Pergamon

Tetrahedron Letters, Vol. 38, No. 20, pp. 3553-3556, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00701-6

Enantioselective Acyclic Stereoselection under Catalyst Control. 2.[1] Asymmetric Synthesis of *syn*- and *anti*-1,3-Diols Incorporating an Acetate Equivalent by the Chiral Oxazaborolidinone-Catalyzed Aldol Reaction

Syun-ichi Kiyooka,* Takafumi Yamaguchi, Hirofumi Maeda, Haruhide Kira,
Mostofa Abu Hena†, and Michio Horiike†

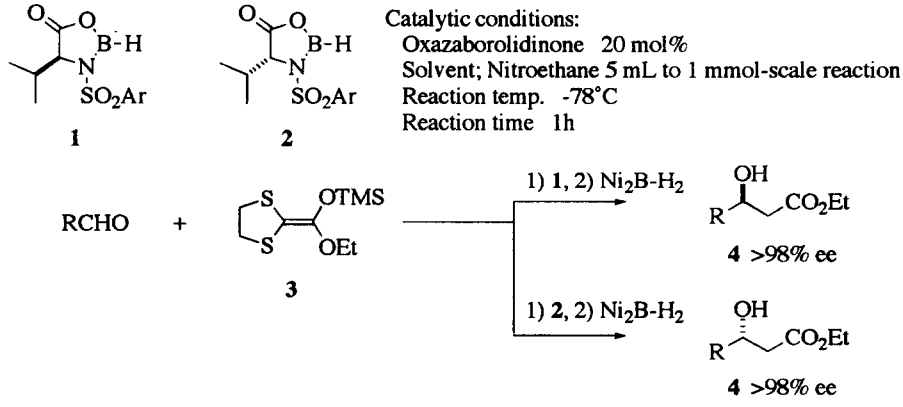
Department of Chemistry, Kochi University
Akebono-cho, Kochi 780, Japan
†Department of Biosources Science, Kochi University
B200 Monobe, Nankoku, Kochi 783, Japan

Dedicated to Prof. Clayton H. Heathcock

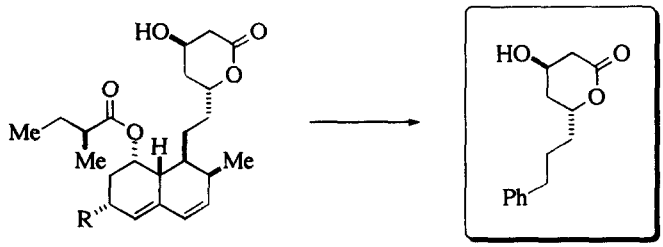
Abstract: The chiral oxazaborolidinone-catalysed aldol reaction of a silyl ketene acetal involving a dithiolane moiety with β-silyloxy aldehyde resulted in the production of *syn*- and *anti*-1,3-diols with complete stereoselection by the choice of the stereochemistry of the catalyst. This reaction is an elegant example of enantioselective acyclic stereoselection under catalyst control. © 1997 Elsevier Science Ltd.

Acyclic stereoselection developed in the past two decades has been mostly attained by means of using diastereoselective inter- and/or intramolecular chirality transfer of the stereochemistry of the first supplied chiral center; consequently, the stereoselective construction of acyclic systems involving multiple chiral centers was always affected by the stereochemistry of the substrates used in the reaction.[2] It might be expected for acyclic stereoselection to evolve to highly intensive stages provided that enantioselective carbon-carbon bond formation reactions proceed under complete catalyst control without any stereochemical disturbance caused by the substrates. We have previously reported a chiral oxazaborolidinone (**1** and **2**), which was prepared from *N*-*p*-nitrobenzenesulfonamide of valine and BH_3·THF, catalyzed aldol reaction with silyl ketene acetal **3** containing a dithiolane ring which allows the production of acetate aldols **4** ,via dithiolane aldols ,with the level of almost complete enantioselectivity . The opposite stereochemistry of acetate aldols **4** can be easily obtained using chiral

Scheme 1



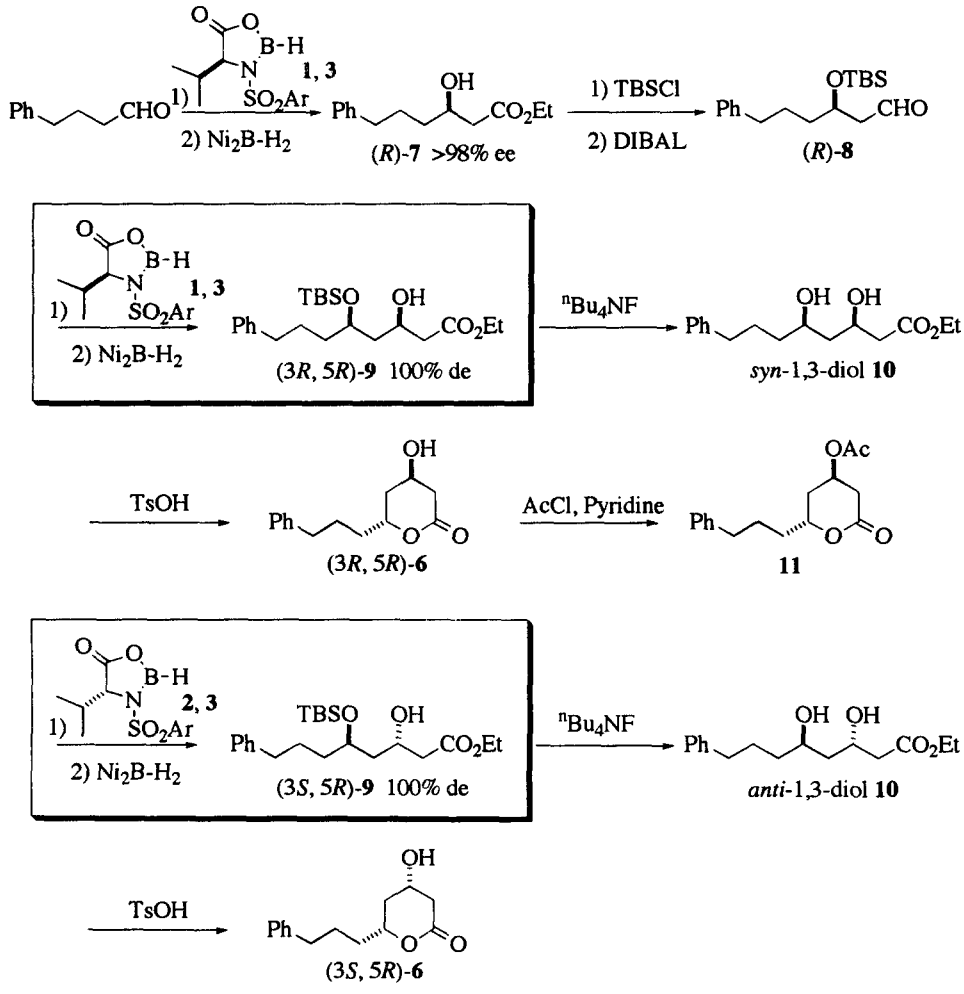
Scheme 2



5a R=H **Mevinolin**
5b R=CH_3 **Compactin**

6

Scheme 3



borane **2** (Scheme 1).[3] Here, if the chirality of the β-hydroxy aldehyde used in the reaction does not affect the stereochemical course of the aldol reaction , we can exploit the strategy to achieve the synthesis of enantiopure *syn*- and *anti*-1,3-diols. We disclose herein such an evolved example of acyclic stereoselection in enantioselective synthesis of *syn*- and *anti*-1,3-diols, which are known to be fundamental units of 1,3-polyol chain found in the polyene macrolide antibiotics and others.[4]

In order to confirm the effectiveness of the strategy, we chose lactone **6**[5] involving a *syn*-1,3-diol unit, which is known as a mevinic acid lactone derivative of HMG-CoA reductase inhibitors, mevinolin (**5a**) and compactin (**5b**) (Scheme 2).[6] According to the above procedures, silyl ketene acetal **3** was condensed with 4-phenylbutanal in the presence of **1** to give the corresponding α-dithiolane aldol in 86% yield (the standard conditions of the aldol reaction are presented in Scheme 1) which was converted to acetate aldol **7** in 96% yield upon treatment with nickel boride under a hydrogen atmosphere. The value of enantiomeric excess of **7** was determined to be >98 % by HPLC with Daicel Chiralcel OD. After TBS protection, the following DIBAL reduction gave β-silyloxy aldehyde **8** of *R* configuration (in 85% yield from **7**), which is a starting compound for the enantiodivergent synthesis of 1,3-diols. If the sequence of the above aldol reaction and the following reactions with aldehyde (*R*)-**8** is repeated accompanied by the same level of enantioselectivity , only one isomer is detectable in the possible diastereomeric 3,5-diol ester derivatives (*R,R* : *R,S* : *S,R* : *S,S* = 99 x 99 : 99 : 99 : 1).

Next we examined the following chiral oxazaborolidinone-promoted aldol reactions of silyl ketene acetal **3** with β-chiral aldehyde (*R*)-**8** in the presence of chiral boranes **1** and **2**. In each case, (*R*)-**8** underwent the aldol reaction, followed by desulfurization to give the corresponding TBS-mono-protected aldols (**9**) in 77- 83% yields; after deprotection, chiral borane **1** led to the production of enantiomeric pure *syn*-1,3-diol (3*R*,5*R*)-**10** and chiral borane **2** led to the production of enantiomeric pure *anti*-1,3-diol (3*S*,5*R*)-**10**, respectively (Scheme 3). No detectable amounts of the other isomers were observed in both HPLC modes of determining the ratios of diastereomer and enantiomer, so that further purification procedures with column chromatography were not required. The result provides the rationale that the chiral center at the β-position of the aldehyde did not affect the stereoselection at the newly-created chiral center at all, which is really controlled only by the stereochemistry of the used chiral borane. *This is an excellent example of enantioselective acyclic stereoselection under catalyst control.* The reason why the complete stereocontrol takes place with the catalyst is presumably explained by a mechanism associated with a more converged transition state assembly involving the chiral borane, which is consequently far from the adjacent β-chiral center of the aldehyde. The treatment of (3*R*,5*R*)-**9** with tetrabutylammonium fluoride gave a mixture of lactone (3*R*,5*R*)-**6** and *syn*-1,3-diol **10** which was converted to the lactone by *p*-toluenesulfonic acid (70% yield, from **9** to **6**).[7] Acetylation of (3*R*,5*R*)-**6** gave acetate **11** which was identical with the previously reported result.[5] The epimer lactone (3*S*,5*R*)-**6** was also prepared via *anti*-1,3-diol **10** according to similar procedures, mentioned above.

In conclusion, our strategy using the chiral oxazaborolidinone-promoted aldol reaction with complete enantioselectivity opens up a novel access to acyclic stereoselection for the synthesis of 1,3-diol systems. Further applications of this method are in progress for constructing more complicated 1,3-polyol skeletons.

Acknowledgment: This work was supported by Grant-in-Aid for Scientific Research (Nos. 7640790 and 8245239) from the Ministry of Education.

References and Notes

1. Presented in part at the 11th international conference on organic synthesis (ICOS-11), Amsterdam, June 30-July 4, 1996. For part 1, see: Kiyooka, S. -i.; Kira, H.; Hena, M. A. *Tetrahedron Lett.* **1996**, 37, 2597-2600. Our results on chiral oxazaborolidinone-

promored aldol reactions: (a) Kiyooka, S. -i.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, 56, 2276-2278. (b) Kiyooka, S. -i.; Kaneko, Y.; Kume, K. i., *Tetrahedron Lett.* **1992**, 33, 4927-4930.

2. (a) Gawley, R. E.; Aubé, J. *Principles of Asymmetric Synthesis*, Pergamon, Oxford (1996). (b) Santelli, M.; Pons, J. -M. *Lewis Acids and Selectivity in Organic Synthesis*, CRC press, Boca Raton (1995). (c) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, John Wiley & Sons, New York (1995).
3. Kiyooka, S. -i.; Hena, M. A. *Tetrahedron: Asymmetry* **1996**, 7, 2181-2184.
4. A variety of papers on stereoselective 1, 3-diol syntheses: (a) McGarvey, G. J.; Mathys, J. A.; Wilson, K. J.; Overly, K. R.; Buonora, P. T.; Spoors, P. G. *J. Org. Chem.* **1995**, 60, 7778-7790. (b) Menges, M.; Brückner, R. *Synlett.* **1994**, 809-813. (c) Kaneko, Y.; Matsuo, T.; Kiyooka, S. -i.; *Tetrahedron Lett.* **1994**, 35, 4107-4110. (d) Poss, C. S.; Rychnovsky, S. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, 115, 3360-3361. (e) Rychnovsky, S. D.; Skalitzky, D. J. *J. Org. Chem.* **1992**, 57, 4336-4339. (f) Mohr, P. *Tetrahedron Lett.* **1992**, 33, 2455-2458. (g) Evans, D. A.; Gauchet-Prunet, J. A.; Carreira, E. M.; Charette, A. B. *J. Org. Chem.* **1991**, 56, 741-750. (h) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635-645. (i) Mori, Y.; Suzuki, M. *Tetrahedron Lett.* **1989**, 30, 4387-4388. (j) Nakata, T.; Suenaga, T.; Oishi, T. *Ibid.* **1989**, 30, 6525-6528. (k) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Ibid.* **1988**, 29, 5419-5422. (l) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, 110, 3560-3578. (m) Reetz, M. T.; Jung, A.; Bolm, C. *Tetrahedron* **1988**, 44, 3889-3898. (n) Schreiber, S. L; Goulet, M. T.; Schulte, G. *J. Am. Chem. Soc.* **1987**, 109, 4718-4720. (o) Schreiber, S. L.; Goulet, M. T. *Tetrahedron Lett.* **1987**, 28, 6001-6004. (p) Kiyooka, S. -i.; Kuroda, H.; Shimasaki, Y. *Ibid.* **1986**, 27, 3009-3012. (q) Nakata, T.; Nagao, S.; Oishi, T. *Ibid.* **1985**, 26, 75-78. (r) Lipshutz, B. H.; Kozlowski, J. A. *J. Org. Chem.* **1984**, 49, 1147-1149. (s) Narasaka, K.; Pai, F. -C. *Tetrahedron* **1984**, 40, 2233-2238. (t) Kiyooka, S. -i.; Sasaoka, H.; Fujiyama, R.; Heathcock, C. H. *Tetrahedron Lett.* **1984**, 25, 5331-5334. (u) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, 105, 4833-4835. (v) Kiyooka, S. -i.; Heathcock, C. H. *Tetrahedron Lett.* **1983**, 24, 4765-4768. (w) Nakata, T.; Takao, S.; Fukui, M.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, 24, 3873-3876. (x) Hirama, M.; Uei, M. *Ibid.* **1982**, 23, 5307-5310. (y) Ma, P. Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, 47, 1378-1380. (z) Nicolaou, K. C.; Uenishi, J. *J. Chem. Soc., Chem. Commun.* **1982**, 1292-1293.
5. Lautens, M.; Ma, S.; Yee, A. *Tetrahedron Lett.* **1995**, 36, 4185-4188.
6. Synthetic works related to mevinic acid lactones: (a) Hiyama, T.; Minami, T.; Takahashi, K. *Bull. Chem. Soc. Jpn.* **1995**, 68, 364-372. (b) Hiyama, T.; Reddy, G. B.; Minami, T.; Hanamoto, T. *Ibid.* **1995**, 68, 350-363. (c) Gijsen, H. J. M.; Wong, C. -H. *J. Am. Chem. Soc.* **1994**, 116, 8422-8423. (d) Kumar, A.; Dittmer, D. C. *J. Org. Chem.* **1994**, 59, 4760-4764. (e) Menges, M.; Brückner, R. *Synlett.* **1993**, 901-905. (f) Hanessian, S.; Roy, P. J.; Petrini, M.; Hodges, P. J.; Fabio, R. D.; Carganico, G. *J. Org. Chem.* **1990**, 55, 5766-5777. (g) Wess, G.; Kesseler, K.; Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Jendralla, H.; Bock, K.; Holzstein, G.; Kleine, H.; Schnierer, M. *Tetrahedron Lett.* **1990**, 31, 2545-2548. (h) Rosen, T.; Heathcock, C. H. *Tetrahedron* **1986**, 42, 4909-4951.
7. *Syn*-1,3-diol **10**: $[\alpha]^{24}_{D}$ +4.3 (c = 0.472, $CHCl_3$). IR (neat) 3397, 1732, 850, 748, 700cm^{-1}. ^{1}H NMR (500MHz) ($CDCl_3$) δ 1.27 (3H, t, *J* = 7.0Hz), 1.45-1.58 (4H, m), 1.27 (3H, t, *J* = 7.0Hz), 1.45-1.58 (4H, m), 1.65-1.69 (1H, m), 1.74-1.78 (1H, m), 2.46 (1H, d, *J* = 5.2Hz, 1H, d, *J* = 7.0Hz), 2.63 (2H, t, *J* = 7.6Hz), 3.26 (1H, bs), 3.76 (1H, bs), 3.89 (1H, quintet, *J* = 6.5Hz), 4.16 (2H, q, *J* = 7.0Hz), 4.25 (1H, quintet, *J* = 6.2Hz), 7.17-7.28 (5H, m);. ^{13}C NMR (125 MHz) ($CDCl_3$) δ 172.54, 142.30, 128.39, 128.27, 125.71, 71.97, 69.08, 60.78, 42.27, 41.66, 37.33, 35.81, 27.10, 14.13.
Anti-1,3-diol **10**: $[\alpha]^{24}_{D}$ +10.0 (c = 1.105, $CHCl_3$). IR (KBr) 3531, 3460, 3362, 3271, 837, 750, 700cm^{-1}. ^{1}H NMR (500MHz) ($CDCl_3$) δ 1.27 (3H, t, *J* = 7.3Hz), 1.51 (1H, quintet, *J* = 5.2Hz), 1.56-1.61 (2H, m), 1.63-1.71 (2H, m), 1.79 (1H, dddd, *J* = 21.4, 10.7, 5.6, 2.9Hz), 2.42 (1H, d, *J* = 4.9Hz), 2.46 (1H, dd, *J* = 16.5, 4.0Hz), 2.52 (1H, dd, *J*= 16.5, 8.9Hz), 2.64 (2H, ABq, apparent t, *J* = 7.6, 7.3Hz), 3.40 (1H, d, *J* = 3.4Hz), 3.94 (1H, ddd, *J*= 15.9, 7.9, 2.1Hz), 4.17 (2H, dd, *J* = 14.3, 7.0Hz), 4.33 (1H, ddd, *J* = 15.9, 8.5, 3.7Hz), 7.16-7.29 (5H, m);. ^{13}C NMR (125 MHz) ($CDCl_3$) δ 172.90, 142.28, 128.39, 128.30, 125.75, 68.73, 65.67, 60.77, 42.01, 41.22, 37.03, 35.81, 27.49, 14.16.
Mevinic lactone derivative, (3*R*,5*R*)-**6**. The following data provided definitive evidence of the existence of two conformational isomers: $[\alpha]^{24}_{D}$ +14.6 (c = 1.78, $CHCl_3$). IR (neat) 3396, 1732, 850, 748, 700cm^{-1}. ^{1}H NMR (500MHz) ($CDCl_3$) δ 1.47-1.81 (m), 1.84-1.94 (m), 2.38 (bs), 2.52 (bs), 2.59 (ddd, *J* = 17.7, 3.7, 1.8Hz), 2.64 (ABq, apparent t, *J* = 7.5, 7.3Hz), 2.69 (dd, *J* = 17.7, 5.2, 4.9Hz), 3.80 (ddd, *J* = 15.0, 7.9, 4.3, 4.0), 3.85-3.89 (m), 4.34 (quintet, *J* = 3.8Hz), 4.69 (ddt, *J* = 16.5, 4.9, 2.8Hz), 7.16-7.29 (m);. ^{13}C NMR (125 MHz) ($CDCl_3$) δ 170.57, 142.20, 141.75, 128.38, 128.35, 128.33, 128.28, 125.85, 125.75, 75.69, 72.09, 62.57, 61.76, 38.58, 38.18, 37.26, 35.83, 35.75, 35.47, 34.93, 27.25, 26.52.
Epimer lactone, (3*S*,5*R*)-**6**: $[\alpha]^{22}_{D}$ +32.3(c = 1.24, $CHCl_3$). IR (neat) 3429, 1730, 752, 700cm^{-1}. ^{1}H NMR (500MHz) ($CDCl_3$) δ 1.55 (1H, ddd, *J* = 13.7, 11.6, 9.2Hz), 1.62-1.68 (2H, m), 1.69-1.77 (2H, m), 1.84-1.88 (1H, m), 2.21 (1H, dddd, *J* = 12.5, 5.2, 2.7, 1.2Hz), 2.33 (1H, bs), 2.43 (1H, dd, *J* = 17.1, 7.9Hz), 2.64 (2H, ABq, apparent t, *J* = 7.3Hz), 2.86 (1H, ddd, *J* = 17.1, 6.1, 1.2, 0.9Hz), 4.15-4.24 (2H, m), 7.16-7.29 (5H, m);. ^{13}C NMR (125 MHz) ($CDCl_3$) δ 170.69, 141.64, 128.36, 128.30, 125.91, 77.10, 63.81, 39.48, 37.79, 35.44, 34.98, 26.52.
Acetate **11**: $[\alpha]^{22}_{D}$ +10.4 (c = 0.77, $CHCl_3$). IR (neat) 1738, 750, 702cm^{-1}. ^{1}H NMR (500MHz) ($CDCl_3$) δ 1.62-1.68 (1H, m), 1.70-1.80 (4H, m), 1.85-1.93 (1H, m), 2.07 (3H, s), 2.66 (2H, ABq, apparent t, *J* = 7.3, 7.0), 2.66 (1H, ddd, *J* = 18.0, 3.4, 1.5), 2.76 (1H, dd, *J* = 18.0, 5.5Hz), 4.55 (1H, dt, *J* = 7.3, 7.0Hz), 5.23 (1H, dt, *J* = 8.9, 8.5, 3.5Hz), 7.16-7.29 (5H, m);. ^{13}C NMR (125 MHz) ($CDCl_3$) δ 169.93, 168.84, 141.60, 128.37, 125.93, 75.92, 65.55, 35.48, 35.33, 34.94, 32.97, 26.46, 21.00.

(*Received in Japan* 14 *March* 1997; *revised* 9 *April* 1997; *accepted* 10 *April* 1997)