Stereocontrolled Synthesis of Four Possible Stereoisomers of Vicinal Diol Derivatives *via* Relative 1,2-Asymmetric Induction. Preparation of Optically Active *exo*- and *endo*-Brevicomin

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Four possible stereoisomers of vicinal diol derivatives were synthesized stereoselectively by nucleophilic addition to α-alkoxy-β-trimethylsilyl-β,γ-unsaturated carbonyl compounds and this reaction was applied to the synthesis of *exo*- and *endo*-brevicomin.

Highly diastereoselective addition reactions of Grignard reagents with α-alkoxyketones or organocuprates with β-alkoxyaldehydes have been achieved and have been used for the synthesis of a number of natural products.[1] High stereoselectivity in reactions of α-alkoxy aldehydes with organometallic compounds which constitutes a valuable procedure for the stereoselective synthesis of vicinal diol derivatives, however, is more difficult to attain.[2]

Previously we have reported a highly diastereoselective addition reaction of nucleophiles with α-alkyl-β-trimethylsilyl-β,γ-unsaturated carbonyl compounds.[3] Thus, for example, 2-methyl-3-trimethylsilylalk-3-enals (**1**) react with Grignard

Table 1. Reactions of (**4**) and (**6**) with nucleophiles.[a]

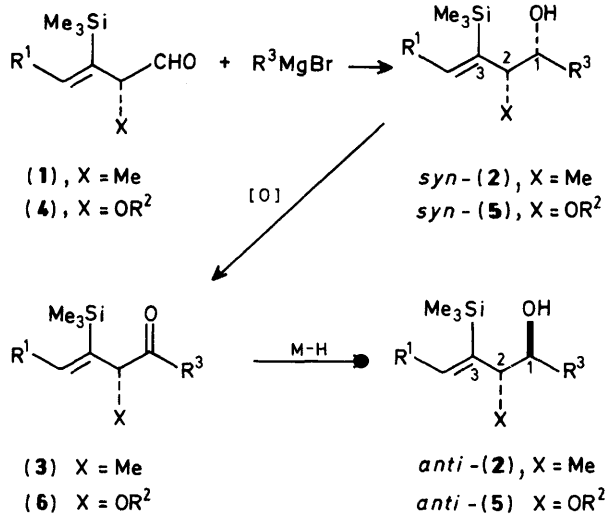
Run		Substrate R¹	R²	R³	Reaction conditions Nucleophile	Solvent	Product (**5**) *syn* : *anti*	Yield (%)
1	(**4a**)	H	Bn		EtMgBr	THF	1 : 1	63
2	(**4a**)	H	Bn		EtMgBr	Et_2O	14 : 1	87
3	(**4b**)	H	Me		EtMgBr	THF	9 : 1	68
4	(**4b**)	H	Me		EtMgBr	Et_2O	>99 : <1[b]	92
5	(**4c**)	Bu^n	Me		EtMgBr	Et_2O	>99 : <1	82
6	(**6a**)	H	Bn	Et	L-Selectride	Et_2O	<1 : >99	91
7	(**6b**)	H	Me	Et	L-Selectride	Et_2O	<1 : >99[c]	83
8	(**6c**)	Bu^n	Me	Et	L-Selectride	Et_2O	<1 : >99	83

[a] Reactions were carried out at −78 °C for 1 h. Bn = benzyl. [b] *syn*-(1*S*,2*R*)-(**5b**) [from (*R*)-(**4b**)]: $[\alpha]_D^{25}$ +44.8° (*c* 1.00, $CHCl_3$). *syn*-(1*R*,2*S*)-(**5b**) [from (*S*)-(**4b**)]: $[\alpha]_D^{25}$ −46.4° (*c* 1.11, $CHCl_3$). [c] *anti*-(1*R*,2*R*)-(**5b**): $[\alpha]_D^{25}$ +66.4° (*c* 0.452, $CHCl_3$). *anti*-(1*R*,2*R*)-(**5b**): $[\alpha]_D^{25}$ −67.6° (*c* 0.71, $CHCl_3$).

Table 2. Overall yield and specific rotation of brevicomin.

Brevicomin	Configuration	Overall yield (%) from (**4a**)	$[\alpha]_D$ (*c* in Et_2O, temp./°C) Observed	Lit.[a]
(+)-*exo*	(1*R*,7*R*)	49	+80.9° (2.18, 25)	+84.1° (2.2, 26)
(−)-*exo*	(1*S*,7*S*)	52	−80.3° (2.23,25)	−80.0° (1.6, 24)
(+)-*endo*	(1*S*,7*R*)	32	+96.6° (0.98, 25)[b]	
(−)-*endo*	(1*R*,7*S*)	36	−93.1° (1.01, 25)[b]	

[a] See ref. 12. [b] The highest $[\alpha]_D$ values reported so far were +74 and −76.7° for *endo*-brevicomin; see ref. 13.



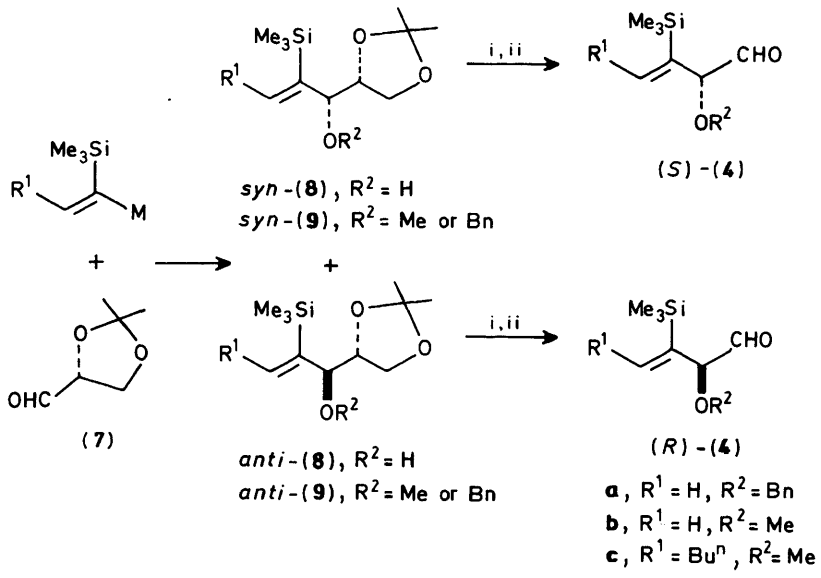
Scheme 1

reagents to afford 'Cram products' *syn*-(**2**) with >99% selectivity, and *syn*-(**2**) thus prepared can be readily converted to >99% pure *anti*-(**2**) (Cram products) *via* oxidation and subsequent reduction of the resulting ketones (**3**) with a metal hydride reagent (Scheme 1). We expected a similar high diastereoselectivity in the reaction of α-alkoxy-β-trimethylsilyl-β,γ-unsaturated carbonyl compounds with nucleophiles. This communication reports the selective preparation of both (*R*)- and (*S*)-2-alkoxy-3-trimethylsilylalk-3-enals (**4**) and the diastereoselective synthesis of four possible stereoisomers of 2-alkoxyalk-3-enols (**5**) according to Scheme 1. The utility of the reaction is also demonstrated by the preparation of *exo*- and *endo*-brevicomin.

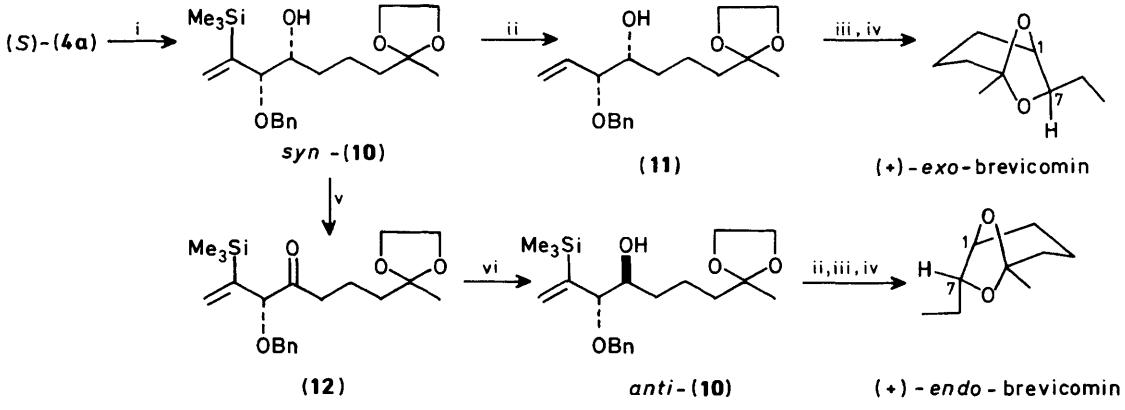
Compounds (**4**) were synthesised as shown in Scheme 2 starting with the readily available (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**7**).[4] Reaction of (**7**) with 1-trimethylsilylvinyl organometallic compounds afforded a mixture of *syn*- and *anti*-addition products (**8**). They were converted into methyl or benzyl ethers (**9**), which were then separated by column chromatography. The separated products (**9**) were converted into the aldehydes (**4**)† by successive treatment with aqueous HCl and $NaIO_4$ [50—65% overall yields from (**8**)]. Enantiomeric purity of both (*R*)- and (*S*)-(**4**) was confirmed to be >99% by ^1H n.m.r. spectroscopy using the chiral shift reagent (+)-tris[bis(perfluoro-2-propoxypropionyl)methanato]praseodymium(III).[5] Reaction of (**7**) with 1-trimethylsilylvinylmagnesium bromides in tetrahydrofuran (THF)–hexamethylphosphoramide (HMPA) (3 : 1) afforded *anti*-addition products (**8**) predominantly (*syn* : *anti* ≈1 : 3, >85% yields),[6] while reaction of (**7**) with 1-trimethylsilylvinylcopper compounds, prepared *in situ* from the corresponding Grignard reagents and CuI in THF–Me_2S (5 : 1)‡ afforded *syn*-addition products (**8**) with >98% selectivity in >85% yield.[7] Thus it is possible to prepare either (*R*)- or (*S*)-(**4**) selectively. It should also be noted that various 1-trimethylsilylvinyl Grignard reagents can be readily prepared by hydromagnesiation of 1-trimethylsilylalk-1-ynes.[8]

† The specific rotations $[\alpha]_D^{25}$ (conc.) in $CHCl_3$ of the aldehydes (**4**) are as follows: (*R*)-(**4a**), +10.4° (1.00); (*S*)-(**4a**), −10.3° (1.03); (*R*)-(**4b**), +3.4° (1.00); (*S*)-(**4b**), −2.8° (1.07); (*R*)-(**4c**), −9.4° (1.38); (*S*)-(**4c**), +9.0° (1.24).

‡ When the Grignard reagent was prepared in Et_2O, the ethereal solution was added to CuI dissolved in THF–Me_2S.



Scheme 2. *Reagents:* i, HCl; ii, $NaIO_4$. Bn = $PhCH_2$.



Scheme 3. *Reagents:* i, $BrMg[CH_2]_3\overline{C(Me)OCH_2CH_2O}$; ii, NaH, HMPA; iii, HCl, iv, H_2, Pd–C; v, $CrO_3 \cdot HCl \cdot$ pyridine; vi, L-Selectride. Bn = $PhCH_2$.

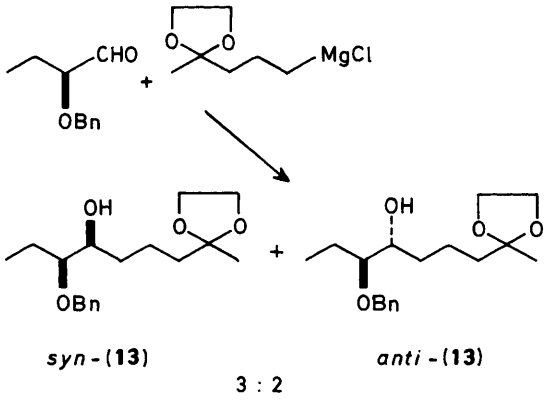
The results of the reaction of (**4**) with ethylmagnesium bromide (Scheme 1) are summarized in Table 1. When diethyl ether was used as a solvent, the reaction proceeded highly stereoselectively affording *syn*-(**5**) either predominantly [for (**4a**)] or exclusively [for (**4b**) and (**4c**)]. The degree of diastereoselectivity was, however, highly dependent on the solvent used and poor selectivity was observed in THF.

Oxidation of the alcohols (**5**) (80—90%) followed by reduction of the resulting ketones (**6**) with L-Selectride afforded *anti*-(**5**) exclusively (Scheme 1). These results are also summarized in Table 1.

It is thus possible to prepare all the four possible stereoisomers of the alcohols (**5**) as required. To show the utility of the present reaction we tried to prepare brevicomin. *exo*- and *endo*-Brevicomin are produced by males of *Dryocetes confusus* and by males and females of three species of *Dendroctonus* beetles, among them the mountain pine beetle *D. ponderosae*, the major insect pest in Western North America.[9] Our synthetic route to brevicomin[10] is illustrated in Scheme 3.

The Grignard reagent prepared from 2-(3-bromopropyl)-2-methyl-1,3-dioxolane reacted with (*S*)-(**4a**) in Et_2O to afford the *syn*-alcohol (**10**) exclusively; the ^1H n.m.r. spectrum of the crude product showed only the signals due to *syn*-(**10**). Compound *syn*-(**10**) was readily protodesilylated by treatment with NaH–HMPA[11] to give the alcohol (**11**), from which naturally occurring (+)-*exo*-brevicomin was produced by a sequence of conventional reactions (deacetalization followed by simultaneous debenzylation and hydrogenation). For preparation of (+)-*endo*-brevicomin, the major component of natural *endo*-brevicomin, *syn*-(**10**) was first oxidized to the ketone (**12**). Reduction of (**12**) with L-Selectride gave *anti*-(**10**) which was found to be homogeneous within the limits of ^1H n.m.r. analysis. The *anti*-alcohol (**10**) was transformed into (+)-*endo*-brevicomin as described above. (−)-*exo*- and (−)-*endo*-Brevicomin were also synthesized starting with (*R*)-(**4a**) using the same method mentioned above. Overall yields and the specific rotations of brevicomin thus prepared are summarized in Table 2. The specific rotations of (+)- and (−)-*exo*-brevicomin are identical to those of the enantiomerically pure compound.[12] The specific rotations of (+)- and (−)-*endo*-brevicomin showed the highest values reported so far.[13] We believe that they are enantiomerically pure because the intermediate *anti*-(**10**) was not contaminated by *syn*-(**10**).

Previously, Grasselli *et al.* reported in their synthesis of *endo*-brevicomin[13] that the diastereoselectivity observed in the addition of α-benzyloxybutanal with the Grignard reagent



Scheme 4

derived from 2-(3-chloropropyl)-2-methyl-1,3-dioxolane was only 3:2 where the *syn*-adduct (**13**) was a major product (Scheme 4). This finding strongly indicates that in the present nucleophilic addition reaction with α-alkyl-β-trimethylsilyl-β,γ-unsaturated carbonyl compounds, the 1-trimethylsilyl-vinyl group is indispensable for getting high diastereoselectivity.

In summary, a practical method for the synthesis of (*R*)- and (*S*)-aldehydes (**4**) has been developed, which allowed all the four possible stereoisomers of vicinal diols to be prepared by stereoselective addition of nucleophiles.

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