Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 3883–3886

TETRAHEDRON: *ASYMMETRY*

Highly stereocontrolled reduction of 1,3-cyclopentanediones using oxazaborolidine–BH_3

Makoto Shimizu,* Shunsuke Yamada, Yoshifumi Fujita and Fumiko Kobayashi

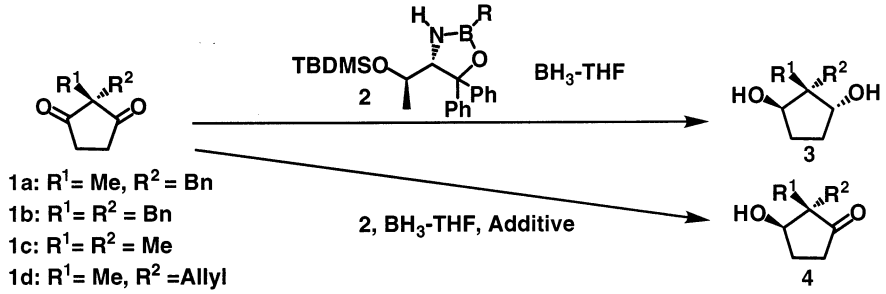
Department of Chemistry for Materials, Mie University, Tsu, Mie 514-8507, Japan

Received 4 September 2000; accepted 18 September 2000

Abstract

Highly enantioselective reduction of 1,3-cyclopentanediones was conducted using an oxazaborolidine derived from L-threonine and a borane complex to give either 1,3-cyclopentanediols or 3-hydroxycyclopentanones in high enantiomeric purity by choosing appropriate reduction conditions.

Widespread occurrence of cyclopentane derivatives in many biologically interesting materials[1] coupled with recent interest in the oxazaborolidine-mediated selective reduction[2] prompts us to report our results from asymmetrization of 1,3-cyclopentanediones using such a reduction methodology. For the preparation of useful chiral synthons possessing multiple stereogenic centers leading to the synthesis of cyclopentanoides, asymmetrization of *meso*-compounds offers one of the most convenient approaches.[3] We have already reported that *meso*-dicarboxylic anhydrides are readily converted into chiral monoesters by the action of zinc reagents in the presence of a cinchona alkaloid as a chiral auxiliary,[4] and have also disclosed very recently that the oxazaborolidine-mediated reduction is a useful tool for the reduction of *meso*-imides, leading to a short-step synthesis of (+)-deoxybiotin, a precursor of (+)-biotin, with high enantiomeric excess.[5] However, difficulty was encountered in the selective reduction of 1,3-diketones to 1,3-diols or β-hydroxy ketones due to the susceptibility of β-hydroxy ketones towards further reduction into 1,3-diols. We have now found that the reduction of 1,3-cyclopentanediones with BH_3–oxazaborolidine derived from L-threonine leads to the formation of either 1,3-diols or β-hydroxy ketones by choosing appropriate reduction conditions.

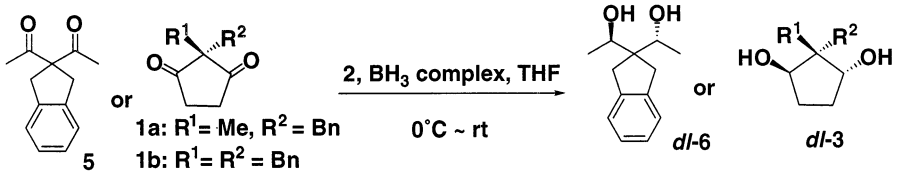


* Corresponding author. Tel/fax: +81 59 231 9413; e-mail: mshimizu@chem.mie-u.ac.jp

0957-4166/00/$ - see front matter
PII: S0957-4166(00)00378-5

An initial examination was carried out for the bis-reduction using diacetylindane **5** as a substrate under the conditions previously reported,[6] except oxazaborolidine **2**, which we have developed,[7] was used. As shown in Table 1, the substituent on the boron atom of the oxazaborolidine **2** was found to be very important in the control of enantioselectivity. Among the derivatives screened, the use of methyl substituted analogue **2** (R = Me) proved to be the most effective, and the use of a stoichiometric amount of the oxazaborolidine **2** (R = Me) was also crucial for the control of the diastereoselectivity (entry 4). We then turned our attention to the stereocontrolled reduction of cyclic substrates, and the results are also summarized in Table 1.

Table 1
Bis-reduction of 1,3-cyclopentanedione **1** to 1,3-diol **3**[a]



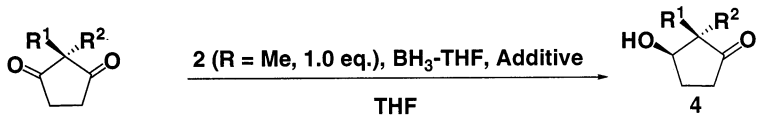
Entry	Diketone	R in ligand **2**	**2** (equiv.)	BH_3 complex	% ee[b]	Yield (%)[c]	*dl*:*meso*[d]
1	**5**	H	0.1	BH_3–SMe_2	8	48	36:64
2	**5**	Me	0.1	BH_3– SMe_2	92	44	23:77
3	**5**	*n*-Bu	0.1	BH_3–SMe_2	66	46	22:78
4	**5**	Me	1.0	BH_3–SMe_2	97	74	69:31
5	**1a**	Me	0.1	BH_3–THF	90	89	65:35
6	**1a**	Me	1.0	BH_3–THF	>99	83	>99:1
7	**1a**	Me	0.1	BH_3–SMe_2	83	72	78:22
8	**1a**	Me	1.0	BH_3–SMe_2	98	80	>99:1
9	**1b**	Me	0.1	BH_3–SMe_2	56	56	79:21
10	**1b**	Me	1.0	BH_3–SMe_2	>99	62	>99:1

[a] The reaction was carried out according to the typical procedure, see Ref. 9.
[b] Determined by HPLC using a chiral stationary column (Daicel OD).
[c] Isolated yields. Determination of the absolute configurations of the products, see Ref. 8.
[d] Determined by HPLC (Kanto Chemicals Mightysil and/or Daicel OD column).

In the presence of a catalytic amount of oxazaborolidine **2** (R = Me), the reduction proceeded to give the diol in good yield with good enantioselectivity, although the diastereoselectivity was not high (entry 5). In contrast, when a stoichiometric amount of **2** was used, both diastereo- and enantioselectivities were excellent, and the reduction gave essentially enantiomerically pure diols (entries 6, 8, and 10).[9] The poor diastereoselectivities observed in the cases with the use of a catalytic amount of **2** may be due to the competing non-diastereoselective reduction of the initially formed hydroxy ketone with BH_3 itself. With these findings in mind we next applied the present procedure to the mono-reduction of 1,3-pentanediols, and the results are shown in Table 2.

As shown in Table 2, reduction in the absence of additives gave the mono-reduction product **4a** with moderate enantiomeric purity in moderate yield. In order to improve both product

Table 2
Mono-reduction of 1,3-cyclopentanedione **1** to β-hydroxy ketone **4**[a]



1a: R^1= Me, R^2 = Bn **1c**: R^1= R^2 = Me
1b: R^1= R^2 = Bn **1d**: R^1= Me, R^2 =Allyl

Entry	**1**	Additive (equiv.)	BH_3–THF (equiv.)	Time (h)	Yield (%)[b]	% ee[c]
1	**1a**	None	1.1	1	58	78
2	**1a**	*N*,*N*-Diethylaniline (0.1)	1.1	19	64	88
3	**1a**	*N*,*N*-Diethylaniline (0.5)	2.0	19	40	86
4	**1a**	*N*-Ethyl-*N*-methylaniline (0.5)	2.0	3	29	84
5	**1a**	*N*,*N*-Diethylaniline (0.5)	2.0	1	70	84
6	**1a**	*N*-Ethyl-*N*-isopropylaniline (0.5)	2.0	1	48	92
7	**1a**	*N*,*N*-Diisopropylaniline (0.5)	2.0	1	44	94
8	**1b**	*N*,*N*-Diethylaniline (2.0)	4.0	19	40	96
9	**1c**	*N*,*N*-Diethylaniline (0.5)	2.0	19	71	88
10	**1d**	*N*,*N*-Diethylaniline (0.75)	3.0	19	63[d]	90

[a] The reaction was carried out according to the typical procedure, see Ref. 12.
[b] Isolated yields. Determination of the absolute configurations of the products, see Ref. 10.
[c] Determined by HPLC using a chiral stationary column (Daicel OD).
[d] No hydroboration at the allyl substituent was observed under the present conditions.

yields and enantiomeric purities, we carried out the reduction under a variety of conditions. Although it was not trivial to stop the reduction at the mono-reduction stage under the typical reduction conditions, the presence of certain amine additives could retard the second reduction.[11] Among the amines screened aniline derivatives were found to be effective.[6] The presence of *N*,*N*-diethylaniline improved the enantiomeric purity of the mono-reduction product up to 88% ee, and *N*,*N*-diisopropylaniline was also effective (entries 2 and 7). In terms of the product yield, the reaction carried out in a short reaction period gave better results, although the enantioselectivity was somewhat lowered (entries 3 and 5). This is due to over-reduction leading to the formation of diols and some other unidentified products. In the presence of *N*,*N*-diethylaniline other 1,3-cyclopentadione derivatives **1b–d** underwent enantioselective mono-reduction to give hydroxy ketones **4b–d** with good enantiomeric purities.[12] In the absence of added amines, the second reduction was relatively fast, giving the diol **3** with good enantiomeric purity and the hydroxy ketone **4** with moderate enantiomeric purity. This is due to the kinetic resolution of the hydroxy ketone **4**, in which the second reduction increases the enantiomeric purity in favor of the diol **3** not of the remaining hydroxy ketone **4**. Therefore, the added amine possesses two roles, the control of enantioselectivity of the first reduction and the suppression of the second one.

In conclusion, the present methodology using asymmetrization of cyclopentan-1,3-diones demonstrates the power of the oxazaborolidine-mediated reduction of symmetrical molecules to give a very useful class of compounds with high enantiomeric excess in a single step. The presence of the added amine makes the selective formation of the mono-reduction product

feasible. Thus, both 1,3-diols and β-hydroxy ketones may be prepared by choosing appropriate reduction conditions.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research on Priority Area from the Ministry of Education, Science, Sports, and Culture of the Japanese Government.

References

1. (a) Pankau, W. M.; Kreiser, W. *Tetrahedron Lett*. **1998**, *39*, 2089–2090. (b) Kreiser, W.; Wiggermann, A.; Kreif, A.; Swinnen, D. *Tetrahedron Lett*. **1996**, *37*, 7119–7122. (c) Breuilles, P.; Uguen, D. *Tetrahedron Lett*. **1988**, *29*, 201–204. (d) Corey, E. J.; Bakshi, R. K.; Shibata. S.; Chen, C. P.; Singh, V. K. *J. Am. Chem. Soc*. **1987**, *109*, 7925–7926. (e) Trost, B. M.; Shimizu, M. *J. Am. Chem. Soc*. **1983**, *105*, 6757–6759, and references cited therein.
2. For reviews, see: (a) Singh, V. K. *Synthesis* **1992**, 605–617. (b) Deloux, L.; Srebnik, M. *Chem. Rev*. **1993**, *93*, 763–784, and references cited therein.
3. (a) Whitesell, J. K. *Chem. Rev*. **1989**, *89*, 1581–1590. (b) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477–511. (c) Harada, T.; Oku, A. *Synlett* **1994**, 95–104, and the references cited therein.
4. Shimizu, M.; Matsukawa, K.; Fujisawa, T. *Bull. Chem. Soc. Jpn*. **1993**, *66*, 2128–2130.
5. Shimizu, M.; Nishigaki, Y.; Wakabayashi, A. *Tetrahedron Lett*. **1999**, *40*, 8873–8876.
6. Quallich, G. J.; Keavey, K. N.; Woodall, T. M. *Tetrahedron Lett*. **1995**, *36*, 4729–4732.
7. (a) Shimizu, M.; Kamei, M.; Fujisawa, T. *Tetrahedron Lett*. **1995**, *36*, 8607–8610. (b) Shimizu, M.; Tsukamoto, K.; Fujisawa, T. *Tetrahedron Lett*. **1997**, *38*, 5193–5196. (c) Shimizu, M.; Tsukamoto, K.; Matsutani, T.; Fujisawa, T. *Tetrahedron* **1998**, *54*, 10265–10274.
8. Absolute configurations of the products were determined by comparison with the authentic samples prepared via baker's yeast reduction of cyclopentan-1,2-diones followed by further reduction with $NaBH_4$ and appropriate functional group transformations. Cf. Brooks, D. W.; Mazdiyasni, H.; Grothaus, P. G. *J. Org. Chem*. **1987**, *52*, 3223–3232.
9. A typical procedure for the reduction of 1,3-diketones into 1,3-diols: A mixture of (2*S*,3*R*)-2-amino-3-(*t*-butyldimethylsiloxy)-1,1-diphenylbutanol (74.2 mg, 0.2 mmol) and methylboronic acid (13.2 mg, 0.22 mmol) in THF (3.0 mL) was heated at 50°C for 5 h in the presence of molecular sieves 4 Å (1.0 g). The resulting mixture was cooled to 0°C and to it was added a solution of **1a** (40.4 mg, 0.2 mmol) in THF (3.0 mL). A solution of $BH_3{\cdot}SMe_2$ complex (0.1 mL, 1.0 mmol) in THF (3.0 mL) was added to the mixture over 3 h at 0°C. After stirring for 13 h at rt, the reaction mixture was quenched by adding 2N HCl, and the repeated extraction with ethyl acetate was followed by usual work-up which gave a crude oil that was purified on preparative TLC (eluent: *n*-Hex/AcOEt = 2/1) to give the diol **3a** as a colorless oil (33.0 mg, 80%).
10. Absolute configurations of the products were determined by comparison with the authentic samples prepared via baker's yeast reduction of cyclopentan-1,2-diones. See Refs. 1a,b and 8.
11. (a) Cai, D.; Tschaen, D.; Shi, Y. J.; Verhoeven, T. R.; Reamer, R. A.; Douglas, A. W. *Tetrahedron Lett*. **1993**, *34*, 3243–3246. (b) Shi, Y. J.; Cai, D.; Dolling, U. H.; Douglas, A. W.; Tschaen, D. M.; Verhoeven, T. R. *Tetrahedron Lett*. **1994**, *35*, 6409–6412. (c) Periosamy, M.; Kanth, J. V. B.; Prasad, A. S. B. *Tetrahedron* **1994**, *50*, 6411–6416. (d) Falorni, M.; Collu, C.; Giacomelli, G. *Tetrahedron*: *Asymm*etry **1996**, *7*, 2739–2742. (e) Saunkhe, A. M.; Burkhardt, E. R. *Tetrahedron Lett*. **1997**, *38*, 1523–1526. (f) Cho, B. T.; Chun. Y. S. *J. Chem. Soc*., *Perkin Trans. 1* **1999**, 2095–2100.
12. A typical procedure for the reduction of 1,3-diketones into β-hydroxy ketones: Compound **2** (R = Me) was prepared as above. The resulting solution of **2** (R = Me) was cooled to 0°C and to it was added a mixture of **1a** (40.4 mg, 0.2 mmol) and *N*,*N*-diethylaniline (1.5 μL, 0.02 mmol) in THF (3.0 mL). A solution of $BH_3{\cdot}THF$ complex (0.22 mL, 0.22 mmol) in THF (0.6 mL) was added to the mixture during 45 min at 0°C. After stirring for 19 h at rt, the reaction mixture was quenched by adding 2N HCl. Usual work-up followed by purification on preparative TLC (eluent: *n*-Hex/AcOEt = 2/1) gave the β-hydroxy ketone **4a** as a colorless oil (25.9 mg, 64%).

.