JOC*Note*

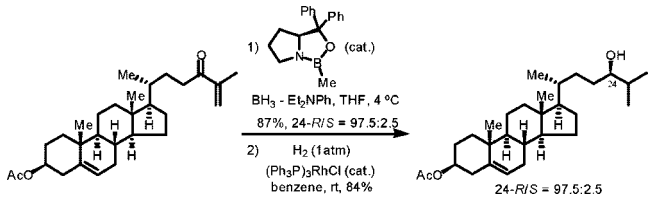
Oxazaborolidine-Catalyzed Enantioselective Reduction of α-Methylene Ketones to Allylic Alcohols

Jun-ichi Matsuo,* Takaaki Kozai, Osamu Nishikawa, Yu Hattori, and Hiroyuki Ishibashi*

Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma machi, Kanazawa 920-1192, Japan

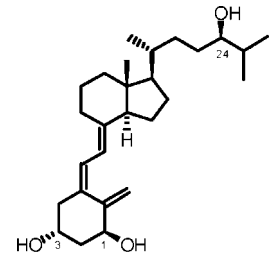
jimatsuo@p.kanazawa-u.ac.jp

Received May 20, 2008



Oxazaborolidine-catalyzed enantioselective reduction of α-methylene ketones was efficiently carried out by using borane−diethylaniline as a stoichiometric reducing agent. The combination of this method and subsequent hydrogenation of thus-formed allylic alcohol improved stereoselectivity in the reduction of 24-oxocholesteryl ester to 24-(*R*)-hydroxycholesteryl ester.

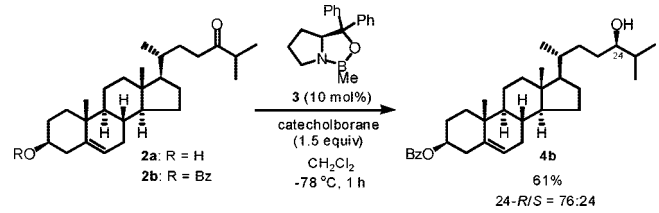
Tacalcitol (1α,24-(*R*)-dihydroxycholecalciferol, **1**) is a pharmacologically active vitamin D_3 analogue (Figure 1).[1,2] We have been studying efficient synthesis of **1** from 24-oxocholesterol (**2a**),[3] and reduction of the 24-keto group of **2a** with high facial selectivity is a difficult issue that remains to be solved. The difficulty was exemplified by reduction of 24-oxocholesteryl benzoate (**2b**) with sodium borohydride, which gave the corresponding alcohol **4b** as a mixture of equal amounts of 24-(*R*) and 24-(*S*)-isomers. Even oxazaborolidine **3**-catalyzed reduction[4,5] of **2b** with catecholborane gave alcohol **4b** in 61% yield with moderate selectivity (24-*R*/*S* = 76:24, Scheme 1)



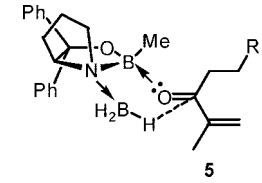
1

FIGURE 1. Tacalcitol (1α,24-(*R*)-dihydroxycholecalciferol).

SCHEME 1. Reduction of 24-Oxochoresterol Derivative



because the sizes of the aliphatic alkyl groups on the 24-keto group were not sufficiently differentiated. Stereoselective reduction of such ketones has been left as an important problem, and some indirect methods have been reported. For example, DeNinno reported a method involving oxazaborolidine-catalyzed reduction of acyl dithianes and reductive removal of the dithiane group.[6] Cho reported **3**-catalyzed reduction of *p*-tolylthiomethyl ketones followed by oxidation to sulfoxide, alkylation, and reductive removal of the sulfinyl group.[7] Crich reported **3**-catalyzed reduction of α,α-disubstituted α-nitroketones followed by removal of the nitro group using AIBN and Bu_3SnH.[8]



5

FIGURE 2. Ternary complex of oxazaborolidine **3**, borane, and α-methylene ketone **5**.

We considered that enone **5** would be a more suitable substrate for oxazaborolidine **3**-catalyzed reduction since lone pair electrons that were anti to the C−C double bond would selectively coordinate to boron (Figure 2)[9] and thus-formed allylic alcohol would be easily hydrogenated to a saturated one. However, there has been only one example of oxazaborolidine-

(1) Review: Nishikawa, O. *Medchem News* **1994**, *4*, 85–90.

(2) (a) Matsui, T.; Nakao, Y.; Kobayashi, N.; Kishihara, M.; Ishizuka, S.; Watanabe, S.; Fujita, T *Int. J. Cancer* **1984**, *33*, 193–202. (b) Matsunaga, T.; Yamamoto, M.; Ohta, T.; Kiyoki, M.; Ohba, T.; Naruchi, T.; Hosoi, J.; Kuroki, T. *J. Dermatol.* **1990**, *17*, 135–142.

(3) (a) Morisaki, M.; Koizumi, N.; Ikekawa, N.; Takeshita, T.; Ishimoto, S. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1421–1424. (b) Nishikawa, O.; Ishimaru, K.; Takeshita, T.; Tsuruta, H. U.S. Patent 4,298,537, 1981. (c) Nishikawa, O.; Ishimaru, K.; Takeshita, T.; Ysuruta, H. U.S. Patent 4,388,243, 1983. (d) Okamoto, M.; Tabe, M.; Fujii, T.; Tanaka, T. *Tetrahedron: Asymmetry* **1995**, *6*, 767–778.

(4) Review: (a) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012. (b) Itsuno, S. *Org. React.* **1998**, *52*, 395–576. (c) Itsuno, S. In *Comprehensive Asymmetric Catalysts*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 3, pp 289−315. (d) Wallbaum, S.; Martens, J. *Tetrahedron: Asymmetry* **1992**, *3*, 1475–1504. (e) Cho, B. T. *Tetrahedron* **2006**, *62*, 7621–7643.

(5) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926.

(6) DeNinno, M. P.; Perner, R. J.; Lijewski, L. *Tetrahedron Lett.* **1990**, *31*, 7415–7418.

(7) (a) Cho, B. T.; Kim, D. J. *Tetrahedron* **2003**, *59*, 2457–2462. (b) Cho, B. T.; Choi, O. K.; Kim, D. J. *Tetrahedron: Asymmetry* **2002**, *13*, 697–703.

(8) Crich, D.; Ranganathan, K.; Rumthao, S.; Shirai, M. *J. Org. Chem.* **2003**, *68*, 2034–2037.

(9) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153–9156.

10.1021/jo8011013 CCC: $40.75
Published on Web 08/07/2008

SCHEME 2. Oxazaborolidine 7-Catalyzed Reduction of α-Methylene Ketone 6

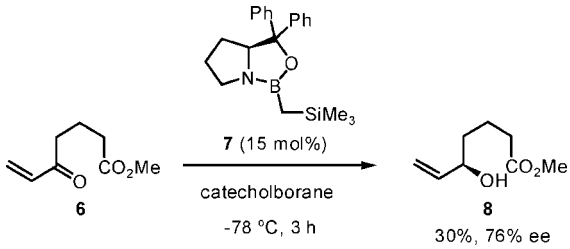
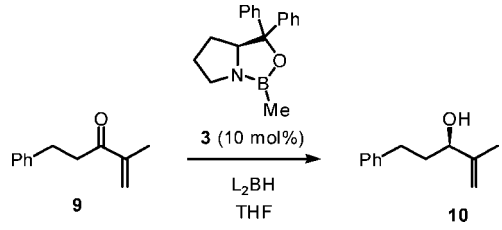


TABLE 1. Effect of Reducing Agents



entry	L_2BH (equiv)	conditions[a]	yield (%)	% ee
1	BH_3−THF (1.0)	4 °C, 10 min	19	63
2	BH_3−Me_2S (1.0)	4 °C, 5 min	29	83
3	BH_3−Et_2NPh (1.0)	4 °C, 2 h	75 (88)[b]	92 (94)[b]
4[c]	catecholborane (1.5)	−78 °C, 3.5 h	90	86

[a] After the slow addition (1.5 h) of **9**. [b] The catalyst **3** (25 mol %) was employed. Conditions: 4 °C for 5 min. [c] Dichloromethane was used as solvent.

catalyzed α-methylene ketones:[10] Corey reported that vinyl ketone **6** was reduced by oxazaborolidine **7**-catalyzed reduction to afford **8** in a low yield (30%) with moderate enantioselectivity (76% ee, Scheme 2). They introduced an Me_3Si or *n*-Bu_3Sn group at the *β*-position of α,*β*-unsaturated ketone **6** for size-differentiation and inhibition of side reactions.[11] We report here an efficient method for enantioselective reduction of α-methylene ketones by oxazaborolidine catalysis with borane−diethylaniline.

Prior to the preparation of 24-(*R*)-hydroxycholesterol, suitable reaction conditions were explored for the reduction of α-methylene ketone **9** using 10 mol % of oxazaborolidine catalyst **3**[11] (Table 1). First, various borane complexes, including borane−THF, borane−Me_2S,[12] borane−diethylaniline,[13] and catecholborane, were employed. It was found that reduction with the relatively reactive reducing agents, borane−THF and borane−Me_2S, gave **10** in 19% and 29% yields, respectively (entries 1 and 2), while the reaction with the mild reducing agents, borane−diethylaniline and catecholborane, gave **10** in 75% and 90% yields, respectively (entries 3 and 4). Milder reducing agents gave allyl alcohol **10** in better chemical yields because they minimized side reactions.[14] It was noted that

TABLE 2. Effect of Amines[a]

entry	ligand	reaction time (h)	yield (%)	% ee
1	$^iPr_2NPh$	5	22	92
2	$^iPrEtNPh$	2	46	88
3	Et_2NPh	1	71	91
4	Me_2NPh	4	22	85
5	2,6-lutidine	2	0	

[a] Enantioselective reduction of **9** to **10** by using **3** (10 mol %) and BH_3−amine complex (1 equiv) in THF at 4 °C.

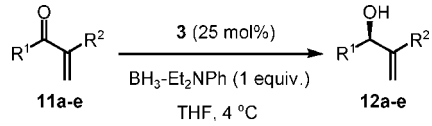
borane−diethylaniline showed better enantioselectivity (92% ee) and the use of 25 mol % of the catalyst **3** gave **10** in 88% yield with 94% ee (entry 3). The increased amount of the catalyst **3** contributed to shortening of the reaction time: the use of 10 mol % of **3** required a long reaction time (2 h), whereas the reduction was completed within 5 min when 25 mol % of **3** was employed. Lowering the reaction temperature did not improve the enantioselectivity (−10 °C: 61% yield, 92% ee; −20 °C: 10% yield, 51% ee). The absolute configuration of **10** was determined by comparison with the reported sign of optical rotation.[15] In Corey's transition state model,[4a] as expected, the isopropenyl group adopts the position anti to lone pair electrons which coordinate to boron (Figure 2). When solvents other than THF were employed in **3**-catalyzed reduction of **9** with borane−diethylaniline, neither better chemical yields nor better enantioselectivities were observed in toluene (31%, 62% ee), CH_2Cl_2 (22%, 51% ee), ^{t}BuOMe (57%, 74% ee), Et_2O (75%, 84% ee), dimethoxyethane (69%, 80% ee), CH_3CN (trace), and $EtNO_2$ (trace).

In order to investigate the effect of amines[16] that coordinated to borane, various borane−amine complexes[17] were prepared by mixing 1.2 equiv of borane−Me_2S[18] and 1 equiv of amine in THF at room temperature for 1 h followed by removal of excess borane−Me_2S in vacuo. The **3**-catalyzed reduction of **9** with BH_3−diethylaniline complex prepared by this method gave results similar to those obtained with commercially available borane−diethylaniline[13] (Table 2, entry 3 vs Table 1, entry 3). Investigation of the effects of *N*-substituents of *N*,*N*-substituted anilines revealed that there was no notable influence on enantioselectivity, whereas chemical yield of **10** was influenced by the amine ligands (entries 1−4). The use of dimethylaniline and 2,6-lutidine gave **10** in low yields because they coordinated to borane more strongly than did diethylaniline and their complexes reduced **9** more slowly than did borane−diethylaniline.

Scope and limitations of the present method were surveyed by using 25 mol % of catalyst **3** and commercially available borane−diethylaniline[13] (Table 3). Various alkyl isopropenyl ketones **11a**−**d** were reduced by the present method to give the corresponding allylic alcohols **12a**−**d** in good yields with around 90% ee's (entries 1−4). Alkyl vinyl ketone **11e** was reduced by the present method in 81% yield with 70% ee (entry 5). The absolute configuration of **12e** was determined by hydrogenation of **12e** to 1-phenylpentan-3-ol (H_2, Pd/C, EtOH) and by comparison with the reported sign of optical rotation.[19]

(10) Corey, E. J.; Guzman-Perez, A.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1997**, *119*, 11769–11776.
(11) A solution of **3** in toluene was prepared by the reported procedure, see: Xavier, L. C.; Mohan, J. J.; Mathre, D. J.; Thompson, A. S.; Carroll, J. D.; Corley, E. G.; Desmond, R. *Org. Synth.* **1997**, *74*, 50.
(12) Mincione, E. *J. Org. Chem.* **1978**, *43*, 1829–1830.
(13) Purchased from Aldrich. For employment of borane−diethylaniline in oxazaborolidine-catalyzed reduction, see: (a) Periasamy, M.; Kanth, J. V. B.; Prasad, A.S. B. *Tetrahedron* **1994**, *50*, 6411–6416. (b) Salunkhe, A. M.; Burkhardt, E. R. *Tetrahedron Lett.* **1997**, *38*, 1523–1526.
(14) It is known that BH_3−THF complex reduces α,*β*-unsaturated carbonyl compounds with a formation of saturated carbinols. (a) Klein, J.; Dunkelblum, E *Tetrahedron Lett.* **1966**, *604*, 7–6049. (b) Klein, J.; Dunkelblum, E. *Tetrahedron* **1968**, *24*, 5701–5710. (c) Dunkelblum, E.; Levene, R.; Klein, J. *Tetrahedron* **1972**, *28*, 1009–1024.
(15) Shibata, T.; Nakatsuki, K.; Soai, K. *Inorg. Chim. Acta* **1999**, *296*, 33–36.
(16) (a) Cai, D.; Tschaen, D.; Shi, Y.-J.; Verhoeven, T. R.; Reamer, R. A.; Douglas, A. W. *Tetrahedron Lett.* **1993**, *34*, 3243–3246. (b) Falorni, M.; Collu, C.; Giacomelli, G. *Tetrahedron: Asymmetry* **1996**, *7*, 2739–2742. (c) Yeung, Y.-Y.; Chein, R.-J.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 10346–10347.
(17) Brown, H. C.; Murray, L. T. *Inorg. Chem.* **1984**, *23*, 2746–2753.
(18) The use of borane−THF complex did not give a satisfactory result.
(19) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. J. *Am. Chem. Soc.* **1986**, *108*, 6071–6072.

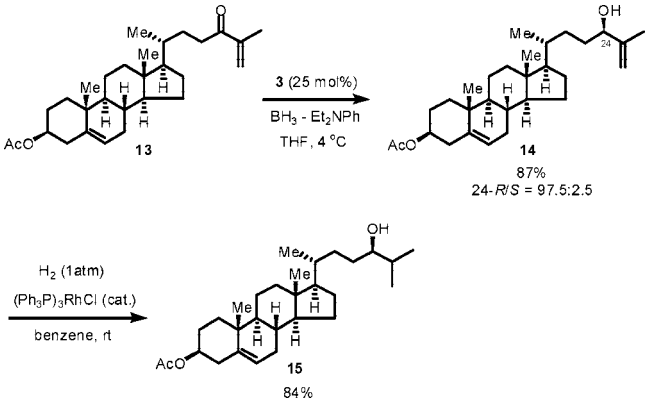
TABLE 3. Oxazaborolidine 3-Catalyzed Enantioselective Reduction of Various α-Methylene Ketones 11a−e to Allylic Alcohols 12a−e with Borane−Diethylaniline



entry	11	R^1	R^2	12	yield (%)	% ee
1	**11a**	$Ph(CH_2)_3$	Me	**12a**	83	90
2	**11b**	$CH_3(CH_2)_6$	Me	**12b**	82	92
3	**11c**	*c*-$HexCH_2$	Me	**12c**	82	87[a]
4	**11d**	*c*-$Hex(CH_2)_2$	Me	**12d**	85	95[b]
5	**11e**	$Ph(CH_2)_2$	H	**12e**	81	70

[a] ee was determined by HPLC after derivatization to *p*-methoxybenzoate. [b] ee was determined by HPLC after derivatization to benzoate.

SCHEME 3. Stereoselective Synthesis of 15 from 13



It was then found that the absolute configuration of **12e** was *R* and even the vinyl group tended to adopt the same position as the 2-propenyl group in the transition state as shown in Figure 2.

Oxazaborolidine **3**-catalyzed reduction of **13** under optimized reaction conditions gave allylic alcohol **14** in 87% yield with high facial selectivity (24-*R*/*S* = 97.5:2.5) (Scheme 3).[20] Stereoselective synthesis of 24-(*R*)-hydroxycholesteryl acetate **15** was accomplished by regioselective hydrogenation of the *exo*-methylene group of **14** by using H_2 and Wilkinson's catalyst (84% yield).

Thus, highly enantioselective reduction of 2-propenyl ketones to the corresponding allylic alcohols was efficiently carried out by oxazaborolidine **3**-catalyzed reduction with borane−diethylaniline in THF. It was found that diethylaniline made the reactivity of borane suitable for reduction of α-methylene ketones. The present method will be useful for oxazaborolidine-catalyzed reduction of α-methylene ketones because the introduction and removal of trimehylsilyl or tributylstannyl group at the β-position of enones are not required. The combination of the present procedure and hydrogenation of the C−C double bond is an effective method for preparing chiral secondary alcohols in high enantiomeric purity compared with reduction of aliphatic isopropyl ketones.

Experimental Section

General Procedure for Oxazaborolidine 3-Catalyzed Enantioselective Reduction of α-Methylene Ketones with Borane−Diethylaniline. To a stirred solution of **3** (0.5 M in toluene,[11] 0.29 mL, 0.145 mmol) in THF (2 mL) was added BH_3-Et_2NPh (0.1 mL, 0.576 mmol) at 4 °C (ice−water), and the solution was stirred for 30 min at 4 °C. A solution of **9** (101.4 mg, 0.581 mmol) in THF (5 mL) was then added through a cannula for 1.5 h at 4 °C, and complete disappearance of **9** was confirmed by TLC analysis (it took 5 min at 4 °C). The reaction was quenched with 1 N hydrochloric acid, and the mixture was extracted with ethyl acetate (three times). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified with preparative TLC (hexane/ethyl acetate = 7:1) to afford **10**[21] (90.3 mg, 88%) as a colorless oil. The enantiomeric excess (94% ee) was determined by HPLC analysis using a chiral column (Daicel Chiralpak AS-H 46 × 150 mm, 254 nm UV detector, room temperature, eluent: hexane/*i*-PrOH = 20:1, flow rate: 0.5 mL/min, retention time (min) 8.1 (*S* isomer), 8.6 (*R* isomer)): $[\alpha]^{23}_D = +26.2$ (*c* 1.20, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 1.51 (1H, brs), 1.75 (3H, s), 1.83−1.91 (2H, m), 2.58−2.76 (2H, m), 4.04−4.14 (1H, m), 4.87−4.88 (1H, m), 4.96−4.97 (1H, m), 7.16−7.31 (5H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.6, 31.9, 36.5, 75.2, 111.2, 125.8, 128.4, 128.4, 142.0, 147.4.

Acknowledgment. The authors are grateful for the financial support from Takeda Science Foundation and a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

Supporting Information Available: Experimental procedures and full characterization of data for all new compounds; ^1H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8011013

(20) For asymmetric reduction of a compound similar to **13** with (*R*)-(+)-binaphthol−$LiAlH_4$, see: Ishiguro, M.; Koizumi, N.; Yasuda, M.; Ikekawa, N. *J. Chem. Soc. Chem. Commun.* **1981**, 115–117.

(21) Bonnert, R. V.; Jenkins, P. R. *J. Chem. Soc., Perkin Trans. 1* **1989**, 413–418.