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A Versatile Synthesis of (*E*)- and (Z)-1-Halo-2-(alkoxymethyl)-1,3-butadienes and their Condensation with Aldehydes

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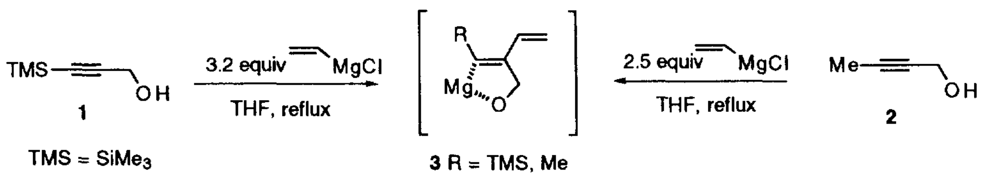
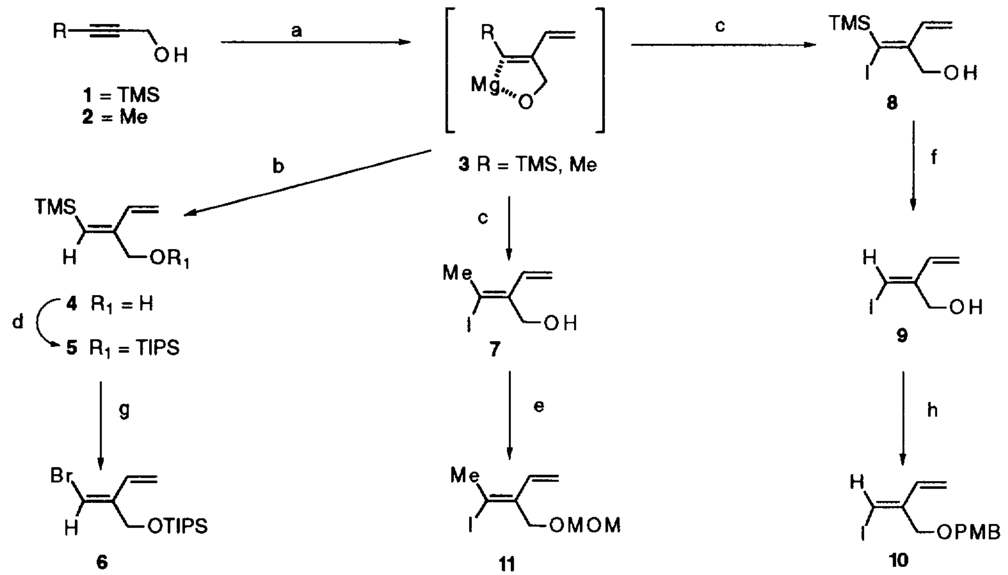
Abstract: The direct synthesis of various stereodefined dienes **4-11** from propargyl alcohols upon direct addition of vinylmagnesium chloride and manipulation of the resulting magnesium chelate **3** is described. These halo-dienes provided access to the corresponding dienyllithium reagents which were condensed with the aldehydes **13, 15, 17,** and **19** to provide the secondary alcohols **14, 16, 18, 20,** and **21**, respectively, in a stereoselective manner.

The continued popularity of the Diels-Alder reaction and its many synthetic applications has required the development of direct routes to stereodefined dienes.[1] In addition, these building blocks are of interest for the study of transition metals with unsaturated systems and their synthetic application.[2] Motivated by our interest in the total synthesis of the potent anti-tumor agent paclitaxel (Taxol®)[3-5] and the synthetic application of [4 + 2] cycloadditions,[6] we required a versatile route to various dienes. We have described previously the synthesis of *E*- and *Z*-substituted 1-trimethylsilyl-1,3-butadienes via Pd(0) mediated coupling of functionalized alkenes and their halodesilylation products.[7] A more direct entry to these and related dienes may be achieved by the direct addition of vinyl Grignard reagents to 3-trimethysilylpropargyl alcohol (**1**) or 2-butyn-1-ol (**2**).[8] As illustrated, the addition of vinylmagnesium chloride[9] (3.2 equiv., THF, reflux) to either **1** or **2** (2.5 equiv.) provided direct access to the magnesium chelate **3**.[10]



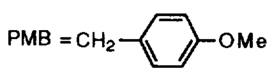
Subsequent addition of a suitable electrophile determined the product and the stereochemistry of the resulting diene. For example, protonation in the trimethylsilyl series generated the diene **4**, in which the primary alcohol was protected as the triisopropylsilyl ether **5**. Treatment of **5** with *N*-bromosuccinimide resulted in the smooth replacement of the trimethylsilyl group with retention of stereochemistry.[11] This provided (*E*)-1-bromo-2-(triisopropylsiloxy)methyl-1,3-butadiene (**6**) in 88% yield. Direct entry to the corresponding *Z*-iodides was achieved by quenching the reaction mixture with iodine to afford the iodo-alcohols **7** and **8** depending upon the substrate selected. Protodesilylation[11h] of **8** under basic conditions generated **9**. A more efficient procedure, particularly on a larger scale, was to employ the crude product **8** directly in the desilylation step to give the iodo-diene **9** (65-77% from **1**). This iodo-alcohol was unstable and thus was protected directly as the *p*-methoxybenzyl ether to give the desired diene (*Z*)-1-iodo-2-(*p*-methoxybenzyloxy)methyl-1,3-butadiene (**10**) in 75% overall yield from **1**. A related sequence provided the diene-methoxymethyl ether **11**. The availability of these vinyl halides set the stage for their addition to aldehydes.

Scheme 1. Halodiene Syntheses



TIPS = Si(^{i}Pr)$_3$

MOM = CH_2OMe

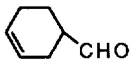
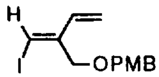
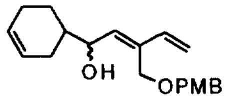
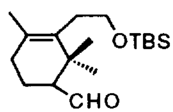
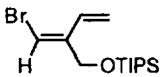
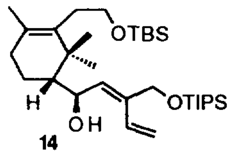
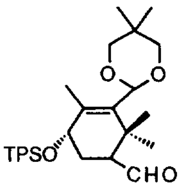
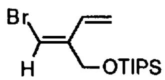
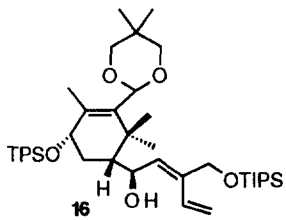
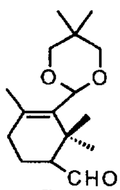
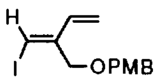
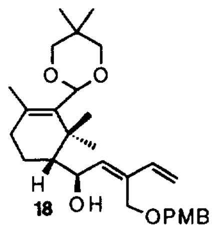
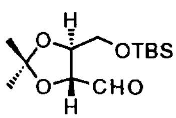
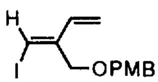
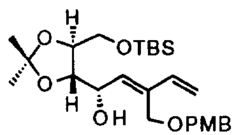
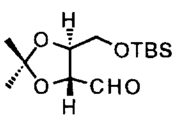
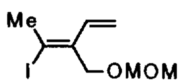
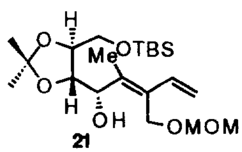


(a) CH_2=CHMgCl, THF, 0-67 °C, 16 h; (b) Aq. NH_4Cl, 0 °C, 2 min., 75%; (c) I_2, THF, -78 °C, 1.5 h, 53-60%; (d) TIPSCl, imidazole, CH_2Cl_2, 0 °C, 2.3 h, 88%; (e) CH_3OCH_2Cl, ^{i}Pr$_2$NEt, CH_2Cl_2, 15 h, 94% ; (f) MeOH, NaOMe, 65 °C, 45 min., 87%; (g) NBS, DMF, 21 °C, 1 h, 87%; (h) NaH, THF, 0 °C, DMF, 4-MeOBnCl, 21 °C, 18 h, 97%.

The standard conditions employed for the halogen-metal exchange involved treatment of the selected halo-diene with *s*-butyllithium in THF at -78 °C followed by addition of the appropriate aldehyde. As summarized in Table 1, the diastereoselectivity of the condensations depended upon the steric environment of the aldehyde substrates. For example, with aldehydes such as **13, 15** and **17**, required for our taxane studies, the selectivity improved to approximately 5:1 with good isolated yields (81-99%). The relative stereochemistry of the major secondary alcohols related to **16** and **20** was establish by X-ray analysis of subsequent intermediates. In an attempt to improve these ratios the $CrCl_2$/$NiCl_2$ mediated coupling protocol[12] was examined, but with both **12** and **19** a 1:1 mixture of epimers was obtained and the same reaction failed with **15** and **17**. The *L*-tartaric acid derived aldehyde **19**[13] afforded a 2:1 epimeric ratio with **10** and 3:1 with **11**.[14] However, Lewis acid complexation ($ZnBr_2$), unlike a related case,[15] failed to improve the ratio of **20**.

In summary, the direct route described to these stereodefined halo-diene building blocks will permit their application to a variety of synthetic objectives. In addition to the condensations illustrated below, the modification of the alkoxymethyl function, by either oxidation or substitution, will provide entry to more complex systems.

Table 1. Diene Additions to Aldehydes

Aldehyde	Diene	Product	Yield	Ratio*
 12	 10		98%	1:1
 13	 6	 14	99%	6:1
 15	 6	 16	81%	5:1
 17	 10	 18	85%	6:1
 19	 10	 20	93%	2:1
 19	 11	 21	63%	3:1

*Ratios determined by ^{1}H and/or ^{13}C NMR spectroscopy TBS = SiMe$_2$^{t}Bu; TPS = SiPh$_2$^{t}Bu

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10. The exact nature of this intermediate is unknown but the reactivity pattern observed is consistent with a solvated species related to **3**.

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