Tetrahedron Letters, Vol.32, No.11, pp 1479-1482, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

STEREOSPECIFIC CONSTRUCTION OF THREE CONTIGUOUS ASYMMETRIC CENTERS *via* CYCLIC HYDROBORATION

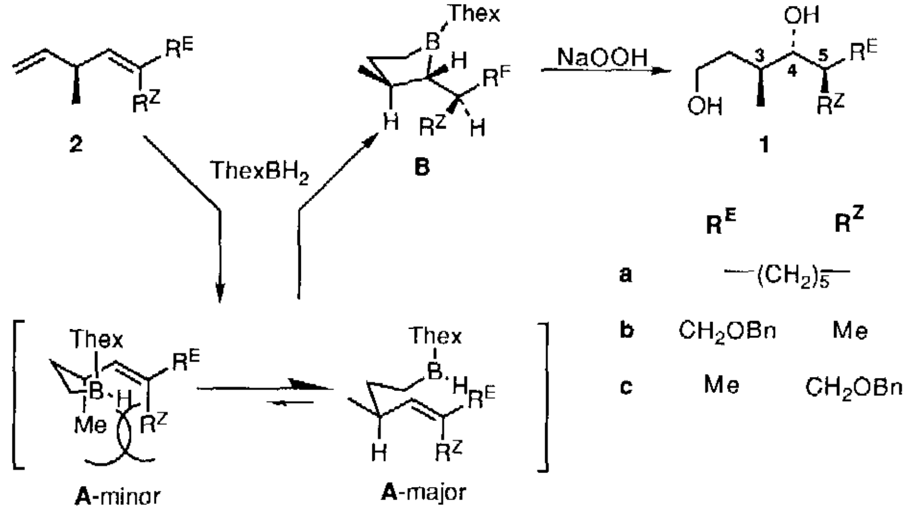
Yasushi Yokoyama,* Hideyuki Kawashima, Masaaki Kohno,
Yoshiko Ogawa, and Soichi Uchida

Department of Materials Science, Faculty of Engineering,
Yokohama National University,
Tokiwadai, Hodogaya-ku, Yokohama 240, Japan

Abstract: Diastereospecific construction of three contiguous asymmetric centers assembled in optically active 1,4-diols, cyclopentanones, and δ-lactones have been achieved *via* $A^{(1,3)}$-strain controlled cyclic hydroboration.

Recently we have reported the synthesis of 3,4-*anti*-4-cyclohexyl-3-methylbutane-1,4-diol **1a** in 96/4 *anti*/*syn* ratio by a treatment of 4-cyclohexylidene-3-methyl-1-butene **2a** with thexylborane.[1,2] The origin of the high diastereoselectivity is that the intermediate **A** takes the conformation with the least $A^{(1,3)}$-strain[3,4] as depicted in Scheme 1. We here report the application of this strategy to the diastereospecific construction of three different types of optically active compounds possessing three contiguous asymmetric centers.

Scheme 1.

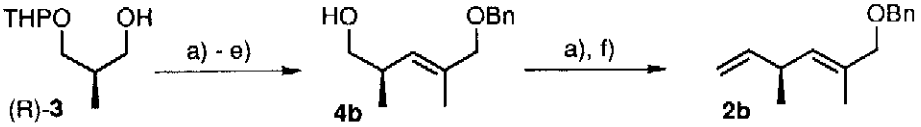


	R^E	R^Z
a	$-(CH_2)_5-$	
b	CH_2OBn	Me
c	Me	CH_2OBn

As the hydroboration proceeds in a *syn* addition manner, control of the geometry of the trisubstituted double bond of the 1,4-diene **2** directly results in the 4,5-*anti*/*syn*-selective preparation of the 3,4-*anti*-1,4-diol **1**. Accordingly, it was decided to apply this methodology to chiral 1,4-dienes **2b** and **2c**, from which 1,4-diols **1b** and **1c**, potential synthons of polypropionate natural products, were expected.

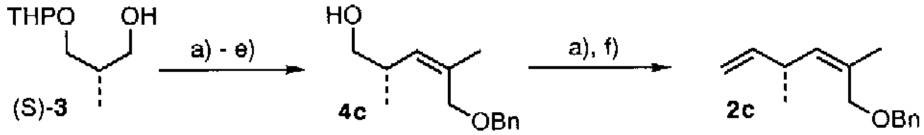
Synthesis of the diene **2b** was started from the known alcohol (R)-**3**,[5] obtained from methyl (S)-3-hydroxy-2-methylpropanoate.[6] Swern oxidation[7a] followed by Wittig reaction, reduction, benzylation, and cleavage of THP ether afforded an alcohol **4b** in 74% yield for 5 steps (Scheme 2). The E/Z ratio of the double bond of **4b** was determined by GC analysis to be >99/1. Swern oxidation[7a] followed by Wittig methylenation afforded **2b** in 99% yield in 2 steps. Geometrically isomeric 1,4-diene **2c** was obtained from (S)-**3** by Swern oxidation[7b] and Horner-Emmons reaction,[8] followed by the same reaction sequence[7b] for the synthesis of **2b** described above in 52% yield in 7 steps (Scheme 3). The E/Z ratio of the trisubstituted double bond of **4c** was 2/98.

Scheme 2.



a) DMSO, $(COCl)_2$, CH_2Cl_2; Et_3N. b) $Ph_3P{=}C(CH_3)CO_2Et$, THF (86% in 2 steps). c) $LiAlH_4$, THF (93%). d) BnBr, NaH, THF (97%). e) *p*-TsOH. MeOH (96%). f) $Ph_3P{=}CH_2$, THF (99% in 2 steps).

Scheme 3.



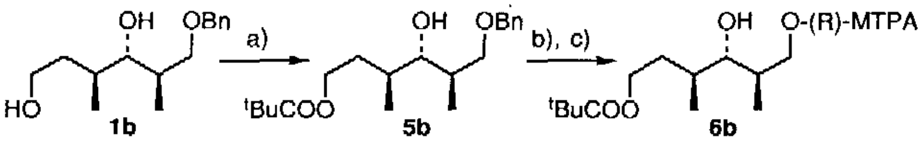
a) DMSO, $(COCl)_2$, CH_2Cl_2; N methylmorpholine. b) $(MeO)_2P(O)CH(CH_3)CO_2Me$, NaH, THF (67% in 2 steps). c) $LiAlH_4$, THF (84%). d) BnBr, NaH, THF (93%). e) *p*-TsOH, MeOH (100%). f) $Ph_3P{=}CH_2$, THF (100% in 2 steps).

Treatment of **2b** in THF (0.1 mol dm^{-3} concentration) at -78°C with thexylborane (1.3 eq, prepared from borane-dimethylsulfide complex and 2,3-dimethyl-2-butene in THF) followed by oxidation afforded, after chromatographic purification, a mixture of 1,4-diols in 75% yield. The diastereomeric purity (3,4-*anti*-4,5-*anti* (**1b**) *vs.* 3,4-*syn*-4,5-*anti*(**1d**)) was shown to be 96/4 by ^1H NMR.[9] The other compound isolated was a 1,4-diol derived from olefinic isomer (*i.e.*, the enantiomer of **1c** described below).

All attempts to determine the optical purity of the monopivalate **5b** (lanthanide induced chiral shift reagent experiment) or (R)-MTPA ester **6b** (^1H, ^{13}C, ^{19}F NMR, and GC analysis) failed to give any definite e.e. value due to interference by the inseparable *syn-anti* stereoisomer derived from **1d**.[10] The three-step conversion depicted in Scheme 4, however, showed a convenient differentiation method of the hydroxyl groups.

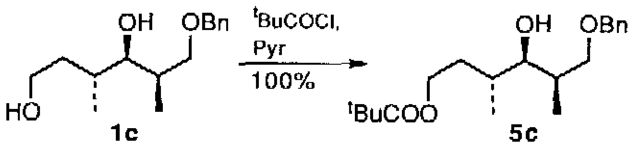
Similar treatment of **2c** with thexylborane followed by chromatographic purification gave 1,4-diol **1c**[9] in 95% yield. The diastereomeric ratio 3,4-*anti*-4,5-*syn* *vs.* 3,4-*syn*-4,5-*syn* was shown to be >98/<2 since only a trace amount of other diastereoisomers could be isolated. Lanthanide-induced shift experiment of ^1H NMR of **5c** using $Eu(TFC)_3$ proved the optical purity of **1c** to be 98% e.e.[10a]

Scheme 4.



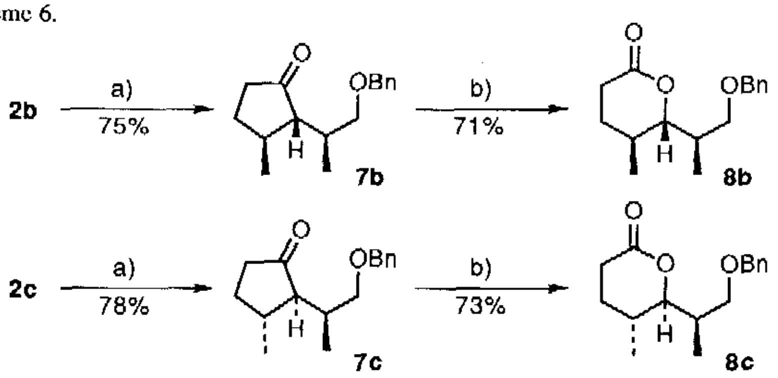
a) ᵗBuCOCl, Pyr (98%). b) Pd/C, H_2, AcOEt .
c) (R)-(+)-MTPA, DCC, DMAP, CH_2Cl_2 (89% in 2 steps).

Scheme 5.



The borolane **B**, an unisolated intermediate of the cyclic hydroboration depicted in Scheme 1, was known to give a cyclopentanone[1] by treatment with NaCN and $(CF_3CO)_2O$ followed by alkaline hydrogen peroxide.[11] Thus, the 1,4-diene **2b** was successively reacted with the following reagents in one flask: (1)thexylborane, (2)NaCN, (3)$(CF_3CO)_2O$, (4)NaOOH. After chromatographic purification, cyclopentanone **7b**[9] was obtained in 75% yield. Oxidation of **7b** with mCPBA gave δ-lactone **8b**[9] in 71% yield. Similarly, **2c** gave a cyclopentanone **7c**[9] in 78% yield, which was oxidized to δ-lactone **8c**[9] by *m*CPBA in 73% yield. Synthesis of racemic **8c** had been reported by Wuts *et al.* and had been converted to Prelog-Djerassi lactonic acid.[12]

Scheme 6.



a) $ThexBH_2$, THF; NaCN; $(CF_3CO)_2O$; NaOOH. b) *m*CPBA, CH_2Cl_2.

Utilization of these compounds in natural product synthesis is now in progress in this laboratory.

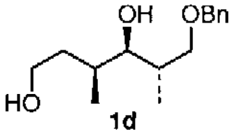
This work was partially supported by a Grant-in-Aid for Scientific Research No. 63740281 from the Ministry of Education, Science, and Culture of Japan, and by The Foundation "Hattori-Hokokai", which are greatly acknowledged.

References and Notes

1. Y. Yokoyama, H. Kawashima, and H. Masaki, *Chem. Lett.*, **1989**, 453.
2. Two other A(1,3)-strain controlled cyclic hydroboration processes have been reported on 1,5-dienes: a) D. J. Morgans, Jr., *Tetrahedron Lett.*, **1981**, *22*, 3721; b) W. C. Still and K. R. Shaw, ibid., **1981**, *22*, 3725.
3. F. Johnson, *Chem. Rev.*, **1968**, *68*, 375.
4. R. W. Hoffmann, *Chem. Rev.*, **1989**, *89*, 1841.
5. K. Mori and S. Senda, *Tetrahedron*, **1985**, *41*, 541.
6. Both enantiomers of methyl 3-hydroxy-2-methylpropanoates were kindly provided by Kanegafuchi Chemical Industry Co., which is greatly acknowledged.
7. a) In order to avoid racemization of the asymmetric center, the triethylamine hydrochloride formed was rapidly removed from the reaction mixture. *See*; K. Suzuki, K. Tomooka, E. Katayama, T. Matsumoto, and G. Tsuchihashi, *J. Am. Chem. Soc.*, **1986**, *108*, 5221.

   b) N-methylmorpholine was used instead of triethylamine for Swern oxidation. *See*; S. F. Martin, G. J. Pacofsky, R. P. Gist, and W. -C. Lee , *J. Am. Chem. Soc.*, **1989**, *111*, 7634.
8. G. Schmid, T. Fukuyama, K. Akasaka, and Y. Kishi, *J. Am. Chem. Soc.*, **1979**, *101*, 259.
9. These new compounds showed satisfactory ^{1}H and ^{13}C NMR, IR, and high resolution mass spectral data.
10. a) In the preparation of the dienes **2b** and **2c**, Swern oxidation - Wittig type reaction combination was carried out twice. Extreme care was taken to avoid racemization of the inherent chiral center on the labile intermediate β,γ-unsaturated aldehyde which supposedly could be caused by the second Swern oxidation.[7]

    b) All of the analyses showed the existence of only one other stereoisomer which was believed to be derived from the inseparable diastereomeric diol **1d**. We therefore assume that e.e. of **1b** is close to unity.

    1d
11. A. Pelter, K. Smith, M. G. Hutchings, and K. Rowe, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 129.
12. P. G. M. Wuts, M. L. Obrzut, and P. A. Thompson, *Tetrahedron Lett.*, **1984**, *25*, 4051.

(Received in Japan 1 December 1990)