Highly Diastereofacial Selective Addition of Nucleophiles to 2-Alkyl-3-trimethylsilylalk-3-enyl Carbonyl Compounds. Stereoselective Preparation of β-Methylhomoallyl Alcohols and β-Hydroxy-α-methyl Ketones

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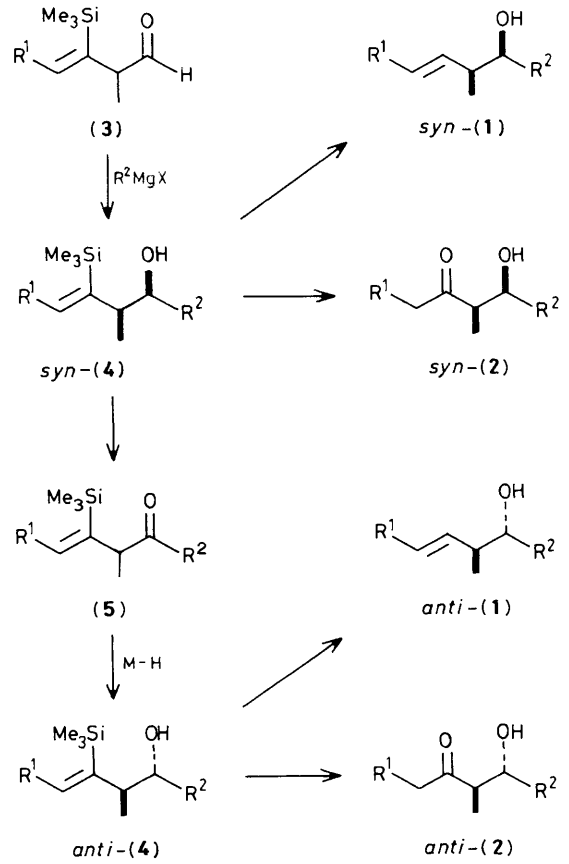
Nucleophiles react with 2-alkyl-3-trimethylsilylalk-3-enyl carbonyl compounds to afford 'Cram' products with high diastereoselectivity; this allows the stereoselective preparation of β-methylhomoallyl alcohols and β-hydroxy-α-methyl ketones.

There has been a great deal of interest in the diastereoselective formation of the β-methylhomoallyl alcohols (**1**) and the β-hydroxy-α-methyl ketones (**2**), because these structural units are potentially useful in the synthesis of macrolide and ionophore antibiotics.[1] Compounds (**1**) have been prepared by diastereoselective addition of allyl metal compounds to aldehydes[2] or *via* sigmatropic rearrangements,[3] and compounds (**2**) have been prepared effectively by stereoregulated aldol condensations.[4] In this communication, we report an efficient, highly selective method for the preparation of compounds (**1**) and (**2**), which is based on diastereoselective addition of nucleophiles to chiral aldehydes or ketones.

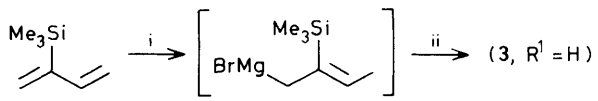
The addition reaction of nucleophiles with carbonyl compounds is one of the most powerful construction methods available to synthetic organic chemists. In carbonyl compounds having an α-asymmetric centre, the two faces of the carbonyl group are diastereotopic and addition of nucleophiles gives rise to a pair of diastereoisomers. In such a case, the major and minor isomers may generally be predicted by Cram's rule for asymmetric induction or one of its descendants, thus they are called 'Cram' and 'anti-Cram' products, respectively.[5] The diastereoselectivity of the reaction is generally expected to increase as the difference in the steric bulk of the groups attached to a chiral centre increases, and, thus, nucleophilic addition to 20-keto-steroids has been used for the stereoselective construction of the acyclic side chain of steroids.[6] Nucleophilic additions to chiral carbonyl compounds having α- or β-oxygen substituents proceed stereoselectively and have been employed for the synthesis of a number of natural products.[7] However, there are few precedents for the highly selective synthesis of compounds (**1**) and (**2**) using this type of relative 1,2-asymmetric induction.[8]

If one considers the 2-methyl-3-trimethylsilylalk-3-enals (**3**), it would appear that (**3**) would react with Grignard reagents with high diastereoselectivity, owing to the steric bulk of the trimethylsilyl group, affording the 'Cram' products *syn*-(**4**),[9] possible precursors of *syn*-(**1**) and *syn*-(**2**).[10] Furthermore, *syn*-(**4**) could be selectively converted into the diastereoisomers *anti*-(**4**) ('Cram' products) *via* oxidation to the ketones (**5**) followed by reduction with a metal hydride (Scheme 1). Herein we report the successful realization of such an approach.†

The aldehyde (**3**, R^1 = H) was prepared as shown in Scheme 2. Titanium-catalysed hydromagnesiation of 2-trimethylsilylbuta-1,3-diene[11] followed by reaction with the magnesium salt of formic acid afforded (**3**, R^1 = H) in 46—55% yield.[12,13] The results of the reaction of (**3**, R^1 = H) with several representative Grignard reagents are given in Table 1. The reactions were carried out by adding an ethereal solution of the Grignard reagent (3 equiv.) to (**3**) in Et_2O at −78 °C and stirring for 2 h. It can be seen from Table 1 that in every case except with methylmagnesium iodide, the 'Cram' products *syn*-(**4**) were obtained in >99% purity [confirmed by ^1H and ^{13}C n.m.r. spectroscopy, and also by g.l.c. analysis of the protodesilylated products (*vide infra*)]. With methylmagnesium iodide, the diastereoselectivity was lower and about 9% of the 'anti-Cram' product was produced, presumably owing to the lower steric demand of the methyl group. Compounds *syn*-(**4**) were oxidized to the ketones (**5**) with pyridinium chlorochromate (PCC) (95—100% yield). The reduction of (**5**) with $NaBH_4$ in MeOH at −10 °C proceeded with high stereoselectivity to give the 'Cram' products *anti*-(**4**) with >99% purity except for (**5a**) (the results are summarized in Table 1).



Scheme 1



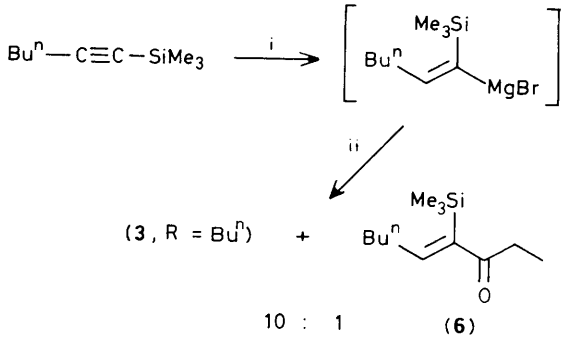
Scheme 2. i, Bu^tMgBr, $(\eta\text{-}C_5H_5)_2TiCl_2$; ii, HCO_2MgBr.

† Parts of this report were presented at the 49th Annual Meeting of the Japan Chemical Society, April 1984, Tokyo. Similar results were also reported (K. Suzuki, E. Katayama, and G. Tsuchihashi).

Table 1. Results of nucleophilic addition to (**3**, R^1 = H) and (**5**, R^1 = H), and protodesilylation[a] of (**4**, R^1 = H) to (**1**, R^1 = H).

Carbonyl compound			Product (**4**)[b]				Product (**1**)[c,d]	
	R^2	Nucleophile		R^2	*syn* : *anti*[e]	Yield (%)[f]		Yield (%)[f]
(**3**)		MeMgI	(**4a**)	Me	91 : 9	84	(**1a**)	46[g]
(**5a**)	Me	$NaBH_4$	(**4a**)	Me	5 : 95	98	(**1a**)	40[g]
(**3**)		EtMgBr	(**4b**)	Et	>99 : <1	92	(**1b**)	86
(**5b**)	Et	$NaBH_4$	(**4b**)	Et	<1 : >99	97	(**1b**)	90
(**3**)		Pr^iMgBr	(**4c**)	Pr^i	>99 : <1	91	(**1c**)[h]	88
(**5c**)	Pr^i	$NaBH_4$	(**4c**)	Pr^i	<1 : >99	96	(**1c**)[h]	85
(**3**)		PhMgBr	(**4d**)	Ph	>99 : <1	94	(**1d**)	90
(**5d**)	Ph	$NaBH_4$	(**4d**)	Ph	<1 : >99	92	(**1d**)	93
(**3**)		CH_2=C(Me_3Si)MgBr	(**4e**)	CH_2=C(Me_3Si)	>99 : <1	93	—	—

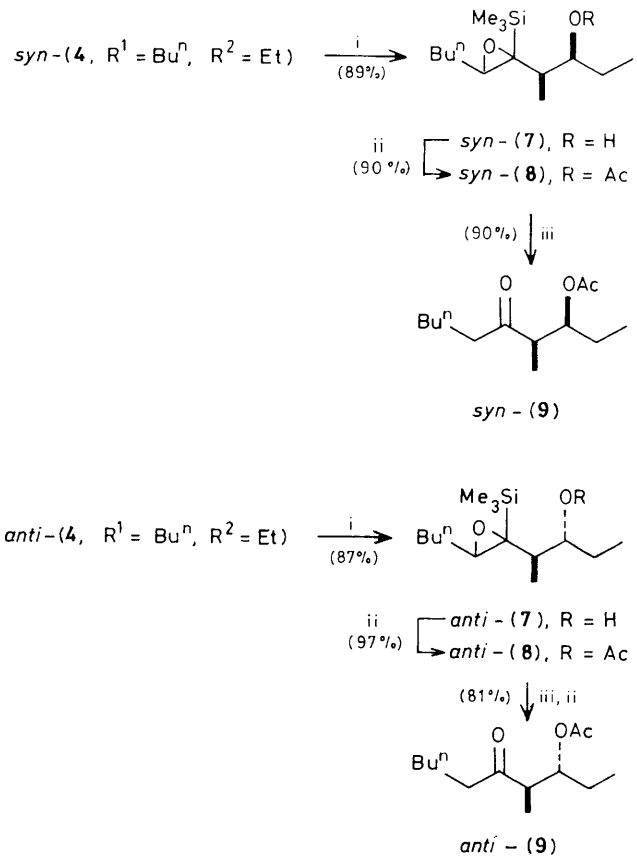
[a] NaH (1 equiv.) in HMPA–THF (3 : 2 v/v), at 30 °C for 2 h, unless otherwise stated. [b] The structures and ratio of the products were determined by ^1H and ^{13}C n.m.r. spectroscopy, and/or by g.l.c. analysis of their protodesilylated products (**1**). [c] All products were fully identified by spectroscopic methods and by comparison with the authentic materials (see refs. 15, 16). [d] The *syn*/*anti* ratio is the same as that of (**4**). [e] Except for (**4a**), no trace of diastereoisomers was found at the limit of our analytical methods. [f] Isolated yield after chromatography on silica gel. [g] Comparatively lower yields were presumably due to the volatility of the products. [h] KH was used instead of NaH.



Scheme 3. i, Bu^iMgBr, $(\eta\text{-}C_5H_5)_2TiCl_2$; ii, MeCH(Br)CHO.

Compounds *syn*- and *anti*-(**4**) were readily protodesilylated to *syn*- and *anti*-(**1**), respectively, on treatment with NaH or KH in hexamethylphosphoramide (HMPA)–tetrahydrofuran (THF) (Table 1). It is noteworthy that NaH (or KH)–HMPA is effective for the protodesilylation of γ-trimethylsilylhomoallyl alcohols as well as β-trimethylsilylallyl alcohols.[14] The β-methylhomoallyl alcohols thus prepared were characterized by ^1H n.m.r. spectroscopy, and also by g.l.c. analysis compared with the authentic materials;‡ except for (**1a**), diastereoisomers were not detected.

Next, we attempted to prepare the aldehyde (**3**, R^1 = alkyl). Titanium-catalysed hydromagnesiation of 1-trimethylsilylhex-1-yne§ followed by treatment with 2-bromopropanal gave the expected aldehyde (**3**, R^1 = Bu^n)[18] along with (**6**) in a ratio of 10 : 1 and about 50% total yield (Scheme 3). Efforts to separate (**3**) and (**6**) were not successful, however, (**3**) was found to react preferentially with a Grignard reagent. The mixture of (**3**) and (**6**) was treated with ethylmagnesium bromide at −78 °C for 2 h to yield *syn*-(**4**, R^1 = Bu^n, R^2 = Et) in 83% yield as the sole product, while (**6**) remained unchanged and was readily separated. The product *syn*-



Scheme 4. i, Bu^tOOH, $VO(MeCOCHCOMe)_2$ (ref. 21); ii, AcCl, C_5H_5N; iii, H_2SO_4, MeOH.

(**4**, R^1 = Bu^n, R^2 = Et) was converted into its diastereoisomer *anti*-(**4**, R^1 = Bu^n, R^2 = Et) in 90% overall yield by oxidation with PCC followed by reduction with $NaBH_4$. Both *syn*- and *anti*-(**4**, R^1 = Bu^n, R^2 = Et) are diastereoisomerically homogeneous as judged by ^1H and ^{13}C n.m.r. spectroscopy. Protodesilylation of *syn*- and *anti*-(**4**, R^1 = Bu^n, R^2 = Et) with NaH–HMPA afforded pure *syn*- and *anti*-(**1**, R^1 = Bu^n, R^2 = Et) in high yields, respectively (checked by ^1H n.m.r. spectroscopy and g.l.c. analysis). Conversion of the vinyl-

‡ The alcohols *anti*-(**1**) were prepared by our method published earlier (ref. 15). Mixtures of *syn*- and *anti*-(**1**) were obtained by the standard literature procedure (ref. 16).

§ Previously, we reported that the hydromagnesiation of a 1-trimethylsilylalk-1-yne proceeded with about 95% selectivity (ref. 17), however, it has become clear that if the reaction is carried out at 25 °C for 6 h, the selectivity is near 100% (ref. 14).

silane moiety in (**4**, $R^1 = Bu^n$, $R^2 = Et$) into a carbonyl group was carried out in three steps according to Stork's procedure (Scheme 4).[19] [We did not attempt to convert (**4**, $R^1 = H$) into (**2**) directly, since compounds (**1**, $R^1 = H$) have been shown to be converted into (**2**) by the Wacker oxidation.[20]] It should be mentioned that direct treatment of (**7**) with H_2SO_4 afforded (**2**, $R^1 = Bu^n$, $R^2 = Et$) in only poor yield.¶

In conclusion, almost perfect stereoselective production of both *syn*- and *anti*-(**1**) and -(**2**) has been achieved. However, compounds (**4**) are, in some cases, even more versatile than (**1**) or (**2**) in that (i) the vinylsilyl group itself rather than the carbonyl group can be preserved during the multistep transformations of other functional groups in this precursor, and (ii) olefins having a $SiMe_3$ group react with an electrophile more regio- and stereo-selectively than those without a $SiMe_3$ group.**

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¶ The ^1H n.m.r. spectrum of *syn*-(**9**) was identical with that of the authentic material obtained by acetylation of *syn*-(**2**, $R^1 = Bu^n$, $R^2 = Et$), which was prepared as a *syn–anti* mixture by the method of Yamamoto (ref. 22) and separated by chromatography.

** Sharpless epoxidation (ref. 21) of *syn*-(**4**) afforded single isomers in good yields. This result will be published in due course.