Stereoselective Preparation of Deuteriated Dienes by Ring Fragmentation of Metallated Cyclopropylcarbinols

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Abstract: The hydroalumination reaction of cyclopropenylcarbinols initially leads to the alumino-cyclopropylcarbinol derivatives, which is followed by an elimination reaction to give the corresponding substituted dienes as unique isomers and in good yields. The use of $LiAlD_4$ as reducing agent provides stereoselectively substituted deuteriodienes.

Key words: dienes, deuteriodienes, reducing agent, cyclopropane, cyclopropene

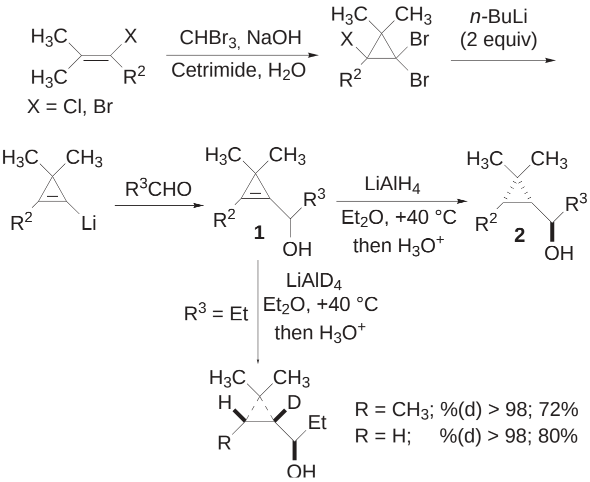
As the conjugated diene system represents not only an important structural feature of many insect pheromones and other biologically active compounds[1] but also a versatile building skeleton for the construction of complicated molecules via the Diels–Alder reaction,[2] numerous methods have been developed for their stereoselective synthesis. These methodologies are based on either the Wittig-type approach,[3] the selective reduction of acetylenic units of 1,3-enynes[4] or the direct coupling reaction of two vinyl groups. The latter method, namely the metal-catalyzed cross-coupling reaction between a stereodefined vinyl halide with a stereodefined alkenyl organometallic compound such as vinylborane,[5] -zinc,[6] -cuprates,[7] -aluminum,[8] -zirconium,[9] -magnesium[10] or -tin[11] reagents, has found outstanding applications in organic synthesis.

The stereoselective preparation of deuterium-labelled dienyl systems is particularly important for the structural determination of fragments in mass spectroscopy,[12] and is generally more troublesome since pure stereospecifically deuteriated alkenyl halides and/or alkenyl metals have to be synthesized.[13] In this letter, we would like to report an unusual but straightforward stereoselective preparation of deuteriated dienes in only a few chemical steps from commercially available starting materials.

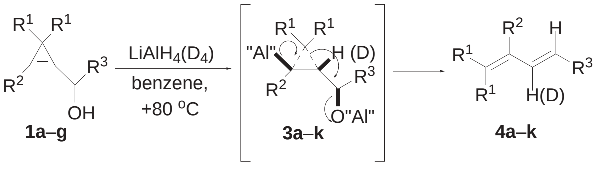
We have recently developed the diastereoselective reduction of cyclopropenylcarbinol **1** to *anti*-cyclopropylcarbinol derivatives **2** (Scheme 1);[14] the cyclopropenylcarbinols **1** are themselves obtained from 1,1,2-trihalocyclopropanes (prepared by reaction of substituted vinyl bromide derivatives with bromoform) by treatment with two equivalents of *n*-BuLi and reaction with various aldehydes as summarized in Scheme 1.[15]

The reduction of **1** occurs diastereoselectively in Et_2O at 40 °C to yield the *anti*-cyclopropylcarbinol **2** as a single diastereoisomer. The regioselectivity of the hydroalumination on the cyclopropenyl ring has been mapped out by deuterium labeling experiments (Scheme 1).

However, when the reaction mixture is heated at higher temperature (80 °C in benzene) or in Et_2O for a longer period of time, the intermediate cyclopropylaluminum species **3a**–**k** undergo an elimination reaction to yield the corresponding dienes **4a**–**k** in excellent yields and as unique geometrical isomers (Scheme 2).[16]



Scheme 1



Scheme 2

The scope of the reaction is rather broad as compiled in Table 1.

The reaction was first tested with non-deuteriated $LiAlH_4$ on the fully substituted cyclopropenylcarbinol **1a** ($R^1 = R^2 = Me$, $R^3 = Ph$, entry 1, Table 1). After heating for 19 hours in benzene, the corresponding diene **4a** was obtained in 85% yield as unique (*E*)-isomer ($J = 16$ Hz).

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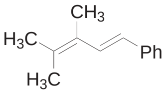
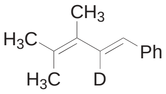
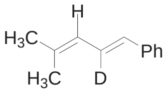
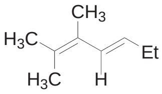
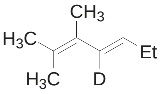
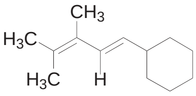
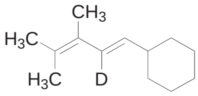
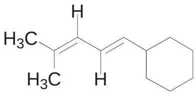
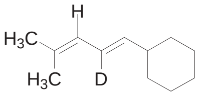
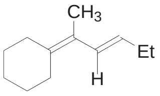
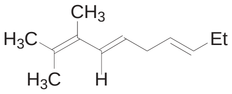
Table 1 Stereoselective Preparation of Dienes

Entry	R^1	R^2	R^3	$LiAlH_4$/$LiAlD_4$	Product	Yield (%)[a]
1	CH_3	CH_3	C_6H_5	$LiAlH_4$	 **4a**	85
2	CH_3	CH_3	C_6H_5	$LiAlD_4$	 **4b**	84
3	CH_3	H	C_6H_5	$LiAlD_4$	 **4c**	80
4	CH_3	CH_3	C_2H_5	$LiAlH_4$	 **4d**	75
5	CH_3	CH_3	C_2H_5	$LiAlD_4$	 **4e**	67
6	CH_3	CH_3	c-C_6H_{11}	$LiAlH_4$	 **4f**	75
7	CH_3	CH_3	c-C_6H_{11}	$LiAlD_4$	 **4g**	70
8	CH_3	H	c-C_6H_{11}	$LiAlH_4$	 **4h**	65
9	CH_3	H	c-C_6H_{11}	$LiAlD_4$	 **4i**	65
10	$(CH_2)_5$		C_2H_5	$LiAlH_4$	 **4j**	55
11	CH_3	CH_3	$CH_2CH{=}CHC_2H_5$	$LiAlH_4$	 **4k**	65

[a] Yields determined after purification by chromatography on silica gel.

When the reduction is performed with $LiAlD_4$ (Table 1, entry 2), the deuteriated diene is similarly obtained and in comparable yield with more than 98% of deuterium incorporation (both $LiAlH_4$ and $LiAlD_4$ are used in solution in Et_2O from commercially available sources). The cyclopropenylcarbinol can also bear three substituents as in **1c** (Table 1, entry 3, R^1 = Me, R^2 = H, R^3 = Ph) or be substituted by a primary (entries 4 and 5 for $LiAlH_4$ and $LiAlD_4$ respectively, R^1 = Me, R^2 = Me, R^3 = Et) or a secondary alkyl group (entries 6 and 7 for $LiAlH_4$ and $LiAlD_4$ respectively, R^1 = Me, R^2 = Me, R^3 = cyclohexyl) at the preexisting stereogenic center without altering the efficiency of the reaction; dienes **4d** and **4f**, as well as dienes specifically labeled in 2-positions such as **4c**, **4e** and **4g**, are consistently obtained in good yields and as unique geometrical isomers. The combination of a cyclopropenylcarbinol with three substituents with a secondary alkyl group for R^3 also leads to the diene **4h** and deuteriodiene **4i** as unique isomers (Table 1, entries 8 and 9). The *gem*-dimethyl group for R^1 can also be replaced by other substituents such as a cyclohexyl ring [Table 1, entry 10, R^1 = $(CH_2)_5$]; **4j** was isolated in 55% yield as a unique isomer. Additional functionality, such as (*E*)-double bond (Table 1, entry 11, R^1 = Me, R^2 = Me, R^3 = CH_2CH=CHEt), can be present on the carbon skeleton of the cyclopropenylcarbinol. The reduction occurs chemoselectively at the double bond of the three-membered ring unit and by subsequent thermal elimination, the skipped triene **4k** was obtained as a single isomer (Table 1, entry 11).

In conclusion, from common commercially available starting materials (vinyl bromides, $HCBr_3$, aldehydes and $LiAlH_4$ or $LiAlD_4$), the corresponding alumino-cyclopropylcarbinol derivatives are easily obtained by reduction of the internal double bond in very few chemical steps. Just by heating these intermediates, an elimination reaction occurs in all cases to lead to diversely substituted dienes. The major advantage of this methodology is that the preparation of regiospecific deuteriodienes is easily achieved.[17]

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(17) General Procedure for the Preparation of Dienes from Cyclopropenylcarbinols **1a**–**g**: $LiAlH_4$ (or $LiAlD_4$, 1 M solution in Et_2O, 1 mmol) was added to a stirred solution of **1a**–**g** (1 mmol) in 5 mL of benzene at 5 °C. The reaction mixture was then heated to 80 °C for several hours and the sequential reduction and elimination reactions were followed by TLC. When the transformation was complete, 1 M aq solution of HCl (3 mL) was added and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure. Chromatography on silica gel (eluent: hexane) gave the dienes **4a**–**k** in yields indicated in Table 1.