43	>20:1

Dianions of carboxylic acids were also examined as nucleophiles in the three-component coupling process. The products, γ, δ; ε, ζ unsaturated acids were again mixtures of (*E,Z*) and (*E,E*) isomers, with the former predominating. The dianion of acetic acid failed to yield a diene product, but couplings with both propanoic and *n*-hexanoic acids were successful. These results are summarized in Table 2.

Table 2. Dienes Prepared by Three-Component Coupling with 1 Using the Dianion of a Carboxylic Acid as the Nucleophile.

Entry	Nucleophile	Aldehyde	Major Product		Yield (%)	(*E*,*Z*:*E*,*E*) Ratio
1				**(14)**	55	8:1
2				**(15)**	50	2:1
3				**(16)**	47	8:1
4				**(17)**	44	2.4:1
5				**(18)**	67	2:1

α-Anions derived from sulfones were reactive in the diene synthesis yielding γ, δ; ε, ζ unsaturated sulfones. These results are summarized in Table 3. Only monoanions were employed in these studies. When the dianion of methyl phenyl sulfone was reacted with **1** and then with isobutyraldehyde, the yield of diene fell to 26%. Stereoselectivity was lower in the case of sulfonyl anions and was found to be independent of the structure of the aldehyde. The monoanion of acetonitrile (entry 6) gave a result similar to those obtained with sulfones.

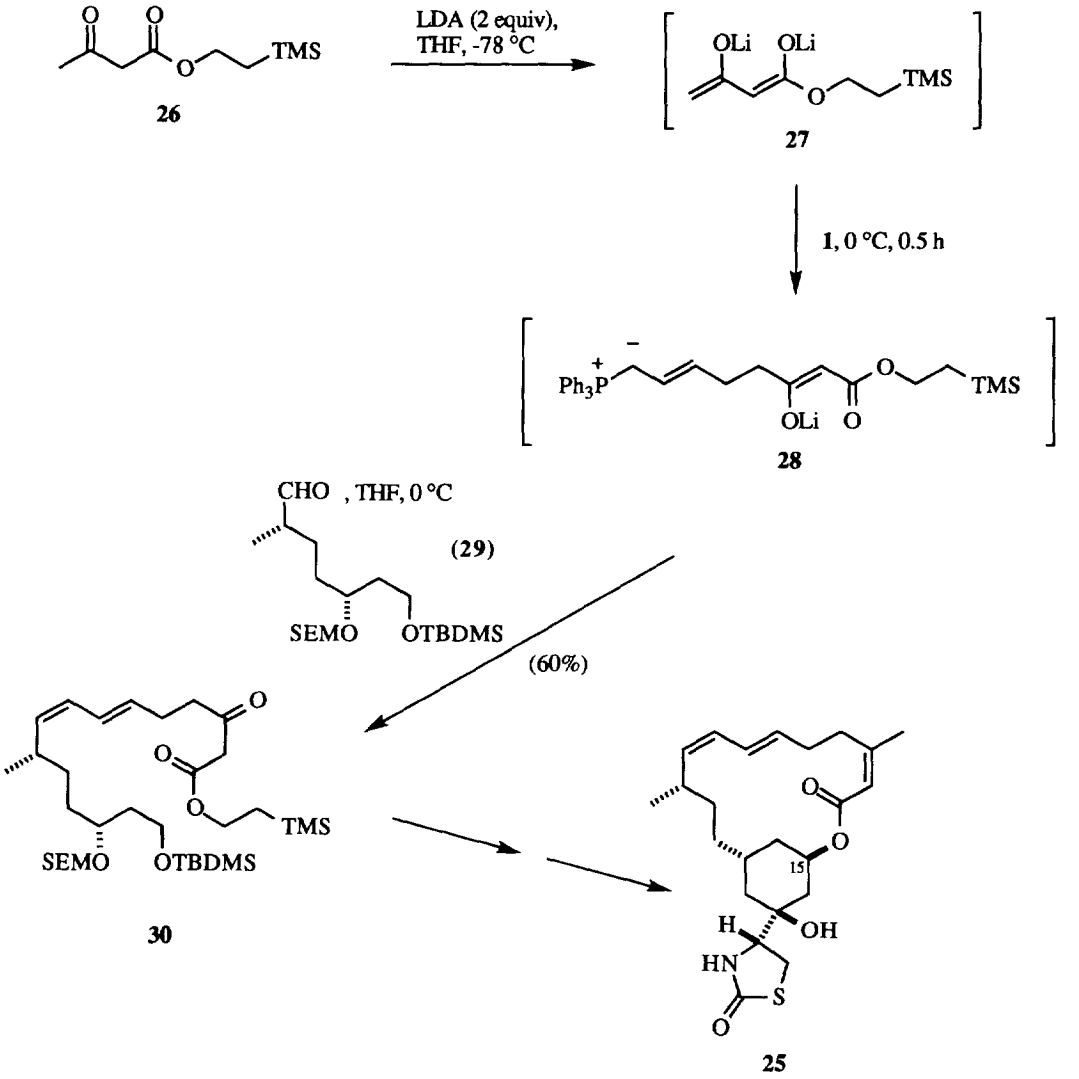
Several general observations emerge from the foregoing study. First, the failure to detect (*Z*,*E*) or (*Z*,*Z*) diene products in any of the reactions is consistent with the view that ylide **2** is generated exclusively with (*E*) configuration and that it reacts without detectable isomerization to the (*Z*) allylphosphorane. This is in accord with results obtained by Pattenden who showed that, under certain conditions, (*E*) or (*Z*) allylphosphoranes can be used in Wittig reactions with complete retention of olefin geometry in the allyl unit.[20] Second, it is apparent that best results are obtained with powerful nucleophiles. This probably reflects the potential

reversibility of the first step in eq (1), weak nucleophiles being unable to produce a sufficient concentration of ylide to promote the subsequent Wittig olefination. The inherent advantage of β-dicarbonyl dianions is that the nucleophilic component of **2** retains enolate character, thus protecting itself against the intramolecular Wittig reaction seen by Fuchs.[13] Finally, it is clear from entries 1, 3, 5, and 7 in Table 1 and from entries 1 and 3 in Table 2 that α-branched aldehydes afford superior (*E,Z:E,E*) ratios with β-dicarbonyl and carboxylate dianions as nucleophiles. Straight-chain aldehydes give lower, though still useful proportions of (*E,Z*) dienes. Sulfonyl anions (Table 3) consistently produced a 1.5:1 – 2:1 mixture of (*E,Z:E,E*) dienes.

Table 3. Dienes Prepared by Three-Component Coupling with 1 Using the Anion of a Sulfone or Nitrile as the Nucleophile.

Entry	Nucleophile	Aldehyde	Major Product		Yield (%)	(*E,Z:E,E*) Ratio
1	$PhSO_2\bar{C}H_2$	CHO	SO_2Ph	**(19)**	50	2:1
2	$PhSO_2\bar{C}H_2$	CHO	SO_2Ph	**(20)**	53	1.5:1
3	$PhSO_2\bar{C}HCH_3$	CHO	SO_2Ph	**(21)**	50	2:1
4	$PhSO_2\bar{C}HCH_3$	CHO	SO_2Ph	**(22)**	60	2:1
5	$PhSO_2\bar{C}HCH_3$	CHO	SO_2Ph	**(23)**	57	1.5:1
6	$\bar{C}H_2CN$	CHO	CN	**(24)**	57	2:1

The diene construction represented in Table 1 was a key strategic element of our recent synthesis of the ichthyotoxic macrolide latrunculin A (**25**).[21] Thus, the dilithio dianion **27** of β-keto ester **25** was reacted with **1**, and the resultant ylide **28** was then treated with aldehyde **29**. (*E,Z*)-Diene **30** was produced in 56% yield with only a trace of the (*E,E*) isomer, and was transformed to both **25** and its C-15 epimer.



26 **27** **28** **30** **25**

In summary, the unique three-component coupling described herein leads to conjugated dienes of predominantly (*E,Z*) configuration in practical yields and with useful stereoselectivity in certain cases. The reaction is strongly dependent on the nature of the nucleophilic component as well as the aldehyde partner.

EXPERIMENTAL SECTION

Melting points were measured using a Büchi melting point apparatus and are uncorrected. Infrared spectra were recorded with a Nicolet 5DXB FT-IR spectrometer. Carbon and proton nuclear magnetic resonance spectra were measured using either a Bruker AC-300 or Bruker AM-400 spectrometer. Chemical shifts are reported in parts per million downfield from tetramethylsilane using the δ scale. ^{1}H NMR data are reported in the order of chemical shift, number of protons, multiplicity, (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and b=broad) and coupling constant in Hertz (Hz). Electron impact (EI) mass spectra were determined using a Varian MAT 311 spectrometer. Chemical ionization (CI) mass spectra were obtained with a Finnigan 4023 spectrometer, and fast atom bombardment (FAB) mass spectra were measured with a Kratos MS-50 RFTC mass spectrometer.

(*E*)-4-Bromo-2-butenyltriphenylphosphonium Bromide (5). To a solution of 1,4-dibromo-2-butene (**4**) (8.56 g, 40.00 mmol) in benzene (20 mL) was added a solution of triphenylphosphine (10.49 g, 40.00 mmol) in benzene (20 mL) dropwise over 2 h, and the resulting white suspension was stirred at room temperature for 24 h. The white solid was collected, rinsed with benzene (20 mL), and dried in a desiccator to give 16.66 g (88%) of **5** as a colorless powder : mp 187.5-189.0 °C; ^{1}H NMR ($CDCl_3$) δ 3.84 (2H, dd, J=17, 3 Hz), 4.97 (2H, dd, J=15, 7 Hz), 5.71 (1H, ddt, J=15, 7, 3 Hz), 6.20 (1H, ddt, J=15, 7, 5 Hz), 7.61-7.67 (6H, m), 7.73-7.82 (9H, m); ^{13}C NMR ($CDCl_3$) δ 27.0, 27.7, 31.0, 116.9, 118.1, 120.0, 120.2, 130.2, 130.4, 133.8, 133.9, 135.0, 135.5, 136.6; MS (FAB) *m/z* 397, 395, 315, 262, 183; HRMS *m/z* 395.0563 (calcd for $C_{22}H_{21}BrP$: 395.0564).

(*E*)-1,3-Butadienyltriphenylphosphonium Bromide (1). To a solution of **5** (2.81 g, 5.90 mmol) in chloroform (20 mL) was added anhydrous sodium carbonate (1.88 g, 17.71 mmol), and the suspension was stirred for 18 h at room temperature. The solid was filtered and the filtrate was evaporated to leave a syrup which was crystallized from chloroform and ether to yield 4.40 g (94%) of **1** as a colorless solid: mp 187-189 °C (lit[13] mp 186-188.5 °C); ^{1}H NMR ($CDCl_3$) δ 5.56 (1H, d, J=17 Hz), 5.66 (1H, dd, J=10, 3 Hz), 6.81 (1H, ddd, J=21, 16, 12 Hz), 7.29 (1H, ddt, J=17, 10, 2 Hz), 7.67-7.84 (15H, m), 8.19 (1H, dd, J=21, 16 Hz); ^{13}C NMR ($CDCl_3$) δ 109.2, 110.3, 117.6, 118.8, 129.2, 130.4, 130.5, 133.8, 134.0, 135.0, 135.2 (x2), 135.5, 135.8, 156.3 (x2); MS (FAB) *m/z* 315, 262, 183, 108; HRMS *m/z* 315.1301 (calcd for $C_{22}H_{20}P$: 315.1303). This material was erroneously reported to be unstable in ref 15 (footnote 7).

(6*E*,8*Z*)-*tert*-Butyl 10-Methyl-3-oxo-6,8-undecadienoate (6). To a solution of diisopropylamine (0.14 mL, 1.0 mmol) in tetrahydrofuran (2 mL) at -78 °C was added dropwise *n*-butyllithium (0.63 mL of a 1.6 M solution in hexane, 1.0 mmol). After 10 min, the resulting solution was added dropwise to a stirred suspension of **5** (476 mg, 1.0 mmol) in tetrahydrofuran (3 mL) at -78 °C. The resulting brown mixture was allowed to warm to -40 °C over 30 min. In a separate flask, *n*-butyllithium (1.26 mL of a 1.6 M solution in

hexane, 2.0 mmol) was added dropwise to a solution of diisopropylamine (0.28 mL, 2.0 mmol) in tetrahydrofuran (3 mL) at -78 °C. After 10 min, the resulting solution was added to *tert*-butyl acetoacetate (166 μL, 1.0 mmol) in tetrahydrofuran (2 mL) at -78 °C. After a further 10 min, the bright yellow solution was transferred via cannula to the flask containing the brown mixture containing **1**. The solution turned deep red while warming to 0 °C over 1 h. A solution of isobutyraldehyde (27 μL, 0.3 mmol) in tetrahydrofuran (3 mL) was added dropwise and the red color of the phosphorane faded rapidly . After 10 min, the solution was poured into ice-cold 1% hydrochloric acid. The aqueous phase was extracted with ether (3 x 25 mL), and the combined extracts were washed with brine and dried (magnesium sulfate). The solvent was removed and the residual oil was chromatographed on silica, using 10% ethyl acetate in hexane as eluant, to give 54.2 mg (62%) of a 16:1 mixture of (*E,Z*) and (*E,E*) isomers, respectively. Data for **6**: IR (neat) 2963, 2931, 2871, 1738, 1718, 1644, 1257, 1153, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (6H, d, J=7 Hz), 1.14 (9H, s), 2.38 (2H, dt, J=7, 7 Hz), 2.62 (2H, t, J=7 Hz), 2.72 (1H, dq, J=9, 7 Hz), 3.33 (2H, s), 5.14 (1H, dd, J=10, 10 Hz), 5.56 (1H, dt, J=15, 7 Hz), 5.78 (1H, dd, J=11, 11 Hz), 6.32 (1H, dd, J=15, 11 Hz); ^{13}C NMR ($CDCl_3$) δ 23.1 (x2), 26.6, 26.9, 27.9 (x3), 42.4, 50.6, 90.7, 125.8, 126.7, 131.7, 138.4, 166.3, 202.4.

(6*E*,8*Z*)-*tert*-Butyl 3-Oxo-6,8-pentadecadienoate (7). The reaction was carried out as for **6** on a 1 mmol scale using *n*-heptanal (34 mg, 0.30 mmol) to give 57.4 mg (62%) of a 6:1 mixture of (*E,Z*) and (*E,E*) dienes, respectively. Data for **7**: IR (neat) 3018, 3006, 2979, 2959, 2929, 2871, 2856, 1738, 1716, 1650, 1644, 1369, 1319, 1252, 1165, 1149 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3H, m), 1.28 (8H, m), 1.46 (9H, s), 2.14 (2H, m), 2.39 (2H, dt, J=7, 7 Hz), 2.64 (2H, t, J=7 Hz), 3.35 (2H, s), 5.34 (1H, dt, J=11, 8 Hz), 5.61 (1H, dt, J=15, 7 Hz), 5.91 (1H, dd, J=11, 11 Hz), 6.33 (1H, dd, J=15, 11 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 26.6, 27.7, 28.0 (x3), 28.9, 29.6, 31.7, 42.5, 50.7, 82.0, 126.8, 128.0, 131.2, 131.6, 166.4, 202.5.

(6*E*,8*Z*)-*tert*-Butyl 9-Cyclohexyl-3-oxo-6,8-nonadienoate (8). The reaction was carried out as for **6** on a 1 mmol scale using cyclohexanecarboxaldehyde (36 μL, 0.30 mmol) to give 48.2 mg (53%) of a 11:1 mixture of (*E,Z*) and (*E,E*) dienes, respectively. Data for **8**: IR (neat) 2979, 2926, 2851, 1740, 1716, 1645, 1368, 1319, 1253, 1151 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03-1.32 (6H, m), 1.46 (9H, m), 1.65 (4H, m), 2.38 (3H, m), 2.63 (2H, m, J=7Hz), 3.34 (2H, s), 5.18 (1H, dd, J=10, 10 Hz), 5.60 (1H, dt, J=15, 7 Hz), 5.80 (1H, dd, J=10, 10 Hz), 6.32 (1H, dd, J=15, 10 Hz); ^{13}C NMR ($CDCl_3$) δ 25.8, 25.9 (x2), 26.6, 27.9 (x3), 33.2 (x2), 36.7, 42.5, 50.7, 82.0, 126.2, 126.9, 131.7, 137.1, 166.4, 202.5; MS (EI) *m/z* 306, 250, 233, 148; HRMS *m/z* 306.2196 (calcd for $C_{19}H_{30}O_3$: 306.2196).

(6*E*,8*Z*)-*tert*-Butyl 9-Phenyl-3-oxo-6,8-nonadienoate (9) and (6*E*,8*E*)-*tert*-Butyl 9-Phenyl-3-oxo-6,8-nonadienoate (10). The reaction was carried out as for **6** on a 1 mmol scale using benzaldehyde (30.5 μL, 0.30 mmol) to give 36 mg (40%) of a 2:1 mixture of (*E,Z*) and (*E,E*) dienes, respectively. These were separated by preparative HPLC.

9: IR (neat) 2979, 1737, 1716, 1643, 1369, 1319, 1255, 1152, 989, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (9H, s), 2.42 (2H, q, J=7 Hz), 2.65 (2H, t, J=7 Hz), 3.35 (2H, s), 5.83 (1H, dt, J=15, 7 Hz), 6.18 (1H, t, J=11 Hz), 6.34 (1H, d, J=11 Hz), 6.61 (1H, dd, J=12, 14 Hz), 7.29 (5H, m); ^{13}C NMR ($CDCl_3$) δ 26.6, 27.9 (x3), 42.2, 50.7, 82.0, 126.8, 127.5, 128.2 (x2), 128.5, 128.9 (x2), 129.9, 135.1, 137.5, 166.4, 202.4.

10: IR (neat) 3024, 3003, 2979, 2932, 1737, 1714, 1643, 1597, 1368, 1319, 1254, 1149, 989, 749, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (9H, s), 2.44 (2H, q, J=7 Hz), 2.67 (2H, t, J=7 Hz), 3.36 (2H, s), 5.79 (1H, dt, J=15, 7 Hz), 6.23 (1H, dd, J=12, 5 Hz), 6.46 (1H, d, J=16 Hz), 6.72 (1H, dd, J=16, 5 Hz), 7.58 (5H, m); ^{13}C NMR ($CDCl_3$) δ 26.5, 27.9 (x3), 42.2, 50.6, 81.9, 126.1 (x2), 127.2, 128.5 (x2), 128.7, 130.8, 131.5, 132.8, 137.3, 166.3, 202.3.

(2*E*,4*Z*)-Ethyl 3-(6-Methyl-2,4-heptadienyl)-2-oxocyclopentanecarboxylate (11). The reaction was carried out as for **6** on a 3 mmol scale using ethyl 2-oxocyclopentanecarboxylate (0.44 mL, 3.0 mmol) and isobutyraldehyde (0.30 mL, 3.3 mmol) to give 417 mg (48%) of a 12:1 mixture of (*E,Z*) and (*E,E*) dienes, respectively. Data for **11**: IR (neat) 3018, 2961, 2935, 2910, 2870, 1754, 1726, 1659, 1621, 1253, 1191 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (6H, d, J=7 Hz), 1.28 (3H, dt, J=7, 2 Hz), 2.10-2.37 (5H, m), 2.54 (1H, m), 2.74 (1H, m), 3.10 (1H, m), 4.18 (2H, m), 5.17 (1H, dd, J=11, 11 Hz), 5.55 (1H, dt, J=15, 7 Hz), 5.80 (1H, dd, J=11, 11 Hz), 6.34 (1H, dd, J=15, 11 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1, 23.0 (x2), 24.9, 26.7, 26.9, 32.6, 49.2, 55.0, 61.2, 125.6, 127.9, 130.0, 138.7, 169.4, 212.3; MS (EI) *m/z* 263, 247, 235, 219, 199, 169, 153; HRMS *m/z* 264.1726 (calcd for $C_{16}H_{24}O_3$: 264.1725).

(2*E*,4*Z*)-Ethyl 3-(2,4-Undecadienyl)-2-oxocyclopentanecarboxylate (12). The reaction was carried out as described for **11** on a 3 mmol scale using *n*-heptanal (0.17 mL, 1.2 mmol) to give 206.3 mg (54%) of a 5:1 mixture of (*E,Z*) and (*E,E*) dienes, respectively. Data for **12**: IR (neat) 3020, 2958, 2928, 2872, 2857, 1754, 1727, 1661, 1655, 1621, 1456, 1191 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (3H, t, J=5 Hz), 1.27 (13H, m), 1.51 (1H, m), 2.02-2.36 (6H, m), 2.53 (1H, m), 4.18 (2H, m), 5.34 (1H, dt, J=11, 8 Hz), 5.55 (1H, dt, J=15, 7 Hz), 5.91 (1H, m), 6.34 (1H, dd, J=15, 11 Hz); ^{13}C NMR ($CDCl_3$) δ 14.1 (x2), 22.6, 25.0, 26.7, 27.7, 28.9, 29.6, 31.7, 32.7, 49.2, 55.0, 61.3, 128.0, 130.0, 130.3, 131.4, 169.4, 212.4.

(7*E*,9*Z*)-11-Methyl-7,9-dodecadien-2,4-dione (13). To a solution of diisopropylamine (0.14 mL, 1.0 mmol) in tetrahydrofuran (2 mL) at -78 °C was added dropwise *n*-butyllithium (0.63 mL of a 1.6 M solution in hexane, 1.0 mmol). After 10 min, the resulting solution was added dropwise to a stirred suspension of **5** (476 mg, 1.0 mmol) in tetrahydrofuran (3 mL) at -78 °C. The resulting brown mixture was warmed to -40 °C over 30 min. In a separate flask, *n*-butyllithium (1.26 mL of a 1.6 M solution in hexane, 2.0 mmol) was added dropwise to a solution of diisopropylamine (0.28 mL, 2.0 mmol) in tetrahydrofuran (3 mL) at -78 °C. After 10 min, the mixture was added to a solution of 2,5-pentanedione (105 μL, 1.0 mmol) in tetrahydrofuran (2 mL) at -78 °C. After 1 h, the yellow solution was transferred via cannula to the brown mixture containing **1**. The solution turned deep red while warming to 0 °C over 1 h. A solution of isobutyraldehyde (27 μL, 0.3 mmol) in tetrahydrofuran (3 mL) was added dropwise, and the red color of the phosphorane faded rapidly. After 10 min, the solution was poured into ice-cold 1% hydrochloric acid. The aqueous phase was extracted with ether (3 x 25 mL) and the combined extracts were washed with brine and dried (magnesium sulfate). The solvent was removed and the residual oil was chromatographed on silica, using 10% ethyl acetate in hexane as eluant, to give 27.0 mg (43%) of a >20:1 mixture of (*E,Z*) and (*E,E*) dienes, respectively. Data for **13**: IR (neat) 3019, 3002, 2960, 1728, 1707, 1683, 1612, 1461, 1423, 1361, 985, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.97 (6H, d, J=7 Hz), 2.05 (3H, s), 2.39 (4H, m), 2.74 (1H, m), 5.17 (1H, dd, J=10, 10 Hz), 5.50 (1H, s, enol form), 5.62

(1H, dt, J=15, 8 Hz), 5.81 (1H, t, J=11 Hz), 6.35 (dd, J=15, 11 Hz); ^{13}C NMR ($CDCl_3$) δ 23.0 (x2), 24.8, 26.9, 28.6, 37.9, 99.8, 125.7, 126.7, 131.7, 138.5, 191.1, 193.2.

(4*E*,6*Z*)-2,8-Dimethyl-4,6-nonadienoic Acid (14). To a solution of diisopropylamine (0.14 mL, 1.0 mmol) in tetrahydrofuran (2 mL) at -20 °C was added dropwise *n*-butyllithium (0.63 mL of a 1.6M solution in hexane, 1.0 mmol). After 10 min, the resulting solution was added dropwise to a stirred suspension of **5** (476 mg, 1.0 mmol) in tetrahydrofuran (3 mL) at -78 °C, and the resulting brown mixture was warmed to -40 °C over 30 min. In a separate flask, *n*-butyllithium (1.26 mL of a 1.6M solution in hexane, 2.0 mmol) was added dropwise to a solution of diisopropylamine (0.28 mL, 2.0 mmol) in tetrahydrofuran (3 mL) at -20 °C. After 10 min, propionic acid (75 μL, 1.0 mmol) and hexamethylphosphoramide (18 μL, 1.0 mmol) were added and the resulting solution was warmed to room temp. After 40 min, the pale yellow solution was transferred via cannula to the brown mixture containing **1**. The solution turned orange while warming to 0 °C over 1 h. A solution of isobutyraldehyde (73 μL, 0.8 mmol) in tetrahydrofuran (10 mL) was added, and the mixture turned from orange to brown. After stirring for 10 min, the mixture was poured into ice-cold 1% hydrochloric acid and was extracted with ether (3 x 25 mL). The combined extracts were washed with brine and dried (magnesium sulfate), and the solvent was removed. The residual oil was chromatographed on silica, using ethyl acetate in hexane (1:2) as eluant, to give 80.5 mg (55%) of an 8:1 mixture of (*E,Z*) and (*E,E*) dienes, respectively. Data for **14**: IR (neat) 3000, 1907, 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (6H, d, J=7 Hz), 1.18 (3H, d, J=7 Hz), 2.26 (1H, m), 2.51 (2H, m), 2.75 (1H, dq, J=10, 7 Hz), 5.18 (1H, dt, J=10, 10 Hz), 5.59 (1H, dt, J=15, 7 Hz), 5.83 (1H, dd, J=11, 11 Hz), 6.36 (1H, ddd, J=15, 11, 1 Hz); ^{13}C NMR ($CDCl_3$) δ 16.4, 23.1 (x2), 27.0, 36.5, 39.5, 125.8, 128.0, 130.0, 138.7, 182.4.

(4*E*,6*Z*)-2-Methyl-4,6-tridecadienoic Acid (15). The reaction was carried out as described for **14** on a 1 mmol scale using *n*-heptanal (107 μL, 0.80 mmol) to give 87.3 mg (50%) of a 2.3:1 mixture of (*E,Z*) and (*E,E*) dienes, respectively. Data for **15**: IR (neat) 3063, 2927, 1709, 1655, 1464, 1236, 949 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, J=5 Hz), 1.18 (3H, d, J=7 Hz), 1.27, (8H, m), 2.26-2.01 (3H, m), 2.54 (2H, m), 5.36 (1H, dt, J=11, 8 Hz), 5.59 (1H, m), 5.98 (1H, dd, J=12, 12 Hz), 6.34 (1H, dd, J=15, 11 Hz); ^{13}C NMR ($CDCl_3$) δ 14.0, 16.3, 22.5, 27.6, 28.8, 29.5, 31.6, 36.4, 39.4, 128.0, 128.1, 129.9, 131.3, 182.4.

(4*E*,6*Z*)-2-*n*-Butyl-8-methyl-4,6-nonadienoic Acid (16). The reaction was carried out as described for **14** on a 1 mmol scale using *n*-hexanoic acid (125 μL, 1.0 mmol) to give 84.6 mg (47%) of a 8:1 mixture of (*E,Z*) and (*E,E*) dienes, respectively. Data for **16:** IR (neat) 3091, 2950, 2933, 2872, 1708, 1466, 1241, 984 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, m), 0.97 (6H, d, J=7 Hz), 1.31 (6H, m), 2.29 (1H, m), 2.43 (2H, m), 2.75 (1H, m), 5.18 (1H, dd, J=10, 10 Hz), 5.58 (1H, dt, J=15, 7 Hz), 5.82 (1H, dd, J=11, 11 Hz), 6.35 (1H, dd, J=15, 11 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9, 22.6, 23.1 (x2), 27.0, 29.3, 31.2, 35.1, 45.5, 125.9, 128.0, 130.1, 138.6, 182.2; MS (EI) *m/z* 224, 179, 163, 123, 108; HRMS *m/z* 224.1777 (calcd for $C_{14}H_{24}O_2$: 224.1776).

(4*E*,6*Z*)-2-*n*-Butyl-4,6-tridecadienoic Acid (17). The reaction was carried out as described for **16** on a 1 mmol scale using *n*-heptanal (107 μL, 0.8 mmol) to give 93.1 mg (44%) of a 2.4:1 mixture of (*E,Z*) and (*E,E*) dienes, respectively. Data for **17**: IR (neat) 3083, 3080, 3065, 3020, 2958, 2932, 2928, 2873, 2859, 1709, 1466, 1242, 986 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (6H, m), 1.31 (14H, m), 2.04 (1H, q, J=7 Hz), 2.14 (1H, q,

J=7 Hz), 2.29 (1H, m), 2.43 (2H, m), 5.35 (1H, dt, J=11, 8 Hz), 5.61 (1H, m), 5.93 (1H, dd, J=11, 11 Hz), 6.35 (1H, dd, J=15, 11 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.1, 22.5, 22.6, 27.7, 28.9, 29.3, 29.6, 31.2, 31.7, 35.3, 45.5, 128.0, 128.1, 130.0, 131.3, 182.2; MS (EI) *m/z* 266, 182, 151, 150, 137, 123, 109, 95, 81, 67; HRMS *m/z* 266.2247 (calcd for $C_{17}H_{30}O_2$: 266.2246).

(4*E*,6*Z*)-2-*n*-Butyl-9,13-dimethyl-4,6-tetradecadienoic Acid (18). The reaction was carried out as described for **16** on a 1 mmol scale using (*R*)-(+)-citronellal (54 μL, 0.3 mmol) to give 61.6 mg (67%) of a 2:1 mixture of (*E,Z*) and (*E,E*) dienes, respectively. Data for **18**: IR (neat) 3079, 3021, 2959, 2927, 2872, 2861, 1706, 1456, 1378, 1288, 987 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (6H, m), 1.17 (1H, m), 1.30 (6H, m), 1.51 (2H, m), 1.60 (3H, s), 1.68 (3H, s), 1.98 (3H, m), 2.14 (1H, m), 2.41 (3H, m), 5.10 (1H, t, J=8 Hz), 5.36 (1H, dt, J=11, 8 Hz), 5.59 (1H, dt, J=15, 7 Hz), 5.99 (1H, dd, J=11, 11 Hz), 6.35 (1H, dd, J=15, 11 Hz); ^{13}C NMR ($CDCl_3$) δ 13.9, 17.6, 19.4, 22.6, 25.6, 25.7, 29.3, 31.2, 33.1, 34.8, 35.1, 36.7, 45.5, 124.8, 128.1, 129.0, 129.8, 130.1, 131.1, 182.3; MS (EI) *m/z* 306, 263, 210, 191, 163, 149, 147, 135, 121, 109, 95, 81, 69, 55; HRMS *m/z* 306.2560 (calcd for $C_{20}H_{34}O_2$: 306.2559).

(3*E*,5*Z*)-1-Phenylsulfonyl-7-methyl-3,5-octadiene (19). To a solution of diisopropylamine (0.14 mL, 1.0 mmol) in tetrahydrofuran (2 mL) at -20 °C was added dropwise *n*-butyllithium (0.63 mL of a 1.6 M solution in hexane, 1.0 mmol). After 10 min, the resulting solution was added dropwise to a stirred suspension of **5** (476 mg, 1.0 mmol) in tetrahydrofuran (3 mL) at -78 °C. The resulting brown mixture was warmed to -40 °C over 30 min. In a separate flask *n*-butyllithium (0.63 mL of a 1.6 M solution in hexane, 1.0 mmol) was added to a solution of methyl phenyl sulfone (156 mg, 1.0 mmol) in tetrahydrofuran (3 mL) at 0 °C. Stirring was continued for 45 min and the solution was added to the brown mixture containing **1**. The resulting mixture was warmed to 0 °C over 1 h and a solution of isobutyraldehyde (27 μL, 0.3 mmol) in tetrahydrofuran (3 mL) was added. After 10 min, the mixture was poured into ice (125 g) and was extracted with ether (3 x 25 mL). The combined extracts were washed with brine and dried (magnesium sulfate), and the solvent was removed. The residual oil was chromatographed on silica, using 14% ethyl acetate in hexane as eluant, to give 38.8 mg (50%) of a 2:1 mixture of (*E,Z*) and (*E,E*) dienes, respectively. Data for **19**: IR (neat) 2960, 1447, 1307, 1293, 1149, 1187, 988, 735, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (6H, d, J=7 Hz), 2.51 (2H, m), 2.69 (1H, m), 3.15 (2H, m), 5.19 (1H, t, J=10 Hz), 5.48 (1H, dt, J=15, 7 Hz), 5.74 (1H, t, J=11 Hz), 6.31 (1H, m), 7.58 (2H, m), 7.67 (1H, m), 7.91 (2H, m); ^{13}C NMR ($CDCl_3$) δ 23.0 (x2), 27.0, 29.7, 55.7, 125.2, 128.0, 128.1 (x2), 129.3 (x3), 133.7, 139.0, 139.7.

(3*E*,5*Z*)-1-Phenylsulfonyl-3,5-dodecadiene (20). The reaction was carried out as described for **19** on a 1 mmol scale using *n*-heptanal (40 μL, 0.3 mmol) to give 49.1 mg (53%) of a 1.5:1 mixture of (*E,Z*) and (*E,E*) dienes, respectively. Data for **20**: IR (neat) 3066, 3021, 3007, 2956, 2927, 2870, 2856, 1479, 1466, 1458, 1447, 1319, 1307, 1148, 1087, 600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, m), 1.31 (8H, m), 2.08 (2H, m), 2.49 (2H, m), 3.14 (2H, m), 5.39 (1H, m), 5.48 (1H, dt, J=15, 7 Hz), 5.86 (1H, m), 6.32 (1H, dd, J=15, 11 Hz), 7.58 (2H, m), 7.67 (1H, m), 7.91 (2H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 26.1, 27.7, 28.8, 29.5, 31.7, 55.7, 125.7, 127.4, 128.1 (x2), 129.3 (x2), 132.4, 133.7, 134.9, 138.9.

(3*E*,5*Z*)-2-Methyl-8-phenylsulfonyl-3,5-nonadiene (21). The reaction was carried out as described for **19** on a 1 mmol scale using ethyl phenyl sulfone (170 mg, 1.0 mmol) to give 38.1 mg (50%) of a 2:1 mixture of (*E,Z*) and (*E,E*) dienes, respectively. Data for **21**: IR (neat) 2961, 1583, 1459, 1447, 1305, 1147, 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.96 (6H, t, J=7 Hz), 1.24 (3H, d), 2.15 (1H, m), 2.72 (1H, m), 2.77 (1H, m), 3.07 (1H, m), 5.20 (1H, dd, J=10, 10 Hz), 5.45 (1H, m), 5.77 (1H, dd, J=11, 11 Hz), 6.33 (1H, dd, J=15, 11 Hz), 7.56 (2H, m), 7.66 (1H, m), 7.88 (2H, m); ^{13}C NMR ($CDCl_3$) δ 13.0, 23.1 (x2), 27.0, 32.8, 59.9, 125.3, 127.5, 129.0 (x2), 129.1 (x2), 129.5, 133.7, 137.1, 139.6; MS (EI) *m/z* 278, 136, 121, 107, 93, 77; HRMS *m/z* 278.1342 (calcd for $C_{16}H_{22}O_2S$: 278.1341).

(1*Z*,3*E*)-1-Cyclohexyl-6-phenylsulfonyl-1,3-heptadiene (22). The reaction was carried out as described for **21** on a 1 mmol scale using cyclohexanecarboxaldehyde (36 μL, 0.3 mmol) to give 56.9 mg (60%) of a 2:1 mixture of (*E,Z*) and (*E,E*) dienes, respectively. Data for **22**: IR (neat) 2925, 2850, 1447, 1086, 999, 951, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03-1.27 (7H, m), 1.62 (6H, m), 2.15 (1H, m), 2.37 (1H, m), 2.78 (1H, m), 3.06 (1H, m), 5.22 (1H, dd, J=10, 10 Hz), 5.45 (1H, m), 5.79 (1H, dd, J=11, 11 Hz), 6.36 (1H, dd, J=15, 11 Hz), 7.57 (2H, m), 7.66 (1H, m), 7.88 (2H, m); ^{13}C NMR ($CDCl_3$) δ 13.0, 25.7 (x2), 25.8, 32.7, 33.2 (x2), 36.8, 59.9, 125.7, 127.5, 129.0 (x2), 129.1 (x2), 129.7, 133.7, 137.1, 138.2; HRMS *m/z* 318.1665 (calcd for $C_{19}H_{26}O_2S$: 318.1654).

(4*E*,6*Z*)-2-Phenylsulfonyl-4,6-tridecadiene (23). The reaction was carried out as for **21** on a 1 mmol scale using *n*-heptanal (40 μL, 0.3 mmol) to give 54.7 mg (57%) of a 2:1 mixture of (*E,Z*) and (*E,E*) dienes, respectively. Data for **23**: IR (neat) 3018, 2963, 2928, 2872, 2857, 1656, 1583, 1307, 1147, 987 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (3H, t, J=7 Hz), 1.24 (11H, m), 2.02 (1H, q, dt, J=7, 7 Hz), 2.12 (2H, m), 2.78 (1H, m), 3.06 (1H, m), 5.45 (1H, m), 5.60 (1H, dt, J=14, 7 Hz), 5.97 (1H, m), 6.32 (1H, dd, J=14, 9 Hz), 7.56 (2H, m), 7.65 (1H, m), 7.86 (2H, m); MS (EI) *m/z* 320, 179, 178, 149, 135, 121, 110, 107; HRMS *m/z* 320.1810 (calcd for $C_{19}H_{28}O_2S$: 320.1810).

(3*Z*,5*E*)-8-Cyano-2-methyl-3,5-octadiene (24). To a solution of diisopropylamine (0.28 mL, 2.0 mmol) in tetrahydrofuran (4 mL) at -78 °C was added dropwise *n*-butyllithium (1.26 mL of a 1.6 M solution in hexane, 2.0 mmol). The resulting solution was added dropwise to a stirred suspension of **5** (952 mg, 2.0 mmol) in tetrahydrofuran (6 mL) at -78 °C, and the resulting brown mixture was warmed to -40 °C over 30 min. In a separate flask, *n*-butyllithium (1.26 mL of a 1.6 M solution in hexane, 2.0 mmol) was added dropwise to a solution of diisopropylamine (0.28 mL, 2.0 mmol) in tetrahydrofuran (4 mL) at -78 °C. After 10 min, the solution was added to a solution of dry acetonitrile (105 μL, 2.0 mmol) in tetrahydrofuran (4 mL) at 0 °C. The mixture was stirred for 20 min and was transferred via cannula to the brown mixture containing **1**, after which the mixture was warmed to 0 °C during 1 h. A solution of isobutyraldehyde (54 μL, 0.6 mmol) in tetrahydrofuran (4 mL) was added dropwise, and the mixture was stirred for 10 min. The mixture was poured into ice-cold 1% hydrochloric acid and was extracted with ether (3 x 25 mL). The combined extracts were washed with brine and dried (magnesium sulfate), and the solvent was removed. The residual oil was chromatographed on silica, using 10% ethyl acetate in hexane as eluant, to give 51.3 mg (57%) of a 2.3:1 mixture of (*E,Z*) and (*E,E*) isomers, respectively. Data for **24**: IR (neat) 2961, 2930, 2869, 2246, 1463, 988,

950 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (6H, d), 2.31-2.56(4H, m), 2.76 (1H, m), J=7 Hz), 5.73 (1H, dd, J=10, 10 Hz), 5.61 (1H, m), 5.81 (1H, dd, J=11, 11 Hz), 6.42 (1H, dd, J=15, 11 Hz).

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