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Reassignment of the absolute configuration of the baker's yeast reduction of (±)-ethyl 1-allyl-2-oxocyclopentanecarboxylate

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Abstract

The baker's yeast reduction of (±)-ethyl 1-allyl-2-oxocyclopentanecarboxylate under aqueous conditions in the presence of CuO yields (1*S*,2*S*)-(+)-ethyl 1-allyl-2-hydroxycyclopentanecarboxylate and the unreacted enantiomer (1*R*)-(−)-ethyl 1-allyl-2-oxocyclopentanecarboxylate. The absolute configuration of the secondary alcohol was determined from the X-ray crystal structure of the (1*S*)-10-camphorsulfonyl derivative of (1*S*,2*S*)-(+)-ethyl 1-allyl-2-hydroxycyclopentanecarboxylate. This refutes configurational claims based on CD/ORD and chemical affiliation techniques currently reported in the literature for this reaction. © 1999 Elsevier Science Ltd. All rights reserved.

In a project related to the synthesis of enantiopure *cis*,*cis*-spiro[4.4]nonane-1,6-diol,[1] we repeated the procedure reported by Fraga and Barreiro[2,3] in which they report that (±)-ethyl 1-allyl-2-oxocyclopentanecarboxylate (±)-**1** can be selectively reduced by *Saccharomyces cerivisiae* (baker's yeast) in the presence of CuO to give (1*R*,2*R*)-(+)-ethyl 1-allyl-2-hydroxycyclopentanecarboxylate (+)-**2** and the unreacted enantiomer of the β-ketoester (1*S*)-(−)-**1** (top arrow of Scheme 1). We provide evidence herein that the kinetic reduction of (±)-**1** with baker's yeast provides (1*S*,2*S*)-(+)-**2** ($[\alpha]_D^{20.6}$ +27.9 (c=1.2, $CHCl_3$)) and (1*R*)-(−)-**1** ($[\alpha]_D^{21.1}$ −33.4 (c=1.2, $CHCl_3$)) (bottom arrow of Scheme 1).

The previously claimed configuration of secondary alcohol (+)-**2** was assigned by default after the absolute stereochemistry of (−)-**1** was determined by: (1) measuring the CD/ORD spectrum of (−)-**1**; and (2) by comparing the sign of the optical rotation of (+)-**3**, which was prepared from (−)-**1** in three steps, with the known diester (1*S*)-(+)-**4**[4] (Scheme 2). Based on this correlation, Fraga et al. claimed this reduction with baker's yeast was an exception to Prelog's rules.[5]

Because (+)-**2** is a key starting material for our synthesis of spirodiols, we decided to unambiguously assign the absolute configuration in (+)-**2**. To ensure the correct absolute configuration of (+)-**2** and (−)-**1**, we treated (±)-**1** under the same aqueous enzymatic reducing conditions described by Fraga et al. (bottom arrow of Scheme 1) and treated the secondary alcohol (+)-**2** with (1*S*)-(+)-10-camphorsulfonyl chloride in the presence of NEt_3 in CH_2Cl_2 (Scheme 3).[6] This provided **5** as a solid. The X-ray crystal structure[7]

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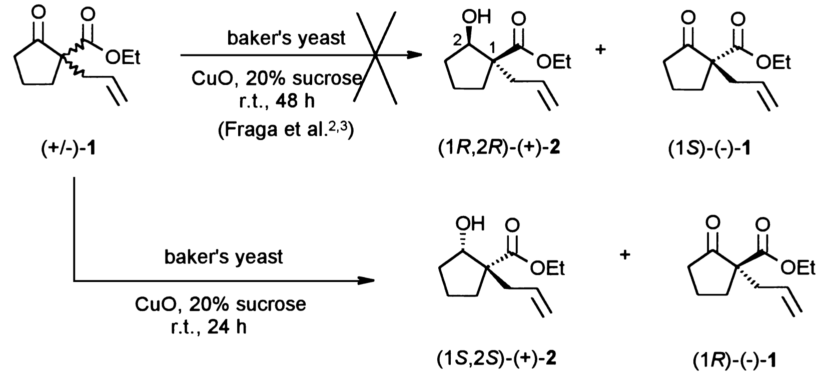
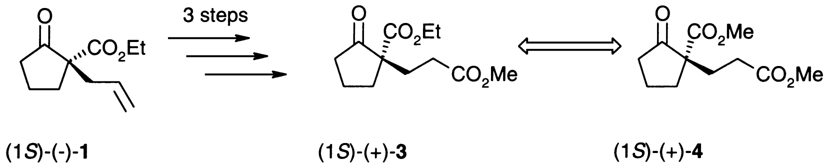
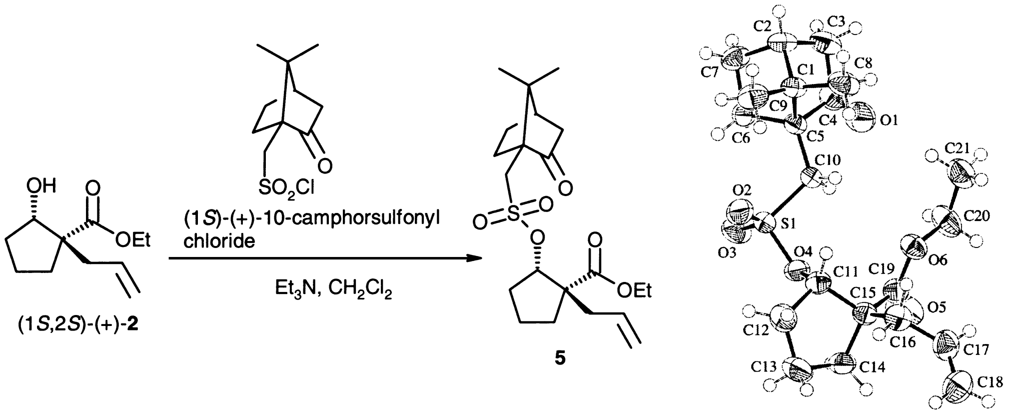


Scheme 1.



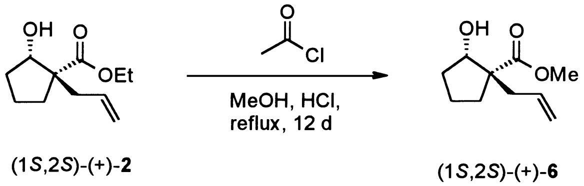
Scheme 2.

of ester **5** clearly showed that the absolute configuration of (+)-**2** was in fact the product predicted by Prelog's rules, notably (1*S*,2*S*)-(+)-ethyl 1-allyl-2-hydroxycyclopentanecarboxylate. To be sure that the camphorsulfonyl chloride shipped[8] to us was indeed the (1*S*)-(+)-enantiomer of 10-camphorsulfonyl chloride, the optical rotation was measured and found to be $[\alpha]_D^{19.6}$ +30.9 (c=0.990, $CHCl_3$), which compared favorably to the literature value of $[\alpha]_D^{25.0}$ +32.1 (c=1, $CHCl_3$).[9] To further confirm the absolute configuration of **5**, a Bijvoet[10] analysis was conducted on the cyrstal of **5**, which confirmed the absolute configuration as that shown in Scheme 3.



Scheme 3.

As secondary proof of the absolute configuration of (+)-**2**, we decided to convert (1*S*,2*S*)-(+)-**2** into (1*S*,2*S*)-(+)-**6**, whose absolute configuration has been reported.[11] Transesterification of (1*S*,2*S*)-(+)-**2** with HCl in refluxing MeOH in the presence of acetyl chloride for 12 days yielded methyl ester (1*S*,2*S*)-(+)-**6** (Scheme 4). Compound (1*S*,2*S*)-(+)-**6** had an optical rotation of $[\alpha]_D$ +25.6 (c=1.875, $CHCl_3$) that closely matched the optical rotation reported by Seebach $[\alpha]_D$ +26.3 (c=1.87, $CHCl_3$) thereby further confirming the absolute configuration of (1*S*,2*S*)-(+)-**2**.



Scheme 4.

It should also be noted that significant improvements on the reported yield of the baker's yeast reduction of (±)-**1** were achieved. The reaction was carried out under the same conditions outlined by Fraga et al. with the exception that we only let the reaction run for 24 h instead of 48 h. In addition to the ethyl acetate extraction of the reaction filtrate, the yeast residues were subjected to Soxhlet extraction in chloroform. Yields of 39% and 40% were obtained for (−)-**1** and (+)-**2**, respectively, which compare favorably with yields reported for the organic phase baker's yeast reduction of (±)-**1**.

Therefore we have shown that the baker's yeast reduction of (±)-**1** actually produces (1*S*,2*S*)-(+)-**2** and (1*R*)-(−)-**1**. In addition, the kinetic reduction with baker's yeast follows Prelog's rules for the prediction of the absolute configuration for the formation of β-hydroxyesters from β-ketoesters as reported by others.[12]

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7. Compound **5**: monoclinic $P2_1$ (#4); a=6.877(4) Å, b=8.638(1) Å, c=18.258(5) Å, β=94.96(3)°; V=1080.5(5) Å^3; Z=2; R=0.042; R_w=0.095; Flack parameter [Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876–878]=0.02(2). Bijvoet analysis was performed. A refinement of the inverted structure was carried out which converged with R=0.052, R_w=0.126 and the Flack parameter=0.88(3), and was therefore rejected as the absolute configuration present in the crystal.
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