JOC Article

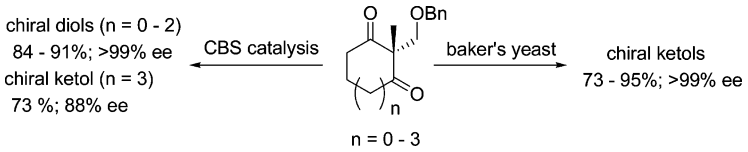
Preparation of New Chiral Building Blocks: Highly Enantioselective Reduction of Prochiral 1,3-Cycloalkanediones Possessing a Methyl Group and a Protected Hydroxymethyl Group at Their C2 Position with Baker's Yeast or CBS Catalyst

Hideaki Watanabe, Mitsuhiro Iwamoto, and Masahisa Nakada*

Department of Chemistry, School of Science and Engineering, Waseda University, 3-4-1, Ohkubo, Shinjuku, Tokyo 169-8555, Japan

mnakada@waseda.jp

Received February 24, 2005



Highly enantioselective reduction of five-, six-, seven-, and eight-membered prochiral 1,3-cycloalkanediones possessing a methyl group and a protected hydroxymethyl group at their C2 position with baker's yeast or CBS catalyst and a new efficient and general method for preparing the 1,3-cycloalkanediones have been developed. These baker's yeast mediated reductions were found to produce corresponding ketols with high optical purity (>99% ee) and high yield. All of the prepared ketols and their derivatives, chiral building blocks, have been fully characterized, and their absolute configurations have been determined. These compounds would be useful for the convergent synthesis of complex natural products.

Introduction

In the total synthesis of natural products, especially terpenoids, construction of a stereogenic quaternary carbon is often troublesome. One solution to avoid such trouble is to use the chiral building blocks suitable for the total synthesis of the target molecule; however, such chiral building blocks are often hardly derived from readily available compounds or natural products. Hence, preparation of new chiral building blocks possessing a stereogenic carbon via asymmetric reactions is very important for the enantioselective total synthesis of natural products.[1]

Since some enzyme-mediated reactions are readily carried out, produce chiral compounds easily, and are environmentally benign, preparation of chiral building blocks with a biocatalyst has been extensively studied and applied to asymmetric natural product synthesis.[2]

Baker's yeast is widely utilized because of its availability, easy handling, and broad substrate allowance. Actually, many chiral building blocks have been prepared with baker's yeast;[3] however, some chiral building blocks useful for natural product synthesis have been left unprepared because preparation methods of their substrates have never been developed.

We have reported highly enantioselective reduction of 2-benzyloxymethyl-2-methyl-1, 3-cyclohexanedione **1** with baker's yeast to produce **2** (yield 64%, >99% ee, Scheme 1).[4] This new chiral building block has been utilized in our synthetic studies on Taxol[5a] and convergent asym-

* To whom correspondence should be addressed. Phone and Fax: +813-5286-3240.

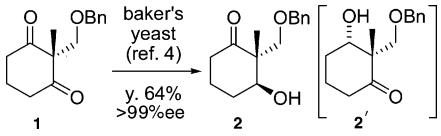
(1) We have also prepared the versatile chiral building blocks via the catalytic asymmetric intramolecular cyclopropanation. See: (a) Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 2860−2861. (b) Honma, M.; Nakada, M. *Tetrahedron Lett.* **2003**, *44*, 9007−9011.

(2) For reviews of biocatalysis, see: (a) Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Msnzocchi, A. *Chem. Rev.* **1992**, *92*, 1071−1140. (b) Robert, S. M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 157−169. (c) Robert, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1−21. (d) Robert, S. M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 611−633. (e) Robert, S. M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1475−1499. (f) Powell, K. A.; Ramer, S. W.; del Cardayré, S. B.; Stemmer, W. P. C.; Tobin, M. B.; Longchamp, P. F.; Huisman, G. W. *Angew. Chem., Int. Ed.* **2001**, *40*, 3949−3959. (g) Nakamura, K.; Yamanaka, R.; Matsuda, T.; Harada, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2659−2681.

(3) For reviews of baker's yeast, see: (a) Servi, S. *Synthesis* **1990**, 1−25. (b) Cusk, R.; Glänzer, B. I. *Chem. Rev.* **1991**, *91*, 49−97. (c) Hoegberg, H.-E.; Berglund, P.; Edlund, H.; Faegerhag, J.; Hedenstroem, E.; Lundh, M.; Nordin, O.; Servi, S.; Voerde, C. *Catal. Today* **1994**, *22* (3), 591−606. (d) Mochizuki, N.; Hiramatsu, S.; Sugai, T.; Ohta, H.; Morita, H.; Itokawa, H. *Biosci. Biotechnol. Biochem.* **1995**, *59* (12), 2282−2291. (e) Bertau, M.; Burli, M. *Chimia* **2000**, *54* (9), 503−507. Recently, Sugai and co-workers reported a new and efficient strategy to prepare new chiral building blocks; see: (f) Fuhshuku, K.; Tomita, M.; Sugai, T. *Tetrahedron Lett.* **2004**, *45*, 1763−1767.

10.1021/jo050349a CCC: $30.25
Published on Web 05/10/2005

SCHEME 1. Baker's Yeast Mediated Reduction of 1



metric total synthesis of allocyatin B_2;[5b] however, five-, seven-, and eight-membered carbocyclic congeners have not been prepared.

Since many terpenoids have a polycyclic ring system in their molecules as shown in Figure 1, chiral building

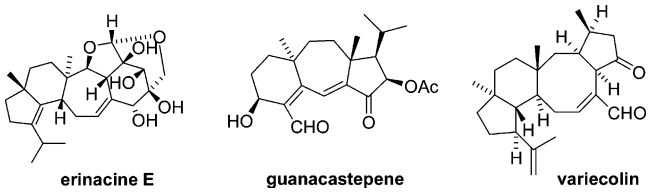


FIGURE 1. Polycyclic terpenoids possessing a stereogenic quaternary carbon.

blocks convertible into their fragments would be beneficial to their syntheses when they could be prepared.

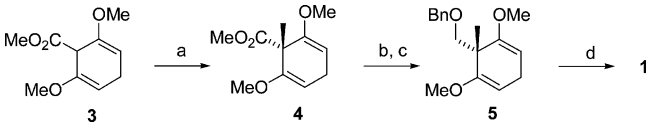
Systematic studies on the baker's yeast mediated reduction of prochiral 2,2-disubstituted-1,3-cycloalkanediones have been reported by Brooks;[6a,b] however, no results have been reported for substrates with two one-carbon units at the C2 position. One reason for this situation is that such substrates are hard to prepare; actually, enolates of prochiral 1,3-cycloalkanediones possessing a substituent at their C2 position are easily *O*-alkylated even with ethyl iodide.[7]

Although the baker's yeast mediated reduction of prochiral 2,2-disubstituted-1,3-cycloalkanediones produces a mixture of diastereomeric products in most cases, the products are obtained with very high optical purity and yield.[6] Hence, the baker's yeast mediated reduction of prochiral 2,2-disubstituted-1,3-cycloalkanediones with two one-carbon-units at its C2 position was surmised to be a powerful protocol for preparing the chiral building blocks when the diastereoselectivity is improved.

We have found that the baker's yeast mediated reduction of **1** affords a single product with exceptionally high diastereo- and enantioselectivity,[4] so we decided to investigate further the scope and generality of the baker's yeast mediated reduction of the congeners of **1**, possessing different ring sizes.

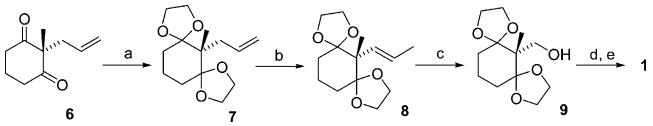
We report herein highly enantioselective reduction of prochiral 1,3-cycloalkanediones with two one-carbon-units, a methyl group, and a protected hydroxymethyl group at their C2 position, with baker's yeast or CBS catalyst, and a new effective and general preparation of the prochiral 1,3-cycloalkanediones.

SCHEME 2. Preparation of 1[a]



[a] Reagents and conditions: (a) LDA, HMPA, THF, −78 °C, 10 min, then MeI, −78 to 0 °C, 1 h, 96%; (b) DIBAL-H, CH_2Cl_2, −78 °C, 15 min, 96%; (c) BnBr, NaH, TBAI, THF, DMF, 10 h, 89%; (d) 2 N HCl, THF, 15 min, 95%.

SCHEME 3. New Preparation of 1[a]



[a] Reagents and conditions: (a) cat. *p*-TsOH, $HOCH_2CH_2OH$, $CH(OEt)_3$, CH_2Cl_2, reflux; (b) cat. $PdCl_2(CH_3CN)_2$, benzene, reflux; (c) O_3, MeOH, −78 °C; $NaBH_4$, rt; (d) NaH, BnBr, TBAI, THF/DMF (10:1), rt; (e) THF/2N HCl (2:1), reflux, 64% (five steps).

Results and Discussion

A New Preparation of 2-Benzyloxymethyl-2-methyl-1,3-cyclohexanedione and Its Improved Enantioselective Reduction with Baker's Yeast. A preparation of **1** reported previously[4] is shown in Scheme 2. Compound **3** was prepared by Birch reduction of 2,6-dimethoxybenzoic acid and subsequent methyl ester formation.[8] Then, **3** was methylated by MeI and LDA to afford **4** (96%), followed by reduction with DIBAL-H (96%) and benzylation (89%) to produce **5**. Finally, acid-catalyzed hydrolysis of the alkenyl ethers of **5** successfully afforded the desired 1,3-diketone **1** (95%).

This method is applicable only for the synthesis of **1** because other 2,2-disubstituted 1,3-cycloalkanediones cannot be prepared via Birch reduction. Accordingly, we started to develop a new general method for preparing **1**, which is applicable to the preparation of other prochiral 1,3-cycloalkanediones possessing a methyl group and a protected hydroxymethyl group at their C2 position.

Initial attempts to introduce a protected hydroxymethyl group to the C2 position of 2-methyl-1,3-cyclohexanedione byalkylation proved fruitless because the *O*-alkylated product formed exclusively. Hence, synthesis of **1** was started from known compound **6** (Scheme 3). Thus, **6**[6b,9] was protected as bis-ketal **7**, and the double bond in **7** was successfully isomerized with the palladium catalyst to afford thermodynamically more stable **8** as a single isomer.[10] Then, ozonolysis of **8**, and the following reductive workup with $NaBH_4$, benzylation of the resulted alcohol **9**, and removal of the ketals under acidic conditions gave **1** (64%, five steps). Since purification by silica gel chromatography was unnecessary during this

(4) Iwamoto, M.; Kawada, H.; Tanaka, T.; Nakada, M. *Tetrahedron Lett.* **2003**, *44*, 7239−7243. Our recent investigation improved the yield of the product **2** to 90%.

(5) (a) Kawada, H.; Iwamoto, M.; Utsugi, M.; Miyano, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 4491−4494. (b) Takano, M.; Umino, A.; Nakada, M. *Org. Lett.* **2004**, *6*, 4897−4900.

(6) (a) Brooks, D. W.; Mazdiyasni, H.; Sally, P. *J. Org. Chem.* **1985**, *50*, 3411−3414. (b) Brooks, D. W.; Mazdiyasni, H.; Grothaus, P. G. *J. Org. Chem.* **1987**, *52*, 3223−3232. For extensive studies on the prochiral 2,2-disubstituted-1,3-cyclohexanediones, see: (c) Fuhshuku, K.-I.; Funa, N.; Akeboshi, T.; Ohta, H.; Hosomi, H.; Ohba, S.; Sugai, T. *J. Org. Chem.* **2000**, *65*, 129−135. (d) Wei, Z.-L.; Li, Z.-Y.; Lin, G.-Q. *Synthesis* **2000**, 1673−1676.

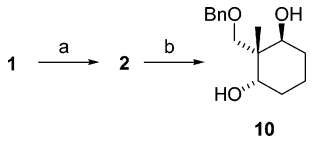
(7) Mori, K.; Fujiwara, M. *Tetrahedron* **1988**, *44*, 343−354.

(8) Tamai, Y.; Mizutani, Y.; Hagiwara, H.; Uda, H.; Harada, N. *J. Chem. Res., Synop.* **1985**, 148−149.

(9) Newman, M. S.; Manhart, J. H. *J. Org. Chem.* **1985**, *50*, 2113−2114.

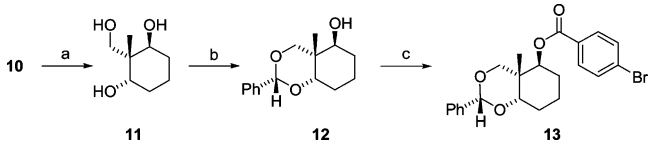
(10) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673−1675.

SCHEME 4. Conversion of 1 to 10[a]



[a] Reagents and conditions: (a) baker's yeast, 91% (93% conversion), >99% ee; see the Supporting Information for the conditions; (b) $Me_4NBH(OAc)_3$, AcOH, DMF, rt, 4 d, 83%.

SCHEME 5. Preparation of Crystalline 13[a]



[a] Reagents and conditions: (a) H_2, Raney-Ni, MeOH, rt, 10 h, quant; (b) PhCHO, cat. CSA, CH_2Cl_2, reflux, 10 h, 98%; (c) *p*-BrBzCl, DMAP, CH_2Cl_2, rt, 10 h, 89%.

synthesis except for the last step, this preparation method is suitable for a large-scale preparation.

We found that the baker's yeast reduction of **1** in the presence of yeast extract improved the yield. Thus, **1** (140.0 mg, 0.57 mmol) was stirred with baker's yeast (1.0 g, Oriental), 0.2% Triton X-100 in ethanol (0.3 mL), sucrose (2.25 g), and yeast extract (0.1 g) in water (30 mL) at 30 °C. After 48 h, the reaction mixture was worked up, and the crude product was purified by silica gel chromatography to afford **2** (119.5 mg, 91% (93% conversion), >99% ee). Although the reason has not been clarified, addition of yeast extract certainly increased yield of the baker's yeast reduction of **1** because the baker's yeast reduction without yeast extract afforded **2** in 64% yield. Interestingly, no other product was obtained in this reaction.

Product **2** was converted to some crystalline derivatives; however, any crystals suitable for X-ray crystallographic analysis were not prepared. Hence, the structure elucidation of **2** required several steps conversion and the X-ray crystallographic analysis as described below.

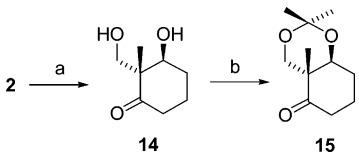
Reduction of ketone **2** with $Me_4NBH(OAc)_3$[11] afforded **10** exclusively (83%, >99% de) (Scheme 4), and the optical purity of **10** (>99% ee) was determined by HPLC of its bis-3,5-dinitrobenzoate. This result indicates that the baker's yeast reduction of **1** proceeds with high enantioselectivity (>99% ee).

As shown in Scheme 5, hydrogenolysis of **10** quantitatively afforded triol **11**, and formation of benzylidene acetal produced **12** as a sole product (98%). Benzylidene acetal **12** was transformed to crystalline *p*-bromobenzoate **13** (89%), and its whole structure was successfully determined by X-ray crystallographic analysis.[12] The X-ray crystal structure clearly shows that relative configuration of the two hydroxy groups is *anti*. Furthermore, **12** has a *cis*-fused bicyclic ring structure, suggesting that the benzylidene acetal formed in a kinetically controlled manner.

(11) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

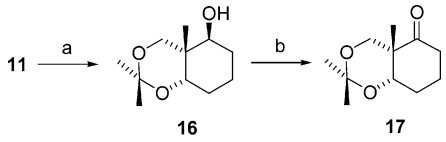
(12) See the Supporting Information.

SCHEME 6. Preparation of Acetonide 15[a]



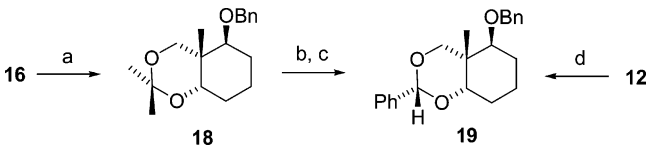
[a] Reagents and conditions: (a) H_2, Pd/C, MeOH, rt, 5 h, quant; (b) acetone, cat. CSA, rt, 3 h, 65%.

SCHEME 7. Preparation of Acetonide 17[a]



[a] Reagents and conditions: (a) acetone, cat. CSA, rt, 2 h, 94%; (b) Dess−Martin periodinane, CH_2Cl_2, rt, 1 h, 99%.

SCHEME 8. Preparation of Benzylidene Acetal 19[a]



[a] Reagents and conditions: (a) BnBr, NaH, TBAI, THF, DMF, 36 h, 99%; (b) *p*-TsOH, MeOH, 60 °C, 6 h, 92%; (c) PhCHO, cat. CSA, CH_2Cl_2, reflux, 10 h, quant; (d) BnBr, NaH, TBAI, THF, DMF, 15 h, 69%.

Although the (1*S*,3*S*)-configuration of **10** was expected on the basis of Prelog's rule,[13] the absolute configuration of **10** was unambiguously confirmed as described above. However, the structure of **2** was still undetermined because the possibility that the diol **10** had been obtained from **2′** (Scheme 1) remained.[14]

Preparation of a crystalline derivative of **2** for X-ray crystallographic analysis failed as mentioned above. Furthermore, we were not able to elucidate the structure of **2** by a comparison of NMR data between **2** and **2′** as well as their NOE and NOESY experiments. Hence, the structure of **2** was determined by comparing the derivative of **2** with the derivative of triol **11** because the structure of **11** had been elucidated.

As shown in Scheme 6, hydrogenolysis of **2** afforded diol **14** (quant), and the reaction of **14** with acetone under acidic condition gave acetonide **15** (65%). On the other hand, **11** was transformed to acetonide **16** (94%) (Scheme 7), followed by Dess−Martin oxidation[15] to generate ketone **17** (99%). The structure of **17** was proved to be different from that of **15** via spectroscopic analysis.

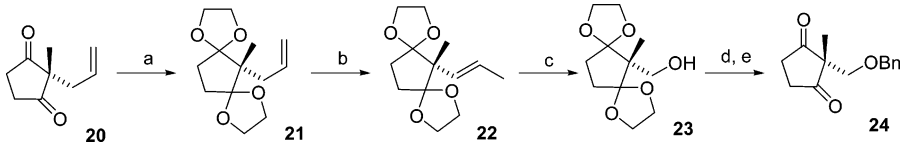
Then, as shown in Scheme 8, **16** was converted to benzyl ether **18** (99%), followed by removal of acetonide (92%), and subsequent benzylidene formation gave **19** (quant) as a sole product. The ^1H NMR, ^{13}C NMR, IR, $[\alpha]_D$, and mass spectral data of **19** are the same as those

(13) Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119−130.

(14) A yeast strain showing an opposite enantiotopic group selectivity toward similar cyclic diketones has been reported. See: Fuhshuku, K.; Tomita, M.; Sugai, T. *Adv. Synth. Catal.* **2003**, *345*, 766−774.

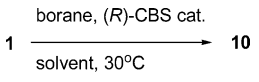
(15) (a) Dess, D. E.; Martin, J. C. *J. Org. Chem.* **1991**, *56*, 7277−7287. (b) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537−4538.

SCHEME 9. Preparation of 2-Benzyloxy-2-methyl-1,3-cyclopentanedione 24[a]



[a] Reagent and conditions: (a) cat. *p*-TsOH, $HOCH_2CH_2OH$, $CH(OEt)_3$, CH_2Cl_2, reflux; (b) cat. $PdCl_2(CH_3CN)_2$, benzene, reflux, (**21**/**22** = 1:26); (c) O_3, MeOH, −78 °C; $NaBH_4$, rt; (d) NaH, BnBr, TBAI, THF/DMF (10:1), rt; (e) THF/2 N HCl (2:1), reflux, 52% (five steps).

TABLE 1. Enantioselective Reduction of 1 with (*R*)-CBS Catalyst



entry	solvent.	(*R*)-CBS (equiv)	concn (L)	time[a] (h)	yield[b] (%)	ee[c] (%)
1[d,e]	THF	0.10	0.04	2	64	24
2[f]	CH_2Cl_2	0.10	0.04	2	72	>99
3[f]	CH_2Cl_2	0.15	0.15	10	91	>99

[a] Time required for the addition by a syringe pump. [b] Isolated yield. [c] ee determined by HPLC. For HPLC conditions, see the Supporting Information. [d] BH_3·THF (2.4 equiv) was used. [e] *meso*-Diol (6.4%) was also obtained. [f] BH_3·SMe_2 (2.4 equiv) was used.

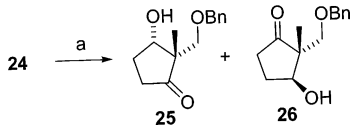
of the benzyl ether of structurally elucidated **12** (Scheme 5); hence, the absolute structure of **16** was confirmed as shown in Scheme 7. From the results of the transformations shown in Schemes 4−7, the structure of **2** was determined as shown in Scheme 1.

Reduction of **2** with $Me_4NBH(OAc)_3$ produced **10** with high diastereoselectivity (>99% de) (Scheme 4); however, this reduction proceeded sluggishly and required 4 days to complete. Therefore, we investigated an alternative method, selecting that using the CBS catalyst[16] from many enantioselective reduction methods because of its wide applicability.

First, enantioselective reduction of **1** was examined with BH_3·THF and (*R*)-CBS catalyst in THF (Table 1, entry 1). A solution of **1** in THF was slowly added to a mixture of BH_3·THF (2.4 equiv) in the presence of (*R*)-CBS catalyst (0.1 equiv) in THF at 30 °C over 2 h by means of a syringe pump. However, the optical purity of **10** obtained was unexpectedly low (24% ee, 64%), and *meso*-diol (6.4%) was obtained as a byproduct.

After optimization of the conditions, we found the optical purity of **10** dramatically increased to >99% ee (72% yield) without generating *meso*-diols when the reduction was carried out using CH_2Cl_2 and BH_3·SMe_2 (Table 1, entry 2). Solvent effect on the enantioselectivity of the oxazaborolidine reduction has been reported;[16e,f] however, to the best of our knowledge, such a dramatic improvement using CH_2Cl_2 as solvent has not been reported. Finally, when a solution of **1** in CH_2Cl_2 was added over 10 h, the yield of **10** was gratifyingly improved to 91% (Table 1, entry 3). The absolute structure of **10** was confirmed by comparison of its ^1H NMR, ^{13}C NMR, IR, $[\alpha]_D$, and mass spectral data with those of **10** prepared as described in Scheme 4.

SCHEME 10. Baker's Yeast Mediated Reduction of 24[a]



[a] Reagents and conditions: (a) baker's yeast, **25** (73%, >99% ee), **26** (6%, >99% ee), **24** (18%); see the Supporting Information for the conditions.

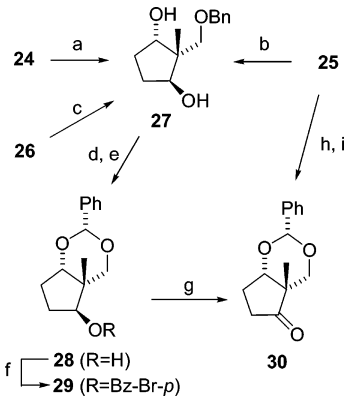
Preparation and Enantioselective Reduction of 2-Benzyloxymethyl-2-methyl-1,3-cyclopentanedione 24. Introduction of a protected hydroxymethyl group to the C2 position of 2-methyl-1,3-cyclopentanedione by alkylation afforded the *O*-alkylated product exclusively, too. Hence, the synthesis of **24** was started from known compound **20** according to the newly developed method for **1** (Scheme 9). As a result, **24** was successfully prepared from **20** (52%, five steps), revealing the wide applicability of this new method. It should be noted that purification by silica gel chromatography was again unnecessary during this synthesis except for the last step.

Baker's yeast mediated reduction of **24** was carried out under the same conditions as those for **1**, affording **25** in 73% yield along with its diastereomer **26** (6%) and the recovered starting material **24** (18%) (Scheme 10). Optical purity of **25** was difficult to determine by HPLC analysis; hence, **25** was selectively reduced to **27** with $Me_4NBH(OAc)_3$ (93%, >99% de), and the ee of **27** was determined successfully by HPLC analysis, indicating the ee of **27** was >99%. Reduction of **26** with $Me_4NH(OAc)_3$ similarly afforded **27** (93%, >99% de). The absolute configuration of **27** was proposed as shown in Scheme 11 because **27** was alternatively prepared from **24** with (*R*)-CBS catalyst. The absolute configuration of **27** was in agreement with Prelog's rule, too; however, we decided to confirm the absolute structure of **27** by X-ray crystallographic analysis of its derivative.

We succeeded in preparing a single crystal of *p*-bromobenzoate **29**, which was obtained from **27** via **28** (88%, three steps, Scheme 11) by the same method as that for preparing **13** in Scheme 5, and its whole structure was gratifyingly determined by the X-ray crystallographic analysis.[12] However, the structure of **25** must be elucidated by further studies because the same problem that arose in the structure determination of **2** remained; that is, regioselectivity of the reduction must be determined. Oxidation of **28** afforded **30** (94%), and

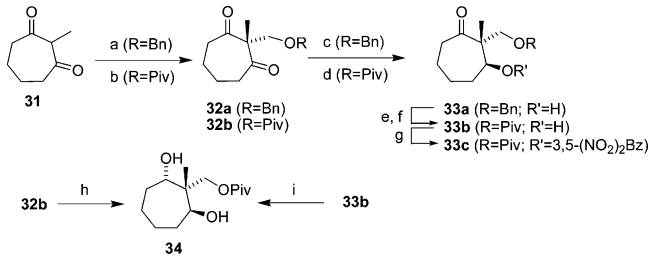
(16) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553. (b) Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751−762. (c) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012. For enantioselective reduction of 2,2-disubstituted-1,3-cyclopentanediones, see: (d) Shimizu, M.; Yamada, S.; Fujita, Y.; Kobayashi, F. *Tetrahedron: Asymmetry* **2000**, *11*, 3883−3886. For solvent effect in CBS catalysis, see: (e) Chan-Mo, Y.; Chunsan, K.; Jae-Hong, K. *Chem. Commun.* **2004**, *21*, 2494−2495. (f) Nathan, J. G.; Simon, J. *Tetrahedron: Asymmetry* **2003**, *14* (15), 2115−2118.

SCHEME 11. Transformations of 24−26 to 27−30[a]



[a] Reagents and conditions: (a) BH_3·SMe_2, (*R*)-CBS cat., CH_2Cl_2, 30 °C, 91% (>99% ee); (b) $Me_4NH(OAc)_3$, AcOH, DMF, rt, quant, (>99% de); (c) $Me_4NBH(OAc)_3$, AcOH, DMF, rt, 93%, (>99% de); (d) H_2, Raney-Ni, MeOH, rt; (e) PhCHO, cat. CSA, CH_2Cl_2, reflux, 97% (two steps); (f) *p*-BrBzCl, DMAP, CH_2Cl_2, rt, 91%; (g) DMP, CH_2Cl_2, rt, 94%; (h) H_2, Pd/C, MeOH, rt; (i) PhCHO, cat. CSA, CH_2Cl_2, reflux, 97% (two steps).

SCHEME 12. Baker's Yeast Mediated Reduction of 25[a]

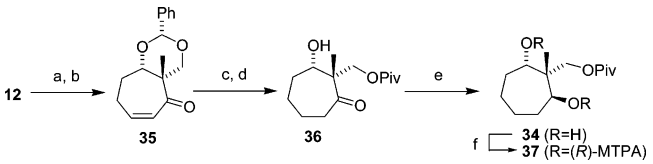


[a] Reagents and conditions: (a) NaH, $BnOCH_2Cl$, NaI, THF, 50 °C; 2 N HCl, 75% (25% conv); (b) NaH, $PivOCH_2I$, THF, 50 °C; 2 N HCl, 86% (65% conv); (c) baker's yeast, 91%, >99% ee; see the Supporting Information for the conditions; (d) baker's yeast, 95%, >99% ee; (e) H_2, Pd/C, MeOH, rt; (f) PivCl, Py, CH_2Cl_2, rt, 89% (two steps); (g) 3,5-dinitrobenzoyl chloride, DMAP, CH_2Cl_2, rt, 87%; (h) BH_3·SMe_2, (*R*)-CBS cat., CH_2Cl_2, 30 °C, 84%, >99% ee; (i) BH_3·SMe_2, (*R*)-CBS cat., CH_2Cl_2, 30 °C, 86%, >99% ee.

two-step conversion of **25** as shown in Scheme 11 afforded the same compound **30** (97%); hence, the structure of **25** was clearly elucidated as shown in Scheme 10.

Preparation and Enantioselective Reduction of 2-Benzyloxymethyl-2-methyl-1,3-cycloheptanedione, 2-Methyl-2-pivaloyloxymethyl-1,3-cycloheptanedione, and 2-Methyl-2-pivaloyloxymethyl-1,3-cyclooctanedione. Compounds **32a** and **32b** were prepared by *C*-alkylation of 2-methyl-1, 3-cycloheptanedione **31**[6a,17] as shown in Scheme 12. Alkylation using benzyl-chloromethyl ether afforded the *O*-alkylated product as its major product, but we found that use of iodomethyl pivalate[18] as the alkylating reagent increases the formation of the *C*-alkylated product. Although the *O*-alkylated product was generated, it was hydrolyzed under the acidic conditions in Scheme 12 to afford the starting material **31**.

SCHEME 13. Preparation of Bis-MTPA Ester 37[a]



[a] Reagents and conditions: (a) Dess−Martin periodinane, CH_2Cl_2, rt, 92%; (b) TMSOTf, Et_3N, CH_2Cl_2; Et_2Zn, CH_2I_2, benzene, reflux; $FeCl_3$, DMF, 50 °C, 39%; (c) H_2, Pd/C, MeOH, rt; (d) PivCl, Py, CH_2Cl_2, rt, 79% (two steps); (e) BH_3·SMe_2, (*R*)-CBS cat., CH_2Cl_2, 30 °C, 86%; (f) (*S*)-MTPACl, DMAP, CH_2Cl_2, rt, 76%.

Baker's yeast mediated reduction of **32a** and **32b** afforded **33a** (91%, >99% ee) and **33b** (95%, >99% ee) as a sole product, respectively. Hydrogenation and the following pivaloylation of **33a** produced **33b** (89%, two steps), and optical purity of **33b** was determined by HPLC of its 3,5-dinitrobenzoate **33c**; hence, optical purities of **32a** and **32b** were determined as mentioned above.

Since no derivatives of **33a** and **33b** crystallized, we determined their absolute configuration based on Mosher's method.[19] For this purpose, **33a** and **33b** were transformed to their derivatives as shown in Schemes 12 and 13. While reduction of **33a** and **33b** with $Me_4NBH(OAc)_3$ afforded no product, CBS reduction of **32b** and **33b** with the (*R*)-catalyst gave **34** in 84% and 86% yields (>99% de), respectively.

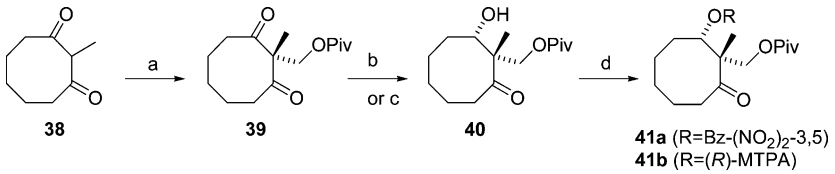
On the other hand, since the structure of **12** had been determined, **12** was transformed to **36**. That is, **12** was oxidized to the corresponding ketone by Dess−Martin periodinane (92%), which was converted to the silyl enol ether, followed by a ring-expansion reaction[20] to generate **35** (36%, four steps) (Scheme 13). Enone **35** was transformed to **36** by the hydrogenation accompanying hydrogenolysis and the following selective pivaloylation (79%, two steps). Compound **36** was converted to **34** by CBS reduction with the (*R*)-catalyst (86%, >99% de), and all the spectral data of **34** thus prepared was identical with those of **34** prepared as described in Scheme 12; hence, the absolute configuration of **34** was determined as shown in Scheme 12. Furthermore, bis-(*R*)-MTPA ester **37**[19] was prepared from **34** with (*S*)-MTPACl (76%), and Mosher's method supported the absolute configuration of **37** shown in Scheme 13 as well.

Since all of the spectral data of **36** proved that its structure is nonidentical to that of **33b**, the structure of **33b** was elucidated as shown in Scheme 12. At the same time, the structure of **33a** was also elucidated as shown in Scheme 12 because **33a** was converted to **33b** as shown in Scheme 12. The absolute configuration of **33a** and **33b** was also in agreement with Prelog's rule.

Eight-membered 1,3-diketone **39** was also easily prepared by the *C*-alkylation of 2-methyl-1,3-cyclooctanedione **38**[6a,17] (86% at 81% conversion) as shown in Scheme 14, and baker's yeast mediated reduction of **39** afforded **40** as almost a sole product in 93% yield at 86% conversion. The ee of **40** (>99% ee) was determined by

(17) Lewicka-Piekut, S.; Okamura, W. H. *Synth. Commun.* **1980**, *10*, 415−20.
(18) Bodor, N.; Solan, K. B.; Kaminiski, J. J.; Shih, C.; Pogany, S. J. *J. Org. Chem.* **1983**, *48*, 5280−5284.
(19) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512−519.
(20) Ito, Y.; Fujii, S.; Nakatsuka, M.; Kawamoto, F.; Saegusa, T. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, pp 327−333.

SCHEME 14. Preparation of Bis-MTPA Ester 37[a]



[a] Reagents and conditions: (a) NaH, $PivOCH_2I$, THF, 50 °C; 2 N HCl, 86% (81% conv); (b) baker's yeast, 93% at 86% conversion, >99% ee; see the Supporting Information for the conditions; (c) $BH_3{\cdot}SMe_2$, (*R*)-CBS cat., CH_2Cl_2, 30 °C, 73%, 88% ee; (d) for **41a**: 3,5-dinitrobenzoyl chloride, DMAP, CH_2Cl_2, rt, 92%; for **41b**: (*S*)-MTPACl, DMAP, CH_2Cl_2, rt, 93%.

HPLC of the 3,5-dinitrobenzoate **41a**, but unfortunately, **41a** did not crystallize. Hence, (*R*)-MTPA ester **41b** was prepared from **40**, and the absolute configuration of **41b** was determined by Mosher's method as well as NOE experiments (see the Supporting Information) on **40** and **41a**, elucidating the absolute structure of **40** as shown in Scheme 14.

Interestingly, CBS reduction of **39** with the (*R*)-CBS catalyst afforded ketol **40** (73%) with rather low 88% ee. This monoreduction would be rationally explained by the transannular interaction, which is often observed in the eight-membered ring system; that is, the first reduction occurs smoothly, but the second reduction of **39** could be very slow because formation of the product, the corresponding diol, would suffer from the transannular interaction. Regioselectivity of the CBS reduction of **39** would be explained by the steric factor; thus, the ketone was reduced from the less hindered side. This was consistent with the fact that reduction of **39** with $NaBH_4$ afforded racemic **40** preferentially (**40**/diastereomers = 2.4:1, see the Supporting Information).

In summary, highly enantioselective reduction of five-, six-, seven-, and eight-membered prochiral 1, 3-cycloalkanediketones possessing a methyl group and a protected hydroxymethyl group at their C2 position with baker's yeast, and a new efficient and general method for preparing the 1,3-cycloalkanediketones have been developed. These baker's yeast mediated reductions were found to produce corresponding ketols with high optical purity (>99% ee) and high yield. In addition, a highly enantioselective reduction of prochiral 1, 3-diketones to the corresponding diol has been alternatively accomplished by use of the CBS catalysis. All of the chiral building blocks reported herein would be useful for enantioselective total synthesis of complex natural products, and such projects are now underway in our laboratory.

Experimental Section

6-Allyl-6-methyl-1,4,8,11-tetraoxadispiro[4.1.4.3]tetradecane (7). To a solution of 2-methyl-2-(3-propenyl)-1,3-cyclohexadienone **6** (5 g, 30.1 mmol) in CH_2Cl_2 (100 mL) were added *p*-toluenesulfonic acid (572 mg, 3.01 mmol), ethylene glycol (15.1 mL, 271 mmol), and triethyl orthoformate (37.5 mL, 226 mmol), and the reaction mixture was refluxed for 24 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL) at ambient temperature and then extracted with CH_2Cl_2 (25 mL × 2), and the combined organic layer was dried over Na_2SO_4, filtered, and evaporated to give the crude **6** (7.65 g, 30.1 mmol). This crude **6** was sufficiently pure and was used for the next step without further purification: R_f = 0.33 (hexane/ethyl acetate = 3/1); mp 37.5−39.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.98 (1H, m), 4.91 (2H, m), 4.06−3.82 (8H, m), 2.36 (2H, d, J = 7.3 Hz), 1.70−1.50 (6H, m), 1.15 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 114.1, 113.0, 65.3, 63.8, 49.7, 35.0, 30.2, 18.6, 17.3; IR (KBr) ν_{max} 2959, 2883, 1735, 1636, 1459, 1335, 1194, 1142, 1065 cm^{-1}; HRMS(FAB) [M + H]$^+$ calcd for $C_{14}H_{23}O_4$ 255.1596, found 255.1587.

(*E*)-6-Methyl-6-(1-propenyl)-1, 4, 8, 11-tetraoxadispiro-[4.1.4.3]tetradecane (8). To a solution of crude **7** (7.65 g, 30.1 mmol) in benzene (75 mL) was added $PdCl_2(CH_3CN)_2$ (78.0 mg, 0.301 mmol), and the mixture was refluxed for 48 h. The reaction mixture was filtered and evaporated to give crude **8** (7.65 g, 30.1 mmol). This crude **8** was used for the next step without further purification: R_f = 0.33 (hexane/ethyl acetate = 3/1); mp 74.9−76.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (1H, dd, J = 15.9, 1.5 Hz), 5.63 (2H, dq, J = 15.9, 6.3 Hz), 4.00−3.83 (8H, m), 1.73 (3H, dd, J = 6.3, 1.5 Hz), 1.72−1.58 (6H, m), 1.18 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.1, 126.2, 112.4, 65.1, 65.0, 52.4, 30.8, 18.9, 18.8, 15.1; IR (KBr) ν_{max} 2959, 2874, 1655, 1474, 1249, 1155, 1067, 1034 cm^{-1}; HRMS(FAB) [M + H]$^+$ calcd for $C_{14}H_{23}O_4$ 255.1596, found 255.1593.

(6-Methyl-1,4,8,11-tetraoxadispiro[4.1.4.3]tetradec-6-yl)methanol (9). A solution of crude **8** (7.65 g, 30.1 mmol) in methyl alcohol (250 mL) cooled to −78 °C was bubbled into excess ozone for 4 h. N_2 gas was bubbled into the reaction mixture to purge ozone, and then to this reaction mixture was added $NaBH_4$ (2.41 g, 63.6 mmol) portionwise. After the reaction mixture was warmed to room temperature, solvent was removed under reduced pressure, and to the residue were added EtOAc (100 mL) and saturated aqueous NH_4Cl (100 mL). The aqueous layer was extracted with EtOAc (25 mL × 2), and the combined organic layer was dried over Na_2SO_4, filtered, and evaporated to give crude **9** (5.54 g, 22.7 mmol). This crude **9** was used for the next step without further purification: R_f = 0.21 (hexane/ethyl acetate = 1/1); mp 41.3−43.7 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00−3.88 (8H, m), 3.79 (2H, d, J = 5.4 Hz), 3.12 (1H, t, J = 5.4 Hz), 1.68−1.52 (6H, m), 1.07 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.9, 65.1, 64.9, 64.6, 50.5, 30.4, 18.8, 12.6; IR (KBr) ν_{max} 3488, 2958, 2874, 1735, 1637, 1459, 1349, 1227, 1125, 1065, 953 cm^{-1}; HRMS-(FAB) [M + H]$^+$ calcd for $C_{12}H_{21}O_5$ 245.1389, found 245.1397.

6-Benzyloxymethyl-6-methyl-1,4,8,11-tetraoxadispiro-[4.1.4.3]tetradecane. To a suspension of NaH (60%, 998 mg, 24.9 mmol) and TBAI (838 mg, 2.27 mmol) in THF (50 mL) was added a solution of crude **9** (5.54 g, 22.7 mmol) in THF (10 mL × 1, 5 mL × 2) via a cannula at 0 °C. To this reaction mixture was added a solution of benzyl bromide (2.83 mL, 23.8 mmol) in DMF (5 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with MeOH (0.2 mL). Saturated aqueous NH_4Cl (100 mL) was added to the mixture, and the aqueous layer was extracted with EtOAc (25 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated to give crude 6-benzyloxymethyl-6-methyl-1,4,8,11-tetraoxadispiro[4.1.4.3]-tetradecane (7.60 g, 22.7 mmol): R_f = 0.33 (hexane/ethyl acetate = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.22 (5H, m), 4.52 (2H, s), 3.97−3.83 (8H, m), 3.64 (2H, s), 1.83 (2H, m), 1.70−1.53 (4H, m), 1.06 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 128.0, 127.1, 127.0, 112.3, 73.4, 72.0, 65.1, 64.6, 50.9, 31.4, 18.7, 14.1; IR (neat) ν_{max} 3428, 2964, 2892, 1712, 1560,

1458, 1336, 1320, 1270, 1224, 1182, 1130, 1072, 1034 cm^{-1}; HRMS(FAB) $[M + H]^+$ calcd for $C_{19}H_{27}O_5$ 335.1858, found 335.1851.

2-Benzyloxymethyl-2-methylcyclohexane-1,3-dione (1). To a solution of crude 6-benzyloxymethyl-6-methyl-1,4,8,11-tetraoxadispiro[4.1.4.3]tetradecane obtained as above (7.60 g, 22.7 mmol) in THF (50 mL) was added 2 N HCl (25 mL), and the reaction mixture was refluxed for 3 h. After the mixture was cooled to room temperature, the aqueous layer was extracted with EtOAc (125 mL × 2). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 6/1) to afford **1** (4.76 g, 64% (five steps)) as a white solid: R_f = 0.37 (hexane/ethyl acetate = 3/1); mp 52.0−52.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.20 (m, 5H), 4.41 (s, 2H), 3.69 (s, 2H), 2.73−2.59 (m, 4H), 2.11−2.02 (m, 1H), 1.94−1.83 (m, 1H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7, 137.4, 128.2, 127.5, 127.2, 76.2, 73.4, 63.5, 39.6, 17.7, 16.9; IR (KBr) ν_{max} 3035, 2957, 2932, 2907, 2866, 1694, 1458 cm^{-1}; HRMS(FAB) $[M + H]^+$ calcd for $C_{15}H_{19}O_3$ 247.1334, found 247.1331.

(2*R*,3*S*)-2-Benzyloxymethyl-3-hydroxy-2-methylcyclohexanone (2). A solution of sucrose (2.25 g), baker's yeast (1.00 g, Oriental Yeast Co.), and yeast extract (0.10 g) in H_2O (30 mL) was stirred at 30 °C, when brisk fermentation took place. After 10 min, a solution of **1** (0.14 g, 0.57 mmol) in EtOH (0.15 mL) and 0.2% Triton X-100 (0.3 mL) were added to the reaction mixture. The mixture was stirred for 48 h at 30 °C. Et_2O (1.2 mL) and Celite (0.6 g) were then added to the mixture, which was allowed to stand for 12 h. The mixture was filtered through a pad of Celite, and the residue was washed with ethyl acetate. The organic layer was separated, washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 20/1 to 10/1) to afford of **2** (119.5 mg, 91% (93% conversion), >99% ee) as an oil: R_f = 0.52 (hexane/ethyl acetate/CH_2Cl_2 = 1/1/1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 4.56 (d, 1H, J = 12.0 Hz), 4.53 (d, 1H, J = 12.0 Hz), 3.98 (dd, 3.46, 1H, J = 11.0 Hz), 3.78 (d, 1H, J = 9.4 Hz), 3.72 (d, 1H, J = 9.4 Hz), 3.50 (s, 1H), 2.50 (td, 1H,, J = 13.8, 6.4 Hz), 2.20 (m, 1H), 1.95 (m, 2H), 1.78 (m, 1H), 1.53 (m, 1H), 1.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.9, 137.5, 128.5, 127.9, 127.6, 76.4, 75.8, 73.9, 54.1, 37.3, 28.5, 20.4, 14.8; IR (thin film) ν_{max} 2944, 1706, 740 cm^{-1}; HRMS(FAB) $[M + H]^+$ calcd for $C_{15}H_{23}O_3$ 249.1491, found 249.1490; $[\alpha]^{25}_D$ +33.8 (*c* 1.6, $CHCl_3$).

(1*S*,3*S*)-2-Benzyloxymethyl-2-methylcyclohexane-1,3-diol (10). From 2 with $Me_4NBH(OAc)_3$. A solution of **2** (4.2 mg, 1.7×10^{-2} mmol) in DMF (2 mL) was treated with $Me_4NHB(OAc)_3$ (0.201 g, 7.6×10^{-1} mmol) and AcOH (0.029 mL, 0.51 mmol) at room temperature. The reaction mixture was stirred for 4 days. The reaction was quenched with saturated NH_4Cl (4 mL) at 0 °C. After dilution with Et_2O (10 mL), the organic layer was separated, washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1 to 1/1) to afford **10** (3.5 mg, 83%, >99% de) as a white solid.

From 1 with CBS Catalyst. A solution of **1** (2.54 g, 10.3 mmol) in CH_2Cl_2 (100 mL) was added to a mixture of 0.5 N (*R*)-CBS (3.09 mL, 1.55 mmol) and 90% BH_3·SMe_2 (2.61 mL, 24.7 mmol) in CH_2Cl_2 (250 mL) via a syringe pump at 30 °C over 10 h. The reaction was quenched with MeOH (5 mL), 2 N HCl (30 mL) was added to the reaction mixture, and then the resulting solution was stirred for 10 h at room temperature. After dilution with Et_2O (200 mL), the organic layer was separated, washed with brine (250 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 10/1 to 1/1) to afford **10** (2.30 g, 91%, >99% ee) as a white solid. The ee was determined by HPLC (254 nm); Dicel Chiral Cell AS-H 0.46 cm i.d. × 25 cm; hexane/2-propanol = 14/1; flow rate = 0.3 mL/min); retention time 37.5 min for (*R*,*R*)-**10**, 41.5 min for (*S*,*S*)-**10**. Racemic **10** was prepared from **1** with *dl*-CBS catalyst and was used as an authentic sample for HPLC: R_f = 0.43 (hexane/ethyl acetate/CH_2Cl_2 = 1/1/1); mp 76.5−77.8 °C (recrystalized by ethylmethyl ketone/hexane); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 4.59 (d, 1H, J = 12.0 Hz), 4.53 (d, 1H, J = 12.0 Hz), 4.15 (dd, 1H, J = 11.2, 4.4 Hz), 3.80 (s, 1H), 3.68 (d, 1H, J = 9.0 Hz), 3.56 (d, 1H, J = 9.0 Hz), 3.34 (s, 1H), 1.89 (br, 1H), 1.89−1.72 (m, 2H), 1.66−1.60 (m, 2H), 1.58−1.43 (m, 3H), 0.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.6, 128.5, 127.9, 127.6, 77.3, 75.9, 73.7, 69.1, 43.0, 29.8, 28.4, 18.7,14.4; IR (KBr) ν_{max} 2944, 1454,1047, 742 cm^{-1}; HRMS-(FAB) $[M + H]^+$ calcd for $C_{15}H_{23}O_3$ 251.1647, found 251.1642; $[\alpha]^{22}_D$ +18.6 (*c* 1.0, $CHCl_3$).

Acknowledgment. We thank the Material Characterization Central Laboratory, Waseda University, for technical support of the X-ray crystallographic analysis. We also thank Professor Takeshi Sugai (Department of Chemistry, Keio University) for helpful discussions about baker's yeast reduction. This work was financially supported in part by the Uehara Memorial Foundation, a Waseda University Grant for Special Research Projects, and a Grant-in-Aid for Scientific Research on Priority Areas (Creation of Biologically Functional Molecules (No. 17035082)) from the Ministry of Education, Science, Sports, Culture and Technology, Japan. We are also indebted to 21COE "Practical Nano-Chemistry."

Supporting Information Available: Synthesis and full characterization of compounds in Scheme 2, 3, and 5−14; X-ray crystal structures of **13** and **29** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO050349A