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SYNTHESIS OF OPTICALLY ACTIVE ALKYNYL ALCOHOLS BY MICROBIAL ASYMMETRIC HYDROLYSIS OF THE CORRESPONDING ACETATES

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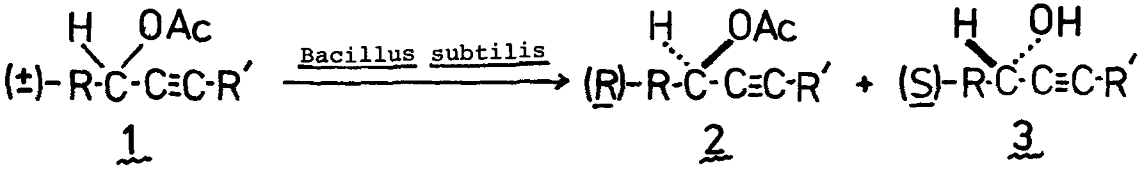
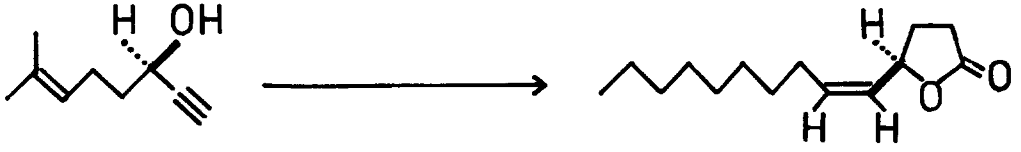
In spite of plenty of works concerning applications of biochemical systems in organic chemistry,[1] there are still vast possibilities of employing microorganisms or enzymes in executing preparative organic transformations. Obviously the most noteworthy feature of a microbial reaction is its enantioselectivity. Here we report our findings on the asymmetric hydrolysis of acetates of racemic alkyl alkynyl carbinols by Bacillus subtilis var. Niger. This bacterium is known to effect asymmetric hydrolysis of acetates of some terpene alcohols.[2]



Optically active alkynyl alcohols are useful intermediates in natural products syntheses,[3,4,5] and can be prepared either by optical resolution of the racemates or by asymmetric reduction of the corresponding acetylenic ketones in the presence of (+)-(2S, 3R)-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (Darvon alcohol).[4] However, the resolution is tedious and the reduction requires rather inaccessible "Darvon alcohol."

When acetates of racemic alkyl alkynyl carbinols (**1**) were shaken for 3 days at 30° with *Bacillus subtilis* var. *Niger* grown in a 2% nutrient broth, optically active (*R*)-alkynyl acetates (**2**) and (*S*)-alkynyl alcohols (**3**) were obtained as shown in the TABLE.

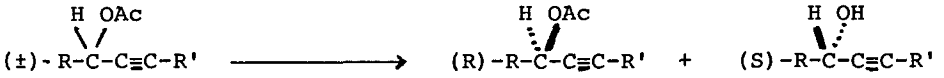
The absolute configuration of the hydrolysis products (**3**) was assigned to be *S* by correlation with the reported data in the cases of **3a**,[6] **3b**,[7] and **3e**.[3] The *S* absolute stereochemistry of (-)-**3d** was deduced by the conversion of 90% optically pure (+)-**3d** to (*S*)-(+)-decan-3-ol.[8] The (+)-enyne alcohol **3f** also belonged to the (*S*)-series, since 90% optically pure (-)-**3f**[9] yielded the natural enantiomer (85% optical purity, $[\alpha]_D^{22}$ - 59.4° (c=1.04, $CHCl_3$)) of the Japanese beetle pheromone (**4**, (*R*, *Z*)-5-(1-decenyl)dihydro-2(3H)-furanone, lit. $[\alpha]_D^{26}$ - 69.6° (c=5, $CHCl_3$)).[10] In any of the above cases, the NMR signal due to the O*Me* protons of the (*S*)-(-)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) ester[11] of an (*S*)-alcohol (**3**) appeared at a higher field than that of the enantiomeric (*R*)-alcohol in the presence of the Sievers' reagent, $Eu(fod)_3$. By this correlation, it was possible to deduce the absolute configuration of **3c** to be *S*.



(*R*)-**3f** (*R*)-(*Z*)-**4**

The optical purities of the products were determined by the NMR measurement and GLC analysis of the (*S*)-(-)-MTPA esters of the alcohols (**3**). An acetate (**2**) with unknown optical purity was hydrolyzed to compare the $[\alpha]_D$ value of the corresponding alcohol with that of the enantiomeric alcohol whose optical purity was determined by the MTPA-ester method. In this manner the optical purities of all of the products were clarified and shown in the TABLE. The acetates with smaller alkyl groups (**1a**, **1b** and **1e**) yielded products with higher optical purities, while the acetates with larger alkyl groups (**1c**, **1d** and **1f**) gave unsatisfactory results. No hydrolysis took place in the case of **1g** where R and R' were both bulky alkenyl and alkyl groups.

TABLE Asymmetric Hydrolysis of Some Acetates of Racemic Alkyl Alkynyl Carbinols with *Bacillus subtilis* var. *Niger*



1 2 3

Substrate	R	R'	Product ratio[a] 2 : 3	Isolated yield[b] 2 : 3	Obsd $[\alpha]_D$ (optical purities[c]) of Acetate (2)	and Alcohol (3)
1a	Et	H	1 : 2.8	9% : 20%	$+91.6^{\circ}$[d] (72%)	-22.5°[d] (54%)
1b	n-Pr	H	1 : 1.6	22% : 36%	$+88.1^{\circ}$[d] (90%)	-24.0°[d] (68%)
1c	n-Bu	H	1 : 1.3	28% : 28%	$+11.1^{\circ}$[d] (16%)	-3.2°[d] (14%)
1d	n-Oct	H	1 : 0.4	53% : 25%	$+3.2^{\circ}$[d] (7%)	-2.1°[d] (16%)
1e	Me_2CHCH_2	Me	1 : 1.8	25% : 36%	$+78.9^{\circ}$[d] (74%)	-7.6°[e] (54%)
1f	$Me_2C=CH(CH_2)_2$	H	1 : 0.7	28% : 14%	$+17.4^{\circ}$[f] (34%)	-3.2°[f] (40%)
1g	$Me_2C=CH(CH_2)_2$	n-Oct	1 : 0	—— ——	——	——

a As determined by GLC or NMR analyses of the crude products before chromatographic purification. The area ratio of the signals due to C<u>H</u>OH (δ4.2) and C<u>H</u>OAc (δ5.2) protons was compared.

b The microorganism was cultured for 2 days at 30° in a nutrient broth (100 ml containing beef extract (0.33g), peptone (1.11g) and NaCl (0.56g)). Then ca. 2g of 1 was added and the culture medium was shaken for 3 days at 30°. The broth was extracted with ether. The ether extract was washed with brine, dried ($MgSO_4$) and concentrated. The residual oil was chromatographed over neutral alumina (Woelm, grade II). Elution with n-pentane (or hexane) gave 2 Further elution with n-pentane (or hexane)-ether (1:1) gave 3. The yields refer to the pure distilled products. The structures and purities were fully checked (IR, NMR and GLC).

c The optical purities were determined by the NMR analysis of the (<u>S</u>)-(-)-MTPA esters of the alcohols (3) in the presence of $Eu(fod)_3$. Alternatively, the MTPA esters were analyzed by GLC. The retention times of the esters of (<u>S</u>)-alcohols were always shorter than those of the (<u>R</u>)-alcohols. The figures obtained by these two methods were in good accord.

d Measured as ether soln.

e Measured as $CHCl_3$ soln.

f Measured as n-hexane soln.

In summary, the followings were concluded.

(1) Bacillus subtilis var. Niger effects asymmetric hydrolysis of several alkynyl acetates.

(2) The bacterium always preferentially hydrolyzes (S)-acetates to give (R)-acetates and (S)-alcohols, although in varying optical yields. Therefore, by a single fermentation, it is possible to obtain the both enantiomers after chromatographic separation.

(3) The MTPA-ester method (both NMR and GLC) is quite useful in assigning the absolute configuration of the alkyl alkynyl carbinols.

(4) In view of the simplicity of the experimental procedure, this microbial method is an excellent preparative method for chiral alkyl alkynyl carbinols of known absolute configuration.

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