Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 7, pp. 1147-1150, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $7.00+0.00

0957-4166(94)00150-2

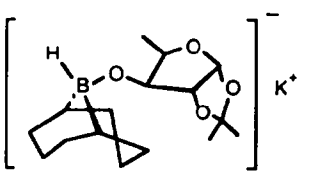
Asymmetric Reduction of α-Keto Acetals with Potassium 9-*O*-(1,2-isopropylidene-5-deoxy-D-xylofuranosyl)-9-boratabicyclo[3.3.1]nonane. Enantioselective Synthesis of α-Hydroxy Acetals with High Optical Purities

Byung Tae Cho* and Yu Sung Chun
Department of Chemisry, Hallym University, Chunchon 200-702, Republic of Korea

Abstract : Asymmetric reduction of α-keto acetals with a chiral borohydride, potassiun 9-*O*-(1,2-isopropylidene-5-deoxy-α-D-xylofuranosyl)-9-boratabicyclo[3.3.1]nonane in THF at -78 ℃ provided the corresponding α-hydroxy acetals with 87 - 99 % ee.

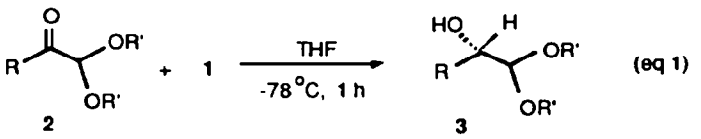
Optically active α-hydroxy aldehydes are useful chiral building blocks for the preparation of natural products such as rhodianose,[1] rocellaric acid,[2] lipoxine A,[3] *endo*-brevicomine,[4] and amino sugars,[5] including ristosamine and daunosamine. These chiral synthons are generally obtained from natural precursors or microbial reduction of α-keto acetals[6] and α-keto thioacetals.[7] One of the most convenient methods for the synthesis of these chiral α-hydroxy aldehydes may be asymmetric reduction of α-keto acetals or α-keto thioacetals. However, to the best of our knowledge, no reports for the asymmetric reduction using chiral hydride reagents are available, although a variety of the hydride reducing agents to give high optical induction for ketones has been reported.[8]

Very recently, we reported the preparation of a chiral borohydride, potassiun 9-*O*-(1,2-isopropylidene-5-deoxy-α-D-xylofuranosyl)-9-boratabicyclo[3.3.1]nonane (1), which showed high enantioselectivity for aromatic and hindered aliphatic ketones.[9] In the course of study on the asymmetric reduction of



K xylide, 1

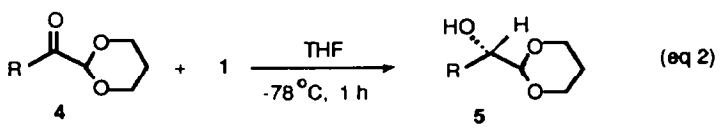
prochiral ketones containing functional groups with this chiral hydride reagent, we discovered that this reagent reduced a α-keto acetal 1-phenyl-2,2-dimethoxyethanone **2e** in THF at -78 °C to the corresponding α-hydroxy acetal **3e** with 92 % ee. Encouraged by this, we decided to investigate the asymmetric reduction of other α-keto acetals using **1** under the same reaction condition. In the reduction of α-keto acetals, it seems reasonable that the degree of optical induction should depend on the steric inequality of the two moieties attached to the carbonyl group. Accordingly, we examined the effects of variations in the steric bulk of both these moieties in a systematic manner. For the R groups in $RCOCH(OMe)_2$, we selected methyl, *n*-butyl, *i*-propyl, *tert*-butyl, phenyl and 2-naphthyl (eq 1). The reductions were carried out at -78 °C in THF with 1.1 equiv of **1**. All the reductions examined were



(eq 1)

a : R = Me, R' = Me ; **b** : R = *n*-Bu, R' = Me ; **c** : R = *i*-Pr, R' = Me ;
d : R = *tert*-Bu, R' = Me ; **e** : R = Ph, R' = Me ; **f** : R = Ph, R' = Et ;
g : R = 2-naphthyl, R' = Me

complete within 1 h to give the corresponding α-hydroxy acetals. Thus, 1,1-dimethoxy-2- propanone (**2a**) underwent rapid reduction (< 40 min) to give (S)-(-)-1,1-dimethoxy-2-propanol (**3a**) with 87 % ee. The optical induction for 1,1-dimethoxy-2-hexanone (**2b**) increased significantly, affording **3b** with 95 % ee. The reduction of even more hindered α-ketoacetals such as 1,1-dimetoxy-3-methyl-2-butanone (**2c**) and 1,1-dimethoxy-3,3-dimethyl-2-butanone (**2d**) provided high optical inductions (90 % ee). Similarly, in the reduction of aromatic α-ketoacetals, high optical yields were obtained, such as 92 % ee for 1-phenyl-2,2-dimethoxyethanone (**2e**), 93 % ee for 1-phenyl-2,2-diethoxyethanone (**2f**) and 92 % ee for 1-(2-naphthyl)-2,2-dimethoxyethanone (**2g**). When the dialkoxy group in $RCOCH(OR)_2$ (**4**, R = Me or Ph)



(eq 2)

a : R = Me ; **b** : R = Ph

was changed from the dimethoxy group to a cyclic alkoxy group, 1,3-propanedioxy moiety, the optical induction increased dramatically to > 99 % ee for 2-acetyl-1,3-dioxane (**4a**) and 96 % ee for 1-benzoyl-1,3-dioxane (**4b**) (eq 2). The stereochemical direction of reduction was constant with all the α-hydroxy acetals (**3** and **5**) obtained being enriched in the S enantiomers.[11] The results are summarized in Table 1. The following procedure is representative. Under a stream of nitrogen, 2.2 mmol of K xylide **1** in

Table 1. Asymmetric Reduction of Representative α- Keto Acetals with **1** in THF at -78 °C.[a]

α-keto acetals	time	optically active α-hydroxy acetals (**3** and **5**)			
		yield(%)[b]	$[\alpha]^{25}_D$	% ee	abs confg.
2a	40 min	70	- 12.15 (*c* 3.21, MeOH)	87[c]	S[i]
2b	1 h	80	- 41.41 (c 1.1, CH_2Cl_2)	95[d]	S[j]
2c	40 min	72	- 10.24 (*c* 2.1 CH_2Cl_2)	90[e]	S[k]
2d	1 h	76	10.16 (*c* 3.2 CH_2Cl_2)	90[d]	l
2e	1 h	81	13.57 (*c* 5.0, $CHCl_3$)	92[f]	S[m]
2f	1 h	80	18.57 (*c* 5.0, $CHCl_3$)	93[f]	S[k]
2g	1 h	87	2.36 (*c* 5.2, $CHCl_3$)	92[g]	S[k]
4a	1 h	72	- 11.40 (*c* 2.1, CH_2Cl_2)	>99[d]	S[k]
4b	1 h	83	3.21 (*c* 5.1, $CHCl_3$)	96[h]	S[k]

[a] [H^-/α-keto acetals] = 1.1 ; [α-keto acetals] = 0.3 M. [b] Isolated yields. [c] By capillary GC analysis of its (-)-menthyl carbonate. [d] By GC analyses using a 20 m Chiraldex GTA capillary column. [e] By GC analysis of its trifluoroacetate using a 20 m Chiraldex GTA capillary column. [f] By HPLC analyses with a Chiralcel OD (Daicel Co.) column using hexane/2-propanol (40/1) as eluent. [g] By HPLC analysis with Chiralcel OT (Daicel Co.) column using hexane/2-propanol (9/1) as eluent. [h] By HPLC analysis with a Chiralcel OD (Daicel Co.) column using hexane/2-propanol (9/1) as eluent. [i] Based on (R)-(+)-1,1-dimethoxy-2-propanol : ref. 10. [j] Based on (S)-(-)-1,1-dimethoxy-2-hexanol : ref. 6. [k] Absolute cofiguration is unknown, but probably S, based on comparison of the order of elution in HPLC or capillary GC analysis and the sign of optical rotation with those of **3a**, **3b** and **3e**. [l] Unknown. [m] Based on S-(-)-1-phenyl-2,2-dimethoxyethanol : ref. 6.

THF (5 ml) was transferred to the flask. The solution was cooled to -78 °C. To this was added 2 mmol of **2e** in THF (1.6 ml) precooled to -78 °C *via* a double-ended needle. After the reaction mixture was stirred at -78 °C for 1 h, the excess hydride was destroyed by the addition of methanol (1 ml) at -78 °C. The volatiles were pumped off at aspirator pressure. The product **3e** was isolated by bulb-to-bulb distillation (bp 132-134 °C/40 mmHg) : 295 mg (81 % yield).[12] The product was further purified by silica gel column chromatography using hexane-ether (1 : 1) as eluent and the optical rotation was measured: $[\alpha]_D^{24}$ 13.57 (*c* 5.0, $CHCl_3$), which revealed (S)-configuration.[6] HPLC analysis with a Chiralcel OD column using hexane/2-propanol (40/1) as eluent showed a composition of 96 %, S and 4 %, R (*i.e.*, 92 % ee).

Acknowledgment. We are grateful to the Organic Chemistry Research Center / KOSEF for financial support.

References and Notes

1. Kelly, T. R.; Kauel, P. L. *J. Org. Chem.* **1983**, *48*, 2775.
2. Mulzer, J.; Salimi, N.; Hartl, H. *Tetrahedron: Asymmetry*, **1993**, *4*, 457.
3. Okamoto, S.; Shimazaki,T.; Kitano, Y.; Kobayashi, Y.; Sato, F. *J. Chem. Soc. Chem. Commun.* **1986**, 1352.
4. Noda, Y.; Kikuchi, M. *Chem. Lett.* **1989**, 1755.
5. (a) Hanessian, S.; Kloss, J. *Tetrahedron Lett.* **1985**, *26*, 1261. (b) Brandänge, B.; Lindvquist, B. *Acta Chem. Scand. B*, **1985**, *39*, 589.
6. Ferraboschi, P.; Santaniello, E.; Tingoli, M.; Aragozzini, F.; Molani, F. *Tetrahedron: Asymmetry*, **1993**, *4*, 1931.
7. (a) Bianchi, D.; Cesti, P.; Golini, P. *Tetrahedron*, **1989**, *45*, 869. (b) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1986**, *27*, 3547.
8. For a review of recent work, see: (a) Singh, V. K. *Synthesis*, **1992**, 605. (b) Midland, M. M. In *Asymmetric Synthesis* ; Morrison, J. D. Ed.; Academic Press: New York 1983; vol. 2, chapt. 2. (c) Grandbois. E. R.; Howard, S. I.; Morrison, J. D. ref. 8b, chap. 3.; (d) Haubenstock, H. *Top. Stereochem.* **1983**, *14*, 231. (e) ApSimon, J. W.; Collier, T. L. *Tetrahedron*, **1986**, *42*, 231. (f) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry*, **1992**, *3*, 1475. For a comparison work, see: (g) Brown, H. C.; Park, W. S.; Cho, B. T.; Ramachandran, P. V. *J. Org. Chem.* **1987**, *52*, 5406.
9. Cho, B. T.; Chun, Y. S. *Tetrahedron: Asymmetry*, **1992**, *3*, 73.
10. Takahashi, H.; Moromoto, T.; Achiwa, K. *Chem. Lett.* 1987, 855.
11. Although absolute configurations of the α-hydroxy acetals (**3** and **5**) obtained with the exception of **3a**, **3b** and **3e** have not been reported, they are assigned to (S) configurations on the basis of comparison of the order of elution in HPLC or capillary GC analyses and the signs of optical rotation with those of the known compounds.
12. For **3e**, IR (neat, cm^{-1}), 3435, 2929, 1493, 1451, 1187, 1121, 1080, 971, 759, 697; ^1H NMR (300 MHz, $CDCl_3$, TMS) δ 2.64-2.65 (br s, 1 H, O<u>H</u>), 3.28 (s, 3 H, OC<u>H</u>$_3$), 3.48 (s, 3 H, OC<u>H</u>$_3$), 4.30 [d, 1 H, J = 6.4 Hz, C<u>H</u>(OMe)$_2$], 4.62 (d, J = 6.3 Hz, C<u>H</u>OH), 7.27-7.44 (m, 5 H, aromatic H); ^{13}C NMR (75.46 MHz, $CDCl_3$, TMS) δ 140.0, 128.4, 127.8 and 127.6 (aromatic-C), 108.1 [<u>C</u>H(OMe)$_2$], 74.3 (<u>C</u>HOH), 58.2 and 57.6 (O<u>C</u>H$_3$); Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91 ; H, 7.75. Found : C, 65.80 ; H, 7.94.

(*Received in Japan* 6 *April* 1994; *accepted* 6 *May* 1994)