Regiospecific Synthesis of 1,4-Dienes by Alkylation–Reduction of α,β,γ,δ-Unsaturated Ketones[1]

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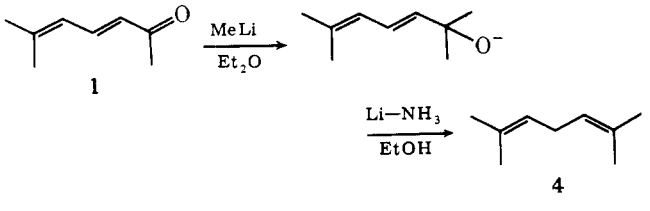
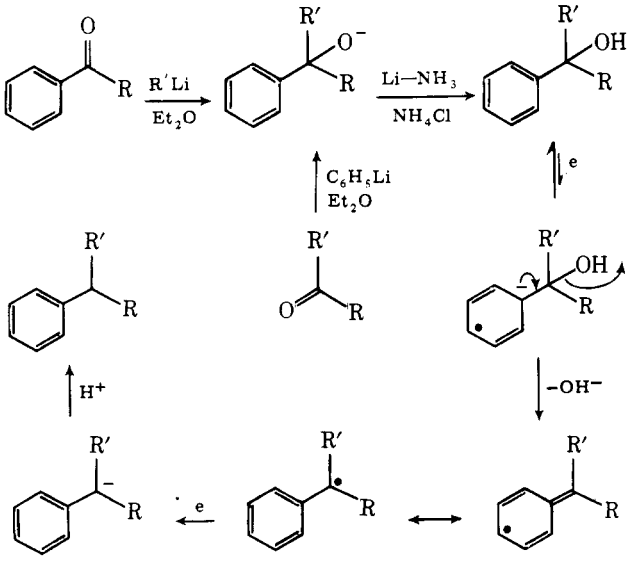
1,4-Dienes are conveniently prepared from α,β,γ,δ-unsaturated ketones by tandem alkylation–reduction. By this procedure substituted 1,3-diene 5-alkoxides, generated in situ by alkylation of α,β,γ,δ-unsaturated ketones, are reduced by lithium–ammonia–ethanol to the corresponding substituted 1,4-dienes. Examples include the synthesis of 2,6-dimethyl-2,5-heptadiene (**4**), 2,6-dimethyl-2,5-decadiene (**5**), and 2,6,7,7-tetramethyl-2,5-octadiene (**6**) by the methylation–, *n*-butylation–, and *tert*-butylation–reduction of 6-methyl-3,5-heptadien-2-one (**1**), respectively. By this procedure 2,6,10-trimethyl-2,5,9-undecatriene (**7**), 2,6,10-trimethyl-2,6,9-tetradecatriene (**8**), and 2,6,10,11,11-pentamethyl-2,6,9-dodecatriene (**9**) were also prepared from 6,10-dimethyl-3,5,9-undecatrien-2-one (pseudoionone, **2**), as well as 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-2-butene (**10**), 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-2-heptene (**11**), and 1-(2,2,6-trimethyl-1-cyclohexen-1-yl)-3,4,4-trimethyl-2-pentene (**12**) from β-ionone (**3**).

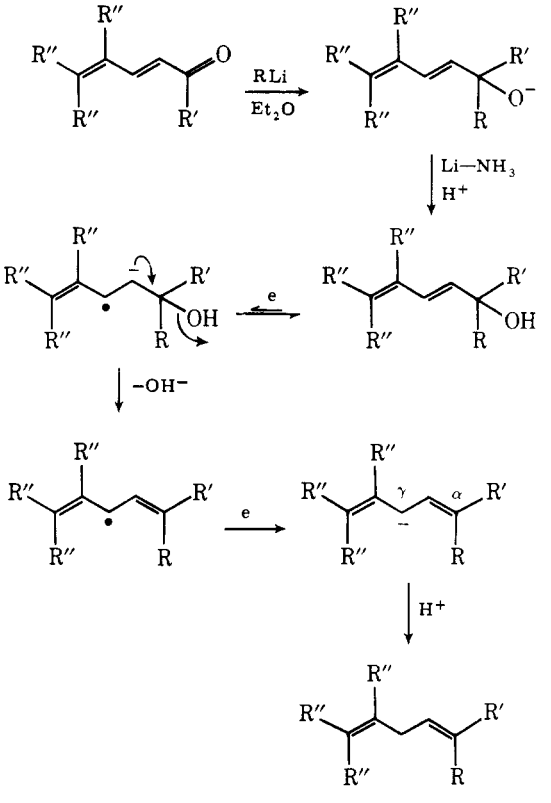
This laboratory has demonstrated the application of tandem alkylation–reduction of aromatic carbonyl systems[2] and phenylation–reduction of aldehydes and ketones[3] as a convenient method of preparing aromatic hydrocarbons. These methods have involved the lithium–ammonia–ammonium chloride reduction of a benzyl alkoxide that was generated in situ by alkylation or phenylation. In all of these studies, the presence of the aromatic ring as an electron acceptor was essential for the reduction of the benzyl alcohol to the benzyl group to be effected (see Scheme I). Since substituted 1,3-dienes can also accept an electron in metal–ammonia solutions and in the presence of an added proton source are reduced to an olefin by 1,2-addition to the less substituted double bond,[3b,4] it was of interest to examine the alkylation–reduction of substituted α,β,γ,δ-unsaturated carbonyl systems as a potentially selective procedure to prepare substituted 1,4-dienes (see Scheme II). Herein, we report such a study that results in the regioselective synthesis of 1,4-dienes when α,β,γ,δ-unsaturated ketones are subjected to tandem alkylation–reduction conditions.



Scheme I



Scheme II



The general procedure, which is performed in a single reaction vessel and requires only a few hours, is to generate a diene alkoxide in a metal–ammonia reaction vessel by the addition of the α,β,γ,δ-unsaturated ketone to an alkyllithium in ether. Ammonia is subsequently distilled into the vessel, lithium is added, and then the resulting dark blue mixture is quenched with ethanol or *tert*-butyl alcohol.[5] Table I is a listing of the unsaturated ketones subjected to this procedure, along with the products. In all cases the isolated yield of the 1,4-diene is excellent. The position of the 1,4-diene system is predictable according to the mechanism outlined in Scheme II. Where applicable, the 1,4-diene is a mixture of the *E* and *Z* stereoisomers at the newly developed double bond.[6] More acidic proton sources such as ammonium chloride were not effective at all since only the alkylated diene alcohol was isolated, indicating that the reaction of this proton source with the lithium–ammonia solution is much faster than electron transfer to the diene system and subsequent loss of hydroxide ion.

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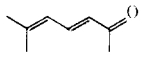
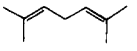
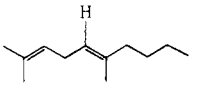
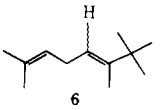
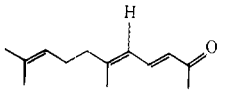
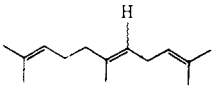
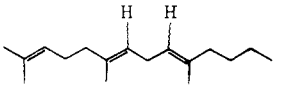
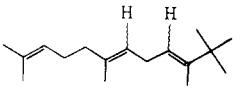
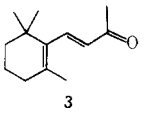
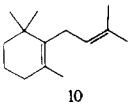
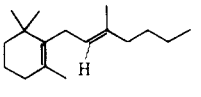
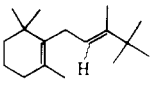
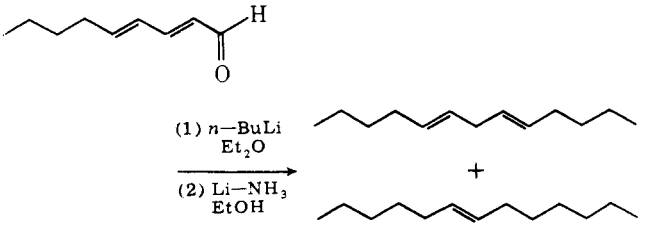
Table I. Alkylation–Reduction of α,β,γ,δ-Unsaturated Ketones[a]

α,β,γ,δ-unsat. ketone	alkylating agent	product[b]	isolated yield,[c] %
 1	CH_3Li	 4	98
	n-C_4H_9Li	 5	99
	t-C_4H_9Li[d]	 6	97
 2	CH_3Li	 7	94
	n-C_4H_9Li	 8	98
	t-C_4H_9Li[d]	 9	93
 3	CH_3Li	 10	96
	n-C_4H_9Li	 11	99
	t-C_4H_9Li[d]	 12	91

[a] See Expermiental Section for details. [b] All products gave satisfactory composition analyses (±0.4% for C, H). [c] Column chromatography. [d] The alkylation step was allowed to stir for an additional 15 min at room temperature to insure complete alkylation before adding ammonia. [e] Pseudoionone (2) is an E/Z isomeric mixture at C-5.

Application of this tandem alkylation–reduction procedure to α,β,γ,δ-unsaturated aldehydes is not synthetically useful since a diene–olefin mixture is formed. For example, when 2,4-nonadienal is butylated–reduced, a 1:1 mixture of 5,8-tridecadiene and 6-tridecene is isolated. Evidently, with al-



dehydes (R′ = H in Scheme II) the protonation of the diene anion occurs not only at the γ position (as is the case with the ketones) but at the α position as well. The latter produces a 1,3-diene that is rapidly reduced to the olefin.

The diene system of the intermediate diene alkoxide (Scheme II) is essential since attempts to extend this synthetically useful tandem alkylation–reduction 1,4-diene synthesis sequence to α,β-unsaturated systems to prepare olefins failed. For example, methylation–reduction of (*E*)-4-cyclohexyl-3-buten-2-one using these reaction conditions resulted in the isolation of only the corresponding alkylated product (*E*)-4-cyclohexyl-2-methyl-3-buten-2-ol.

Experimental Section[7]

General Comments. The alkylation reaction sequence is performed under a static nitrogen atmosphere by connecting a N_2 gas source to a T-tube that is connected to the reaction assembly and a soda lime drying trap, which is in turn connected in series to an oil bubbler, and sweeping N_2 through the system at a moderate flow rate. When ammonia is to be added, the N_2 source is disconnected and a soda lime drying tube is attached to the exit of the Dewar condenser and used for the duration of the reduction. All glassware was oven-dried, cooled to room temperature in a box desiccator, and then quickly assembled. Anhydrous ether was used directly from freshly opened containers. 6-Methyl-3,5-heptadien-2-one (1) was from ICN Pharmaceuticals, Inc. Pseudoinonone (2, a mixture of *E* and *Z* stereoisomers at C-5) and β-ionone (3) were from Hoffmann-La Roche Inc. Methyllithium (2 M solution in Et_2O, lithium bromide complex) was from Aldrich Chemical Co., Inc.; *tert*-butyllithium (1.6 M solution in *n*-pentane) was from Ventron Corp.; and *n*-butyllithium (1.4 M solution in hexane) was from Foote Mineral Co. Lithium wire (0.32 cm, high purity, Foote Mineral Co.) was wiped free of oil, rinsed in hexane, and cut into small pieces just prior to use. Anhydrous am-

monia was distilled, through a tower of KOH pellets, directly into the reaction vessel. Gas chromatography (GLC) analyses were performed on a 100 × 0.4 cm (i.d.) glass column packed with 5% silicone OV-225 (25% phenyl, 25% cyanopropyl, methyl) supported on 60–80 mesh Chromosorb W. Purification of the product(s) by column chromatography was accomplished on 80–200 mesh adsorption alumina (Fisher Scientific Co.) by elution with hexane. Evaporative distillations, samples for microanalyses, were performed in a Kugelrohr oven. The assigned structure of each product or product mixture (*E* and *Z*) was consistent with the spectral data. Satisfactory composition analyses (±0.4% for C, H) on all products were submitted to the Editor. The methylation–reduction of 6-methyl-3,5-heptadien-2-one (**1**) is described, in detail, to illustrate the procedure.

Methylation–Reduction of 6-Methyl-3,5-heptadien-2-one (1). 2,6-Dimethyl-2,5-heptadiene (4). To a stirred suspension (−50 °C) of methyllithium (5 mmol, 2.5 mL of a 2 M solution) in 20 mL of Et_2O was added a solution of 310 mg (2.50 mmol) of 6-methyl-3,5-heptadien-2-one (**1**) in 10 mL of Et_2O in a metal–ammonia reaction vessel. After 15 min, the dry ice–isopropyl alcohol bath was removed and the reaction mixture was allowed to warm to ambient temperature (30 min), during which time the white suspension turned a yellow color. Ammonia (~60 mL) was carefully, to prevent excessive splattering, distilled into the mixture and 104 mg (15 mg-atom, 6 pieces) of lithium wire added. 5 min after the dark blue color of the mixture was established, 3 mL of absolute EtOH was added (~30 s) and within 5 min the reaction mixture had turned white. After the ammonia was allowed to evaporate, the residue was partitioned between ether and water. The organic phase was dried ($MgSO_4$), filtered, and concentrated at water aspirator pressure, and then the crude yellow oil was analyzed (GLC). Following column chromatography, 365 mg (98%) of 2,6-dimethyl-2,5-heptadiene (**4**) was obtained as a colorless oil: bp 65 °C (22 torr); IR (film) 3020 sh, 2955, 2910, 2860, 1455, 1373, 963, 898 cm^{-1}; NMR ($CDCl_3$) δ 5.10 (2 H, t, J = 7.3 Hz), 2.67 (2 H, t, J = 7.3 Hz), 1.68 (6 H, s), 1.63 (6 H, s); MS *m/e* (rel intensity) 124 (M^+, 46), 109 (50), 81 (53), 69 (24), 67 (59), 56 (40), 55 (100), 43 (59), 41 (24).

2,6-Dimethyl-2,5-decadiene (5): bp 73–75 °C (2 torr); IR (film) 3060 sh, 3020 sh, 2940, 2910, 2850, 1470, 1385, 970, 735 cm^{-1}; NMR ($CDCl_3$, *E/Z* mixture) δ 5.10 (2 H, t, J = 7.0 Hz), 2.67 (2 H, t, J = 7.5 Hz), 1.97 (2 H, m), 1.68 (3 H, s), 1.62 (6 H, s), 1.50–1.10 (4 H, m), 0.91 (3 H, perturbed t); MS *m/e* (rel intensity) 166 (M^+, 1), 109 (52), 95 (30), 81 (54), 69 (44), 67 (100), 55 (61), 43 (52), 41 (98).

2,6,7,7-Tetramethyl-2,5-octadiene (6): bp 58–62 °C (2 torr); IR (film) 3040 sh, 2960, 2930, 2870, 1475, 1385, 1370 cm^{-1}; NMR ($CDCl_3$, *E/Z* mixture) δ 5.17–5.01 (2 H, m), 2.67 (2 H, t, J = 6.6 Hz), 1.68 (3 H, br s), 1.61 (6 H, br s), and sharp singlets at 1.02 (5.7 H) and 1.00 (3.3 H) for the *E* and *Z* isomers; MS *m/e* (rel intensity) 123 (7), 109 (46), 95 (27), 79 (12), 69 (30), 67 (57), 57 (68), 55 (34), 43 (63), 41 (100).

2,6,10-Trimethyl-2,5,9-undecatriene (7): bp 65–67 °C (1 torr); IR (film) 3050, 2980, 2970, 1460, 1385, 1110, 830 cm^{-1}; NMR ($CDCl_3$, *E/Z* mixture) δ 5.10 (3 H, t, J = 7.2 Hz), 2.67 (2 H, t, J = 7.1 Hz), 2.2–1.7 (4 H, m), 1.68 (9 H, s), 1.61 (6 H, s); MS *m/e* (rel intensity) 192 (M^+, 1), 152 (5), 138 (5), 123 (11), 109 (16), 95 (22), 81 (22), 69 (100), 55 (33), 45 (30), 43 (50).

2,6,10-Trimethyl-2,6,9-tetradecatriene (8): bp 68–70 °C (1 torr); IR (film) 3040 sh, 2970, 2930, 2870, 1455, 1380, 1260, 1110, 805 cm^{-1}; NMR ($CDCl_3$, *E/Z* mixture) δ 5.10 (3 H, superficial t, J = 7.0 and 8.8 Hz), 2.68 (2 H, superficial t, J = 7.0 and 8.6 Hz), 2.01 (6 H, br m), 1.67 (6 H, br s), 1.60 (6 H, br s), 1.30 (4 H, complex m), 0.87 (3 H, perturbed t, J = 6.6 Hz); MS *m/e* (rel intensity) 234 (M^+, 1), 191 (4), 177 (4), 151 (6), 138 (6), 123 (18), 109 (41), 95 (41), 81 (52), 69 (100), 55 (51), 43 (39), 41 (51).

2,6,10,11,11-Pentamethyl-2,6,9-dodecatriene (9): bp 67–70 °C (2 torr); IR (film) 3050 sh, 2980, 2960, 1450, 1380, 1365, 1105, 815 cm^{-1}; NMR ($CDCl_3$, *E/Z* mixture) δ 5.10 (3 H, superficial t, J = 6.2 Hz), 2.68 (2 H, superficial t, J = 7.2 Hz), 2.01 (4 H, m), 1.68 (6 H, br s), 1.61 (6 H, br s), and sharp singlets at 1.00 (2.1 H), 0.91 (1.8 H), 0.88 (3.6 H), and 0.86 (1.5 H); MS *m/e* (rel intensity) 123 (14), 121 (10), 109 (30), 95 (22), 81 (42), 69 (100), 67 (37), 57 (70), 55 (59), 43 (50).

1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-2-butene (10): bp 78–80 °C (2 torr); IR (film) 3040 sh, 2960, 2920, 2870, 1465, 1380, 1375, 1360, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.97 (1 H, t, J = 6.5 Hz), 2.68 (2 H, apparent d, J = 5.9 Hz), 1.92 (2 H, apparent t, J = 3.9 Hz), 1.66 (6 H, br s), 1.54 (3 H, s) superimposed on 1.47 (4 H, m), 0.97 (6 H, s); ^{13}C NMR ($CDCl_3$, broad-band proton decoupling) δ 136.67, 129.15, 127.15, 125.39, 39.88, 34.93, 32.91, 28.65, 28.31, 27.38, 25.60, 22.51, 19.65, 17.73 ppm; MS *m/e* (rel intensity) 192 (M^+, 1), 136 (5), 122 (12), 107 (22), 94 (21), 81 (35), 69 (39), 67 (22), 55 (40), 43 (73), 41 (100).

1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-2-heptene (11): bp 68–70 °C (2 torr); IR (film) 3050 sh, 2970, 2940, 2880, 1460, 1385, 1370, 1120, 730 cm^{-1}; ^1H NMR ($CDCl_3$, *E/Z* mixture) δ 4.96 (1 H, t, J = 6.5 Hz), 2.69 (2 H, d, J = 6.6 Hz), 1.94 (4 H, m), 1.63 (3 H, br s) and 1.54 (3 H, br s) superimposed on 1.7–1.1 (8 H, m), 0.96 (6 H, s) superimposed on 0.88 (3 H, perturbed t, J = 5.4 Hz); ^{13}C NMR ($CDCl_3$, broad-band proton decoupling) δ 136.89, 136.83, 133.68, 133.23, 127.13, 127.07, 125.76, 125.30, 39.89, 39.40, 34.94, 32.90, 31.70, 30.33, 29.93, 29.42, 28.60, 28.34, 27.27, 26.97, 26.39, 23.26, 22.85, 22.39, 19.66, 15.92, 14.12, 14.02 ppm; MS *m/e* (rel intensity) 234 (M^+, 16), 219 (12), 191 (5), 177 (16), 163 (12), 149 (16), 137 (15), 135 (22), 123 (100), 121 (68), 109 (48), 107 (95), 95 (68), 93 (63), 81 (90), 69 (85), 55 (85), 43 (63), 41 (74).

1-(2,2,6-Trimethyl-1-cyclohexen-1-yl)-3,4,4-trimethyl-2-pentene (12): bp 69–72 °C (2 torr); IR (film) 3040 sh, 2970, 2930, 2880, 1470, 1385, 1370 cm^{-1}; NMR ($CDCl_3$, *E/Z* mixture) δ 4.96 (1 H, t, J = 5.8 Hz), 2.69 (2 H, d, J = 5.8 Hz), 1.92 (2 H, m), 1.64 (3 H, br s) and 1.53 (3 H, br s) superimposed on 1.6–1.1 (4 H, m), 1.01 (6 H, s), and sharp singlets at 0.95 (5 H) and 0.94 (4 H) for the *E* and *Z* isomers; MS *m/e* (rel intensity) 234 (M^+, 18), 219 (4), 177 (58), 163 (14), 149 (10), 135 (24), 123 (56), 121 (60), 109 (40), 107 (58), 97 (20), 95 (58), 93 (38), 83 (22), 81 (42), 69 (80), 57 (100), 43 (38), 41 (64).

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Registry No.—**1,** 1604-28-0; (*E,E*)-**2,** 3548-78-5; (*E,Z*)-**2,** 13927-47-4; **3,** 79-77-6; **4,** 6090-16-0; (*E*)-**5,** 68965-65-1; (*Z*)-**5,** 68965-66-2; (*E*)-**6,** 68974-94-7; (*Z*)-**6,** 68974-95-8; (*E*)-**7,** 68974-96-9; (*Z*)-**7,** 68974-97-0; **8,** 68965-67-3; **9,** 68965-68-4; **10,** 51468-96-3; (*E*)-**11,** 68965-69-5; (*Z*)-**11,** 68965-70-8; (*E*)-**12,** 68965-71-9; (*Z*)-**12,** 68965-72-0.

References and Notes

(1) Part 10 in the series, "Alkylation–Reduction of Carbonyl Systems". For part 9, see S. T. Srisethnil and S. S. Hall, *J. Org. Chem.*, **42,** 4266 (1977).
(2) (a) S. S. Hall, C.-K. Sha, and F. Jordan, *J. Org. Chem.*, **41,** 1494 (1976); (b) S. D. Lipsky and S. S. Hall, *Org. Synth.*, **55,** 7 (1976); (c) *J. Org. Chem.*, **38,** 1735 (1973).
(3) (a) F. J. McEnroe, C.-K. Sha, and S. S. Hall, *J. Org. Chem.*, **41,** 3465 (1976); (b) S. S. Hall and F. J. McEnroe, *ibid.*, **40,** 271 (1975).
(4) W. Hückel and H. Bretschneider, *Justus Liebigs Ann. Chem.*, **540,** 157 (1939).
(5) Ethyl alcohol is the proton source of choice since *tert*-butyl alcohol is inconvenient to manipulate because it solidifies around room temperature and is difficult to remove in vacuo without losing some of the volatile product material.
(6) This mixture of *E* and *Z* stereoisomers is most readily discerned in the ^1H NMR spectrum of olefins **6, 9,** and **12,** where the sharp singlets for the *tert*-butyl groups are an indication of the number of isomers. Examination of the olefinic region of the ^{13}C NMR spectrum of olefin **11** (as compared to that of **10**) also indicates a mixture (60:40) of *E* and *Z* isomers.
(7) GLC analyses were determined on a Hewlett-Packard Model 7610A (flame detector) chromatograph. The IR spectra were determined with a Beckman Model AccuLab 6 infrared recording spectrophotometer. The ^1H NMR spectra were determined at 100 MHz with a JEOL Model JNM-PS-FT-100 fast Fourier transform NMR spectrometer, and the ^{13}C NMR spectra were determined at 25.2 MHz with a Varian Model XL-100 NMR spectrometer. The chemical shifts are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were determined with an AEI Model MS-30 mass spectrometer (70 eV) to which was interfaced a Pye Unicam Model 104 gas chromatograph.