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Microbially-aided Preparation of (S)-2-Methoxycyclohexanone Key Intermediate in the Synthesis of Sanfetrinem

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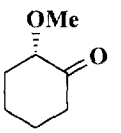
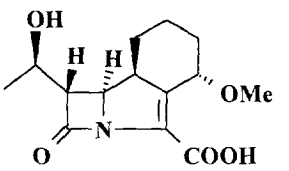
Abstract: (*S*) 2-Methoxycyclohexanone **1**, useful intermediate in the synthesis of Sanfetrinem **2**, is obtained from (*S*) α-benzylidene cyclohexanol **4**, derived from the ketone **3** through a short sequence involving as key step yeast reduction of the carbonyl group. The (*R*) enantiomer of **1** is similarly accessible from the (*R*) enantiomer of **4** obtained either upon *Candida lipolytica*-mediated reduction of **3** or from (*R,S*)-**4** by porcine pancreatic lipase catalyzed acetylation with vinyl acetate. Also the saturated carbinols **7** and **8**, which accompany **4** in the microbial reduction of **3**, are converted into **1** through unexceptional steps. *Nocardia opaca*, *Pichia etchelsii* and *Mucor subtilissimus* provide from **3** upon reduction (*S*)-configurated **4**, **7** and **8** possessing moderate-high *ee* values.

For some years now extensive studies have been performed on the mode of transformation of multifunctional unnatural carbonyl compounds by microorganisms[1] and by baker's yeast in particular.[2] As a result, a whole set of optically active compounds became available by these means. However, most of these materials seemed, up to now, to be not susceptible of practical applications in the synthesis of enantiopure compound of industrial interest. Important exception to this trend is the synthesis of ephedrine[2] and of the steroid *trimegestone* [3]. Recently[4] the utility of (*S*) 2-methoxycyclohexanone **1** in the synthesis of the trinem antibiotic sanfetrinem **2** has been described. Reportedly, ketone **1** is obtained upon Swern oxidation of (+)-(1*S*,2*S*)-2-methoxycyclohexanol prepared by enzymic resolution of the racemic material. Since the (-)-(1*R*,2*R*) isomer is available from enzymatic hydrolysis of trans-racemic esters as reported in the literature[5] , the (+)-(1*S*,2*S*)-alcohol was secured by enzymatic

acylation of the unwanted isomer and separation from the ester formed[6]. Alternatively *trans* racemic 2-methoxycyclohexanol was esterified with L-valine, the diastereomeric esters purified by crystallization and the required alcohol obtained by subsequent hydrolysis in about 25% yield[6]. This report suggested us the use as alternative precursor of **1** (*S*) α-benzylidene cyclohexanol **4**, recently characterized as one of the educts of the baker's yeast mediated transformation of α-benzylidene cyclohexanone **3**[7]. Since enzymic carbonyl reduction compares favorably in terms of precursor utilization with respect to enzymic kinetic resolution of a racemic material in the production of enantiomerically pure carbinols, we explored an approach to (*S*) **1** based on the microbial reduction of **3** to **4** and we present now the results.



1



2

In the first instance, the enantiomerically pure, yeast-generated (*S*) carbinol **4** was converted (NaH/THF, then MeI) into the O-methyl ether **5** in 95% yield. This material, on ozonolysis in methylene chloride at low temperature and PPh_3 treatment, provided in high yield the desired (*S*) 2-methoxycyclohexanone **1**, $[\alpha]^{D}_{20}$ -71 (c 1, $CHCl_3$), separated from the accompanying benzaldehyde by column chromatography. The substantial enantiomeric purity of product **1** obtained by these means was determined by multidimensional GLC analysis and comparison with the racemic material.[8] When the ozonolytic cleavage of **5** was performed as above but using methylene chloride/methanol 4:1 as solvent , the dimethoxyketal of **1** in racemic form was isolated.

Thus, from a synthetic viewpoint product **4** appears a convenient precursor of **1**. However, baker's yeast out of **3** produces the allylic alcohol **4** in 2:3 ratio with the saturated ketone **6**. This kind of product distribution is probably dependent upon the inhibitory effect of the enone moiety of **3** towards carbonyl reduction.[9] In fact, racemic saturated ketone **6** on yeast treatment rapidly affords[7] a 1:1 mixture of enantiomerically pure (1*S*,2*R*) **7** and (1*S*,2*S*) **8** in high yield. Accordingly, we thought worthwhile to explore the conversion of **7** and **8** into **1** *via* i) O-methylation, ii) benzylic bromination, iii) dehydrobromination, and iv) ozonolysis.

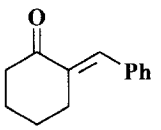
To this end, the saturated carbinols **7** and **8,** in separate experiments, were converted into the O-methyl ethers **9** and **10**, as indicated for **4**. Bromination of the above materials using N-bromosuccinimide in CCl_4 afforded a 1:1 mixture of two products by TLC and GLC analysis, unseparable by column chromatography. NMR studies indicated the presence of two diastereoisomers identified as the two couples of 1'-bromoderivatives **11** and **12.**. Indeed, in the spectrum of **11** relevant distinct signals were observed for the O-Me group at 3.3 and 3.5 ppm (1.5 hydrogen atom each) and for the hydrogen atom linked to the oxygen-bearing carbon atom at position 1 at 2.6

and 3.2 ppm (0.5 hydrogen atom each), respectively. For compound **12** the two sets of signals appeared at 2.9, 3.4, 2.85 and 4 ppm, respectively.

The dehydrobromination of the two couple of diastereoisomers **11** and **12** using DBU in refluxing acetonitrile proceeded in different ways. The former material, possessing 1,2- *anti*-located substituents on the cyclohexane ring, rapidly provided on basic treatment the (*E*) allylic ether **5** as exclusive transformation product. Conversely, the diastereomeric mixture **12** reacted at much lower rate, with one of the two diastereoisomers reacting faster, and eventually gave a 1:1 mixture of the stereoisomeric (*E*) and (*Z*) olefins **5** and **13**.
Finally, product **5** obtained from 7and the mixture **5**+**13** derived from **8**, upon ozonolysis provided enantiomerically pure **1**.

This sequence thus allows the conversion into the enantiomerically pure ketone **1** of the two sets of enantiomerically pure carbinols accessible from **3** upon baker's yeast reduction.

Thus, in the above mentioned routes, the allylic alcohol **4** accessible from **3** in baker's yeast close to the racemic saturated ketone **6** (2:3 ratio) provides **1** in two steps, whereas the saturated enantiomerically pure carbinols **7** and **8**, obtained as exclusive materials of bioreduction of the saturated ketone **6**, are converted into the same target molecule in four steps.



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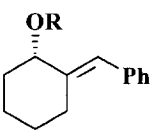
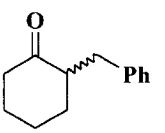
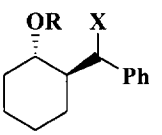


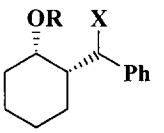
4 R=H
5 R=CH_3



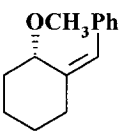
6



7 R=X=H
9 R=CH_3; X=H
11 R=CH_3; X=Br



8 R=X=H
10 R=CH_3; X=H
12 R=CH_3; X=Br



13

Since the mode of transformation of α,β-unsaturated carbonyl compounds structurally related to **3** is strongly dependent upon the microorganism used,[10] we performed a screening in the expectation to identify a microorganism able to selectively transform **3** either into the allylic alcohol **4** or into the saturated carbinols **7** and **8**. Of the many microorganisms tested, few showed interesting selectivity. The most outstanding result was obtained with *Candida lipolytica* CBS 2074 which afforded, as the only transformation product of **3**, in 40% yield,

the allylic carbinol, shown to contain 93% excess of the (*R*) enantiomer of **4**. Conversely, *Nocardia opaca* DSM 43205, *Pichia etchelsii* CBS 2011 and *Mucor subtilissimus* CBS 735.70 under identical conditions provided mixtures of (*S*) configurated unsaturated and saturated alcohols, possessing different enantiomeric composition (Table 1).

Entry	*Microorganism*	**Product**, %, (*ee*)		
		4	**7**	**8**
1	*Nocardia opaca*	23.6 (*0.26*)	53 (*0.47*)	23.4 (*0.84*)
2	*Pichia etchelsii*	19 (*0.67*)	57.9 (*0.99*)	23.1 (*0.85*)
3	*Mucor subtilissimus*	6.8 (*0.50*)	80 (*0.97*)	13.2 (*0.53*)

Table 1. Product distribution and enantiomeric composition of the alcohols derived from ketone **3** in *Nocardia opaca*, *Pichia etchelsii* and *Mucor subtilissimus* (1g/l and 24 h incubation)

Inspection of the results in Table 1 shows rather variable and modest *ee* values for the allylic carbinol **4** produced by microbial reduction of **3**. Conversely, the *ee* values of the *anti* carbinol **7** resulted modest (entry 1) or very high (entries 2 and 3). The reverse is partially true for the *syn* diastereoisomer **8**, produced in high enantiomeric purity only by the two former microorganisms. Seen together, these results thus indicate that in the transformation of **3** baker's yeast is still superior in chemo and enantioselectivity to other microorganisms.

In the reported[3] and in the present synthesis of (*S*) α-methoxycyclohexanone **1** the carbonyl group is revealed at the latest stage of the process by Swern oxidation of a carbinol obtained by enzymic kinetic resolution and by ozonolysis of the double bond of **5** derived from **3** by baker's yeast reduction, respectively. We considered the mode of production of **1** from **5** here reported easy to execute and susceptible of large scale application. Accordingly, we thought of possible interest also an access to **1** from the allylic carbinol **4** produced by resolution of a racemic mixture. To this end, (*R*,*S*) **4** was incubated in the presence of PPL (Sigma type II) in *i*-Pr_2O[10] with vinyl acetate, obtaining at *ca.* 30% conversion, the corresponding enantiomerically pure (*R*) acetate ester, $[\alpha]^{D}_{20}$ +35.5 (c 1, $CHCl_3$). Basic hydrolysis of the latter material, followed by methylation and ozonolysis, afforded the (*R*) enantiomer of **1**. This experiment, considered together with those reported above, thus indicates an access to **1**

and to its enantiomer from the (*S*) and (*R*) enantiomerically pure forms of **4** produced by baker's yeast reduction of **3** and enzymic kinetic resolution of the racemic allylic alcohol, respectively.

The use of a baker's yeast mediated transformation in the preparation of (*S*) 2-methoxycyclohexanone **1**, key intermediate in a new synthesis of sanfetrinem **2** here reported, further supports the significance in the chemistry of certain β-lactam antibiotics of the microbial and enzymic methods. Indeed, the optically active acetoxyazetidinone used to construct the 'left' part of **2** has been already prepared using baker's yeast mediated processes[12] and enzymic systems.[13]

Acknowledgments: We thank Mrs. Rosanna Bernardi for the multidimensional GLC analyses performed.

Experimental

(E)(S) α-benzylidene cyclohexyloxymethyl ether (**5**). (*S*) α-benzylidene cyclohexanol **4**[7] (1.88 g, 10 mmol) in THF (30 ml) under stirring at 0°C was treated with NaH (0.24 g, 10 mmol). The reaction mixture was kept at r.t. for 2 h and then reacted at 0°C with MeI (1.4 ml, 21 mmol). After 2 h stirring the precipitated NaI is filtered and the reaction mixture is diluted with AcOEt (100 ml), washed with water, dried and evaporated. The oily residue was chromatographed on a short path of SiO_2 with hexane/AcOEt 9:1 to provide **5**, oil, 1.9 g (94% yield), $[\alpha]^D_{20}$ +7.3 (c 1, $CHCl_3$). ^1H NMR: δ_H ($CDCl_3$) 0.9-2.5 (8H, $4CH_2$, m), 3.3 (3H, OCH_3, s), 3.7 (1H, C*H*OCH_3, t), 6.4 (1H, H vinyl, s), 7.1-7.4 (5H, ArH, m). Anal. calcd. for $C_{14}H_{18}O$: C, 83.11; H, 8.98. Found: C, 83.18; H, 8.94.

(S) 2-methoxycyclohexanone (**1**). Ozonized oxygen was passed through a solution of the O-methyl ether **5** (1.82 g, 0.9 mmol) in CH_2Cl_2 (40 ml) at -78°C. At the end of the reaction N_2 was flushed through for 10 min, followed by the addition of PPh_3 (2.4 g, 0.9 mmol). After 30 min at -78°C, the temperature was raised slowly to 20°C and the reaction mixture was evaporated under vacuum. The oily residue was taken up in a small volume of ether/pentane and the precipitated phosphine oxide was removed by filtration. The residue obtained upon evaporation of the organic phase was chromatographed on SiO_2 with increasing amounts of AcOEt in hexane. The desired ketone fraction was further purified by bulb-to-bulb distillation under vacuum (water pump) to provide (*S*) 2-methoxycyclohexanone **1**, oil, 0.96 g (83% yield), $[\alpha]^D_{20}$ = -71° (c 1, $CHCl_3$)[6] ^1H NMR: δ_H ($CDCl_3$) 1.5-2.6 (8H, $4CH_2$, m), 3.45 (3H, OCH_3, s), 3.7 (1H, C*H*OCH_3, t). Anal. calcd. for $C_7H_{12}O_2$: C, 65.60; H, 9.43. Found: C, 65.67; H, 9.41.

(1S,2R) and (1S,2S) 2-benzylcyclohexyloxymethyl ethers (**9**) *and* (**10**). The O-methylation of yeast generated **7** and

8[7] was performed exactly as reported for **5** to provide in *ca.* 90% yield **9**, oil, $[\alpha]^{D}_{20}$ = -25.4° (c 1, $CHCl_3$). ^1H NMR: δ_H ($CDCl_3$) 1.0-2.1 (9H, $4CH_2$+ CH, m), 2.3 (1H, CH-7a, dd), 2.8 (1H, C*H*OCH_3, m), 3.2 (1H, CH-7b, dd), 3.4 (3H, OCH_3, s), 7.1-7.3 (5H, ArH, m). Anal. calcd. for $C_{14}H_{20}O$: C, 82.31; H, 9.89. Found: C, 82.37; H, 9.78.

Product **10**, oil, $[\alpha]^{D}_{20}$ = -12.8° (c 1, $CHCl_3$). ^1H NMR: δ_H ($CDCl_3$) 1.1-2.0 (9H, $4CH_2$+ CH, m), 2.5 (1H, CH-7a, dd), 2.75 (1H, CH-7b, dd), 3.15 (1H, C*H*OCH_3, s), 3.3 (3H, OCH_3, s), 7.1-7.3 (5H, ArH, m). Anal. calcd. for $C_{14}H_{20}O$: C, 82.31; H, 9.89. Found: C, 82.29; H, 9.92.

Bromo derivatives (**11**) *and* (**12**). The O-methyl ether **9** (2 g, 9.8 mmol) in CCl_4 (20 ml) was treated at reflux with NBS (2 g, 10.4 mmol) in the presence of a trace of benzoyl peroxide. After 2 h the reaction is complete (TLC). The filtered solution is washed with water and dil. $NaHSO_3$ solution, dried and evaporated to provide after SiO_2 column chromatography with hexane/AcOEt 3:1, **11**, oil, 2.2 g (80%). ^1H NMR: δ_H ($CDCl_3$) 1.0-2.3 (9H, $4CH_2$+ CH, m), 2.6 and 3.2 (0.5H, C*H*OCH_3, m), 3.3 and 3.5 (1.5H, OCH_3, s), 5.7 and 5.8 (0.5H, CHBr, d), 7.1-7.5 (5H, ArH, m).

In the same manner, from **10** compound **12** was obtained. ^1H NMR: δ_H ($CDCl_3$) 1.0-2.3 (9H, $4CH_2$+ CH, m), 2.85 and 4.0 (0.5H, C*H*OCH_3, s), 2.9 and 3.4 (1.5H, OCH_3, s), 4.95 and 5.1 (0.5H, CHBr, d), 7.1-7.4 (5H, ArH, m). GLC analysis: fused silica capillary column, 25 mt x 0.25 mm i.d., coated with 0.25 μm of cross-linked SE-52 (MEGA, Italy). DANI apparatus (model 8610), equipped with PTV injector and FID detector.Carrier gas: He, 0.9 bar. Temperature program: 80°C 1 min, 10°C/min, 155°C 1 min, 1°C/min, 165°C 2 min, 15°C/min, 250°C. Injector and detector temperatures: 250°C. Compound **11**: two peaks at R_t 25.32 and 25.54min. Compound **12**: single peak at R_t 24.8min.

(E) and (Z) (S) α-benzylidene cyclohexyloxymethyl ethers (**5**) *and* (**13**) *from* (**11**) *and* (**12**) *and their conversion into* (**1**). The bromoderivative **11** (2.83 g, 10 mmol) in CH_3CN (40 ml) was refluxed 1 h in the presence of DBU (4.5 ml, 30 mmol). At the end of the reaction (TLC) the mixture was diluted with AcOEt (150 ml) and washed with water and dil. HCl sol.. GLC analysis (same conditions reported for compounds **11** and **12**) of the residue obtained upon evaporation of the dried organic phase indicated the only presence of the unsaturated product **5**, R_t 17.8 min. This was obtained in pure form, 1.63 g (80%), after SiO_2 column chromatography, $[\alpha]^{D}_{20}$ +7.2 (c 1, $CHCl_3$).^1H NMR spectrum was identical to the same material produced from **4**.

The same reaction conditions were applied to the transformation of **12**. In this instance over 3 h reflux were needed in order to observe complete consumption of the substrate (TLC). GLC analysis of the crude reaction mixture showed the presence, close to **5**, of another component (1:1 ratio): R_t (**13**) 15.7min; R_t (**5**) 17.8min. ^1H NMR of the mixture allowed to identify the presence of **5**: δ_H ($CDCl_3$) 0.9-2.5 (8H, $4CH_2$, m), 3.3 (3H, OCH_3, s), 3.7 (1H,

C*H*OCH_3, t), 6.4 (1H, H vinyl, s), 7.1-7.4 (5H, ArH, m) and of **13**: δ_H ($CDCl_3$) 0.9-2.5 (8H, $4CH_2$, m), 3.1 (3H, OCH_3, s), 4.3 (1H, C*H*OCH_3, t), 6.5 (1H, H vinyl, s), 7.1-7.4 (5H, ArH, m).

Product **5** and the mixture **5+13** so obtained when submitted to ozonolysis, as above, provided (*S*) 2-methoxycyclohexanone **1** in *ca.* 80% yield, shown at the multidimensional GLC analysis to possess over 0.93 *ee*.

Microbial transformation of (**3**) *to* (**4**), (**7**) *and* (**8**): *Pichia etchelsii* CBS 2011, *Candida lipolytica* CBS 2074, *Nocardia opaca* DSM 43205 and *Mucor subtilissimus* CBS 735.70 were grown on conventional MPGB media. After 24 hours of growth **3** was added (1 g/l) and the cultures were afterwards stirred on an orbital shaker (160 rpm) at 28°C for 24 hours. The incubation mixtures were extracted with AcOEt and the dried organic extract was submitted to HPLC and GLC analysis.

Chiral HPLC analysis: CHIRALCEL OD column, Daicel, hexane/i-PrOH 95/5, 0.6 ml/min, UV 254 nm, **3** R_t=11.32 min, (*R*)**4** R_t=15.5 min, (*S*)**4** R_t=20.96 min, (1*R*,2*S*)**7** R_t=13.44 min, (1*S*,2*R*)**7** R_t=41.9 min, (1*R*,2*R*)**8** R_t=10.55 min, (1*S*,2*S*)**8** R_t=14.74 min.

GLC analysis: fused silica capillary column 25m x 0.25 mm i.d. (MEGAWAX) coated with 0.25 μm of polyethyleneglycol. Carrier gas: H_2, 0.7 bar. Temperature program: 70°C 1 min, 10°C/min, 150°C 1 min, 2°C/min, 200°C 2 min, 5°C/min, 210°C 2 min. **3**: R_t=26.52 min, **4**: R_t=27.09 min, **7**: R_t=21.81 min, **8**: R_t=21.06 min.

Acetate ester of (R) α-benzylidene cyclohexanol by enzymic resolution of racemic (**4**). Carbinol **4** (2 g, 10 mmol) and PPL (Sigma Type II) (4 g) were stirred 48 h at r.t. in i-Pr_2O (75 ml) in the presence of vinyl acetate (2.4 ml).The residue obtained upon evaporation of the filtered reaction mixture was chromatographed on SiO_2 (Hexane-AcOEt) to provide the acetate ester of (*R*) **4**, 0.6 g (25%), oil, $[\alpha]^D_{20}$ = +35.5° (c 1, $CHCl_3$), ^{1}H NMR: δ_H ($CDCl_3$) 1.5-2.0 (6H, $3CH_2$, m), 2.1 (3H, CH_3, s), 2.3-2.7 (2H, CH_2, m), 5.35 (1H, OCH, m), 6.4 (1H,H vinyl, s), 7.1-7.4 (5H, ArH, m).Chiral HPLC analysis: the acetyl derivative was hydrolysed with sodium methylate to **4** and analysed as described above: (*R*)**4** R_t=15.5 min. Anal. calcd. for $C_{15}H_{18}O_2$: C, 78.25; H, 7.86. Found: C, 78.30; H, 7.78.

The above ester (2.3 g, 10 mmol) in MeOH (20 ml) was treated at room temperature with a solution of sodium methylate obtained from sodium (*ca.* 100 mg) in 5 ml of methanol. After 1 h at r.t. the hydrolysis was complete (TLC). The reaction mixture was concentrated to a small volume, diluted with water and extracted with AcOEt. The residue obtained upon evaporation of the organic phase left a residue which was crystallized from hexane to provide the (*R*) enantiomer of **4**, 1.4 g (75%), $[\alpha]^D_{20}$ +37 (c 1, $CHCl_3$). ^{1}H NMR: δ_H ($CDCl_3$) 1.4-2.05 (7H, $3CH_2$+OH, m), 2.12 (1H, H-3, m), 2.72 (1H, H-3', m), 4.23 (1H, C*H*OH, m), 6.5 (1H,CH vinyl, s), 7.15-7.35 (5H, ArH, m). Anal. calcd. for $C_{13}H_{16}O$: C, 82.95; H, 8.55. Found: C, 82.89; H, 8.61.

(R) 2-methoxycyclohexanone from the (R) enantiomer of (**4**). The conversion of the above allylic carbinol into 2-

methoxycyclohexanone was performed exactly as described for the enantiomeric series described above. The final product at the multidimensional GLC analysis resulted to be the *(R)* enantiomer of **1**, possessing 0.94 *ee*. $[\alpha]^{D}_{20}$ = +68° (c 1, $CHCl_3$).

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8. Multidimensional GLC analysis of the enantiomeric excess of **1**: fused silica capillary column 25m x 0.25 mm i.d. (MEGA) coated with 0.25 μm of DActBSi-β-cyclodextrin. DANI 6500 apparatus. Carrier gas: H_2, 0.8 bar. 70°C 2 min, 2°C/min, 110°C 0 min, 10°C/min. **1**(*R*): R_t 20.185, **1**(*S*): R_t 21.225.
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