Applications of Baylis–Hillman Coupling Products: a Remarkable Reversal of Stereochemistry from Esters to Nitriles: a Simple Synthesis of (2*E*)-2-Methylalk-2-en-1-ols and (2*Z*)-2-Methylalk-2-enenitriles

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Reaction of methyl 3-acetoxy-2-methylenealkanoates with the reducing agent, lithium aluminium hydride (LAH): ethanol (1 : 1), provides (2*E*)-2-methylalk-2-en-1-ols, whereas, reaction of 3-acetoxy-2-methylenealkanenitriles with the same reagent provides (2*Z*)-2-methylalk-2-enenitriles in high yields.

The Baylis–Hillman coupling reaction is a new, versatile carbon–carbon bond forming reaction providing multifunctional molecules and is of current interest.[1–12] It occurred to us that the coupling products of this reaction could be potential starting materials for the preparation of trisubstituted alkenes with known stereochemistry according to Scheme 1. Synthesis of trisubstituted alkenes of defined stereochemistry has been one of the important objectives of organic chemistry in recent years, because many biologically active compounds occurring in nature possess the structural skeleton of trisubstituted alkenes.[13–16] Herein, we report a remarkable reversal in the stereochemistry of the products formed in the reactions of methyl 3-acetoxy-2-methylenealkanoates and 3-acetoxy-2-methylenealkanenitriles with LAH : EtOH (1 : 1) thus providing a simple synthesis of (2*E*)-2-methylalk-2-en-1-ols and (2*Z*)-2-methylalk-2-enenitriles in high yields.

First, we have examined the reaction of methyl 3-acetoxy-2-methylenenonanoate† with LAH : EtOH (1 : 1) reagent in diethyl ether at −78 °C for 1 h. Usual workup followed by column chromatography provided the (2*E*)-2-methylnon-2-en-1-ol **5c** in 78% yield.‡ The stereochemistry was established by the synthesis of (2*Z*)-2-methylnon-2-en-1-ol following the well known Corey procedure[17] and comparing its ^{13}C NMR spectra with that of **5c**.§ Several examples of (2*E*)-2-methylalk-2-en-1-ols are prepared (Table 1).

Reduction of 3-acetoxy-3-phenyl-2-methylenepropanenitrile with LAH : EtOH gave (2*Z*)-2-methyl-3-phenylprop-2-enenitrile **6d**.¶ The (*Z*)-stereochemistry was assigned by

† Methyl 3-acetoxy-2-methylenealkanoates are obtained by the action of acetyl chloride on methyl 3-hydroxy-2-methylenealkanoates. Hoffmann and Rabe[6] have reported that treatment of these methyl 3-acetoxy-2-methylenealkanoates with $LiBEt_3H$ produces the corresponding methyl (2*E*)-2-methylalk-2-enoates.

‡ *Spectral data* for **5c**: ^1H NMR: ($CDCl_3$) δ 0.88 (t, *J* 6 Hz, 3H), 1.04–1.48 (m, 8H), 1.68 (s, 3H), 1.76–2.28 (m, 3H, 1H D_2O washable), 3.96 (s, 2H), 5.38 (br t, 1H); ^{13}C NMR ($CDCl_3$) δ 12.8, 13.4, 22.2, 27.2, 28.7, 29.1, 31.4, 67.7, 125.4, 134.3; IR: ν_{max}/cm^{-1} (neat) 3350.

§ The two products were also examined on GC (methyl silicone, capillary column) and found to be different, indicating that the molecule **5c** is the (*E*)-isomer.

¶ *Spectral data* for **6d**: ^1H NMR: ($CDCl_3$) δ 2.08 (d, *J* 1.5 Hz, 3H), 6.86 (br s, 1H), 7.24–7.76 (m, 5H); ^{13}C NMR: ($CDCl_3$) δ 21.1, 105.3, 118.5, 127.7, 128.1, 129.1, 133.3, 143.3; IR: ν_{max}/cm^{-1} (neat) 2210.

Table 1 Synthesis of (2*E*)-2-methylalk-2-en-1-ols[a–c]

Allylic acetate	R	Product[d]	Yield (%)[e]
3a	n-C_4H_9	**5a**	76
3b	n-C_5H_{11}	**5b**	65
3c	n-C_6H_{13}	**5c**	78
3d	Ph	**5d**[f]	84
3e	*p*-MeC_6H_4	**5e**	60
3f	3-(4-MeC_6H_4)Bu	**5f**[g]	75
3g	*p*-ClC_6H_4	**5g**	73

[a] ^{13}C NMR spectra indicate the absence of the other isomer. [b] All reactions were carried out on 10 mmol scale using 24 mmol of the reducing agent at −78 °C. [c] All products were characterized by IR, ^1H and ^{13}C NMR spectra. [d] All products except **5g** are obtained as colourless liquids; **5g** is obtained as a low melting solid. [e] Yields of the column chromatography purified products. [f] This reaction was carried out at 0 °C as the ester is the main product at −78 °C. [g] This reaction was carried out at room temp. for 3 h using 10 equiv. of the reducing agent.

Table 2 Synthesis of (2*Z*)-2-methylalk-2-enenitriles[a–c]

Allylic acetate	R	Product[d]	Yield (%)[e]
4a	n-C_4H_9	**6a**	66
4b	n-C_5H_{11}	**6b**	62
4c	n-C_6H_{13}	**6c**	71
4d	Ph	**6d**	77
4e	*p*-MeC_6H_4	**6e**	62
4f	3-(4-MeC_6H_4)Bu	**6f**[f]	64

[a] ^{13}C NMR spectra indicate the absence of the other isomer. [b] All reactions were carried out on 10 mmol scale using 24 mmol of the reducing agent at −78 °C. [c] All products were characterized by IR, ^1H and ^{13}C NMR spectra. [d] All products are obtained as colourless liquids. [e] Yields of the column chromatography purified products. [f] This reaction was carried out at −78 °C using 10 equiv. of the reducing agent.

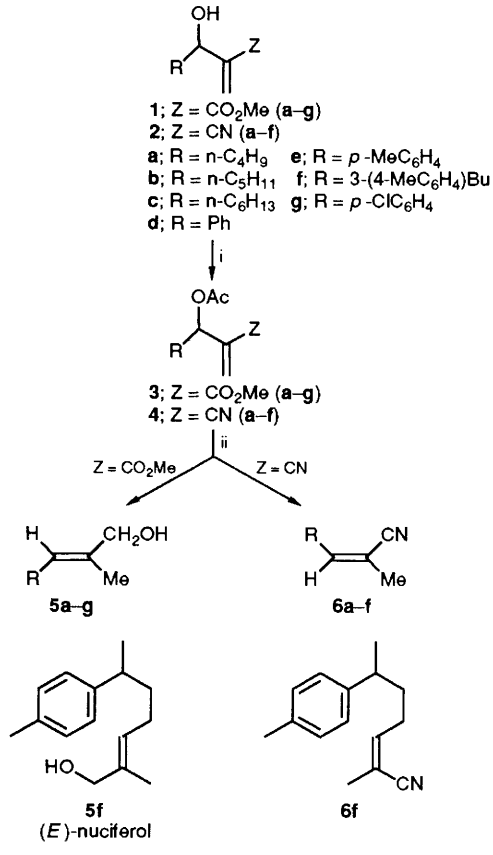
comparing ^1H and ^{13}C NMR spectral data of this molecule with the spectral data of the (*E*) and (*Z*) molecules reported in literature.‖[18,19] A representative class of (2*Z*)-2-methylalk-2-enenitriles were prepared following this strategy (Table 2).

The reversal of stereochemistry in the reactions of **3** and **4** with LAH : EtOH, giving rise to **5** and **6** (Scheme 1) may be due to the elimination of acetate taking place from the sterically preferred conformation of the enolates **7** and **8** (Scheme 2). This may be based upon the fact that the methoxycarbonyl group is bigger than methyl which in turn is bigger than cyano.

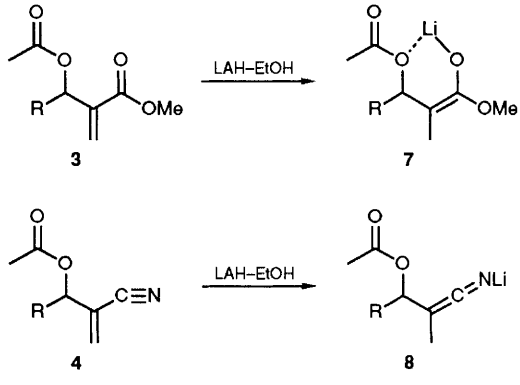
To prove efficacy of this method we have prepared the natural product (*E*)-nuciferol **5f**[20] and (2*Z*)-2-methyl-6-(4-methylphenyl)hept-2-enenitrile **6f**,[20] the precursor of (*Z*)-nuciferol, starting from 4-(4-methylphenyl)pentanal.

The general procedure for the synthesis of (2*E*)-2-methylalk-2-en-1-ols is as follows: LAH : EtOH (1 : 1) reagent in diethyl ether (0.578 mol dm^{-3}, 41.5 ml, 24 mmol) is added to a solution of methyl 3-acetoxy-2-methylenealkanoate (10 mmol) in diethyl ether at −78 °C. After 1 h stirring at the same temperature, the reaction mixture is allowed to warm to 0 °C (15–20 min). Water is added cautiously and usual workup followed by column chromatography (silica gel, 30% ethyl acetate in hexane) provided (2*E*)-2-methylalk-2-en-1-ol. In the case of the nitriles, after the addition of the LAH : EtOH reagent to the substrate at −78 °C, the reaction mixture is stirred for 15 min at the same temperature and water is added cautiously. Usual workup followed by column chromatography (silica gel, 10% ethyl acetate in hexane) provided the required product.

This procedure represents a convenient three step synthesis of (2*E*)-2-methylalk-2-en-1-ols and (2*Z*)-2-methylalk-2-enenitriles from easily available starting materials. We are presently exploring the possibility of employing this methodology for the synthesis of biologically active molecules.



Scheme 1 *Reagents and conditions*: MeCOCl, pyridine; ii, LAH–EtOH, diethyl ether, −78 °C



Scheme 2

‖ Both ^1H[18,19] and ^{13}C NMR[18] spectral data for (*Z*)- and (*E*)-**6d** are reported. Comparison of this data with that of our sample clearly establishes the stereochemistry of our sample to be (*Z*). To double check, we have also prepared a mixture of (*E*)- and (*Z*)-isomers (60 : 40) according to a known procedure.[19] Examination of this mixture and our sample on GC (Carbowax, capillary column) and comparison of ^{13}C NMR spectra of this mixture and our sample further confirms that our sample is the (*Z*)-isomer.

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