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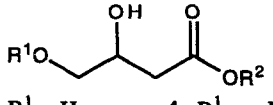
Microbiological Enantioselective Synthesis of (*S*) and (*R*) 4-(*p*-Anisyloxy)-3-hydroxybutyrates as New Chiral Building Blocks for the Synthesis of β-Lactam Antibiotics

Luca Banfi,[a] Giuseppe Cascio,[b] Chiara Ghiron,[a] Giuseppe Guanti,[a]* Elso Manghisi,[b] Enrica Narisano,[a] and Renata Riva[a]

[a]Istituto di Chimica Organica e C.N.R., Centro di Studio per la Chimica dei Composti Cicloalifatici ed Aromatici, corso Europa 26, 16132 GENOVA (Italy)
[b]Luso Farmaco s.p.a.,§ via Carnia 26, 20132 MILANO (Italy)

Abstract: Both enantiomers of 4-*p*-anisyloxy-3-hydroxybutanoates **4** have been prepared in high e.e. by reduction of the corresponding β-ketoesters or β-ketocarboxylates with immobilized fermenting baker's yeast. The utility of these new chiral building blocks in the synthesis of pharmacologically important β-lactam antibiotics has been demonstrated.

During the course of our researches in the field of β-lactam antibiotics,[1] we felt the need of an efficient method for the preparation in high e.e. of both enantiomers of monoprotected β,γ-dihydroxyesters like **2**-**6**. In previous works[1,2] we have obtained (*R*) or (*S*) **2a** and **3a** starting from D or L dimethyl malate, taking advantage of Moriwake's[3] regioselective reduction of C-1 carboxyl, and of subsequent regioselective protection of the primary hydroxyl in the resulting diol **1a**. However, this method was limited by the fact that only few protecting groups could be introduced regioselectively on the primary hydroxyl group of **1** without side reactions.[1] For example, although the *p*-anisyl protecting group[4] appeared to us quite attractive in virtue of its stability under acidic and basic conditions and to its easy removal under neutral oxidative conditions, we did not succeeded in preparing (*R*) or (*S*) **4** by this route.



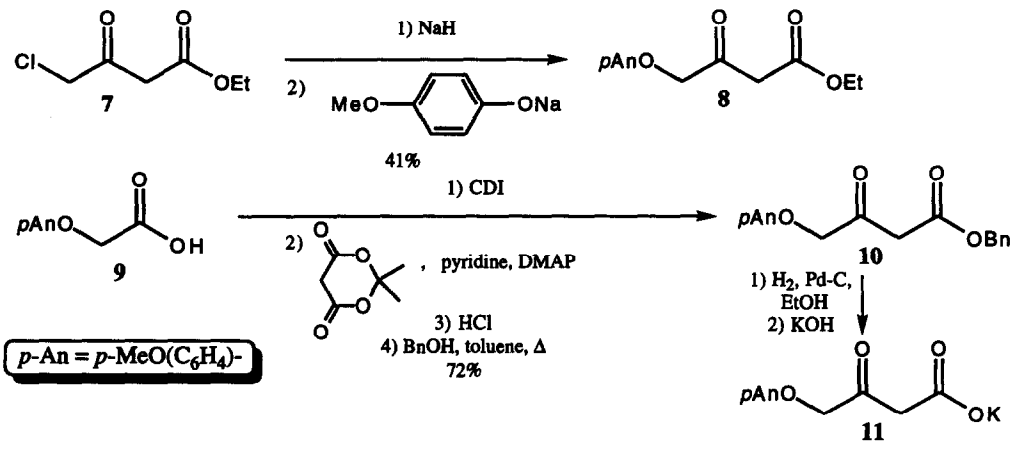
1 $R^1 = H$ **4** $R^1 = p\text{MeOC}_6\text{H}_4\text{-}$
2 $R^1 = Ph_2tBuSi$ **5** $R^1 = t\text{Bu}$
3 $R^1 = Ph_3C$ **6** $R^1 = \text{Bn}$
a: $R^2 = \text{Me}$ **b**: $R^2 = \text{Et}$ **c**: $R^2 = \text{Bn}$

Thus we decided to explore a different strategy for the obtainment of enantiomerically enriched **4**, based on Baker's yeast mediated reduction of the corresponding β-ketoester.[5,6] By this strategy Seebach had already prepared (*R*) **5b** and (*R*) **6b**.[7] However, while the former was guessed to be not ideal for our projected β-lactam syntheses,[8] the latter was produced in only 56% e.e.

The requisite β-hydroxyesters **8** and **10** were prepared as described in Scheme 1, starting from ethyl

§ A company related to "A. Menarini" Industrie Farmaceutiche Riunite s.r.l.

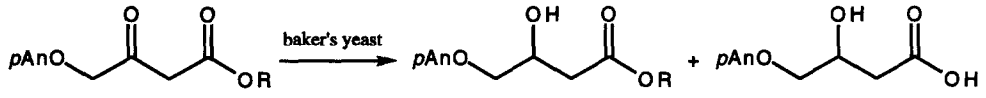
Scheme 1



chloroacetoacetate,[9] or from known *p*-anisyloxyacetic acid **9**.[10,11] The first methodology was less efficient, mainly because of the low stability of the enolate derived from **7**. On the contrary, the second strategy, which employs Meldrum's acid as acetate equivalent,[13] afforded good yields of the desired β-ketoester **10**.[14] We also prepared the potassium carboxylate **11** through hydrogenolysis of **10**.

We next studied baker's yeast reduction of substrates **8**, **10**, and **11** (Table 1). The ethyl ester was reduced with good enantioselection by free baker's yeast (entry 1), provided that high dilution conditions were

Table 1: Baker's Yeast Reduction of 8,10, and 11[a]



8 : R = Et **10** : R = Bn **11** : R =K **4b** : R = Et **4c** : R = Bn **12**

					Hydroxyester **4b,c**			Hydroxyacid **12**		
Entry	Substrate	Yeast[b]	Conditions[c]	Time	Yield	E.e.[d]	Conf.	Yield	E.e.[e]	Conf.
1	**8**	**F**	**A**	20h	48%	85%	*R*	15%	88%	*R*
2	**8**	**F**	**B**	20h	35%	17%	*R*	40%	79%	*R*
3	**8**	**I**	**C**	20h	41%	89%	*R*	40%	94%	*R*
4	**8**	**I**	**D**	36h	61%	89%	*R*	17%	n.d.	n.d.
5	**8**	**I**	**E**	48h	-[f]	n.d.	n.d.	-[f]	n.d.	n.d.
6	**10**	**I**	**C**	23h	70%	91%	*R*	< 15%	n.d.	n.d.
7	**10**	**I**	**F**	68h	69%	91%	*R*	n.d.	n.d.	n.d.
8	**11**	**I**	**C**	36h	-	-	-	70%[g]	90%	*S*

[a] All reactions were performed at 29°C using sucrose as nutrient. [b] **F** = free baker's yeast; **I** = baker's yeast immobilized on calcium alginate. [c] **A**: 15 g yeast, 100 ml H_2O and 10 ml EtOH per mmol substrate. Slow addition of substrate (12 h). **B**: 5 g yeast, 50 ml H_2O and 1 ml EtOH per mmol substrate. Fast addition of substrate. **C**: 7 g yeast, 100 ml H_2O and 10 ml EtOH per mmol substrate. Slow addition of substrate (12 h). **D**: as in C, but in the presence of ethyl chloroacetate (0.2 mmol / g yeast). **E**: as in C, but in the presence of ethyl chloroacetate (1 mmol / g yeast). **F**: 1.5 g yeast, 43 ml H_2O and 9 ml EtOH per mmol substrate. Slow addition of substrate (36 h). [d] Determined by ^1H n.m.r. analysis of the corresponding Mosher's esters (see experimental part). [e] Determined, after conversion into methyl ester **4a**, by ^1H n.m.r. analysis of the corresponding Mosher's esters. [f] Very sluggish reaction. [g] Yield of 2 steps from **10**, including hydrogenolysis.

used. This was realized by slow addition of an ethanolic solution of substrate to the fermenting yeast. On the contrary, by adding all **8** at once, the e.e. dropped significantly (entry 2). The increase of e.e. under higher dilution is in agreement with the behaviour of other β-hydroxyesters.[5] The yield was however only moderate, due to the substantial formation, as by-product, of β-hydroxyacid **12**.[15] We guess that in this case ester hydrolysis occurred after ketone reduction. Reduction after the hydrolysis was indeed expected to lead preferentially to the (*S*) enantiomer (see entry 8). In order to check wether this hydrolysis could be important in increasing the e.e. through a kinetic resolution, we submitted racemic **4b** to the same conditions employed in entry 1. The unreacted substrate turned out to be enriched in the (*S*) enantiomer,[16] showing that (*R*) **4b** is hydrolyzed faster, and that the kinetic resolution is in this case deleterious.

In order to improve the yield and the enantioselectivity, we then explored the effect of reaction conditions.[17,18] In particular it has been reported that the use of baker's yeast immobilized on magnesium or calcium alginate allows easier recovery of reaction products as well as catalyst recycling.[17] Moreover, the eanntioselectivity toward the L [in this case (*R*)] isomer is usually increased.[17d] Finally, the need for high dilution under these conditions is less stringent. In our case, using 1-1.5 mm calcium alginate beads,[17c,h] we actually found an increase of e.e. even using more concentrated conditions and a smaller yeast / substrate ratio (entry 3). We experimented also the use, as additive, of ethyl chloroacetate, which was shown to shift the enantioselectivity towards the L isomer too.[18e] While the effect on the enantioselectivity was negligible, the presence of this additive suppressed in part the competitive ester hydrolysis, bringing about an improvement in the yield (entry 4). The reaction was however slower. By further increasing the ethyl chloroacetate concentration, the reaction became too sluggish (entry 5).

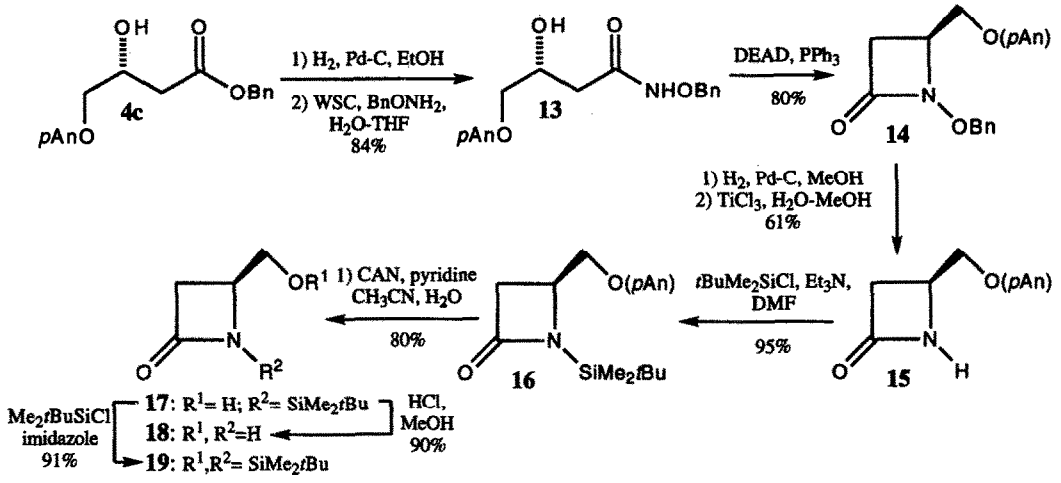
As expected, the benzyl ether **10** proved to be more resistant to ester hydrolysis, thus allowing better yields with e.e.s comparable with those achieved with the ethyl ester (entries 6). We have upscaled this reduction decreasing the yeast amount up to 1.5 g per mmol of substrate (entry 7). Although the reaction was slower, the good yields and e.e.s were maintained.

Finally we subjected to reduction also the potassium carboxylate **11**.[19] With our surprise, a complete reversal of enantioselectivity was found, the (*S*) enantiomer being obtained in good yield and high e.e. (entry 8).[20] This β-hydroxyacid **12** was smoothly converted into the corresponding methyl ester **4a** by treatment with CH_2N_2. Thanks to this unprecedented reversal of enantioselectivity, we have at hand efficient methods for the obtainment of β-hydroxyesters **4** in both enantiomeric forms.

The possibility to reuse the supported yeast was by us verified by consecutively reducing four batches of substrate **10**. The activity was substantially retained. In this case it is however advisable, after complete reduction of each batch, not to wash the catalyst with an organic solvent, like AcOEt, since this operation provokes a decrease of activity.

Having solved the problem of efficient preparation of (*R*) **4c**, we next transformed it into useful intermediate for the synthesis of pharmacologically important β-lactams. For example (Scheme 2), **4c** was converted into hydroxamate **13**, which underwent Miller's biomimetic cyclization[21] to give β-lactam **14** . This reaction was complicated by the competitive formation of elimination products, especially when, using concentrated THF solutions, substrate **13** was not completely dissolved. Although the use of DMF as solvent suppressed this side reaction, the cyclization became too sluggish. Good yields were finally achieved by performing the reaction in THF at high dilution. After removal of benzyloxy and *p*-anisyl groups, 4-(hydroxymethyl)azetidinone **18**[22] was obtained in good overall yield (27%). This compound is a known

Scheme 2

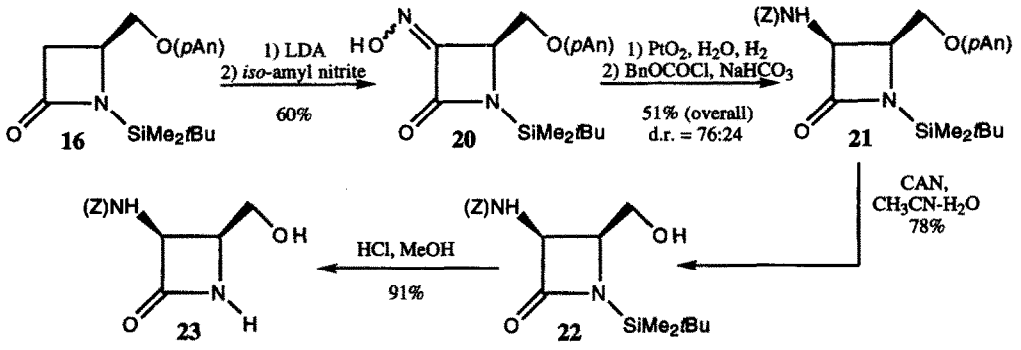


building block for the synthesis of thienamycin,[22a] isoclavams,[23] and other β-lactam antibiotics.[24] Compound **17** was further characterized by conversion into known[25] disilyl derivative **19**.

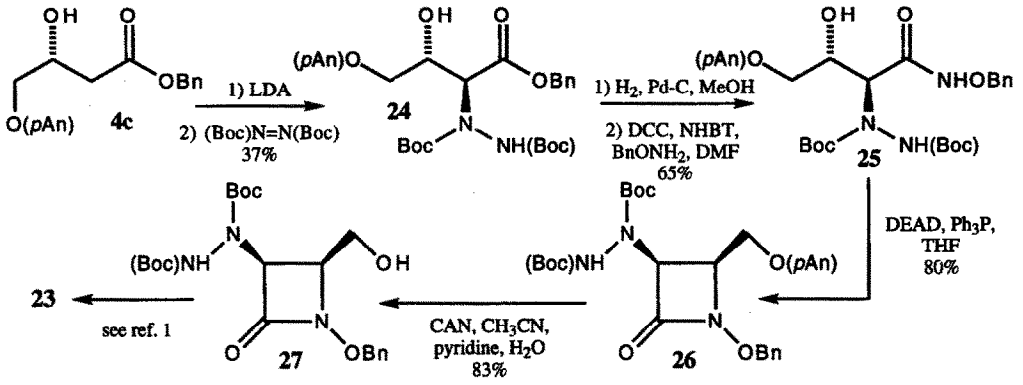
Azetidinone **16** was also used in the synthesis of **23**, which is a known intermediate[1,25] for the synthesis of monocyclic β-lactam antibiotic carumonam[1] (Scheme 3). This was accomplished by "electrophilic amination" of **16** through reaction of the corresponding lithium enolate with *iso*-amyl nitrite followed by hydrogenation of the resulting mixture of oximes and by amine protection.[25] This sequence was moderately stereoselective (about 3.5:1) favouring the *cis* stereoisomer **21**. Deblocking of the *p*-anisyl and Me_2tBuSi groups furnished **23** in good overall yield (6.5% from **4c**).

An alternative synthesis of **23** is shown in Scheme 4. This time the introduction of the amino group was performed through an "electrophilic amination" directly carried out at the level of **4c**. This reaction is a further example of the previously by us described stereoselective condensation of β-hydroxyester dianions with di-*tert*-butyl azodicarboxylate.[26] The *anti* stereoisomer was formed nearly exclusively, although in only moderate yields. The protected hydrazino group introduced in this way may be considered a synthetic equivalent of an amino group, thanks to the possible hydrogenolysis of the N-N bond. Compound **24** was

Scheme 3



Scheme 4



converted *via* Miller's biomimetic cyclization, into azetidinone **26**. Treatment of the latter with cerium ammonium nitrate furnished 4-hydroxymethyl-β-lactam **27**, which has been already transformed by us[1] into **23**.

In conclusion, we have developed an efficient entry into both enantiomers of 4-*p*-anisyloxy-3-hydroxybutanoates by means of microbiological reduction with immobilized baker's yeast of β-ketoesters **8** and **10** and β-ketocarboxylate **11**, respectively. Some possible applications of these new chiral building blocks in the field of β-lactam derivatives have been described.

EXPERIMENTAL

N.m.r. spectra were recorded on a Varian Gemini 200 spectrometer. Tetramethylsilane was used as internal standard for spectra in $CDCl_3$ and d-6 acetone. I.r. spectra were recorded on a Perkin-Elmer 881 instrument as $CHCl_3$ solutions or as nujol dispersion. Elemental analyses were performed with a Perkin-Elmer 240 instrument. Organic extracts were dried over Na_2SO_4 and filtered before removal of solvent under reduced pressure. All reactions employing dry solvents were run under a nitrogen atmosphere. Tetrahydrofuran (THF) was dried over K/benzophenone; CH_2Cl_2, pyridine, and dimethylformamide (DMF) were doubly dried[27] over 4 Å molecular sieves. Chromatographies were carried out on 220-400 mesh silica gel. Thin layer chromatographies were carried out on 0.25 mm silica gel F 254 plates (Merck). Spots were detected at U.V. or, unless otherwise noted, through immersion in a solution of 21 g $(NH_4)_4MoO_4 \cdot 4\ H_2O$ and of 1 g $Ce(SO_4)_2 \cdot 4\ H_2O$ in 469 ml H_2O and 31 ml conc. H_2SO_4, followed by warming on a hot plate. PE = petroleum ether.

Ethyl 4-(4-methoxyphenoxy)-3-oxobutanoate 8. A suspension of NaH (50% in mineral oil) (1.63 g, 34.0 mmol) in dry THF (15 ml), cooled to 0°C, was treated with a solution of 4-methoxyphenol (3.93 g, 31.6 mmol) in dry THF (3 ml). In another flask, a suspension of NaH (1.96 g, 40.8 mmol) in THF (10 ml) was treated, at -30°C, with a solution of ethyl 4-chloroacetoacetate (5 ml, 35.1 mmol) in THF (5 ml). The resulting yellowish solution was slowly added *via* syringe to the solution of sodium 4-methoxyphenoxide, kept at 0°C. At the end of addition the temperature was slowly raised to reflux during 1h, and the solution refluxed for 2h. At this point, another solution of sodium enolate of ethyl 4-chloroacetoacetate [prepared as above described starting from 2.5 ml of acetoacetate (17.6 mmol) and 0.980 g of NaH (20.4 mmol) in 7.5 ml of THF] was

added. After refluxing for 18h, the solution was cooled and poured into 1 N HCl (60 ml). The pH was adjusted to 7, and the mixture extracted with Et_2O to give, after evaporation to dryness and chromatography (PE / Et_2O / CH_2Cl_2 8:2:5) **8**, containing some 4-methoxyphenol (5.67 g). Bulb to bulb distillation gave pure **8** as a colorless liquid (3.26 g, 41%). Found: C, 61.15; H, 6.5%. Calculated for $C_{13}H_{16}O_5$: C, 61.90; H, 6.39%. R_f: 0.56 (PE / Et_2O / CH_2Cl_2 8:2:5). ^1H n.m.r. ($CDCl_3$): δ 6.85-6.80[4 H, m, aromatics]; 4.59 [2 H, s, OCH_2C=O]; 4.18 [2 H, q, OCH_2CH_3, J= 7.1 Hz.]; 3.76 [3 H, s, CH_3O]; 3.62 [2 H, s, CH_2COOEt]; 1.25 [3 H, t, CH_3CH_2, J= 7.1 Hz.].

Benzyl 4-(4-methoxyphenoxy)-3-oxobutanoate 10. A brown solution of 2,2-dimethyl-1,3-dioxan-4,6-dione (6.49 g, 45.0 mmol) in dry CH_2Cl_2 was cooled to 0°C and treated slowly with dry pyridine (7.87 ml, 98.2 mmol). In another flask a suspension of (4-methoxyphenoxy)acetic acid[10] (7.46 g, 40.9 mmol) in CH_2Cl_2 (10 ml) was slowly treated with N,N'-carbonyldiimidazole (7.30 g, 45.0 mmol). When the gas evolution ceased, the resulting solution was added to the reddish solution of Meldrum's acid and pyridine, kept at 0°C. 4-Dimethylaminopyridine (250 mg, 2.05 mmol) was added and the mixture stirred for 1 h at 0°C and for 5h at r.t. After dilution with CH_2Cl_2, the reaction mixture was poured into an Erlenmayer flask containing 2N HCl (70 ml) and some ice, and extracted with CH_2Cl_2. The organic phase was washed with 2N HCl and with saturated brine to give, after evaporation, a crude solid. It was taken up in toluene (30 ml)(it did not dissolve completely) and treated with benzyl alcohol (6.4 ml, 61.4 mmol). The mixture was stirred at 85°C for 45 min. and the solvent evaporated to give a crude solid which was recrystallized from Et_2O / *n*-pentane to give pure **10** as a white solid (7.26 g). The mother liquors afforded, after chromatography and crystallization, another 1.97 g of **10**. Overall yield= 72%. M.p.: 45.4-46.2°. Found: C, 68.6; H, 5.7%. Calculated for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77%. R_f : 0.51 (PE / Et_2O 1:1). ^1H n.m.r. ($CDCl_3$): δ 7.40-7.30 [5 H, m, aromatics of benzyl]; 6.90-6.70 [4 H, m, aromatics of anisyl]; 5.16 [2 H, s, CH_2Ph]; 4.56 [2 H, s, OCH_2C=O]; 3.76 [3 H, s, CH_3O]; 3.68 [2 H, s, CH_2COOBn]. I.r. (nujol): ν_{max}: 1726, 1506, 1324, 1235, 1225, 1195, 1130, 1105, 1072, 1035, 965, 825, 800, 750, 700 cm^{-1}.

(*R*) Benzyl 3-hydroxy-4-(4-methoxyphenoxy)butanoate 4c. A suspension of sodium alginate (35 g) in deionized water (1.8 l) was stirred at 80°C until homogeneous. After cooling to r.t., baker's yeast (Distillerie Italiane)(35 g) was added and the mixture vigourously stirred until homogeneous. It was transferred into a dropping funnel, whose lower end was connected, through a short tube (5 cm), with a needle. The mixture was dropped, under positive pressure, into a vigorously stirred solution of $CaCl_2$ (2% w/w) in water (1.8 l). In this way, beads of approximately 1.5 mm of diameters wre obtained.[17h] They were decanted and suspended in water (1 l). This suspension was warmed to 29°C, treated with sucrose (35 g), and allowed to ferment for 1h. A solution of **10** (2.41 g, 7.67 mmol) in EtOH (70 ml) was slowly added during 8 h. After 14 h, sucrose (35 g) was added and, after 30 min., another solution of **10** (2.41 g, 7.67 mmol) in EtOH (70 ml) was slowly dropped during 8 h. These additions were repeated again after 14 h. Finally the mixture was stirred for 16 h, and the calcium alginate beads removed through decantation. The solution was brought to pH 2 by addition of HCl, and extracted with AcOEt, while the beads were washed with AcOEt (this washing should be avoided if the yeast has to be reused). The reunited organic extracts gave, upon evaporation, a crude product which was chromatographed (PE / Et_2O 1:1 → 4:6) to give pure (*R*) **4c** (5.02 g, 69%). The e.e. was determined to be 91% by conversion into Mosher's esters by reaction with both (*S*) and (*R*) (methoxy)phenyl(trifluoromethyl)acetyl chlorides (4-dimethylaminopyridine, CH_2Cl_2, r.t.) and by their ^1H n.m.r. analysis (integration of CH_2Ph signals). Found: C, 68.0%; H, 6.45%. Calculated for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37%. $[\alpha]_D$ = + 9.0° (c 2, $CHCl_3$). R_f : 0.29 (PE / Et_2O 1:1). ^1H n.m.r. ($CDCl_3$): δ 7.36 [5 H, s, aromatics of benzyl]; 6.82 [4 H, s, aromatics of anisyl]; 5.17 [2 H, s, CH_2Ph]; 4.48-4.35 [1 H, m, CH-OH, mc= 4.42]; 3.95 [2 H, d, *p*AnOCH_2, J=

5.1 Hz.]; 3.76 [3 H, s, C*H*$_3$O]; 2.73 and 2.71 [2 H, AB part of an ABX system, C*H*$_2$COOBn, J not det.]. I.r. ($CHCl_3$): ν_{max}: 3450, 1728, 1505, 1460, 1230, 1165, 1108, 1040, 825, 750, 700 cm^{-1}.

(*R*) Ethyl 3-hydroxy-4-(4-methoxyphenoxy)butanoate 4b. It was prepared in 61% yield by reduction of **8** with immobilized baker's yeast, following a procedure similar to that described for **4c** with these differences: A) 7 g yeast, 100 ml of H_2O, and 10 ml of EtOH were used for each mmol of substrate. B) Slow addition of all substrate was performed during 8 h. Another portion of sucrose was added after 24 h, and the reaction was worked up after 36 h overall. C) 0.2 mmol/ g yeast of ethyl chloroacetate were added just before starting of substrate addition. Yield of pure (*R*) **4b** after chromatography was 61%. The e.e., determined as described for **4c**, was 89% (by integration of C*H*$_3$CH$_2$ signals upon decoupling of CH$_2$C*H*$_3$). Found: C, 61.65; H, 7.35. Calculated for $C_{13}H_{18}O_5$: C, 61.41; H, 7.34%. $[\alpha]_D$= + 9.9° (c 1.5, $CHCl_3$). ^{1}H n.m.r. ($CDCl_3$): δ 6.90-6.76 [4 H, m, aromatics]; 4.45-4.34 [1 H, m, C*H*OH]; 4.22 [2 H, q, C*H*$_2$CH$_3$, J= 6.7 Hz.]; 3.95 [2 H, d, *p*AnOC*H*$_2$, J= 5.2 Hz.]; 3.77 [3 H, s, C*H*$_3$O]; 3.09 [1 H, d, O*H*, J= 4.4 Hz.]; 2.67 and 2.65 [2 H, AB part of an ABX system, C*H*$_2$COOEt, J not det.]; 1.28 [3 H, t, CH$_2$C*H*$_3$, J= 7.1 Hz.].

(*S*) 3-Hydroxy-4-(4-methoxyphenoxy)butanoic acid 12. A solution of **10** (582 mg, 1.85 mmol) in ethanol (15 ml) was hydrogenated for 1.5 h over 10% Pd-C (50 mg). After removal of the catalyst by filtration, the filtrate was treated with 1N KOH in ethanol (1.85 ml, 1.85 mmol). The solvent was evaporated and the residue taken up in H_2O / EtOH 6:1 (30 ml). A suspension of immobilized baker's yeast (obtained from 7 g of yeast using the procedure described above for the synthesis of **4c**) suspended in H_2O (200 ml), was treated at 29°C with sucrose (7 g) and allowed to ferment for 1h. Then, about 70% of the carboxylate solution was slowly added during 6 h to the fermenting yeast. After further stirring for 14h, another portion of sucrose (7 g) was added, and the remaining carboxylate solution added during 6 h. After 10 h., the reaction was worked out as described for the synthesis of **4c**. Chromatography (PE / AcOEt / AcOH 47.5:47.5:5) furnished pure **12** (293 mg, 70%). R_f: 0.42 (PE / AcOEt / AcOH 47.5:47.5:5). $[\alpha]_D$: + 0.5° (c 1.5, MeOH). ^{1}H n.m.r. (CD_3COCD_3): δ 6.80-7.00 [4 H, m, aromatics]; 4.30-4.42 [1 H, m, C*H*OH]; 3.95 [2 H, *p*AnOC*H*$_2$, J= 5.4 Hz.]; 3.74 [3 H, s, C*H*$_3$O]; 2.53 and 2.68 [2 H, AB part of an ABX system, C*H*$_2$COOH, J_{AB}=15.8; J_{AX} and J_{BX}= 4.6 and 8.3 Hz.].

(*R*) Methyl 3-hydroxy-4-(4-methoxyphenoxy)butanoate 4a. A solution of (*R*) **4c** (60 mg, 0.190 mmol) in ethanol (5 ml) was hydrogenated for 2h over 10% Pd/C (10 mg). After removal of the catalyst by filtration, the filtrate was evaporated to dryness, taken up in Et_2O (3 ml) and treated with an ethereal solution of CH_2N_2. Excess reagent was quenched with AcOH and the crude product evaporated to dryness and chromatographed (PE / Et_2O 4:6) to give pure (*R*) **4a** (39 mg, 86%). Found: C, 60.2; H, 6.6%. Calculated for $C_{12}H_{16}O_5$: C, 60.00; H, 6.71%. $[\alpha]_D$ = + 10.8° (c 1.60, $CHCl_3$). R_f:: 0.30 (PE / Et_2O 3:7). ^{1}H n.m.r. ($CDCl_3$): δ 6.84 [4 H, s, aromatics]; 4.41 [1 H, quint. C*H*-OH, J= 5.8 Hz.]; 3.95 [2 H, d, C*H*$_2$O, J= 5.3 Hz.]; 3.77 and 3.74 [2 x 3H, 2s, C*H*$_3$O]; 3.08 [1 H, broad s, O*H*]; 2.69 and 2.67 [2 H, AB part of an ABX system, C*H*$_2$CO$_2$Me, J_{AB}= 16.5; J_{AX} and J_{BX}= ≈ 10.1 and 2.3 Hz.].

(*S*) Methyl 3-hydroxy-4-(4-methoxyphenoxy)butanoate 4a. It was prepared from (*S*) **12** in 90% yield by treatment with CH_2N_2 as above. $[\alpha]_D$= -10.6° (c 1.60, MeOH).

(*R*) Benzyl 3-hydroxy-4-(4-methoxyphenoxy)butanohydroxamate 13. A solution of (*R*) **4c** (4.28 g, 12.8 mmol) in ethanol (100 ml) was hydrogenated over 10% Pd-C (400 mg) for 1 h. After removal of the catalyst by filtration, the filtrate was evaporated to dryness, taken up in H_2O / THF 3:1 (100 ml) and treated with O-benzylhydroxylamine hydrochloride (2.25 g, 14.1 mmol). The pH was adjusted to 4.5 and a solution of N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide (3.70 g, 19.3 mmol) in H_2O (47 ml) was slowly added,

while maintaining the pH constant at 4.5. A white solid gradually formed during this addition. After the end of addition the mixture was stirred for 1 h and filtrated. The mother liquors were extracted with AcOEt, evaporated to dryness, and united to the solid to give a crude product (4.36 g) which was purified by crystallization (AcOEt / *n*-hexane) to give pure **13** as a white solid (3.78 g, 84%). M.p.: 151°C (dec.). Found: C, 64.95; H, 6.2; N, 4.5%. Calculated for $C_{18}H_{21}O_5N$: C, 65.24; H, 6.39; N, 4.23%. $[\alpha]_D$= +17.1° (c 1.54, $CHCl_3$). R_f: 0.49 (PE / AcOEt 2:8). ^1H n.m.r. ($CDCl_3$): 8.20 [1 H, broad s, N*H*]; 7.38 [5 H, s, aromatics of benzyl]; 6.83 [4 H, s, aromatics of anisyl]; 4.94 [2 H, broad s, CH_2Ph]; 4.39-4.27 [1 H, m, C*H*OH]; 3.98-3.82 [2 H, m, *p*AnOCH_2]; 3.77 [3 H, s, OCH_3]; 2.49-2.37 [2 H, m, CH_2CONH].

(*S*) 1-(Benzyloxy)-4-[(4-methoxyphenoxy)methyl]-2-azetidinone 14. To a solution of **13** (2.55 g, 7.69 mmol) and triphenylphosphine (3.03 g, 11.5 mmol) in dry THF (100 ml), diethyl azodicarboxylate (1.70 ml, 10.8 mmol) was slowly added during 15 min. After stirring at r.t. for 30 min. the solvent was evaporated and the crude product was chromatographed (PE / Et_2O 3:7) to give pure **14** as a slightly yellow solid (1.93 g, 80%). Found: C, 68.8; H, 6.2; N, 4.6%. Calculated for $C_{18}H_{19}O_4N$: C, 68.99; H, 6.11; N, 4.47%. $[\alpha]_D$= -37.8° (c 1.77, $CHCl_3$). R_f: 0.28 (PE / Et_2O 2:8). ^1H n.m.r. ($CDCl_3$): δ 7.30-7.45 [5 H, m, aromatics of benzyl]; 6.70-6.90 [4 H, m, aromatics of anisyl]; 4.94 and 4.99 [2 H, AB system, CH_2Ph, J_{AB} = 16.0 Hz.]; 4.00-3.80 [3 H, m, *p*AnOCH_2 and C*H*N]; 3.77 [3 H, s, CH_3O]; 2.79 and 2.65 [2 H, AB part of an ABX system, CH_2O, J_{AB}= 13.6, J_{AX} and J_{BX}= 5.1 and 2.1 Hz.].

(*S*) 4-[(4-Methoxyphenoxy)methyl]-2-azetidinone 15. A solution of **14** (2.23 g, 7.11 mmol) in MeOH (40 ml) was hydrogenated over 10% Pd-C (150 mg) for 1 h. After removal of the catalyst by filtration, the filtrate was evaporated to dryness, taken up in MeOH (30 ml) and treated with a 0.1 N pH 7 buffer solution (KH_2PO_4-K_2HPO_4) (70 ml). The mixture was cooled to 0°C and treated, under vigorous stirring, during 20 min., with a 30% $TiCl_3$ solution in 2N HCl (10.5 ml, 28.4 mmol). During this addition the pH was maintained as near as possible to 7 by continuous addition of 3N NaOH. At the end of the addition, the blue mixture was stirred at r.t. for 30 min., saturated with NaCl, and extracted with AcOEt to give, after evaporation and chromatography (PE / AcOEt 1:9), pure **15** as a white solid (904 mg, 61%). Found: C, 63.95; H, 6.2; N, 6.7.%. Calculated for $C_{11}H_{13}O_3N$: C, 63.76; H, 6.32; N, 6.76%. $[\alpha]_D$= +44.5° (c 1.83, $CHCl_3$). R*f*: 0.45 (AcOEt). ^1H n.m.r. ($CDCl_3$): δ 6.83 [4 H, s, aromatics]; 6.25 [1 H, broad s, N*H*]; 4.06-3.94 [1 H, m, C*H*N]; 4.10 and 3.92 [2 H, AB part of an ABX system, CH_2O*p*An, J_{AB}= 8.3; J_{AX} and J_{BX}= 3.0 and 7.0 Hz.]; 3.77 [3 H, s, CH_3O]; 3.14 [1 H, ddd, C*H*H-CON, J= 15.0, 4.8, and 1.9 Hz.]; 2.79 [1 H, ddd, C*H*H-CON, J= 15.0, 2.2, and 1.6 Hz.]. I.r. ($CHCl_3$): ν_{max}: 3420, 1767, 1500, 1460, 1360, 1337, 1190, 1150, 1110, 1028 cm^{-1}.

(*S*) 1-(*tert*-Butyldimethylsilyl)-4-[(4-methoxyphenoxy)methyl]-2-azetidinone 16. A solution of **15** (682 mg, 3.29 mmol) in dry DMF (16 ml) was cooled to 0°C and treated with Et_3N (0.92 ml, 6.58 mmol) and *tert*-butyldimethylsilyl chloride (992 mg, 6.58 mmol). The temperature was allowed to rise to 20°C and the solution stirred for 2 h. The reaction was quenched with saturated brine and extracted with Et_2O to give, after evaporation and chromatography (PE / Et_2O 4:6), pure **16** (1.00 g, 95%). Found: C, 63.7; H, 8.6; N, 4.25%. Calculated for $C_{17}H_{27}O_3NSi$: C, 63.51; H, 8.47; N, 4.36%. $[\alpha]_D$= -9.0° (c 1.9, $CHCl_3$). R_f: 0.24 (PE / Et_2O 1:1). ^1H n.m.r. ($CDCl_3$): 6.83 [4 H, s, aromatics]; 4.04-3.84 [3 H, m, C*H*N and *p*AnOCH_2]; 3.22 and 2.89 [2 H, AB part of an ABX system, J_{AB}= 15.3; J_{AX} and J_{BX}= 5.4 and 2.6 Hz.]; 0.95 [9 H, s, (CH_3)$_3$C]; 0.25 and 0.28 [2 x 3H, 2s, (CH_3)$_2$Si].

(*S*) 1-(*tert*-Butyldimethylsilyl)-4-hydroxymethyl-2-azetidinone 17. A solution of **16** (114 mg, 0.355 mmol) in CH_3CN / H_2O 1:1 (20 ml) was cooled to 0°C and treated with pyridine (0.228 ml, 2.84 mmol) and cerium ammonium nitrate (973 mg, 1.77 mmol). After 30 min. the reaction was complete and the mixture was diluted with saturated brine, adjusted to pH 6.5 by addition of saturated aqueous $NaHCO_3$, and extracted with

AcOEt. The organic extracts were washed with saturated brine, evaporated, and chromatographed, to give pure **17** (64 mg, 80%). R_f: 0.37 (Et_2O, developed with $KMnO_4$ solution). ^1H n.m.r. ($CDCl_3$): δ 3.88-3.64 [3 H, m, C*H*-CH_2OH]; 3.11 and 2.87 [2 H, AB part of an ABX system, CH_2CON, J_{AB}= 15.3; J_{AX} and J_{BX}= 5.1 and 2.5 Hz.]; 0.97 [9 H, s, (CH_3)$_3$C]; 0.26 and 0.24 [2 x 3H, 2s, (CH_3)$_2$Si].

(*S*) 4-Hydroxymethyl-2-azetidinone 18. A solution of **17** (35 mg, 0.163 mmol) in methanol (1 ml) was cooled to 0°C, and treated with 2N aqueous HCl (60 µl). After stirring for 30 min. at 0°C and at r.t. for 3h, the mixture was neutralized with aqueous saturated $NaHCO_3$, saturated with NaCl, and extracted with AcOEt to give, after evaporation, and chromatography, pure **18** (15 mg, 90%) whose ^1H n.m.r. spectrum was in accord with the previously reported one.[23]

(*S*) 1-(*tert*-Butyldimethylsilyl)-4-[((*tert*-butyldimethylsilyl)oxy)methyl]-2-azetidinone 19. A solution of **17** (60 mg, 0.279 mmol) in dry DMF (2 ml) was cooled to 0°C, and treated with imidazole (96 mg, 1.39 mmol) and *tert*-butyldimethylsilyl chloride (105 mg, 0.696 mmol). After 10 min. at 0°C and 2h at r.t. the reaction was complete and was quenched with saturated brine, extracted with Et_2O, and chromatographed (PE / Et_2O 7:3) to give pure **19** (84 mg, 91%), whose analytical data were in agreement with those reported.[25] $[\alpha]_D$= -26.4° (c 1.36, $CHCl_3$). Lit.: -29.4°[25].

(*E*) and (*Z*) (*S*) 1-(*tert*-Butyldimethylsilyl)-3-(hydroxyimino)-4-[(4-methoxyphenoxy)methyl]-2-azetidinones 20. To a solution of lithium di-*iso*-propylamide in THF/*n*-hexane [prepared from 1.23 ml (8.80 mmol) of di-*iso*-propylamine, 5.0 ml of 1.6M *n*-BuLi in *n*-hexane (8.0 mmol) in 11.5 ml of THF], cooled to -78°C, a solution of **16** (474 mg, 1.47 mmol) in THF (3.8 ml) was added. The temperature was allowed to rise to -50°C (during 45 min.) and stirred at this temp. for 10 min. After cooling again to -78°C, *iso*-amyl nitrite (0.594 ml, 4.42 mmol) was added. After stirring for 1 h at -78°C, the reaction was quenched with AcOH (0.9 ml), allowed to warm to r.t., diluted with saturated NaCl, and extracted with Et_2O. Evaporation and chromatography (PE / Et_2O 4:6) gave a pure mixture (*ca.* 5.5 : 1) of isomeric oximes **20** as a yellow oil (310 mg, 60%). For analytical purposes the two isomers have also been separated. The relative configuration was not assigned. Found: C, 58.5; H, 7.6; N, 7.8%. Calculated for $C_{17}H_{26}N_2O_4Si$: C, 58.26; H, 7.48; N, 7.99%. R_f: 0.42 (major) and 0.31 (minor) (PE / Et_2O 4:6). $[\alpha]_D$= +70.8° (major) (c 1.85, $CHCl_3$). ^1H n.m.r. ($CDCl_3$): **major**: δ 8.85 [1 H, broad s, O*H*]; 6.83 [4 H, s, aromatics]; 4.68 [1 H, dd, C*H*-CH_2O, J= 5.6 and 2.1 Hz.]; 4.40 and 4.16 [2 H, AB part of an ABX system, CH_2O*p*An, J_{AB}= 10.6; J_{AX} and J_{BX}= 1.9 and 5.8 Hz.]; 3.77 [3 H, s, CH_3O]; 0.96 [9 H, s, (CH_3)$_3$C]; 0.33 and 0.30 [2 x 3H, 2s, (CH_3)$_2$Si]; **minor**: δ 8.86 [1 H, broad s, O*H*]; 6.82 [4 H, s, aromatics]; 4.51 [1 H, dd, C*H*-CH_2O, J= 6.2 and 3.1 Hz.]; 4.19 and 4.06 [2 H, AB part of an ABX system, CH_2O*p*An, J_{AB}= 10.4; J_{AX} and J_{BX}= 3.1 and 6.2 Hz.]; 3.77 [3 H, s, CH_3O]; 0.96 [9 H, s, (CH_3)$_3$C]; 0.36 and 0.31 [2 x 3H, 2s, (CH_3)$_2$Si].

(*3S, 4S*) 3-[(Benzyloxycarbonyl)amino]-1-(*tert*-butyldimethylsilyl)-4-[(4-methoxyphenoxy)methyl]-2-azetidinone 21. A solution of the diastereomeric (*E*) and (*Z*) oximes **20** (106 mg, 0.302 mmol) in AcOEt (5 ml) was treated with H_2O (0.3 ml) and hydrogenated over PtO_2 (100 mg) for 12 h. After removal of the catalyst by filtration, the filtrate was evaporated to give a crude 78 : 22 mixture of (*3S*) and (*3R*) 3-aminoazetidinones (determined by weight of isolated isomers). For analytical purposes they could be separated and purified at this level by chromatography [AcOEt / MeOH 95:5. R_f: 0.49 (*3S,4S*) and 0.40 (*3R,4S*)]. The crude mixture was taken up in THF (1.5 ml) and H_2O (4.5 ml) and treated at 0°C with $NaHCO_3$ (28 mg, 0.332 mmol) and benzyl chloroformate (0.047 ml, 0.332 mmol). The mixture was stirred for 45 min. at 0°C, diluted with saturated NaCl, and extracted with AcOEt to give, after evaporation and chromatography (PE / Et_2O 45:55), pure **21** (55.5 mg, 39%)(R_f : 0.26) and its (*3R,4S*) epimer (17 mg, 12%)(R_f : 0.19). Overall yield= 51%. Found: C, 60.8; H, 8.4; N, 8.2%. Calculated for $C_{25}H_{34}N_2O_5Si$: C, 60.68; H, 8.39; N, 8.32.

$[\alpha]_D$= +41.2° (c 1.76, $CHCl_3$). ^1H n.m.r. ($CDCl_3$): δ 7.31 [5 H, s, aromatics of benzyl]; 6.82 [4 H, s, aromatics of anisyl]; 5.58 [1 H, d, N*H*, J= 9.2 Hz.]; 5.34 [1 H, dd, C*H*-NH, J= 5.1 and 9.2 Hz.]; 5.09 [2 H, s, CH_2Ph]; 4.18-4.00 [3 H, m, C*H*-CH_2O]; 3.77 [3 H, s, CH_3O]; 0.94 [9 H, s, $(CH_3)_3$C]; 0.26 and 0.18 [2 x 3H, 2s, $(CH_3)_2$Si]. (*3R,4S*) isomer: δ 7.35 [5 H, s, aromatics of benzyl]; 6.83 [4 H, s, aromatics of anisyl]; 5.35 [1 H, d, N*H*, J= 9.2 Hz.]; 5.12 [2 H, s, CH_2Ph]; 4.64 [1 H, dd, C*H*-NH, J= 6.6 and 2.7 Hz.]; 4.22-4.00 [2 H, m, CH_2O]; 4.04-3.90 [1 H, m, C*H*-CH_2O]; 3.77 [3 H, s, CH_3O]; 0.96 [9 H, s, $(CH_3)_3$C]; 0.30 and 0.25 [2 x 3H, 2s, $(CH_3)_2$Si].

(*3S, 4S*) 3-[(Benzyloxycarbonyl)amino]-1-(*tert*-butyldimethylsilyl)-4-hydroxymethyl-2-azetidinone 22. It was prepared from **21** in 78% yield, by the same procedure employed for the synthesis of **17**. R_f: 0.36 (PE / Et_2O 3:7). ^1H n.m.r. ($CDCl_3$): 7.35 [5 H, s, aromatics]; 5.92 [1 H, d, N*H*, J= 8.8 Hz.]; 5.21 [1 H, dd, C*H*-NH, J= 5.6 and 8.8 Hz.]; 5.11 [2 H, s, CH_2Ph]; 3.98-3.68 [3 H, m, C*H*-CH_2OH]; 2.13 [1 H, broad s, O*H*]; 0.96 [9 H, s, $(CH_3)_3$C]; 0.29 and 0.22 [2 x 3H, 2s, $(CH_3)_2$Si].

(*3S, 4S*) 3-[(Benzyloxycarbonyl)amino]-4-hydroxymethyl-2-azetidinone 23. It was prepared from **22** in 91% yield by the same procedure employed for **18**. This compound had the same spectroscopic, chromatographic, and physical properties as previously reported.[1,25] $[\alpha]_D$= + 8.7° (c 0.685, $CHCl_3$). Lit. +-8.9° (c 1, $CHCl_3$).[25]

(*2S,3R*) Benzyl 2-[N,N'-*bis*(*tert*-butoxycarbonyl)hydrazino]-3-hydroxy-4-(4-methoxyphenoxy)-butanoate 24. To a solution of lithium di-*iso*-propylamide in THF-*n*-hexane [prepared from 1.37 ml (9.80 mmol) of di-*iso*-propylamine and 5.93 ml of 1.6 M *n*-BuLi in *n*-hexane (9.48 mmol) in 12.3 ml of dry THF], cooled to -40°C, a solution of **4c** (1.00 g, 3.16 mmol) in THF (3.5 ml) was added. The mixture was stirred for 5 min. at -40°C and then the temperature was allowed to rise to 0°C during 30 min. After further stirring at this temperature for 30 min., the solution was cooled to -20°C, and treated with di-*tert*-butyl azodicarboxylate (1.46 g, 6.32 mmol) in THF (3.2 ml). The temperature was allowed to rise to 0°C in 30 min. and then the reaction was quenched with AcOH (1.08 ml, 18.9 mmol), diluted with saturated NaCl / saturated NH_4Cl 1:1, and extracted with AcOEt to give, after evaporation and chromatography (PE / Et_2O 8:2 → 1:1) pure **24** as a foam (639 mg, 37%). Found C, 61.2; H, 6.85; N, 5.35%. Calculated for $C_{28}H_{38}N_2O_9$: C, 61.53; H, 7.01; N, 5.12%. R_f: 0.38 (PE / Et_2O 4:6). ^1H n.m.r. (DMSO, 80 MHz., 130°C):[28] δ 8.29 [1 H, broad s, N*H*]; 7.37 [5 H, s, aromatics of benzyl]; 6.85 [4 H, s, aromatics of anisyl]; 5.18 [2 H, s, CH_2Ph]; 4.83 [mc, 1 H, m, C*H*-N]; 4.45-3.87 [3H, m, C*H*-CH_2O]; 3.79 [3 H, s, CH_3O]; 1.41 [18 H, s, $(CH_3)_3$C].

(*2S,3R*) Benzyl 2-[N,N'-*bis*(*tert*-butoxycarbonyl)hydrazino]-3-hydroxy-4-(4-methoxyphenoxy)-butanoahydroxamate 25. The same procedure utilized for the synthesis of **13** was followed, starting from **24**. Yield: 65%. R_f : 0.41 (PE / AcOEt 2:8). ^1H n.m.r. (DMSO, 110°C):[28] δ 8.39 [1 H, broad s, N*H*(Boc)]; 7.48-7.28 [5 H, m, aromatics of benzyl]; 6.86 [4 H, s, aromatics of anisyl]; 4.95 [1 H, broad s, N*H*-OBn]; 4.85 [2 H, s, CH_2Ph]; 4.49 [1 H, d, C*H*-N, J=6.1 Hz.]; 4.36-4.20 [1 H, m, C*H*-OH]; 4.10 and 3.96 [2 H, AB part of an ABX system, CH_2O*p*An, J_{AB}= 9.7; J_{AX} and J_{BX}= 6.3 and 3.5 Hz.]; 3.72 [3 H, s, CH_3O]; 1.42 and 1.39 [2 x 9 H, 2s, $(CH_3)_3$C].

(*3S,4S*) 1-(Benzyloxy)-3-[N,N'-*bis*(*tert*-butoxycarbonyl)hydrazino]-4-[(4-methoxyphenoxy)methyl]-2-azetidinone 26. It was prepared from **25** in 80% yield by the same procedure employed for **14**. Found: C, 61.55; H, 6.65; N, 7.9%. Calculated for $C_{28}H_{37}N_3O_8$: C, 61.87; H, 6.86; N, 7.73%. R_f: 0.61 (PE / Et_2O 3:7). $[\alpha]_D$= + 8.4° (c 1.67, $CHCl_3$). ^1H n.m.r. (DMSO, 80 MHz., 130°C):[28] δ 8.72 [1 H, broad s, N*H*]; 7.38 [5 H, s, aromatics of benzyl]; 6.89 [4 H, s, aromatics of anisyl]; 5.11 [1 H, d, C*H*-N(Boc), J= 5.2 Hz.]; 4.99 [2 H, s,

C*H*$_2$Ph]; 4.44-4.12 [3 H, m, C*H*-C*H*$_2$O*p*An]; 3.74 [3 H, s, C*H*$_3$O]; 1.45 and 1.43 [2 x 9H, 2s, (C*H*$_3$)$_3$C]. I.r. ($CHCl_3$): ν_{max} 3677, 1781, 1750, 1719 cm^{-1}.

(*3S,4S*) 1-(Benzyloxy)-3-[N,N'-*bis*(*tert*-butoxycarbonyl)hydrazino]-4-hydroxymethyl-2-azetidinone 27. It was prepared from **26** in 83% yield by the same procedure employed for **17**. The chromatographic, spectroscopic, and polarimetric data were in agreement with those previously reported.[1]

REFERENCES AND NOTES

1. Guanti, G.; Banfi, L.; Cascio, G.; Manghisi, E.; Narisano, E.; Riva, R. *Tetrahedron* submitted for publication, and refs. therein.
2. Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1989**, *30*, 5507-5510.
3. Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067-4086.
4. **a)** Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291-6292. **b)** Petitou, M.; Duchaussoy, P.; Choay, J. *Tetrahedron Lett.* **1988**, *29*, 1389-1390.
5. Reviews on the subject: **a)** Servi, S. *Synthesis* **1990**, 1-25. **b)** Csuk, R.; Glänzer, B. I. *Chem. Rev.* **1991**, *91*, 49-97.
6. Recent selected papers on baker's yeast reduction of β-ketoesters: **a)** Chenevert, R.; Fortier, G. *Chem. Lett.* **1991**, 1603-1606. **b)** Ghosh, S. K.; Chattopadhyay, S.; Mamdapur, V. R. *Tetrahedron* **1991**, *47*, 3089-3094. **c)** Santaniello, E.; Ferraboschi, P.; Grisenti, P.; Aragozzini, F.; Maconi, F. *J. Chem. Soc., Perkin Trans 1* **1991**, 601-605. See also refs. 17-18.
7. Seebach, D.; Eberle, M. *Synthesis* **1986**, 37-40.
8. We were afraid that the acidic deblocking conditions necessary for removal of *t*-butyl protecting group, which are usually harsher than those utilized for removal of (Boc) groups (see Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, Wiley, New York, 1991), could cause opening of the β-lactam nucleus. Moreover, the *t*-butyl protecting group was incompatible with the route described in Scheme 4.
9. Troostwijk, C. B.; Kellogg, R. M. *J.Chem. Soc., Chem. Commun.* **1977**, 932-933.
10. Sobotka, H.; Austin, J. *J. Am. Chem. Soc.* **1952**, *74*, 3813-3815.
11. **10** was also prepared in similar yield, starting from the known[12] acyl chloride of **9**.
12. *Beilstein Handbuch der Chemie*, *Band 6*, E IV, 5745.
13. **a)** Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087-2088. **b)** Oikawa, Y.; Yohioka, T.; Sugano, K.; Yonemitsu, O. *Org. Synth.* **1984**, *63*, 198-202. **c)** Houghton, R. P.; Lapham, D. J. *Synthesis* **1982**, 451-452.
14. Since the ethyl ester proved to be less useful from a synthetic point of view, we did not optimize its preparation, although most likely also **8** could be prepared more efficiently from **9** by the same route used for benzyl ester **10**.
15. The ability of baker's yeast to hydrolyze esters is well documented: **a)** Glänzer, B. I.; Faber, K.; Griengl, H. *Tetrahedron* **1987**, *43*, 5791-5796. **b)** Brooks, D. W.; Wilson, M.; Webb, M. *J. Org. Chem.* **1987**, *52*, 2244-2248. **c)** Pedrocchi-Fantoni, G.; Servi, S. *J. Chem. Soc., Perkin Trans 1* **1991**, 1764-1765.
16. The e.e. after 50% conversion was however low (24%).
17. Use of baker's yeast immobilized on magnesium or calcium alginate: **a)** Nakamura, K.; Higaki, M.; Ushio, K.; Oka, S.; Ohno, A. *Tetrahedron Lett.* **1985**, *26*, 4213-4216. **b)** Sakai, T.; Nakamura, T.; Fukuda, K.; Amano, E.; Utaka, M.; Takeda, A. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3185-3188. **c)** Naoshima, Y.; Nakamura, A.; Nishiyama, T.; Haramaki, T.; Mende, M.; Munakata, Y. *Chem. Lett.*

1989, 1023-1026. **d)** Nakamura, K.; Kawai, Y.; Oka, S.; Ohno, A. *Tetrahedron Lett.* **1989**, *30*, 2245-2246. **e)** Naoshima, Y.; Nishiyama, T.; Munakata, Y. *Chem. Lett.* **1989**, 1517-1518. **f)** Hannoun, B. J. M.; Stephanopulos, G. *Biotechnol. Prog.* **1990**, *6*, 341-348. **g)** 349-356. **h)** Naoshima, Y.; Nakamura, A.; Munakata, Y.; Kamezawa, M.; Tachibana, H. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1263-1265. **i)** Naoshima, Y.; Maeda, J.; Munakata, Y. *J. Chem. Soc., Perkin Trans 1* **1992**, 659-660.

18. Use of other methods for improving baker's yeast reductions: **a)** Manzocchi, A.; Casati, R.; Fiecchi, A.; Santaniello, E. *J. Chem. Soc., Perkin Trans 1* **1987**, 2753-2757. **b)** Nakamura, K.; Inoue, K.; Ushio, K.; Oka, S.; Ohno, A. *Chem. Lett.* **1987**, 679-682. **c)** Nakamura, K.; Kawai, Y.; Oka, S.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 875-879. **d)** Kometani, T.; Kitatsuji, E.; Matsuno, R. *Chem. Lett.* **1989**, 1465-1466. **e)** Nakamura, K.; Kawai, Y.; Ohno, A. *Tetrahedron Lett.* **1990**, *31*, 267-270. **f)** Nakamura, K.; Kawai, Y.; Miyai, T.; Honda, S.; Nakajima, N.; Ohno, A. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1467-1470. **g)** Spiliotis, V.; Papahatjis, D.; Ragoussis, N. *Tetrahedron Lett.* **1990**, *31*, 1615-1616.

19. Baker's yeast reduction of β-ketoacids or of their salts: **a)** Hirama, M.; Shimizu, M.; Iwashita, M. *J.Chem. Soc., Chem. Commun.* **1983**, 599-600. **b)** Hirama, M.; Noda, T.; Ito, S. *J. Org. Chem.* **1985**, *50*, 127-129. **c)** Afonso, C. M.; Barros, M. T.; Godinho, L.; Maycock, C. D. *Tetrahedron Lett.* **1989**, *30*, 2707-2708. **d)** Watabu, H.; Ohkubo, M.; Matsubara, H.; Sakai, T.; Tsuboi, S.; Utaka, M. *Chem. Lett.* **1989**, 2183-2184.

20. The absolute configuration of **4a-c** and **12** was determined as follows: (*R*) **4c** was correlated chemically with (*S*) **19** and (*3S,4S*) **23** (see Schemes 2-4). It was also transformed into methyl ester (*R*) **4a** by hydrogenolysis (H_2, Pd-C, EtOH) followed by reaction with CH_2N_2. (*R*) and (*S*) **12** were also converted into (*R*) and (*S*) **4a** (CH_2N_2), which were assigned as such by comparison of optical rotations and of Mosher esters ^1H n.m.r. spectra. Finally, (*R*) **12** was transformed into (*R*) **4b** (EtOH, DCC, DMAP, CH_2Cl_2) and compared with (*R*) **4b** derived from yeast reduction.

21. Miller, M. J. *Acc. Chem. Res.* **1986**, *19*, 49-56.

22. Previous enantioselecive syntheses of **18**: **a)** Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161-6163. **b)** Tanner, D.; Somfai, P. *Tetrahedron Lett.* **1987**, *28*, 1211-1214.

23. Brennan, J.; Richardson, G.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans 1* **1983**, 649-655.

24. **a)** McCombie, S. W.; Metz, W.A.; Afonso, A.*Tetrahedron Lett.* **1986**, *27* , 305. **b)** *U.S. Patent 4,491,580* (appl.: 2/4/1982); *Chem. Abs.*, **1985**, *102*, 148994x. **c)** *Eur. Pat. Appl.*, EP 176,369; *Chem. Abs.*, **1986**, *105*, 114833r.

25. Takahashi, Y.; Yamashita, H.; Kobayashi, S.; Ohno, M. *Chem. Pharm. Bull.* **1986**, *34*, 2732-2742.

26. Guanti G., Banfi L., and Narisano E., *Tetrahedron* **1988**, *44*, 5553-5562. See also refs. 1,2.

27. **a)** Burfield, D. R.; Smithers, R. H. *J. Org. Chem.* **1978**, *43* , 3966-3970. **b)** Burfield, D. R.; Lee, K.-H.; Smithers, R. H. *J. Org. Chem.* **1977**, *42* , 3060-3065.

28. At room temperature compounds **23-27** gave unresolved n.m.r. spectra probably due to restricted rotation around the amidic bonds. When ^1H n.m.r. were taken in deuterated DMSO at temperatures >90-100°C, well resolved spectra could be usually obtained.

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