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Enantioselective Reduction of σ-Symmetric Bicyclo[3.3.0]octane-2,8-diones with Baker's Yeast

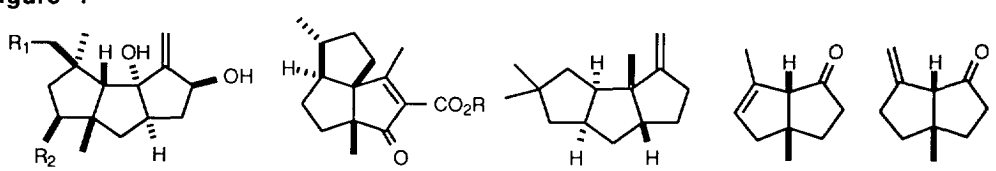
Takehisa Inoue, Kouichi Hosomi, Mamoru Araki, Kiyoharu Nishide and Manabu Node*

Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan

Abstract: σ-Symmetric bicyclic diketones **8a-c** were enantioselectively reduced with baker's yeast to give the chiral hydroxy ketones **7a-c** in 74-100% ee. The reduction product (+)-**7a** and (-)-**7'c** were shown to be the chiral intermediates for the total synthesis of cantabrenonic acids derivatives **3** and hirsutene (**4**), respectively. The subsequent transformation of (+)-**7a** gave the intermediate (+)-**5** for the total synthesis of capnellenols (**1, 2**).

Enantiomerically pure functionalized bicyclo[3.3.0]octanes are important chiral building blocks for the syntheses of tricyclic sesquiterpenoids[1], for example, capnellenols (**1, 2**), cantabrenonic acid (**3a**) and hirsutene (**4**). Asymmetric syntheses of bicyclic intermediates **5** and **6** in the total syntheses[1b] of capnellenols (**1, 2**) were reported by Shibasaki and co-workers using the asymmetric Heck reaction[2], and by Fuji and co-workers using the asymmetric nitroolefination of α-methyl-δ-valerolactone[3]. (±)-Methyl cantabrenonate (**3b**) and its epoxy derivative, and (±)-hirsutene (**4**) were synthesized *via* the bicyclic intermediates **7a**[1j] and **7'c**[1m], respectively. Although the utilization of microorganisms (especially inexpensive baker's yeast) to organic synthesis has been widely studied,[4] only a few examples of the asymmetric reduction of σ-symmetric bicyclic diketones *i.e.* bicyclo[2.2.1]heptane-2,5-diones, bicyclo[2.2.2]octane-2,6-diones have been reported so far.[5] We noticed that bicyclo[3.3.0]octane-2,8-dione derivatives **8** having σ-symmetry were suitable substrates for baker's yeast reduction to give the related intermediates for the asymmetric syntheses of the natural products mentioned above. If it were possible to obtain the hydroxy ketone **7** in excellent enantioselectivity, this methodology would reduce the synthetic steps to these natural products. Here we report the enantioselective reduction of σ-symmetric bicyclo[3.3.0]octane-2,8-diones **8** with baker's yeast.

Figure 1



1 R_1 = H, R_2 = OH
2 R_1 = R_2 = OH

3a,b a R = H
b R = Me

4 **5** **6**

Baker's yeast (*Saccharomyces cerevisiae*) reduction[4] of prochiral ketones is empirically known to give (*S*)-alcohol predominantly (Prelog's rule).[6] Reduction of one carbonyl group on the bicyclic diketone **8a-c** allows theoretically the four enantiomers depicted in Scheme 1 to be obtained. According to Prelog's rule, the hydroxy ketones **7a-c** and **7'a-c** were expected to be produced over *ent*-**7a-c** and *ent*-**7'a-c**. Furthermore, we

counted on the access of the hydride from the less hindered side (convex face) of **8a-c**. We therefore could predict that the optical active hydroxy ketones **7a-c** by enantioface selection of two carbonyl groups of **8a-c** on the treatment of baker's yeast would be obtained exclusively. The results of baker's yeast reduction on **8a-c**[7] were compiled in Table 1.

Scheme 1

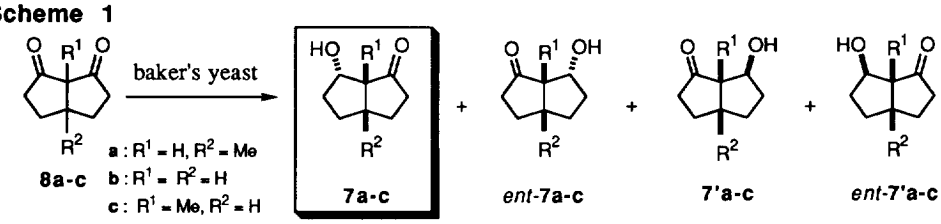


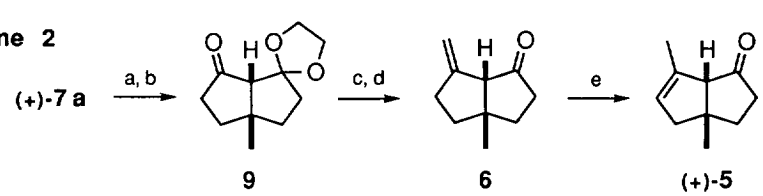
Table 1. Baker's Yeast Reduction of Bicyclo[3.3.0]octane-2,8-diones [a)]

substrate	reaction time	product	yield (%)[b)]	% ee [c)]	$[\alpha]_D^{26}$ ($CHCl_3$)
8a	7 d	**7a**	45	99	+ 163 (*c* 5.3)
8b	8 d	**7b**	41	~100	+ 204 (*c* 5.1)
8c	13 d	**7c**	31	74	+ 136 (*c* 2.0)
		7'c	34	73	- 84 (*c* 1.4)

a) Representative procedure[8]: diketone **8a** (2.07 g) was stirred with baker's yeast (30 g) and D-glucose (30 g) in distilled water (200 ml) for 1 week. Extractive work-up and chromatography on silica gel gave hydroxy ketone **7a** in 45 % yield. b) Isolated yield c) Determined by ^{1}H-NMR with $Eu(hfc)_3$.

The stereochemistry of hydroxy bearing centre in (+)-**7a** has been assigned by Piers and co-workers.[1j] The enantiomeric purity was determined 99% ee by ^{1}H-NMR [$Eu(hfc)_3$] chiral shift experiment. Absolute configuration of (+)-**7a** was determined by its transformation to the intermediate (+)-**5**[2] for the asymmetric synthesis of capnellenols (**1**, **2**), shown in Scheme 2. Protection of carbonyl group in the hydroxy ketone (+)-**7a** with ethylene glycol and subsequent oxidation of alcohol with pyridinium chlorochromate (PCC) gave ketoacetal **9**. Methylenation of **9** by Nozaki-Wittig reagent[9] followed by deprotection of the acetal with pyridinium *p*-toluenesulfonate (PPTS) afforded **6**, while the reaction with the Wittig reagent was unsuccessful. Isomerization of the exo double bond of **6** according to the Shibasaki's procedure[2] gave the intermediate (+)-**5** in 83% yield, of which spectroscopic data and specific rotation {$[\alpha]_D^{22}$ +662 (*c* 2.0, $CHCl_3$) (99% ee), Lit.[2] $[\alpha]_D^{20}$ +532 (*c* 0.85, $CHCl_3$) (80% ee)} were consistent with those of Shibasaki.

Scheme 2

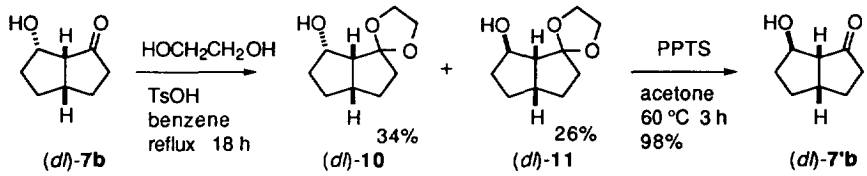


a) $HOCH_2CH_2OH$, cat. TsOH, benzene, reflux, 76%. b) PCC, CH_2Cl_2, r.t., 68%.
c) Zn/CH_2Br_2, $TiCl_4$, CH_2Cl_2, r.t., 82%. d) cat. PPTS, acetone-water (8:1), 60 °C, 98%.
e) DBU, benzene, reflux, 83%

Consequently, the absolute configuration of (+)-**7a** obtained by the asymmetric reduction of **8a** with baker's yeast was determined definitely, and the expeditious relay asymmetric total synthesis of capnellenols (**1**, **2**) was established.

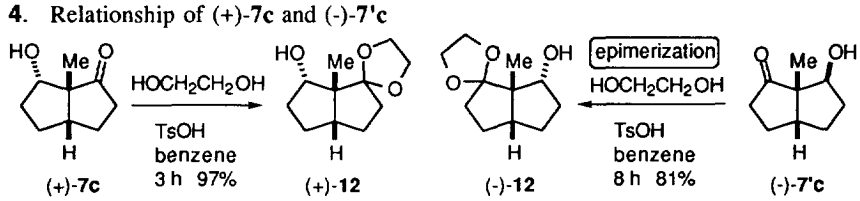
The relative configuration of (+)-**7b**, which has not been clarified on the literature[7a], was determined as follows: (1) racemic **7b**[7] was acetalized with ethylene glycol to give racemic **10** and epimerized[10] **11** by retroaldol-aldol condensation in 34% and 26% yields, respectively. (2) The isolated **11** was deacetalized to afford racemic **7'b** (Scheme 3). The comparison of ^{13}C-NMR shifts on the methine carbon having hydroxyl group of **7b** and **7'b**, which were recorded 74.61 ppm and 76.75 ppm respectively, confirmed the relative configuration of (+)-**7b** on the basis of the report by Paquette.[11] The absolute configuration of the secondary alcohol centre in (+)-**7b** was determined to be *S* by Lightner's method[12] using (*R*)-(+)-MTPA esters and Eu(hfc)$_3$.[13]

Scheme 3



The stereochemistry of the hydroxy ketones (+)-**7c** and (-)-**7'c** having known relative configurations[1m] was reconfirmed by NOESY experiments. The acetalization of (+)-**7c** gave the hydroxy acetal (+)-**12** {$[\alpha]_D^{22}$ + 42.7 (*c* 3.2, MeOH)}, on the other hand the same reaction of (-)-**7'c** afforded the hydroxy acetal (-)-**12** {$[\alpha]_D^{23}$ - 42.0 (*c* 3.0, MeOH)} by the epimerization. Therefore, the diastereomeric and enantiomeric relationship of (+)-**7c** and (-)-**7'c** were clearly assigned as shown in Scheme 4. By the same Lightner's method[11] as **7b**, the absolute configuration of the secondary alcohol centre on (+)-**7c** was concluded to be *S*.

Scheme 4. Relationship of (+)-**7c** and (-)-**7'c**



The products from baker's yeast reduction coincided with those predicted above. The enantiomeric excesses of (+)-**7a** and (+)-**7b** were extremely high. The poor diastereo- and enantioselectivity of the reaction with **8c** was presumably due to bulkiness of the methyl substituent adjacent to the carbonyl group. Thus, the bulkiness of the methyl substituent might reduce the convex and concave face selectivity in bicyclo[3.3.0]octane skeleton as well as the re- and si-face selectivity of the two carbonyl groups.

In summary, we have demonstrated the highly enantioselective reduction of σ-symmetric bicyclo[3.3.0]octane-2,8-diones **8a** and **8b** utilizing baker's yeast. The described hybrid process (the combination of microbial or enzymatic and chemical transformation) should prove to be a powerful tool for the asymmetric total synthesis of capnellenols (**1**, **2**) and cantabrenoic acid derivatives **3** and hirsutene (**4**).

ACKNOWLEDGMENT

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