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SYNTHESIS OF OPTICALLY ACTIVE *t*-BUTYL (*3R,5S*)-3,5-ISOPROPYLIDENEDIOXY-6-HEPTYNOATE THROUGH BAKER'S YEAST REDUCTION OF METHYL 3-OXO-4-PENTYNOATE

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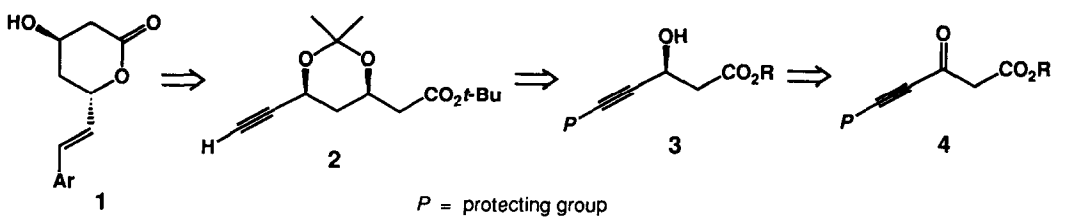
Abstract: Baker's yeast reduction of methyl 3-oxo-4-pentynoate gave the corresponding (*S*)-3-hydroxy ester (80% e.e.), whereas its 5-trimethylsilyl derivative gave the (*R*)-enantiomer (82% e.e.). The (*S*)-alcohol was led to optically active *t*-butyl (*3R,5S*)-3,5-isopropylidenedioxy-6-heptynoate, a versatile synthetic intermediate of artificial HMG-CoA reductase inhibitors.

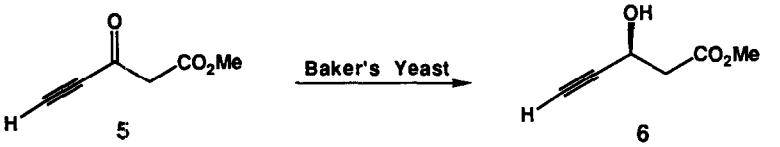
One of the most important and useful chemical transformations of organic compounds is asymmetric reduction of prochiral ketones to optically active secondary alcohols. To this end various chemical or biological methods have been developed, where baker's yeast reduction has played a key role as a ready procedure for optically pure alcohols.[1] Among the many applications of baker's yeast in asymmetric synthesis, the reduction of β-keto esters to the corresponding β-hydroxy esters is one of the most extensively studied microbial transformation for the production of chiral building blocks.[1] As a part of our program aimed at developing useful synthetic methods[2] for the preparation of artificial analogs of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors having a common structure (**1**), we have recently disclosed a new protocol[3] using hydrosilylation and cross coupling methodology where optically pure *t*-butyl (*3R,5S*)-3,5-isopropylidenedioxy-6-heptynoate (**2**) served as a key intermediate. We have since been studying an alternative approach for the synthesis of optically active **2** starting from γ-acetylenic β-hydroxy ester **3** which might be obtained by the asymmetric reduction of γ-acetylenic β-oxo ester **4** such as with baker's yeast in optically active form (Scheme 1). To the best of our knowledge, there is no report in the literature about the asymmetric reduction of prochiral γ-acetylenic β-keto esters to the corresponding alcohols with baker's yeast except one example of microbial resolution of alkynyl esters by lyophilized baker's yeast.[4] In view of our interest to examine for the first time the reduction of γ-acetylenic β-keto esters and in the hope of getting the corresponding

Scheme 1



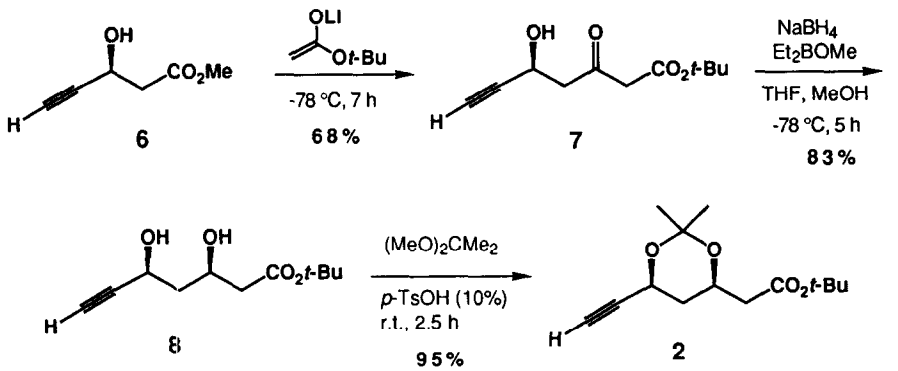
optically active alcohols for our synthetic program of HMG-CoA reductase inhibitors, we studied baker's yeast reduction of methyl 3-oxo-4-pentynoate (**5**)[5] and report herein the results and application of the resulting alcohol **6**[6] to the synthesis of optically active *t*-butyl (*3R,5S*)-3,5-isopropylidenedioxy-6-heptynoate (**2**), a versatile common intermediate of artificial HMG-CoA reductase inhibitors.[7]

Exposure of **5** to a fermentation medium[8] of baker's yeast followed by filtration through a Celite pad, saturation of the filtrate with sodium chloride and ethyl acetate extraction (5 times) gave an alcohol **6** in 46% yield as an oil, $[\alpha]_D^{20}$ -19.15° (*c* 0.71, $CHCl_3$). The enatiomeric excess of **6** was 80% as determined by HPLC analysis of its (*R*)-MTPA ester derivative.[9] The stereochemical assignment was based on its chemical transformation to the corresponding *t*-butyl 3,5-*syn*-isopropylidenedioxy-6-heptynoate (Scheme 2) and comparison of its optical rotation with an authentic sample of (*3R,5S*)-enantiomer **2**.[3]

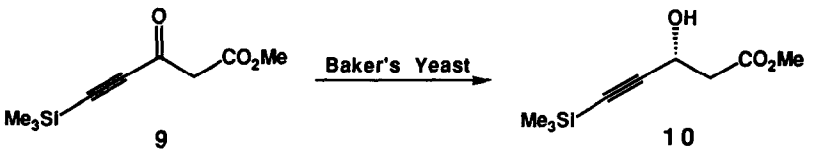


Condensation of *t*-butyl lithioacetate with **6** led to *t*-butyl 3-oxo-5-hydroxy-6-heptynoate **7**. This was reduced with $NaBH_4$ in the presence of Et_2BOMe to give exclusively *syn*-3,5-dihydroxy ester **8** which was protected with $(MeO)_2CMe_2$ (10% *p*-TsOH) to give the desired compound **2** showing $[\alpha]_D^{20}$ -4.15° (*c* 1.01, $CHCl_3$) [lit[3] $[\alpha]_D^{20}$ -4.99° (*c* 1.00, $CHCl_3$)]. Hence, the absolute configuration of the initial yeast reduction product **6** was established to be (*S*).

Scheme 2

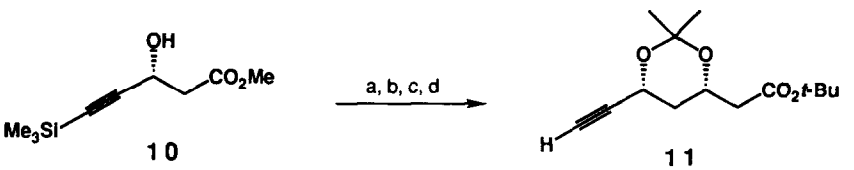


To our surprise, a trimethylsilyl protected substrate **9**[5] afforded an alcohol having an opposite configuration. Reduction of **9** with baker's yeast under the same conditions gave the corresponding β-hydroxy ester **10** (48% isolated yield) as an oil, $[\alpha]_D^{20}$ +19.13° (*c* 1.45, $CHCl_3$), 82% e.e. (determined by HPLC analysis of its (*R*)-MTPA ester). The identity of **10** was proved in a similar way (Scheme 3).



Condensation of *t*-butyl lithioacetate with **10** afforded β-oxo-δ-hydroxy ester, which was reduced by $NaBH_4$ in presence of Et_2BOMe to give exclusively a *syn*-β,δ-dihydroxy ester. Subsequent deprotection and protection led to **11**, $[\alpha]_D^{20}$ +4.18° (*c* 1.29, $CHCl_3$), an enantiomer of **2**.

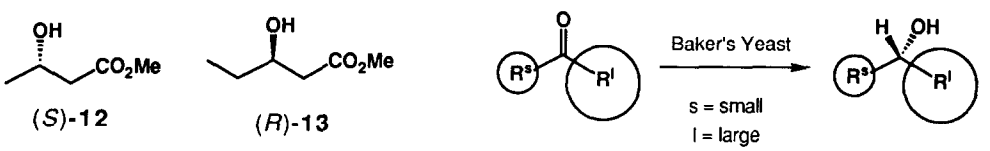
Scheme 3



a: CH_2=C(OLi)O*t*-Bu, -78 °C, 1 h, -15 °C, 30 min, **74%**; b: $NaBH_4$, Et_2BOMe, THF-MeOH, -78 °C, 5 h, **82%**; c: Bu_4NF, THF, 0 °C, 1 h, **78%**; d: $(MeO)_2CMe_2$, *p*-TsOH (10%), r.t., 2.5 h, **98%**

The stereochemical outcome of asymmetric reduction of **5** and **9** by baker's yeast deserves a comment. Reduction process of methyl acetoacetate and methyl 3-oxopentanoate is known to follow the Prelog's rule[10] to give alcohols (*S*)-**12** and (*R*)-**13**, respectively. This rule is presented by Scheme 4 which applies to the reduction of **5** if we assume an ethynyl group is similar to ethyl. However, trimethylsilyl group, apparently larger than ethynyl group, behaved like R^s according to the reduction of **9**. This result should be understood in terms of Sih's rule: kinetic control.[11]

Scheme 4



In summary, we have disclosed here first example of baker's yeast reduction of methyl 3-oxo-4-pentynoates to the corresponding optically active hydroxy esters which provides us with both enatiomers of resulting alcohols depending on the protection of acetylenic terminal. The (*S*)-alcohol was derivatised to an optically active synthetic intermediate **2** of highly potent analog of HMG-CoA reductase inhibitors. Further efforts are in progress to improve the selectivity of the reduction process and to exploit its potential in the synthesis of other natural products.

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5. The β-keto esters **5** and **9** were prepared by the condensation of methyl lithioacetate with corresponding ethyl propiolates (*cf.* Wasserman, H. H.; Frechette, R; Oida, T.; van Duzer, J. H. *J. Org. Chem.* **1989**, *54*, 6012).
6. Following optically active (*S*)-3-hydroxy-4-pentynoates are known: a) *t*-butyl (*S*)-3-hydroxy-5-trimethylsilyl-4-pentynoate: [85% e.e., $[\alpha]_D$ -10.5° (*c* 2, $CHCl_3$)] prepared by asymmetric aldol condensation (Solladie, G.; Hamdouchi, C. *Synthesis*, **1991**, 979); b) ethyl (*S*)-3-hydroxy-4-pentynoate [91% e.e., $[\alpha]_D$ -22.1° (*c* 3.6, $CHCl_3$)].[4]
7. Application of baker's yeast reduction of β-keto esters to the synthesis of natural HMG-CoA reductase inhibitors, see: Hirama, M.; Uei, M. *J. Am. Chem. Soc.*, **1982**, *104*, 4251; Hirama, M.; Shimidzu, M.; Iwashita, M. *J. Chem. Soc., Chem. Commun.*, **1983**, 599.
8. *Typical experimental procedure*: To a suspension of dry baker's yeast (Oriental Yeast Co., Ltd., 9 g) in 400 ml of boiled-cooled water was added glucose (30 g), and the mixture was stirred at 30 °C for 30 min. To this fermentation mixture was added a substrate (3.9 mmol) dissolved in ethanol (2 ml), and the mixture was stirred for 12 h at 30-31°C, treated with Celite (5 g) at ice bath temperature, stirred further for 2 h and filtered through a pre-washed (EtOAc) Celite pad. The Celite was washed with ethyl acetate, and the combined filtrates were saturated with sodium chloride and then extracted with ethyl acetate (5 x 500 ml). The organic layer was washed with water, dried over anhydrous $MgSO_4$ and concentrated to give an oily crude product. Since the crude product was contaminated by higher fatty acids, this was treated with an ethereal solution of diazomethane. Purification by column chromatography using a mixture of hexane and ethyl acetate (3:1; v/v) as eluent to give the pure product, Rf = 0.325 (hexane:ethyl acetate; 2:1).
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