Synthesis of Four Possible Steric Isomers of β-Methylhomoallyl Alcohols[1]

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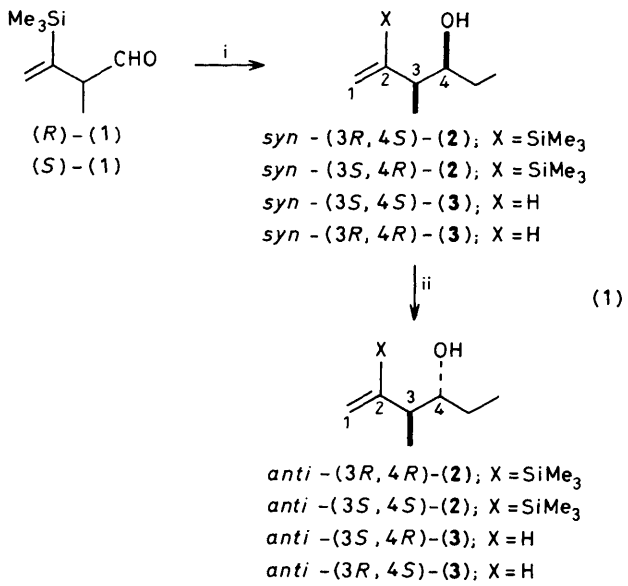
Synthesis of both (*R*)- and (*S*)-2-methyl-3-trimethylsilylbut-3-enal (**1**), and the preparation of the four possible steric isomers of β-methylhomoallyl alcohols (**2**) and (**3**) using (**1**) is decribed.

Enantio-selective preparation of *syn*- and *anti*-β-methylhomoallyl alcohols has attracted much interest in relation to the synthesis of macrolide and ionophore antibiotics. The most attractive approaches to date include addition of optically active but-2-enylboron[2] or but-2-enylsilane derivatives[3] to aldehydes, or *via* [2,3]-Wittig sigmatropic rearrangement of chiral but-2-enyl ethers.[4] However, with both these methods there are difficulties with preparing enantiomerically pure starting materials and/or incomplete chiral selectivity during carbon–carbon bond formation. Recently we have shown that (*RS*)-2-methyl-3-trimethylsilylbut-3-enal (**1**) reacts with Grignard reagents highly selectively affording the corresponding *syn* adducts (**2**), and that *syn*-(**2**) thus prepared can be readily converted into their diastereoisomers, *anti*-(**2**), *via* oxidation and subsequent reduction with metal hydride reagents [equation (1)].[5] We have also shown that protodesilylation of (**2**) to (**3**) proceeds quantitatively with NaH–hexamethylphosphoramide.[5] This communication reports the synthesis of the chiral aldehydes (*R*)-(**1**) and (*S*)-(**1**), and preparation of all four possible steric isomers of (**2**) and (**3**) from (**1**).†

Synthesis of (*R*)-(**1**) began with the optically active epoxide (**4**) [>95% enantiomeric excess (e.e.)] which was prepared by Sharpless asymmetric epoxidation of *trans*-but-2-enol using L-(+)-di-isopropyl tartrate.[6] After protection of (**4**) as a trityl ether (Ph_3CCl, NEt_3, 4-*N*,*N*-dimethylaminopyridine),[7] the resulting (**5**) was treated with 1-trimethylsilylvinylmagnesium bromide in the presence of a catalytic amount of CuI to give alcohol (**6**) as the sole product [equation (2)].[8] Deprotection of crude (**6**) in aqueous $CHCl_2CO_2H$ gave (**7**) [53% overall yield from (**4**)]. Treatment of (**7**) with $NaIO_4$ afforded the optically active aldehyde (*R*)-(**1**) {$[\alpha]_D^{25}$ +77.0° (*c* 1.04, $CHCl_3$)} in 90% yield. Enantiomeric purity of (*R*)-(**1**) was confirmed to be >95% by ^1H n.m.r. spectroscopy using the chiral shift reagent (+)-tris[di(perfluoro-2-propoxypropionyl)methanato]praseodymium(III) [(+)-Pr(DPPM)$_3$].[9] The aldehyde (*S*)-(**1**) (>95% e.e.) {$[\alpha]_D^{25}$ −75.6° (*c* 0.516, $CHCl_3$)} was synthesized using the same method starting from (**8**), which was obtained by epoxidation of *trans*-but-2-enol using D-(−)-di-isopropyl tartrate.[6]



Reagents: i, EtMgBr; ii, for (**2**): CrO_3 then $NaBH_4$.

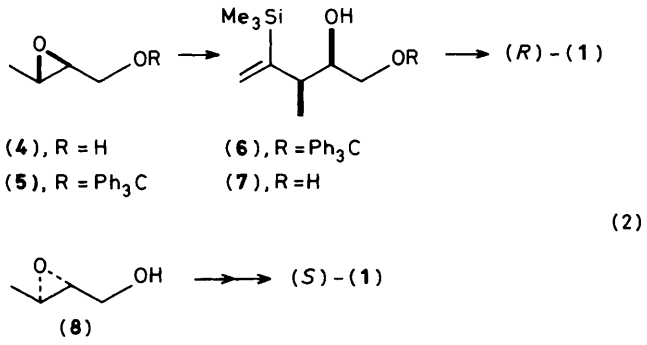
The products *syn*- and *anti*-(**2**) derived from the reaction of (*R*)-(**1**) or (*S*)-(**1**) with ethylmagnesium bromide are summarized in Table 1. The specific rotations of protodesilylated

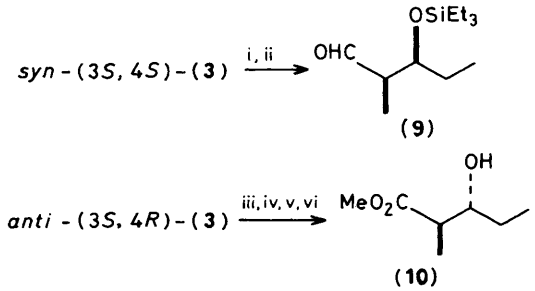
† Parts of this report were presented at the 49th Annual Meeting of the Japan Chemical Society, April 1984, Tokyo.

Table 1. Absolute configuration and rotation of (**2**) and (**3**) prepared by the procedure shown in equation (1).

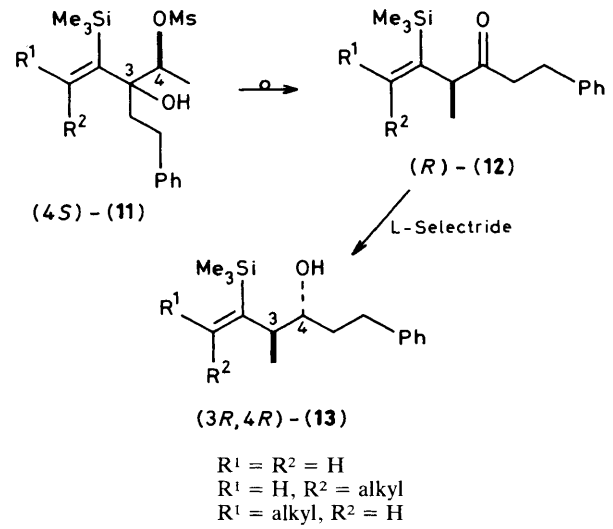
(**2**) (X = $SiMe_3$)			(**3**) (X = H)		
Configuration[a]	$[\alpha]_D^{25}$	(*c* in $CHCl_3$)	Configuration[a]	$[\alpha]_D^{25}$	(*c* in $CHCl_3$)
syn-(3*R*,4*S*)	−26.9°	(1.04)[b]	*syn*-(3*S*,4*S*)	−45.0°	(0.952)[b]
anti-(3*R*,4*R*)	−13.9°	(1.41)[b]	*anti*-(3*S*,4*R*)	−12.2°	(0.426)[b]
syn-(3*S*,4*R*)	+26.2°	(1.00)	*syn*-(3*R*,4*R*)	+45.0°	(0.600)
anti-(3*S*,4*S*)	+14.0°	(0.998)	*anti*-(3*R*,4*S*)	+12.5°	(0.880)

[a] Diastereoisomeric purities were >99%. [b] Optical purities (*ca.* 95% e.e.) were determined by converting them into the known compounds (**9**) and (**10**); see text.





Scheme 1. *Reagents*: i, $ClSiEt_3$, imidazole, *N*,*N*-dimethylformamide; ii, O_3 then Me_2S; iii, $PhCH_2Br$, KH; iv, O_3 then Jones' reagent; v, CH_2N_2; vi, H_2, Pd–C.



products (**3**) are also shown in Table 1. Although the $[\alpha]_D$ values of the pairs of enantiomers indicate that each product has high optical purity, this was confirmed by converting *syn*-(3*S*,4*S*)-(**3**) and *anti*-(3*S*,4*R*)-(**3**) into the known compounds (**9**)[10] and (**10**),[11] respectively, as shown in Scheme 1. Optical purities of (**9**) and (**10**) were found to be *ca.* 95% e.e. by comparison of the rotations with the literature values.‡

Tsuchihashi *et al.* have independently found that reduction of optically active (*R*)-(**12**) with L-Selectride proceeds highly selectively to afford *anti*-products (3*R*,4*R*)-(**13**).[12] They prepared (*R*)-(**12**) by Lewis acid-mediated pinacol type rearrangement of (4*S*)-(**11**).[13]

In summary, enantioselective (*ca.* 95% e.e.) synthesis of all the four possible β-methyl-homoallyl alcohols (**2**) and (**3**) has been achieved.

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‡ (**9**): $[\alpha]_D^{27}$ −47.5° (*c* 0.568, $CHCl_3$) {the enantiomer of (**9**) (ref. 10) $[\alpha]_D^{27}$ −49.8°}. (**10**): $[\alpha]_D^{25}$ −12.2° (*c* 0.82, $CHCl_3$) {the calculated value for pure (**10**) ref. 11: $[\alpha]_D^{25}$ −12.9°}.