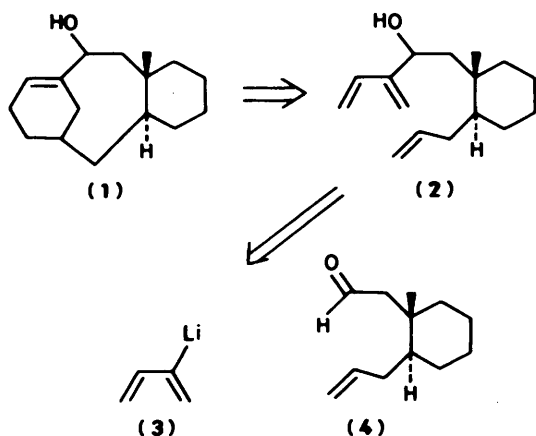


The Generation and Reactions of 2-Lithiobutadiene with Aldehydes

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The tri-isopropylphenylsulphonylhydrazone of methyl vinyl ketone undergoes the Shapiro reaction to give 2-lithiobuta-1,3-diene which reacts with aldehydes to give 2-substituted dienes with high regioselectivity.

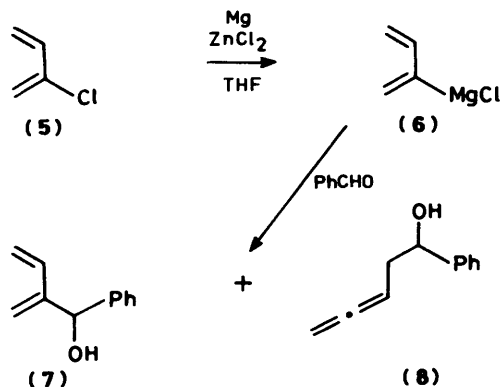
As part of our studies on the synthesis of the taxane ring system (1)¹ we are working on a strategy in which the key step is the intramolecular Diels-Alder reaction of the triene (2). The



Scheme

reaction between 2-lithiobutadiene (3) and the aldehyde (4) would be expected to give the triene (2). 2-Lithiobutadiene (3) is an unknown species,² but the corresponding Grignard reagent,^{3,4} 1-lithiobutadiene,⁵ and an aluminium reagent derived from isoprene⁶ have been reported.

2-Chlorobutadiene (5) is readily converted into 2-(buta-1,3-dienyl)magnesium chloride (6) by a method originally reported by Sultanov;⁴ however, in its reaction with aldehydes,³ e.g. benzaldehyde, a mixture of the diene (7) (30%) and allene (8) (70%) is produced in 68% yield. Clearly the Grignard reagent (6) is not a synthetically useful reagent if it reacts with aldehydes to give a mixture of allene and diene products. Recently it has been shown that Grignard reagent (6) reacts regioselectively as a diene in a conjugate addition to α,β -unsaturated ketones in the presence of $\text{CuBr}\cdot\text{SMe}_2$.⁷

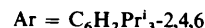
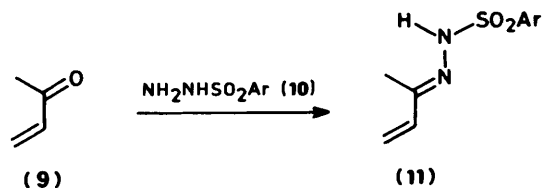


We reasoned that 2-lithiobuta-1,3-diene (3) may have a different profile of reactivity than the corresponding Grignard reagent (6) and that it might show a propensity to react regioselectively with aldehydes giving 2-substituted dienes in a synthetically useful procedure.

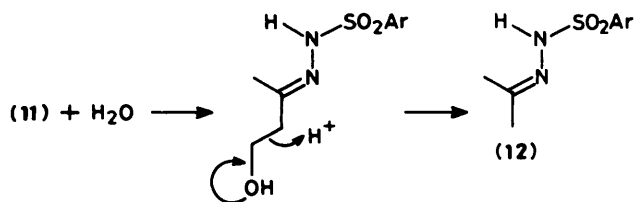
Results and Discussion

Our first attempts to prepare 2-lithiobuta-1,3-diene (3) by lithium halogen exchange on 2-chlorobuta-1,3-diene (5) were unsuccessful. Turning our attention to other methods available for the generation of vinyl-lithium species the Shapiro reaction⁸ appeared to be a useful alternative. The synthetic scope of this reaction has been extended by the elegant studies of Barret⁹ and his co-workers which have recently been applied in a total synthesis of (\pm)-ovalicin.¹⁰ Some examples of the Shapiro reaction on the tosyl hydrazones of α,β -unsaturated ketones have been reported.¹¹ The Shapiro reaction has been much improved by the use of the 2,4,6-tri-isopropylphenylsulphonylhydrazides which avoid *ortho*-metallation of the benzene ring and the consequent need for a large excess of alkyl-lithium reagent.¹²

The sulphonylhydrazone (10)¹³ was condensed with methyl vinyl ketone (9) to give the hydrazone (11).



At first this reaction was unreliable especially when long reaction times were used. One side-reaction involved the conjugate addition of the water generated in the reaction to the hydrazone (11) followed by a retro-aldol like reaction to give acetone hydrazone (12), the structure of this product was proved by independent synthesis.



It was possible to obtain the hydrazone (11) as a crystalline compound in 69% yield by using methyl vinyl ketone as solvent and employing short reaction times to avoid the side reaction.

A series of experiments was carried out to determine the best

Table. The effect of various bases on the Shapiro reaction of the hydrazone (11).

RLi/Solvent	Ratio of (7):(8)	% Yield of (7) + (8)
BuLi/DME	90:10	42
Bu ^t Li/DME	Nil	Nil
LDA/DME	No reaction	
MeLi-LiBr/DME	90:10	46
MeLi-LiBr/DME + TMEDA	93:7	23
MeLi-LiBr/DME + HMPA	Nil	Nil

Nil indicates no (7) or (8) isolated

base and solvent for the Shapiro reaction on (11); the results are summarised in the Table.

Best results were obtained with MeLi-LiBr complex and dimethoxyethane as solvent.⁹ Treatment of (11) with 2 equivalents of MeLi-LiBr at -78°C gave an orange solution which was allowed to warm to 0°C when a gas was evolved and a pink solution produced. This solution was re-cooled to -78°C and benzaldehyde was added. After chromatography a 46% yield of a liquid product was produced which consisted of a 90:10 mixture of diene (7) and allene (8). This mixture could not be separated and the ratio was estimated from the n.m.r. spectrum of the product. Clearly 2-lithiobuta-1,3-diene (3) generated by the Shapiro reaction does indeed have a different profile of reactivity from that of the Grignard reagent (6). In this comparable case (3) shows a definite preference in favour of the formation of the diene (7) over the allene (8).

Exclusive formation of diene products was observed when a solution of 2-lithiobutadiene was treated with the following aldehydes: 3-phenylpropionaldehyde, decanal, phenylacetaldehyde, 4-isopropenylcyclohex-1-enecarbaldehyde, and 3,7-dimethyloct-6-enal. The diene products were separated from a by-product arising from addition of some unchanged MeLi with the added aldehyde in some cases. This may be explained by considering the usual mechanism put forward for the Shapiro reaction,⁸ in which a second deprotonation of (11) occurs at carbon to give a dianion which fragments *via* an aza anion to give 2-lithiobuta-1,3-diene (3). If the second deprotonation is not complete the methyl-lithium will remain unchanged in the solution until the aldehyde is added when it will compete with (3) for this electrophile.

Trapping 2-lithiobuta-1,3-diene (3) with triphenyltin chloride followed by regeneration of (3) with phenyl-lithium failed to give higher yields of diene products compared with the direct Shapiro procedure.

Experimental

All 90 MHz ^1H n.m.r. spectra were recorded on a Varian EM390 spectrometer and all 15 MHz ^{13}C n.m.r. spectra on a Jeol JNM-FX60 Fourier Transform spectrometer. Highfield ^1H n.m.r. (400 MHz) and ^{13}C n.m.r. (100 MHz) spectra were recorded using the highfield n.m.r. service at Warwick University. I.r. spectra were recorded on a Perkin-Elmer 298 spectrometer and mass spectra on a Micromass 16B spectrometer. Accurate mass measurements were made at PCMU Harwell and elemental analysis was carried out by CHN Analysis, Wigston. M.p.s were determined on a Kofler hot-stage and are uncorrected. Flash chromatography was carried out according to the method of Still¹⁴ using silica gel [Merck and Co., Kieselgel 60, 230–240 mesh (ASTM)]. The concentration of butyl-lithium and methyl-lithium-lithium bromide was determined by back titration with 0.1M-HCl from solution in

dibromoethane and water using phenolphthalein as an indicator. All solvents were dried by standard procedures.

N'-But-3-en-2-ylidenehydrazone-2,4,6-tri-isopropylbenzenesulphonohydrazide. (11).—Methyl vinyl ketone (45 ml, 0.55 mol) was added *via* a syringe to 2,4,6-tri-isopropylbenzenesulphonohydrazide¹³ (20.11 g, 67 mmol) at 0°C and under nitrogen. The resulting yellow solution was stirred and the disappearance of starting material monitored by t.l.c. (*ca.* 15 min). The excess of methyl vinyl ketone was then removed under reduced pressure at 0°C and the resulting viscous white solid was triturated with cold hexane (30 ml). It was then filtered off, washed with a further portion of cold hexane (30 ml), and dried *in vacuo* to afford the title compound as a white powder (16.10 g, 69%), m.p. 113–118 $^{\circ}\text{C}$ (decomp.), R_F 0.61 (CH_2Cl_2); ν_{max} (CH_2Cl_2) 3230br (NH), 2955s, 2925m, 2865m, 1595m (C=N), 1325s, 1165s, and 1155s cm^{-1} ; δ_{H} (400 MHz, CDCl_3) 1.24 [d, J 6.9, 6 H, $p\text{-C(H)Me}_2$], 1.27 [d, J 6.7, 12 H, $2 \times o\text{-C(H)Me}_2$], 1.88 (s, 3 H, CH_3), 2.89 [sept, J 6.9, 1 H, $p\text{-CH(Me)}_2$], 4.30 (sept, J 6.7, 2 H, $2 \times o\text{-CH(Me)}_2$), 5.33 (d, $J_{3,4\text{-cis}}$ 11.07, 1 H, 4-H), 5.47 (d, $J_{3,4\text{-trans}}$ 17.80, 1 H, 4-H), 6.32 (dd, J 17.80, 11.07, 1 H, 3-H), 7.17 (s, 2 H, ArH), and 8.30 (br s, 1 H, NH); δ_{C} (100 MHz, CDCl_3) 18.18, 23.38, 24.67, 29.79, 34.02, 123.68, 128.09, 131.27, 137.98, 148.73, 151.25, and 153.11; m/z 350 (M^+ , 4), 282 (35), 267 (100), 266 (32), 189 (42), 148 (30), and 91 (45) (Found: C, 64.9; H, 8.55; N, 7.75; S, 9.05. $\text{C}_{19}\text{H}_{30}\text{N}_2\text{O}_2\text{S}$ requires C, 65.10; H, 8.63; N, 7.99; S, 9.15%).

General Procedure for the Generation of 2-Lithiobuta-1,3-diene (3) and its Reaction with Electrophiles.—MeLi-LiBr complex (5.7 mmol) was added to a stirred solution of the hydrazone (11) (1 g, 2.8 mmol) in DME (20 ml) at -78°C , under nitrogen to give a slight effervescence and precipitation of LiBr. The solution was warmed to 0°C when evolution of nitrogen was accompanied by formation of a characteristic pink colour. The reaction mixture was then re-cooled to -78°C and a solution of the electrophile (4.2 mmol) in DME (5 ml) added, which discharged the pink colour. After being stirred at 0°C for 1 h the mixture was quenched with saturated aqueous NH_4Cl (150 ml) and extracted with ether (3×75 ml). Each extract was washed with saturated brine (75 ml) and the combined extracts were dried (MgSO_4). Removal of the solvent followed by flash chromatography allowed separation of the major products, the dienyl alcohols from excess of aldehyde. In some experiments alcohols arising from MeLi addition to the aldehydes, were detected in minor amounts.

2-Methylene-1-phenylbut-3-en-1-ol.—2-Lithiobutadiene generated by the method described above from MeLi-LiBr (5.7 mmol), and the hydrazone (11) (1 g, 2.8 mmol) was trapped with benzaldehyde (0.43 ml, 4.2 mmol) in DME (5 ml). After work-up and flash chromatography the title compound (7) was obtained as a colourless oil (210 mg, 46%), R_F 0.38 (CH_2Cl_2) which contained 10% of the allenic alcohol (8); ν_{max} (film) 3480br (OH), 1950w (allenic isomer, C=C), 1690w, 1600m (C=C), 1450m, 1010m, and 900s; δ_{H} (90 MHz, CDCl_3) 2.23 (br s, 1 H, OH), 4.98 (d, $J_{3,4\text{-cis}}$ 12, 1 H, 4-H), 5.16 (d, $J_{3,4\text{-trans}}$ 18, 1 H, 4-H), 5.27 (s, 1 H, 1-H), 5.34 (s, 1 H, 2- CH_2), 5.38 (s, 1 H, 2- CH_2), 6.25 (dd, J 18, 12, 1 H, 3-H), and 7.29 (s, 5 H C_6H_5); δ_{C} (15 MHz, CDCl_3) 73.89 (d, C-1), 115.57 ($2 \times t$, 2- CH_2), 126.74 (d), 127.65 (d), 128.30 (d), 135.7 (d), 142.30 (s), and 147.52 (s); m/z 160 (M^+ , 16), 107 (100), 105 (25), 91 (15), and 79 (65); R_t (3% OV17, temp. 162°C) 3.6 min (90%) and 4.8 min [10%, allenic alcohol (8)] (Found: M^+ , 160.0886. $\text{C}_{11}\text{H}_{12}\text{O}$ requires M , 160.0888).

4-Methylene-1-phenylhex-5-en-3-ol.—2-Lithiobutadiene generated by the method described above from MeLi-LiBr (5.7

mmol), and the hydrazone (11) (1 g, 2.8 mmol) was trapped with 3-phenylpropionaldehyde (0.55 ml, 4.2 mmol) in DME (5 ml). After work-up and flash chromatography the title compound was isolated as a colourless oil (293 mg, 55%), R_F 0.39 (CH_2Cl_2); ν_{max} (film) 3 495br (OH), 3 020s, 2 945s, 2 920s, 2 860s, 1 600m ($\text{C}=\text{C}$), 1 495s, 1 450s, 1 070s, 1 030s, and 990s; δ_{H} (90 MHz, CDCl_3) 1.84 (m, 3 H, CH_2 , OH), 2.68 (m, 2 H, CH_2), 4.31 (m, 1 H, 3-H), 5.00 (d, $J_{5,6\text{-cis}}$ 12, 1 H, 6-H), 5.14 (d, $J_{5,6\text{-trans}}$ 18, 1 H, 6-H), 5.1 (s, 1 H, 4- CH_2), 5.2 (s, 1 H, 4- CH_2), 6.28 (dd, J 18, 12, 1 H, 5-H), and 7.16 (s, 5 H, C_6H_5); δ_{C} (15 MHz, CDCl_3) 31.94 (t, CH_2), 37.91 (t, CH_2), 70.51 (d, C-3), 114.14 ($2 \times$ t, $\text{CH}_2=\text{C}$), 125.70 (d), 128.30 ($2 \times$ d), 135.96 (d, C-5), 141.80 (s), and 148.95 (s, C-4); m/z 188 (M^+ , 3), 170 (37), 105 (39), 92 (28), 91 (100), 84 (86), and 83 (39); R_i (3% OV17, temp. 188 °C) 3.6 min (Found: M^+ , 188.1201. $\text{C}_{13}\text{H}_{16}\text{O}$ requires M , 188.1201).

3-Methylenetricidec-1-en-4-ol.—2-Lithiobutadiene generated by the method described above from MeLi–LiBr (5.7 mmol), and the hydrazone (11) (1 g, 2.8 mmol) was trapped with decanal (0.82 ml, 4.2 mmol) in DME (5 ml). After work-up and flash chromatography the title compound was obtained as a colourless oil (294 mg, 49%), R_F 0.34 (CH_2Cl_2 –hexane, 4:1); ν_{max} (film) 3 380br (OH), 2 950s, 2 920s, 2 850s, 1 595m ($\text{C}=\text{C}$), 1 465m, 1 455m, 990m, and 900s; δ_{H} (90 MHz, CDCl_3) 0.85 m, 3 H, CH_3), 1.15–1.75br [17 H, (CH_2)₈, OH], 4.36 (m, 1 H, 4-H), 5.06 (d, $J_{1,2\text{-cis}}$ 11, 1 H, 1-H), 5.11 (s, 1 H, 3- CH_2); 5.30 (d, $J_{1,2\text{-trans}}$ 18, 1 H, 1-H), and 6.30 (dd, J 18, 11, 1 H, 2-H); δ_{C} (15 MHz, CDCl_3) 14.02 (q, CH_3), 22.59 (t), 25.84 (t), 29.60 (t), 31.81 (t), 36.36(t), 71.68 (d, C-4), 114.14 and 113.75 ($2 \times$ t, $\text{CH}_2=\text{C}$), 136.22 (d, C-2), and 149.21 (s, C-3); m/z 210 (M^+ , 2), 119 (95), 117 (100), 93 (40), 91 (20), 84 (82), 83 (65), and 79 (63); R_i (3% OV17, temp. 162 °C) 3.75 min.

3-Methylene-1-phenylpent-4-en-2-ol.—2-Lithiobutadiene generated by the method described above from MeLi–LiBr (5.7 mmol), and the hydrazone (11) (1 g, 2.8 mmol) was trapped with phenylacetaldehyde (0.49 ml, 4.2 mmol) in DME (5 ml). After work-up and flash chromatography the title compound was obtained as a colourless oil (188 mg, 32%), R_F 0.39 (CH_2Cl_2); ν_{max} (film) 3 560m (OH), 3 420br (OH), 3 080m, 3 020m, 2 920m, 1 595m, 1 495s, 1 455s, 1 085s, 1 030s, 990m, and 910s; δ_{H} (90 MHz, CDCl_3) 2.00 (br s, 1 H, OH) 2.68 (dd, $J_{1,1}$ 15, $J_{1,2}$ 9, 1 H, 1-H), 3.00 (dd, $J_{1,1}$ 15, $J_{1,2}$ 4, 1 H, 1-H), 4.55 (dd, J 9, 4, 1 H, 2-H), 5.08 (d, $J_{4,5\text{-cis}}$ 12, 1 H, 5-H), 5.10 (s, 1 H, 3- $\text{CH}_2=\text{C}$), 5.15 (s, 1 H, 3- CH_2), 5.34 (d, $J_{4,5\text{-trans}}$ 18, 1 H, 5-H), 6.34 (dd, J 18, 12, 1 H, 4-H), and 7.18 (s, 5 H, C_6H_5). Samples for accurate mass and ^{13}C n.m.r. decomposed before the results were obtained.

1-(4'-Isopropenylcyclohex-1'-enyl)-2-methylenebut-3-en-1-ol.—2-Lithiobutadiene generated by the method described above from MeLi–LiBr (5.7 mmol) and the hydrazone (11) (1 g, 2.8 mmol) was trapped with 4-isopropenylcyclohex-1-ene-carbaldehyde (0.65 ml, 4.2 mmol) in DME (5 ml). Work-up and flash chromatography afforded the title compound as a colourless oil (220 mg, 40%), R_F 0.31 (hexane–ether, 4:1); ν_{max} (film) 3 380br (OH), 2 960s, 2 850s, 1 640m ($\text{C}=\text{C}$), 1 595m ($\text{C}=\text{C}$), 1 430s, 1 010s, and 900s; δ_{H} (90 MHz, CDCl_3) 1.10–1.60 (m, 2 H), 1.70 (s, 3 H, CH_3), 1.80–2.35 (m, 5 H), 4.68 (br s, 3 H, 4'- $\text{CH}_2=\text{C}$, 1-H), 5.02 (d, $J_{3,4\text{-cis}}$ 12, 1 H, 4-H), 5.22 (s, 1 H, 2- $\text{CH}_2=\text{C}$), 5.25 (s, 1 H, 2- CH_2), 5.30 (d, $J_{3,4\text{-trans}}$ 18, 1 H, 4-H), 5.84

(br s, 1 H, 2-H), and 6.25 (dd, J 18, 12, 1 H, 3-H); δ_{C} (100 MHz, CDCl_3) 20.62 (q, CH_3), 24.24(t), 24.52(t), 27.41(t), 27.70(t), 30.37(t), 30.46(t), 40.86(d, C-4'), 41.09 (d, C-4'), 75.13 (d, C-1'), 75.53 (d, C-1'), 108.51 ($2 \times$ t, 4'- $\text{CH}_2=\text{C}-\text{C}$), 114.55(t), 114.55(t), 114.56(t), 114.71(t), 123.76 (d, C-2'), 124.38 (d, C-2'), 135.77 (d, C-3), 135.95 (d, C-3); 137.50 (s, C-4'), 137.72 (s, C-4'), 146.06 (s, C-1'), 146.33 (s, C-1'), and 149.54 (s, C-2) (the spectrum indicates a 1:1 mixture of diastereoisomers); m/z 204 (M^+ , 3%), 149 (32), 107 (23), 105 (40), 93 (55), 91 (86), 81 (22), and 79 (75) (Found: M^+ , 204.1501. $\text{C}_{14}\text{H}_{20}\text{O}$ requires M , 204.1514).

6,10-Dimethyl-3-methyleneundeca-1,9-dien-4-ol.—2-Lithiobutadiene generated by the method described above from MeLi–LiBr (5.7 mmol), and hydrazone (11) (1 g, 2.8 mmol) was trapped with 3,7-dimethyloct-6-enal (0.76 ml, 4.2 mmol) in DME (5 ml). Work-up and flash chromatography gave the title compound as an oil (282 mg, 49%), R_F 0.4 (CH_2Cl_2); ν_{max} (film) 3 420 br (OH), 2 980s, 2 920s, 1 450s, 1 375s, and 990s; δ_{H} (90 MHz, CDCl_3) 0.85–0.98 ($2 \times$ d, J 6, 3 H, CH_3), 1.10–2.08 (m, 14 H, aliphatic CH, CH_2 , OH, and olefin CH_2), 4.49 (m, 1 H, 4-H), 5.05–5.44 (m, 5 H, $2 \times$ 1-H, 3- CH_2), and 6.30 (dd, $J_{1,2\text{-trans}}$ 18, $J_{1,2\text{-cis}}$ 12, 1 H, 2-H); δ_{C} (100 MHz, CDCl_3) 17.55 (q), 18.90(d), 20.18(d), 36.41(t), 37.76(t), 43.92(t), 44.15(t), 69.21 (d, C-4), 70.12 (d, C-4), 113.45(t), 113.68(t), 113.99(t), 114.31(t), 124.66 (d, C-9), 124.75 (d, C-9), 130.91 (s, C-10), 131.09 (s, C-10), 135.94 (d, C-2), 136.21 (d, C-2), 149.60 (s, C-3), and 149.96 (s, C-3) (the spectrum indicates a 1:1 mixture of diastereoisomers); m/z 208 (M^+ , ca. 1%), 123 (32), 119 (60), 95 (100), 82 (44), and 81 (64).

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