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

Fumie Sato,* Osamu Takahashi, Toshihiko Kato, and Yuichi Kobayashi

Department of Chemical Engineering, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

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]

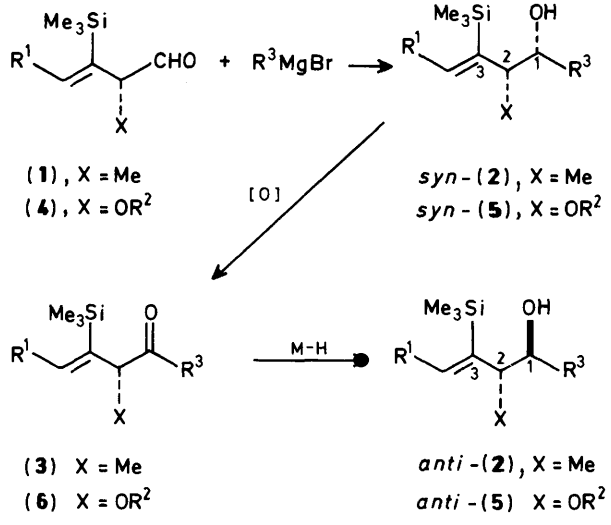
Run		Substrate R¹	R²	R³	Reaction conditions Nucleophile	Solvent	Product (**5**) *syn* : *anti*	Yield (%)
1	(**4a**)	H	Bn		EtMgBr	THF	1 : 1	63
2	(**4a**)	H	Bn		EtMgBr	Et_2O	14 : 1	87
3	(**4b**)	H	Me		EtMgBr	THF	9 : 1	68
4	(**4b**)	H	Me		EtMgBr	Et_2O	>99 : <1[b]	92
5	(**4c**)	Bu^n	Me		EtMgBr	Et_2O	>99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



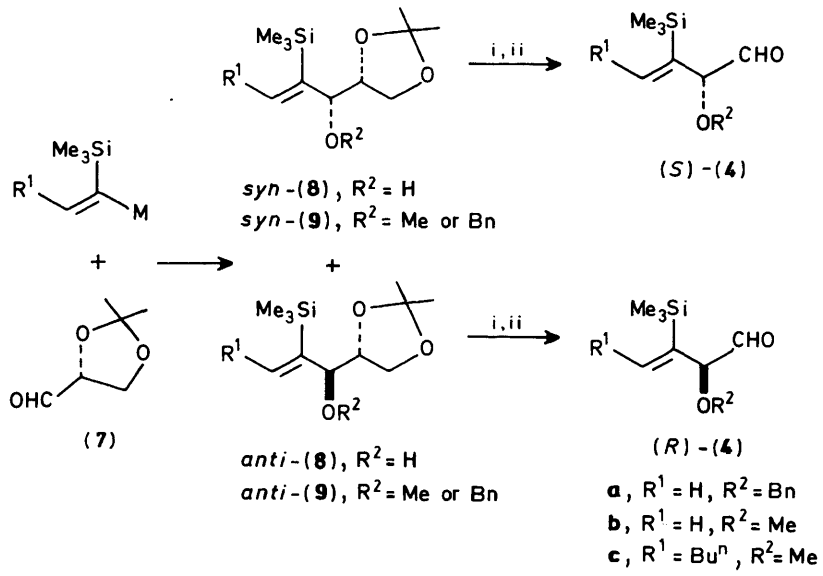
Scheme 1

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.

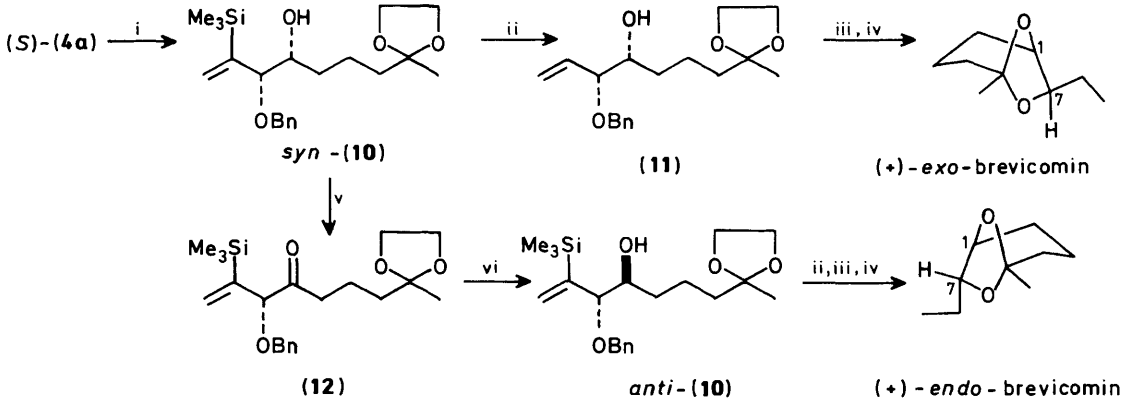
Compounds (**4**) were synthesised as shown in Scheme 2 starting with the readily available (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**7**).[4] Reaction of (**7**) with 1-trimethylsilylvinyl organometallic compounds afforded a mixture of *syn*- and *anti*-addition products (**8**). They were converted 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 = $PhCH_2$.

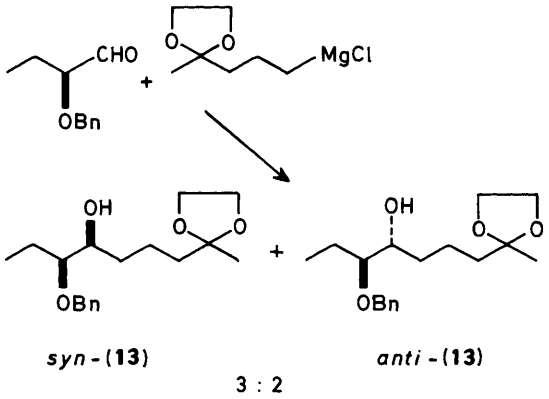
The results of the reaction of (**4**) with ethylmagnesium bromide (Scheme 1) are summarized in Table 1. When diethyl ether was used as a solvent, the reaction proceeded highly stereoselectively affording *syn*-(**5**) either predominantly [for (**4a**)] or exclusively [for (**4b**) and (**4c**)]. The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

We thank Toshiba Silicone Co. Ltd. for a generous gift of trimethylsilyl chloride.

Received, 18th June 1985; Com. 862

References

1 E. L. Eliel, in 'Asymmetric Synthesis,' ed. J. D. Morrison, Academic Press, New York, 1983, vol. 2, part A, ch. 5; P. A. Bartlett, *Tetrahedron*, 1980, **36**, 2; W. C. Still and J. H. McDonald, III, *Tetrahedron Lett.*, 1980, **21**, 1031; W. C. Still and J. A. Schneider, *ibid.*, 1980, **21**, 1035.

2 For recent publications in this area, see: M. Asami and T. Mukaiyama, *Chem. Lett.*, 1983, 93; G. Fronza, C. Fuganti, P. Grasselli, G. P. Faantoni, and C. Zirotti, *ibid.*, 1984, 335; M. T. Reetz, K. Kesseler, S. Schmidtberger. B. Wenderoth, and R. Steinbach, *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 989; M. T. Reetz and K. Kesseler, *J. Chem. Soc., Chem. Commun.*, 1984, 1079; M. T. Reetz, K. Kesseler, and A. Jung, *Tetrahedron Lett.*, 1984, **25**, 729; E. K. Dolence, M. Adamczyk, and D. S. Watt, *ibid.*, 1985, **26**, 1189; G. E. Keck and E. P. Boden, *ibid.*, 1984, **25**, 265, 1879; S. Kiyooka and C. H. Heathcock, *ibid.*, 1983, **24**, 4765; C. H. Heathcock, M. C. Pirrung, S. D. Young, J. P. Hagen, E. T. Jarvi, U. Badertscher, H.-P. Marki, and S. H. Montgomery, *J. Am. Chem. Soc.*, 1984, **106**, 8161; C. H. Heathcock, S. Kiyooka, and T. A. Blumenkopf, *J. Org. Chem.*, 1984, **49**, 4214; L. Banfi, A. Bernardi, L. Colombo, C. Gennari, and C. Scolastico, *ibid.*, 1984, **49**, 3784.

3 F. Sato, M. Kusakabe, and Y. Kobayashi, *J. Chem. Soc., Chem. Commun.*, 1984, 1130.

4 E. Baer and H. O. L. Fischer, *J. Biol. Chem.*, 1939, **128**, 463.

5 N. Ishikawa, H. Honda, and F. Yamaguchi, presented at the Annual Meeting of the Japan Chemical Society, April, 1983, Tokyo.

6 T. Sugiyama and K. Yamashita, *Agric. Biol. Chem.*, 1980, **44**, 1983.

7 F. Sato, Y. Kobayashi, O. Takahashi, T. Chiba, Y. Takeda, and M. Kusakabe, preceding communication.

8 F. Sato, H. Ishikawa, and M. Sato, *Tetrahedron Lett.*, 1981, **22**, 85; F. Sato, *J. Organomet. Chem.*, 1985, **285**, 53.

9 V. Schurig, R. Weber, and G. J. Nicholson, *Naturwissenschaften*, 1983, **70**, 92.

10 For review, see: K. Mori, in 'The Total Synthesis of Natural Products,' ed. J. ApSimon, Wiley, New York, 1981, vol. 4, ch. 1; for recent syntheses of brevicomin, see: M. Larcheveque and J. Lalande, *J. Chem. Soc., Chem. Commun.*, 1985, 83; P. G. M. Wuts and S. S. Bigelow, *ibid.*, 1984, 736, and references cited therein.

11 F. Sato, Y. Tanaka, and M. Sato, *J. Chem. Soc., Chem. Commun.*, 1983, 165.

12 K. Mori, *Tetrahedron*, 1974, **30**, 4223.

13 R. Bernardi, C. Fuganti, and P. Grasselli, *Tetrahedron Lett.*, 1981, **22**, 4021.