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Preparation of new chiral building blocks via asymmetric catalysis

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Abstract—Highly enantio- and stereoselective preparation of some new chiral building blocks with baker's yeast or the CBS catalyst is described.

New chiral building blocks possessing an appropriate carbon skeleton, stereogenic centers, and some functional groups would contribute to a new and convergent asymmetric total synthesis of natural products. These compounds are not readily available, because they are structurally different from naturally occurring compounds, requiring multistep transformations from easily accessible compounds. Hence, preparation of such new chiral compounds via asymmetric synthesis is very important.

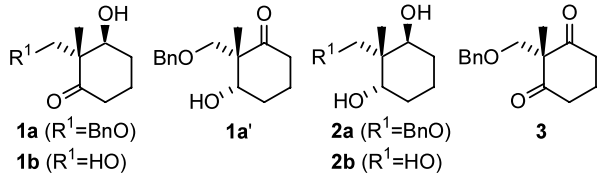
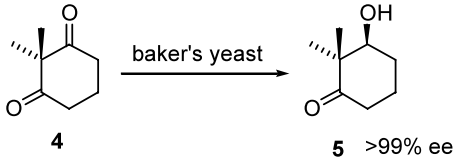


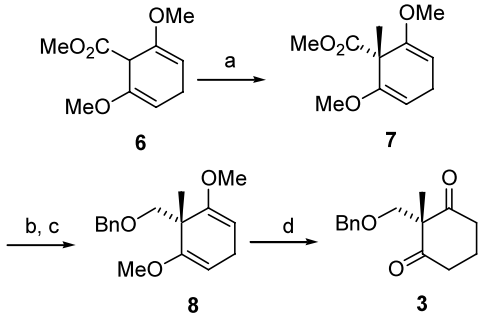
Figure 1. Some new chiral intermediates and common precurser **3**.



Scheme 1.

In our laboratory, synthetic studies on some terpenoids are now in progress, and one problem incurred in their synthesis is the stereoselective construction of the chiral quaternary carbon centers of the target molecule. As a result of our retrosynthetic analysis of some terpenoids, new chiral building blocks, **1a** and **2b** (Fig. 1) possessing a chiral quaternary carbon center were found to be useful for the convergent synthesis. Herein we report highly enantio- and stereoselective preparation of some new chiral building blocks with baker's yeast or the CBS catalyst.

Since **1a** and **2b** were surmised to be prepared from *meso*-1,3-dione **3** by asymmetric reduction, we started the asymmetric reduction of **3** by two methods, that is, one is the method with baker's yeast[1] and the other is the method with the CBS catalyst.[2]



Scheme 2. *Reagents and conditions*: (a) LDA, HMPA, THF, −78°C, 10 min, then MeI, −78°C 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) 2N HCl, THF, 15 min, 95%.

Keywords: asymmetric synthesis; baker's yeast; CBS catalyst; enantioselection; reduction.

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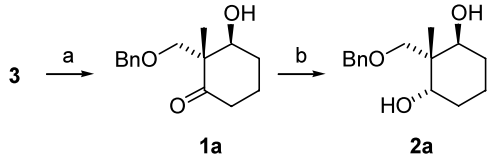
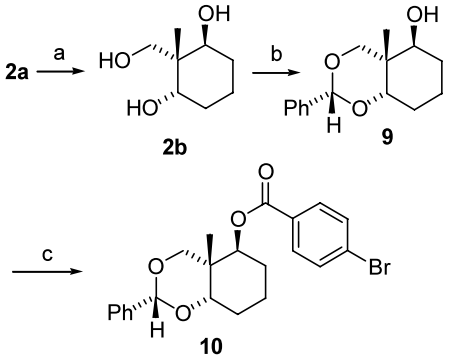
It has been reported that baker's yeast reduction of **4** affords **5** with high enantioselectivity (Scheme 1, >99% ee),[3] hence, baker's yeast reduction of **3** was surmised to give good result. However, it was easily expected that the product obtained by reduction of **3** would be a complex mixture because **3** is a *meso*-1,3-diketone lacking C_2 symmetry, affording four stereoisomers. To our surprise, baker's yeast reduction of **3** has not been reported. Hence, we started an investigation of the stereoselectivity of the baker's yeast reduction of **3**.



Scheme 3. *Reagents and conditions*: (a) baker's yeast, sucrose, Triton X, H_2O, EtOH, 30°C, 48 h, 75% (at 85% conv., >99% ee); (b) $Me_4NH(OAc)_3$, AcOH, DMF, rt, 4 d, 85%.



Scheme 4. *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%.

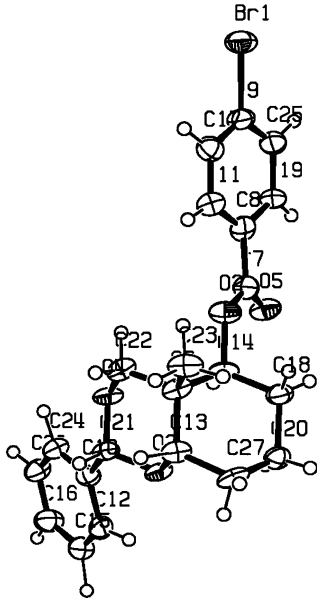


Figure 2. X-Ray crystal structure of **10**.

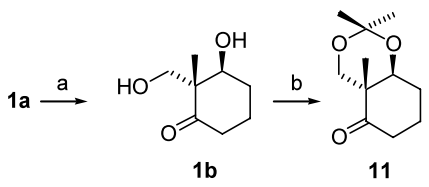
A preparation of **3** is shown in Scheme 2. Compound **6** was prepared by the known method.[4] Thus, Birch reduction of 2,6-dimethoxybenzoic acid, followed by methyl ester formation gave **6**. Then, **6** was methylated by MeI and LDA to afford **7** (96%), and **7** was reduced by DIBAL-H (96%) and benzylated (89%) to give **8**. Finally, acid-catalyzed hydrolysis of the alkenyl ethers of **8** successfully afforded the desired 1,3-diketone **3** (95%).

With the 1,3-diketone **3** in hand, baker's yeast reduction of **3** was investigated. As shown in Scheme 3, the reduction was carried out according to the reported procedure.[3a] Thus, **3** (280.0 mg, 1.14 mmol) was stirred with baker's yeast (2.0 g), 0.2% Triton X-100 in ethanol (0.6 ml), and sucrose (4.5 g) in water (60 ml) at 30°C. After 48 h, the reaction mixture was worked up, and the crude product was purified by silica gel chromatography (hexane:ethyl acetate = 20:1 to 10:1) to afford **1a** (180.7 mg, 64%)[5] and **3** (40.7 mg, 15%). No other product was observed in this reaction. Ketone **1a** was highly diastereoselectively reduced with $Me_4NBH(OAc)_3$[6] to **2a** (>99% de, 85%), and the optical purity of **2a** (>99% ee) was determined by HPLC.[7] This result clearly shows that the baker's yeast reduction of **3** proceeds with high stereoselectivity (>99% ee).

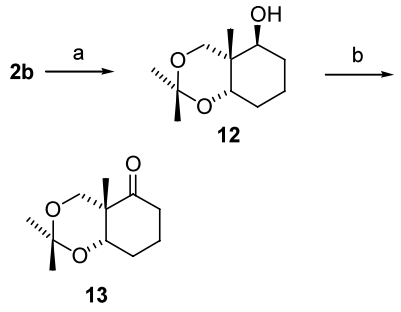
Next, the absolute structure of **1a** was elucidated. Though some crystalline derivatives were prepared starting from **1a**, *p*-bromobenzoate **10** was the only one suitable for X-ray crystallographic analysis. Preparation of **10** is shown in Scheme 4. Thus, hydrogenolysis of **2a** quantitatively afforded triol **2b**, and the reaction of **2b** with benzaldehyde and a catalytic amount of CSA afforded benzylidene acetal **9** as the sole product (98%). Acetal **9** was transformed to crystalline *p*-bromobenzoate **10** (89%), and its whole structure was determined by X-ray crystallographic analysis.[8] The X-ray crystal structure clearly shows that the absolute structure of **10** is as shown in Figure 2, and the relative configuration of the two hydroxy groups is *anti*. Furthermore, **10** has a *cis*-fused bicyclic ring structure, revealing that the benzylidene acetal formed in a kinetically controlled manner.

Though the (*S*)-configuration of **1a** was expected on the basis of Prelog's rule,[9] the absolute configuration of **2a** was unambiguously confirmed as described above. However, the absolute structure of **1a** itself must be determined because the above transformation can not exclude another possibility that the diol **2a** was diastereoselectively obtained from **1a**′.[10] That is, it was not determined which ketone in **3** is selectively reduced. Since the preparation of a crystalline derivative from **1a** for X-ray crystallographic analysis was difficult as stated above, the absolute structure of **1a** was determined by the comparison of the derivative of **1a** with the compound derived from the structurally elucidated triol **2b**.

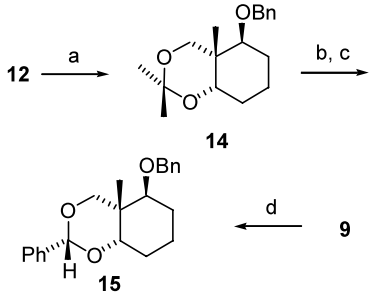
As shown in Scheme 5, a benzyl group of **1a** was removed by hydrogenolysis to give diol **1b** (quant.), followed by the reaction with acetone under acidic condition to afford acetonide **11** (65%).[11]



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



Scheme 6. *Reagents and conditions*: (a) acetone, cat. CSA, rt, 2 h, 94%; (b) DMP, CH_2Cl_2, rt, 1 h, 99%.



Scheme 7. *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%.

On the other hand, **2b** was transformed to acetonide **12** (94%) (Scheme 6). This reaction gave **12** as the sole product, but the structure of **12** was not clearly determined by NMR technique. Hence, the structure of **12** must be elucidated as shown in Scheme 7. Thus, **12** was converted to benzyl ether **14** (99%), followed by deprotection of the acetonide (92%), and benzylidene acetal formation gave **15** (quant.). The ^{1}H NMR, ^{13}C NMR, IR, $[\alpha]_D$, and mass spectral data of **15** are the same as those of the benzyl ether of the structurally elucidated **9** (Scheme 4), determining the absolute structure of **12** as shown in Scheme 6.

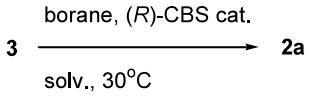
Since the absolute structure of **12** was elucidated, **12** was oxidized by Dess–Martin reagent[12] to generate ketone **13** (99%).[13] The structure of **13** was found to be apparently different from that of **11** as we expected. As the result of transformations shown in Schemes 4–7, the structure of **1a** was proved as shown in Figure 1.

We successfully reduced **1a** to **2a** diastereoselectively (>99% de) with $Me_4NBH(OAc)_3$ (Scheme 3). However, this reduction proceeded sluggishly and required 4 days to complete, so that we were prompted to investigate another method to prepare **2a** from **3**. Among many enantioselective reduction methods we selected the method using the CBS catalyst[2] because of its wide applicability.

First, enantioselective reduction of **3** was examined with BH_3–THF and (*R*)-CBS catalyst in THF (entry 1, Table 1). A solution of **3** in THF was slowly added to a mixture of BH_3–THF (2.4 equiv.) and (*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 **2a** was low (24% ee, 64%) and *meso*-diol (6.4%) was obtained as a by-product.

Next, the solvent and the reducing reagent were changed to CH_2Cl_2 and BH_3–SMe_2, respectively, and the optical purity of **2a** was dramatically increased to >99% ee (72% yield) without generating *meso*-diols (entry 2, Table 1). Finally, when a solution of **3** in CH_2Cl_2 was added over a 10 h period, the yield of **2a** was successfully improved to 91% (entry 3, Table 1). The absolute structure of **2a** was confirmed as shown in Figure 1 by comparison of its ^{1}H NMR, ^{13}C NMR, IR,

Table 1. Asymmetric reduction of **3** with (*R*)-CBS catalyst



Entry	Solv.	(*R*)-CBS (equiv.)	Conc. (mol/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 Ref. 7.
[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.

$[\alpha]_D$, and mass spectral data with those of **2a** prepared as described in Scheme 3.

In summary, highly enantioselective reduction of *meso*-1,3-dione **3** with baker's yeast, affording **1a** (>99% ee), was achieved. Also achieved is the subsequent highly diastereoselective reduction of **1a** with $Me_4NBH(OAc)_3$ generating **2a** (>99% de) and the highly regioselective acetal formation of **2b** giving **9** and **12**. A highly enantioselective reduction of *meso*-1,3-dione **3** generating **2a** directly (>99% ee) is alternatively realized by use of the CBS catalyst.[14,15] The absolute structure of all products was unambiguously determined based on the X-ray crystallographic analysis of **10** and the structure interconversions as shown in Schemes 3–7. The new chiral building blocks reported herein are useful for asymmetric total synthesis of natural products, and such projects are now underway in our laboratory.

Acknowledgements

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References

1. For recent reviews, see: (a) Sugai, T. *Curr. Org. Chem.* **1999**, *3*, 373–406; (b) Kayser, M.; Chen, G.; Stewart, J. *Synlett* **1999**, 153–158; (c) Bortolini, O.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Recent Res. Dev. Pure Appl. Chem.* **1999**, *3*, 137–152; (d) Stewart, J. *Curr. Opin. Biotechnol.* **2000**, *11*, 363–368; (e) Bellgardt, K.-H. In *Bioreaction Engineering*; Schuegerl, K.; Bellgardt, K.-H., Eds.; Springer-Verlag: Berlin, Germany, 2000; pp. 277–320; (f) Cusk, R.; Glanzer, B. I. In *Stereoselective Biocatalysis*; Patel, R. N., Ed.; Marcel Dekker: New York, 2000; pp. 527–578; (g) Santaniello, E.; Manzocchi, A. *Trends Org. Chem.* **2000**, *8*, 21–34.
2. (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.
3. (a) Mori, K.; Mori, H. *Tetrahedron* **1985**, *41*, 5487–5493; (b) For asymmetric reduction of 2-allyl-2-methyl-1,3-cyclohexanedione, see: Brooks, D. W.; Mazdiyasni, H.; Grothaus, P. G. *J. Org. Chem.* **1987**, *52*, 3223–3232. In this baker's yeast reduction, regioselectivity of the reduction was low.
4. Tamai, Y.; Mizutani, Y.; Hagiwara, H.; Uda, H.; Harada, N. *J. Chem. Res. Synop.* **1985**, 148–149.
5. **1a**: a colorless viscous oil; $[\alpha]_D^{25.2}=+33.8$ (*c* 1.6, $CHCl_3$); IR (thin film): 2944, 1706, 740 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.36–7.28 (m, 5H), 4.56 (d, $J=12.0$ Hz, 1H), 4.53 (d, $J=12.0$ Hz, 1H), 3.98 (dd, $J=11.0$, 3.46 Hz, 1H), 3.78 (d, $J=9.4$ Hz, 1H), 3.72 (d, $J=9.4$ Hz, 1H), 3.50 (s, 1H), 2.50 (dt, $J=13.8$, 6.4 Hz, 1H), 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; HRMS (FAB) $[M+H]^+$ calcd for $C_{15}H_{23}O_3$: 249.1491, found: 249.1458.
6. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578.
7. **2a**: a white solid; $[\alpha]_D^{32.1}=+18.6$ (*c* 1.0, $CHCl_3$) (with CBS catalyst), +18.5 (*c* 1.0, $CHCl_3$) (with baker's yeast); mp 76.5–77.8°C (ethyl acetate–hexane); IR (KBr): 2944, 1454, 1047, 742 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.36–7.28 (m, 5H), 4.59 (d, $J=12.0$ Hz, 1H), 4.53 (d, $J=12.0$ Hz, 1H), 4.15 (dd, $J=11.2$, 4.4 Hz, 1H), 3.80 (s, 1H), 3.68 (d, $J=9.0$ Hz, 1H), 3.56 (d, $J=9.0$ Hz, 1H), 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; HRMS (FAB) $[M+H]^+$ calcd for $C_{15}H_{23}O_3$: 251.1647, found: 251.1642. Ee was determined by HPLC (254 nm); Dicel Chiral Cell AS-H 0.46 cm $\phi\times$25 cm; hexane/isopropanol = 14/1; flow rate = 0.3 ml/min); retention time: 37.5 min for (*R*,*R*)-**2a**, 41.5 min for (*S*,*S*)-**2a**.
8. **10**: a white solid; $[\alpha]_D^{25.2}=+124.5$ (*c* 1.0, $CHCl_3$); mp 174.7–175.3°C (ethyl methyl ketone); IR (KBr): 2945, 2867, 1715, 1589, 1397, 1273, 1120, 1095, 1010, 759 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.87 (d, $J=8.7$ Hz, 2H), 7.57 (d, $J=8.7$ Hz, 2H), 7.54–7.52 (m, 2H), 7.39–7.33 (m, 3H), 5.84 (dd, $J=11.6$, 4.85 Hz, 1H), 5.53 (s, 1H), 4.00 (d, $J=11.8$ Hz, 1H), 3.89 (t, $J=2.8$ Hz, 1H), 3.48 (d, $J=11.8$ Hz, 1H), 2.16–2.13 (m, 1H), 1.98–1.91 (m, 1H), 1.81–1.78 (m, 2H), 1.69–1.61 (m, 2H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 138.4, 131.7, 131.0, 129.6, 129.0, 128.3, 127.9, 126.4, 102.2, 81.9, 72.8, 72.3, 36.6, 26.7, 26.6, 19.5, 14.5; HRMS (FAB) $[M+H]^+$ calcd for $C_{22}H_{24}BrO_4$: 431.0858, found: 431.0859.
9. Prelog, V. *Pure Appl. Chem.* **1964**, *9*, 119–130.
10. The yeast strain showing an oppsite enantiotopic-group selectivity toward similar cyclic diketones has been reported, see: Fuhshuku, K.; Tomita, M.; Sugai, T. *Adv. Synth. Catal.* **2003**, *345*, 766–774.
11. **11**: a white solid; $[\alpha]_D^{23.0}=+70.8$ (*c* 1.0, $CHCl_3$); mp 49.5–50.8°C; IR (KBr): 2960, 1703, 1196, 1064 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 4.03 (d, $J=11.9$ Hz, 1H), 3.87 (dd, $J=11.6$, 4.03 Hz, 1H), 3.69 (d, $J=11.9$ Hz, 1H), 2.62 (dt, $J=11.7$, 7.3 Hz, 1H), 2.20–2.16 (m, 1H), 2.05–2.00 (m, 1H), 1.91–1.84 (m, 1H), 1.77–1.74 (m, 1H), 1.66–1.58 (m, 1H), 1.43 (2s, 6H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.9, 99.3, 74.1, 66.6, 48.8, 36.9, 29.6, 25.5, 20.9, 18.9, 15.2; HRMS (FAB) $[M+H]^+$ calcd for $C_{11}H_{19}O_3$: 199.1334, found: 199.1349. Benzylidene group was not selected for the protection because a new stereogenic center forms in the product, rendering the structure elucidation difficult.
12. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1991**, *113*, 7277–7287; (b) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537–4538.
13. **13**: a white solid; $[\alpha]_D^{23.0}=-62.8$ (*c* 1.0, $CHCl_3$); mp 38.3–39.0°C; IR (KBr): 2954, 1710, 1203, 1091 cm^{-1}; ^1H NMR

(600 MHz, $CDCl_3$) δ 4.31 (d, $J=11.7$ Hz, 1H), 4.17 (t, $J=2.8$ Hz, 1H), 3.38 (d, $J=11.7$ Hz, 1H), 2.49–2.43 (m, 1H), 2.41–2.37 (m, 1H), 2.22–2.14 (m, 1H), 2.08–2.02 (m, 1H), 1.86–1.79 (m, 2H), 1.44 (s, 3H), 1.43 (s, 3H), 1.34 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.1, 98.4, 74.7, 64.2, 46.8, 37.7, 29.3, 26.3, 20.4, 19.0, 18.7; HRMS (FAB) $[M+H]^+$ calcd for $C_{11}H_{19}O_3$: 199.1334, found: 199.1311.

14. For enantioselective reduction of 2,2-disubstituted-1,3-cyclopentanediones, see: Shimizu, M.; Yamada, S.; Fujita, Y.; Kobayashi, F. *Tetrahedron: Asymmetry* **2000**, *11*, 3883–3886.
15. Additives that slow down the second reduction of *meso*-diketone **3** were not investigated. For such additives, see Ref. 14 and references cited therein.