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Baker's Yeast Mediated Reduction of Optically Active Diketone

ZHENG, Guo-Jun(郑国君) GAO, Xiao-Lei(高晓蕾) CHEN, Jin-Chun(陈锦春)
LI, Yu-Lin*(李裕林)

State Key Laboratory of Applied Organic Chemistry, Institute of Organic Chemistry, Lanzhou University, Lanzhou, Gansu 730000, China

Baker's yeast mediated reduction of optically active diketone is described. The two keto groups are efficiently differentiated and the *ee* value of the recovered material is considerably raised. It affords highly optically active key intermediates efficiently for the synthesis of natural polyhydroxylated agarofuran products.

Keywords baker's yeast, reduction, agarofuran, sesquiterpenoid

Introduction

9-Oxo-10-epi-α-cyperone (**1a**) is a key intermediate for the synthesis of one kind of natural polyhydroxylated agarofuran sesquiterpenoids.[1-3] To our knowledge, there is no report on the total synthesis of optically active polyhydroxylated agarofuran except our group's work.[2,3] In order to obtain optically pure natural products, raising *ee* value of (—)-**1a** becomes very important. However, the *ee* value of (—)-**1a**, afforded by amino acid catalyzed asymmetric reaction under most favorable conditions, did not exceed 50%. Although some substrates of the similar structure could be easily prepared by asymmetric Robinson annulation with a high value of *ee*,[4-6] it was impossible to obtain (—)-**1a** with high value of *ee* by a similar method. Fortunately, some literatures[7,8] reported baker's yeast mediated reduction to achieve the kinetic resolution of Hajos-Parrish ketone and Wieland-Miescher ketone with structures similar to (—)-**1a**. Therefore, we tried the kinetic resolution of (—)-**1a** by way of baker's yeast mediated reduction to improve the *ee* value, and favorable results were obtained.

Results and discussion

Baker's yeast mediated reduction of synthetic substrate is a useful method for preparing chiral intermediate in synthetic chemistry[9,10] because it is readily available and inexpensive. The reduction proceeds in a highly enantiofacially selective manner, following the Prelog rule,[11] that is, a hydride is transferred to the *re* face of the prochiral ketone to give the corresponding (*S*)-alcohol.[7,8]

Our first attempt was to apply (±)-**1a** as the substrate for baker's yeast (BY) mediated reduction, and (—)-**1a** ($[\alpha]_D^{29}$ —21.0, *c* 1.8, $CHCl_3$) was recovered in 64% isolated yield. It was less than 50% enantiomeric excess and could not meet the needs of synthesis of optically pure aimed compound. In order to get high *ee* value of (—)-**1a**, we applied BY mediated reduction to (—)-**1a** (50% *ee*, $[\alpha]_D^{29}$ —28.0, *c* 2.2, $CHCl_3$), which could be obtained by asymmetric Robinson annulation.[2] According to the general procedure of the reaction, sucrose was firstly used as culture, but the result of only 57% *ee* was not ideal. Then glucose was selected instead of sucrose, and the value of *ee* was raised from 57% to 65% (Entry 1 vs. Entry 2 in Table 1). When the experimental conditions were further optimized, higher value of *ee* was gotten. The results are summarized in Table 1.

From Table 1, it can be concluded that higher concentrations of substrate and BY are favorable (Entries 2—4). Increasing the reaction time properly leads to high value of *ee*, but its further extension leads to the formation of the diol instead of the enhancement of the reaction yield (Entries 1, 4 and 11), while the solvent and addition of non-organic ion almost have no effect on the reaction (Entries 4—7). The best reaction temperature must be 35 ℃ (Entries 4, 8 and 9), which is also observed in the reduction of (—)-**1b**.

By BY mediated reduction, product (+)-**2a** (99% *ee*) was obtained in 20% yield along with (—)-**1a** (89% *ee*) in 63% recovered yield. There was a little amount of (—)-**3a** (84% *ee*) produced at the same time (Scheme 1).

Similarly, when this BY mediated reduction was applied to compound (—)-**1b** (80% *ee*), which was obtained with (—)-**1a** at the same time,[2] nearly all of the compound (+)-**1b** and a little (—)-**1b** were reduced to afford (+)-**2b** (99% *ee*) and (—)-**3b** (89% *ee*) in 9% and 3% yields, respectively. Optically pure (—)-**1b** (99% *ee*) was recovered in 78% yield (Scheme 2). However the experiment processes were somewhat different between (—)-**1a** and (—)-**1b**. For (—)-**1a,** it was

* E-mail: liyl@lzu.edu.cn
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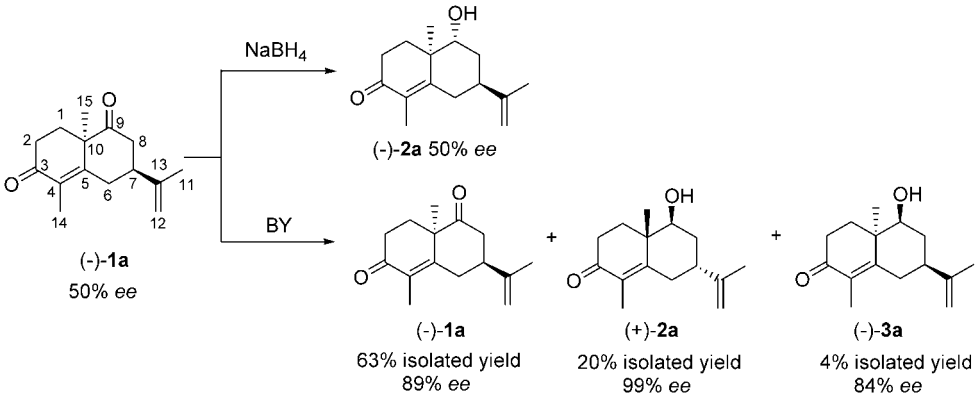
Table 1 Conditions and results of the baker's yeast mediated reduction

Entry	Substrate/ (mmol • L^{-1})	BY/ (g • L^{-1})	Culture solution	Solvent	Temp./℃	Time/d	*ee*/%			Yield/%		
							(−)-**1a**	(+)-**2a**	(−)-**3a**	(−)-**1a**	(+)-**2a**	(−)-**3a**
1	4.3	100	sucrose	EtOH	35	3	57	—	—	88	—	—
2	4.3	100	glucose	EtOH	35	3	65	—	—	87	—	—
3	21.5	100	glucose	EtOH	35	3	74	—	—	85	—	—
4	21.5	500	glucose	EtOH	35	3	89	99	84	63	20	4
5	21.5	500	glucose	DMSO	35	3	85	99	80	64	18	3
6	21.5	500	glucose	Neat	35	3	88	99	83	67	18	4
7	21.5	500	**	EtOH	35	3	88	99	—	60	15	—
8	21.5	500	glucose	EtOH	30	3	88	99	84	66	17	3
9	21.5	500	glucose	EtOH	40	3	87	85	80	75	13	3
10	21.5	500	glucose	EtOH	35	1	75	~100	—	83	12	—
11	21.5	500	glucose	EtOH	35	5	89	83	84	60	22	8

**: 3% glucose, 2% corn starch, 0.1% KH_2PO_4, 0.2% K_2HPO_4, 0.2% HNO_3, 0.05% $MgSO_4$, 0.02% KCl, 0.02% $FeSO_4$.

Scheme 1

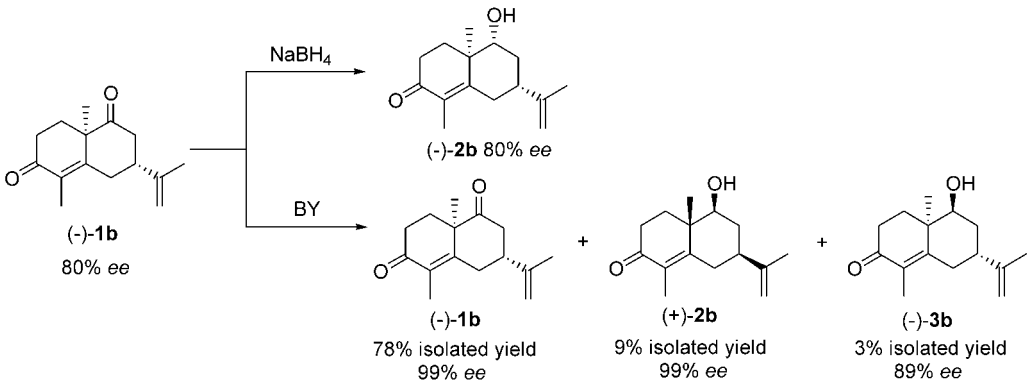


added after BY had been incubated in phosphate buffer solution for 0.5 h when there came out vigorous bubbles, and the reaction went on desirably. But under the same conditions, when (−)-**1a** was displaced by (−)-**1b**, no reaction occured. However, if (−)-**1b** was added after BY had been incubated in the culture for 24 h, the reaction was found to carry out rather favorably. The absolute configurations of (+)-**2a,** (−)-**3a,** (+)-**2b** and (−)-**3b** can be elucidated by comparison of their spectral data with those of the compounds from reducing (−)-**1a** and (−)-**1b** by $NaBH_4$ (Scheme 2).

Experimental

^{1}H NMR spectra were recorded on a Bruker AM-400 spectrometer in $CDCl_3$ using TMS as an internal refer-

Scheme 2



ence. Mass spectra were determined on a HP5988A spectrometer by direct inlet at 70 eV, and signals were given in *m/z* with relative intensity (%) in brackets. Optical rotation measurements were carried out on a Perkin-Elmer 141 polarimeter. Flash chromatography was performed on silica gel, with petroleum benzine (PE) and diethyl ether (Et) mixtures as eluent. The progress of the reactions was monitored by TLC or GC.

The best conditions and steps of BY mediated reduction of (−)-1a (50% *ee*, $[\alpha]_D^{29}$ −28.0, *c* 1.1, $CHCl_3$)

To a phosphate buffer solution (0.1 mol/L, pH=6.5, 20 mL) containing glucose (3 g), Baker's yeast (10 g) was added and the mixture was kept at room temperature until vigorous gas evolution ensued (about 30 min). Then 9-oxo-epi-cyperone (−)-**1a** (50% *ee*, 300 mg) in ethanol (2 mL) was added. The mixture was stirred at 35 ℃ with addition of glucose at intervals when the speed of gas evolution slowed down appreciably. After 3 d the mixture was extracted with EtOAc (3×100 mL). The extraction was washed with water (3×10 mL), sodium chloride solution (3×10 mL) and dried over sodium sulphate successively. After evaporation of the solvent under vacuum, the residue was subjected to chromatography on silica gel (PE∶Et=1∶1, *V*/*V*) to afford (−)-**1a** (89% *ee*, 189 mg, 63%), (−)-**3a** (84% *ee*, 12 mg, 4%) and (+)-**2a** (99% *ee*, 60 mg, 20%) respectively. Spectral data of (−)-**1a** (89% *ee*): $[\alpha]_D^{29}$ −48.0 (*c* 2.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.46 (s, 3H, 10-Me), 1.80, 1.85 (each s, 3H, 11-Me and 4-Me), 1.94—2.05 (m, 1H), 2.16—2.24 (m, 1H), 2.51—2.58 (m, 3H), 2.78—2.87 (m, 2H), 2.90—2.96 (m, 2H), 4.69, 4.85 (each br s, 2H, 12-CH_2); MS (EI) *m/z* (%): 232 (M^+, 18), 190 (100), 175 (23), 147 (45), 121 (45), 93 (71), 79 (45), 41 (38). Spectral data of (+)-**2a** (99% *ee*): $[\alpha]_D^{25}$ +94.2 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.16 (s, 3H, 10-Me), 1.71 (s, 3H, 11-Me), 1.79 (s, 3H, 4-Me), 1.86—1.90 (m, 2H), 2.09—2.14 (m, 2H), 2.30—2.36 (m, 2H), 2.39—2.41 (m, 1H), 2.44—2.49 (m, 1H), 2.57 (s, br, 1H, OH), 2.81—2.89 (m, 1H, 7-CH), 3.50 (dd, *J*=11.1, 5.3 Hz, 1H, 9-CH,), 4.53, 4.74 (each br s, 2H, 12-CH_2); MS (EI) *m/z* (%): 234 (M^+, 25), 219 (10), 191 (72), 178 (19), 138 (100), 109 (42), 93 (40), 67 (35). Spectral data of (−)-**3a** (84% *ee*): $[\alpha]_D^{25}$ −73.3 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.21 (s, 3H, 10-Me), 1.82 (s, 3H, 11-Me), 1.84 (s, 3H, 4-Me), 1.86—2.00 (m, 2H), 2.01—2.04 (m, 2H), 2.09—2.17 (m, 2H), 2.40—2.44 (m, 2H), 2.46 (s, br, 1H, OH), 2.86—2.80 (m, 1H, 7-CH), 3.50 (d, *J*=4.8 Hz, 1H, 9-CH), 4.83, 4.84 (each br s, 2H, 12-CH_2); MS (EI) *m/z* (%): 234 (M^+, 15), 219 (6), 191 (47), 178 (21), 138 (100), 109 (41), 93 (38), 67 (32).

The best conditions and steps of BY mediated reduction of (−)-1b (80% *ee*, $[\alpha]_D^{26}$ −19.1, *c* 1.4, $CHCl_3$)

To 20 mL of culture solution made up of 3% glucose, 2% corn starch, 0.1% KH_2PO_4, 0.2% K_2HPO_4, 0.2% $NaNO_3$, 0.05% $MgSO_4$, 0.01% KCl and 0.02% $FeSO_4$, Baker's yeast (10 g) was added. The mixture was shaken at 35 ℃ for 24 h, then the value of pH was adjusted to 6.5—7.0 using 6 mol/L NaOH. Then (−)-**1b** (80% *ee*) (300 mg) in ethanol (2 mL) was added. The mixture was stirred at 35 ℃ with addition of glucose at intervals to ensure the mixture bubbling all the time. After 3 d, the mixture was extracted with EtOAc (3×100 mL). The extraction was washed with water (3×10 mL), sodium chloride solution (3×10 mL) and dried over sodium sulphate successively. After evaporation of the solvent under vacuum, the residue was subjected to chromatography on silica gel (PE∶Et=1∶1, *V*/*V*) to afford (−)-**1b** (99% *ee*, 234 mg, 78%), (+)-**2b** (99% *ee*, 27 mg, 9%) and (−)-**3b** (89% *ee*, 9 mg, 3%) respectively. Spectral data of (−)-**1b** (99% *ee*): $[\alpha]_D^{26}$ −26.1 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.43 (s, 3H, 10-Me), 1.80, 1.84 (each s, 3H, 11-Me and 4-Me), 2.04—2.13 (m, 2H), 2.46—2.52 (m, 2H), 2.55—2.64 (m, 2H), 2.68—2.69 (m, 1H), 2.70—2.73 (m, 1H), 2.97—3.01 (m, 1H), 4.87, 4.85 (each br s, 2H, 12-CH_2); MS (EI) *m/z* (%): 232 (M^+, 20), 190 (100), 179 (25), 147 (29), 121 (36), 93 (55), 79 (35), 41 (74). Spectral data of (+)-**2b** (99% *ee*): $[\alpha]_D^{25}$ +67.2 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.16 (s, 3H, 10-Me), 1.68—1.72 (m, 1H), 1.75 (s, 3H, 11-Me), 1.76 (s, 3H, 4-Me), 1.79—2.00 (m, 2H), 2.01—2.04 (m, 2H), 2.08—2.16 (m, 1H), 2.36 (s, br, 1H, OH), 2.38—2.43 (m, 2H), 2.64—2.67 (m, 1H, 7-CH), 3.34 (dd, *J*=11.6, 4.3 Hz, 1H, 9-CH), 4.74 (br s, 2H, 12-CH_2); MS (EI) *m/z* (%): 234 (M^+, 45), 219 (4), 191 (43), 178 (10), 138 (59), 109 (38), 93 (32), 77 (46), 67 (37), 41 (100). Spectral data of (−)-**3b** (89% *ee*): $[\alpha]_D^{25}$ −57.4 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (s, 3H, 10-Me), 1.44—1.52 (m, 2H), 1.79 (s, 3H, 11-Me), 1.81 (s, 3H, 4-Me), 1.87—1.93 (m, 2H), 1.97—2.08 (m, 2H), 2.26 (s, 1H, OH), 2.51—2.56 (m, 2H), 2.75—2.79 (m, 1H, 7-CH), 3.69 (t, *J*=2.5 Hz, 1H, 9-CH), 4.82 (s, 2H, 12-CH_2); MS (EI) *m/z* (%): 234 (M^+, 52), 219 (4), 191 (48), 178 (11), 138 (67), 109 (45), 93 (38), 77 (50), 67 (39), 41 (100).

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