Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 2211–2219

TETRAHEDRON: *ASYMMETRY*

Improvement of the chemoenzymatic synthesis of both enantiomers of keto-protected 4-amino-2-pentanone

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Received 6 April 2000; accepted 3 May 2000

Abstract

An improved enantioselective synthesis (five steps, 37–44% yield versus seven to 10 steps, 13.5 and 12% yield, respectively) of both enantiomers of keto-protected 4-amino-2-pentanone has been realized, the key step being the microbiological reduction of 2,4-pentanedione. This study shows that microbiological reductions of the mono acetal-protected 2,4-pentanedione afforded in most cases the corresponding ketol with moderate to excellent enantiomeric excesses, depending on the microorganism used.

1. Introduction

In previous work on the microbiological reduction of monoketone,[1] α- or β-diketones[2,3] and α-substituted ketones,[4] we have shown that by choosing the appropriate microorganism, both enantiomers of the corresponding alcohol could be obtained with high enantiomeric purities. From these chiral alcohols, several new synthons have been prepared and among them, chiral β-aminoketones,[5] which were recently used for the enantioselective synthesis of polysubstituted piperidines.[6]

Both enantiomers of 2-(2-aminopropyl)-2-methyl-1,3-dioxane **1** were prepared through chemoenzymatic pathways starting from ethyl 3-oxobutanoate or 4,4-dimethoxybutan-2-one. The synthetic routes were achieved in 10 and seven steps, giving the desired compound **1** in 12 and 13.5% overall yield, respectively. These moderate yields, due mainly to the length of the sequences

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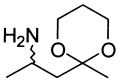
PII: S0957-4166(00)00167-1

together with a limitating step (condensation of methylmagnesium bromide on an aldehyde), greatly decreased the interest of this preparative method.



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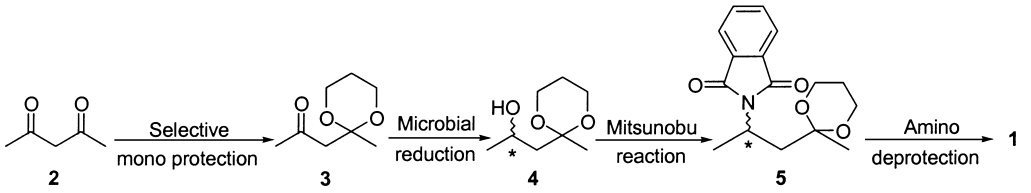
In order to increase the synthetic yield and to make our method more attractive, different routes to compound **1** were considered, a microbiological reduction, allowing the introduction of the stereogenic centre, remaining the key step of the synthesis.

2. Results and discussion

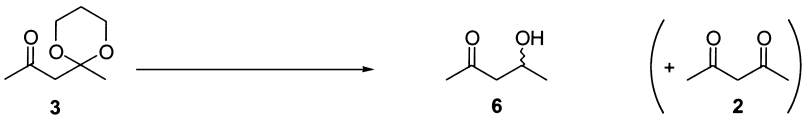
2.1. Microbiological reduction of monoprotected 2,4-pentanedione 3

The new strategy first envisaged for the preparation of **1** (Scheme 1) required four steps from 2,4-pentanedione **2** and involved a microbiological reduction as the key reaction. It started by the selective mono keto-protection, as a dioxane group, of 2,4-pentanedione **2**, then a microbiological reduction of compound **3**, the last steps being a Mitsunobu reaction, using phthalimide as nucleophile, followed by simple amino-deprotection. We thought that this short sequence should permit efficient access to both enantiomers of **1**.



Scheme 1.

Thus, compound **3** was synthesized according to Weiss et al.[7] by reaction of 2,4-pentanedione **2** with 1,3-propanediol (in place of ethanediol) in refluxing chloroform, in the presence of *p*-TSA. It has to be noted that the exchange of a protective group (dioxane instead of dioxolane) dramatically decreased the yield (40% instead of 70%). However, the microbiological reduction of **3** was studied with several microorganisms: yeasts, fungi and a bacterium. Some of the strains tested (baker's yeast under non-fermenting conditions, *Cunninghamella elegans* and the bacterium *Lactobacillus kefir*) did not reduce compound **3**, whose concentration remained unchanged even after 5 days of incubation. Others (baker's yeast under fermenting conditions, *Rhodotorula glutinis*, and the fungi *Aspergillus niger*, *Beauveria bassiana*, *Geotrichum candidum*) yielded, after several days of incubation (3–6 days), a mixture of diketone **2** and deprotected ketol **6** in various ratios depending on the microorganism (Scheme 2). Compound **6** was obtained with an (*R*)- or an (*S*)-absolute configuration, and with poor to excellent enantiomeric excesses depending on the microorganism used.



Baker's yeast (fermentation)	no reaction
Baker's yeast (fermentation)	ee = 60%; (S); 40% yield
Rhodotorula glutinis	ee = 92%; (S); 28% yield
Aspergillus niger	ee = 23%; (R); 15% yield
Beauveria bassiana	ee = 16%; (S); 10% yield
Cunninghamella elegans	no reaction
Geotrichum candidum	ee = 20%; (S); 8% yield
Lactobacillus kefir	no reaction

Scheme 2.

A kinetic study of the reduction with baker's yeast showed that the metabolic pathway goes through the formation of 2,4-pentanedione **2**, which is in its turn reduced to the corresponding ketol **6** (Fig. 1). The fact that **3** was not transformed even after 6 days in water, with or without the strain of microorganisms, revealed that the deprotection reaction is certainly an enzymatic process.

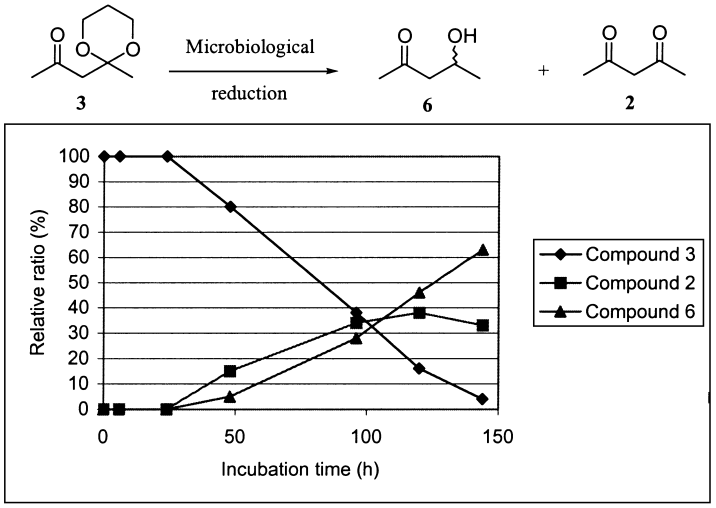


Figure 1. Time courses of compounds **2**, **3** and **6** during the microbiological reduction of **3** by baker's yeast under fermenting conditions

In a chemical approach, the pH of the medium is also very important, as the chemical hydrolysis of acetals occurs in acidic conditions.[8] Some authors[9,10] have already reported the programmed use of acyclic acetals to release the aldehyde function in a controlled manner; in this case the function was not stable in the medium, or was a possible inhibitor of the reductive enzymatic systems. Due to the fermentation process of yeast[9] or *Geotrichum candidum*,[10] the pH of the medium decreased slowly between 3 and 5, leading to the chemical hydrolysis of the acetal. If

such a process can be foreseen for our product in the case of fermenting baker's yeast, the pH of the medium with the other microorganisms would remain between 7 and 8. Pure enzymatic reactions can then be postulated: either enzymatic hydrolysis or *O*-dealkylation catalyzed by a cytochrome P450.[11] This latest has already been reported in the case of 1,3-dioxane and 1,3-oxathiolane derivatives of theophylline, and corresponds to the ring cleavage through the oxidation of the acetalic carbon and subsequent rearrangement.[12] Whatever the enzymatic process is, the product of this microbiological reduction is obtained in too low a yield. To obtain both enantiomers of this product in good yields and with excellent enantiomeric excesses, we finally found it easier to directly reduce 2,4-pentanedione **2**.

2.2. Microbiological reduction of 2,4-pentanedione **2**

The microbiological reduction of several β-diketones has already been reported by some of us.[3,13] The best results, starting from 2,4-pentanedione, were obtained with fresh baker's yeast (leading to enantiomerically pure (*S*)-ketol) and with *Aspergillus niger* ((*R*)-ketol, ee = 95%). In order to improve the enantiomeric purity of the (*R*)-enantiomer, new strains were assayed. The results are listed in Table 1.

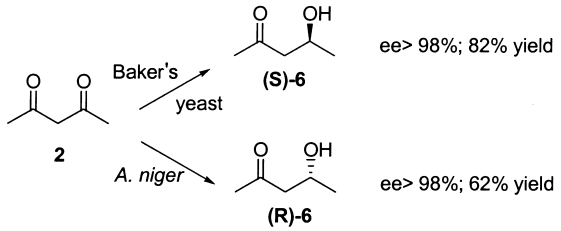
Table 1
Microbiological reductions of 2,4-pentanedione **2**

Microorganisms	Incubation time (days)	4-hydroxy-2-pentanone **6**			
		$[\alpha]_D^{25}$	ee	Absolute Conf.	Yield
Baker's yeast (fermenting conditions)	6	**+ 69**	**> 98 %**	**S**	**82%**
Rhodotorula glutinis	1	+ 53	82%	S	70%
Yamadazyma farinosa (N_2)	0.25	**- 68**	**> 98%**	**R**	**30%**
Aspergillus niger	1	**- 68**	**> 98%**	**R**	**62%**
Beauveria bassiana	2	- 6	9%	R	90%
Cunninghamella elegans	1	+ 34	52%	S	63%
Lactobacillus kefir	3	- 16	25%	R	25%

Most of the microorganisms tested yielded the ketol with moderate enantiomeric excesses. The only ones giving enantiomerically pure compounds remained freeze-dried baker's yeast for the (*S*)-ketol, while *A. niger* and *Y. farinosa* (under anaerobic conditions) yielded the enantiomeric pure (*R*)-ketol. It is worth noting that in these new assays, *A. niger* yielded the enantiomerically pure ketol (Scheme 3).

2.3. Synthesis of (2R)- and (2S)-amine **1**

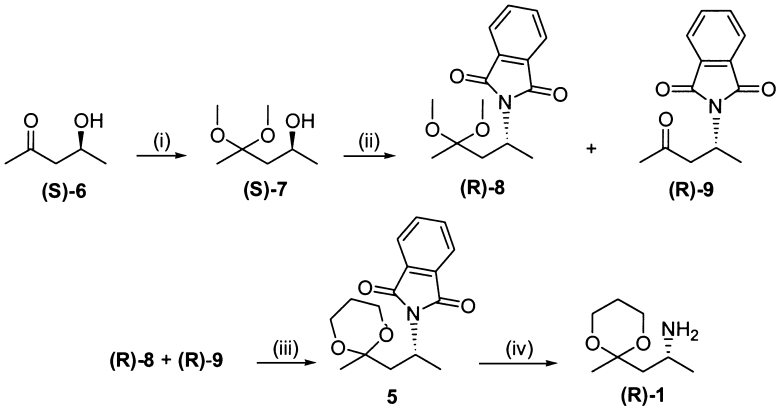
Starting from the (2*R*)- or the (2*S*)-ketol **6**, several synthetic strategies can be proposed for the preparation of **1**. In a first attempt, a Mitsunobu reaction was carried out directly on the ketol, but gave a complex mixture of degradation products. The direct protection of the keto function



Scheme 3.

by treatment with 1,3-propanediol in refluxing toluene in the presence of *p*-TSA, carried out with or without previous alcohol protection by a TBDMS group, was not successful either.

The nature of the acetal had to be changed in order to work under mild conditions (temperature and pH). The new synthetic route is described in Scheme 4.



Scheme 4. Synthetic route for the preparation of **1**. (i) MeOH, $CH(OCH_3)_3$, amberlyst; (ii) DEAD, PPh_3, phthalimide; 71% yield from **6**; (iii) propane-1,3-diol, *p*-TSA, 78% yield; (iv) $NH_2NH_2{\cdot}N_2O$, 98% yield

The ketone function of **6** was protected as a dimethylacetal by treatment with methanol in presence of trimethyl orthoformate according to Ref. 14 using amberlyst in place of *p*-TSA. The pH control was crucial as it was necessary to adjust the pH to 8 by adding triethylamine, prior to the evaporation of the solvent. Compound **7**, thus obtained, was directly used in the second step without purification. The Mitsunobu reaction furnished a (1:1) mixture of two products: the desired phthalimido derivative **8** together with the corresponding keto-deprotected compound **9** in 71% from **6**.

The mixture of **8** and **9** was treated with propane-1,3-diol and afforded compound **5** cleanly, bearing the required protection (yield: 78%). We could verify here that the Mitsunobu reaction took place with complete inversion of configuration by a comparison of the sign and the value of the specific rotation obtained for **5** with those previously described.[5] The last step was the deprotection of the amino function by simple hydrazinolysis (yield: 98%). Comparison of the specific rotation of each enantiomer of **1** with reported data[5] showed that both were prepared enantiomerically pure. The enantiomeric purity of each enantiomer of **1** was easily checked by ^1H NMR realized in the presence of (+)-mandelic acid as chiral solvating agent.[15]

3. Conclusion

This new efficient synthetic route lead to both enantiomerically pure enantiomers of the keto-protected β-aminoketone **1**, in five steps, with overall yields of 44% for (*S*)-**1** and 37% for the (*R*)-enantiomer, the key step being the microbiological reduction of a β-diketone. The improvement of the overall yield obtained (40% instead of 13% in the previous seven-step synthesis) now makes these synthons interesting for further organic synthesis. They have been used for the efficient synthesis of several piperidine alkaloids (see the following paper).

This simple method, involving the microbiological reduction of β-diketones to prepare enantiomerically pure β-aminoketones, will be extended to other parent synthons. Investigations are in progress.

4. Experimental

4.1. General methods

Gas chromatography (GC) was performed using an instrument equipped with a flame ionization detector and a 30 m×0.32 mm capillary column coated with Carbowax 20 M. The carrier gas was hydrogen at 65 kPa. Oven temperature: 40°C for 5 min and then 40°C to 200°C at 5°C/min. For ^{1}H (400.13 MHz) and ^{13}C (100.61 MHz) NMR spectra, the chemical shifts (ppm) were relative to chloroform. Microanalyses were performed by the Service Central d'Analyses du CNRS, Vernaison (France).

Microbiological methods: The microorganisms were all laboratory-grown except freeze-dried baker's yeast which was a commercial product (Vahine, Monteux, France). Preculture, culture and bioconversion conditions for the fungi *Aspergillus niger* ATCC 9142, *Beauveria bassiana* ATCC 7159, *Cunninghamella elegans* ATCC 9245 and *Geotrichum candidum* CBS 233-76, for the yeasts *Rhodotorula glutinis* NRLL Y 1091 and *Yamadazyma farinosa* IFO 10896 and for the bacterium *Lactobacillus kefir* DSM 20587 have already been described elsewhere.[16] The bioconversion conditions are given below:

- For freeze-dried bakers' yeast under fermenting conditions: In a 500 mL conical flask was added, to a solution of 7.5 g of sucrose in 250 mL of distilled water, 12.5 g of baker's yeast. The flask was incubated at 30°C on a rotating table set at 200 rpm. After 30 min of fermentation, 250 μL of substrate was added. Sucrose (7.5 g) was added every 24 h.
- For *Yamadazyma farinosa*: The bioconversion was carried out under anaerobic conditions according to Ohta.[17]
- Other strains: The bioconversion was carried out as previously described.[16]

4.2. Synthesis of 1-(2-methyl-1,3-dioxan-2-yl)-propan-2-one **3**

In a 50 mL round-bottomed flask, equipped with a Dean–Stark apparatus, was refluxed overnight with stirring a mixture of 5.7 g (50 mmol) of freshly distilled 2,4-pentanedione and 3.8 g (50 mmol) of 1,3-propanediol and 50 mg of *p*-toluenesulfonic acid in 20 mL of dry chloroform. The mixture was then washed with a saturated $NaHCO_3$ solution. The aqueous phase was extracted three times with chloroform. The combined organic layers were dried over $MgSO_4$. The solvent

was then removed and the residue was purified over a silica gel column, eluent: pentane:ether, 70:30. Yield: 40% (3.2 g). Retention time: 940 s (P2). ^{1}H NMR (400.13 MHz) δ: 1.42 (s, 3H), 1.45–1.55 (m, 1H), 1.71–1.88 (m, 1H), 2.19 (s, 3H), 2.73 (s, 2H), 3.78–3.88 (m, 2H), 3.88–3.98 (m, 2H). ^{13}C NMR (100.61 MHz) δ: 20.4 (CH_3), 25.1 (CH_3), 31.8 (CH_2 acetal), 53.1 (CH_2), 59.8 (CH_2 acetal), 60.0 (CH_2 acetal), 97.7 (C acetal), 206.4 (CO). Anal. calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.69; H, 8.94.

4.3. Microbiological reduction of 2,4-pentanedione **2**

Varied incubation times are indicated for each microorganism. The product was purified on a silica gel column (eluent: pentane:ether, 70:30). In each case, the yields are overall yields after purification.

- Freeze-dried baker's yeast under fermenting conditions. Incubation time: 6 days. Yield: 82%. (+)-(4S)-**6**: Retention time: 420 s (P2); ^{1}H NMR (400.13 MHz) δ: 1.15 (d, 3H, J = 7.9 Hz), 2.10 (s, 3H), 2.55 (d, 2H, J = 6 Hz), 3.30 (br s, 1H, exchangeable with D_2O), 4.10–4.20 (m, 1H). $[\alpha]_D^{25} = +69$ (*c* 4.1, $CHCl_3$), ee $\geqslant$ 98%. Lit.[3] (–)-(4R)-**6**: $[\alpha]_D^{25} = -60$ (*c* 2.0, $CHCl_3$), ee = 95%.
- *Aspergillus niger*. Incubation time: 24 h. Yield: 62%. $[\alpha]_D^{25} = -68$ (*c* 2.34, $CHCl_3$), ee = > 98%.
- *Lactobacillus kefir*. Incubation time: 3 days. The residue from six flasks consisted of 25% of **2** and 75% of (–)-(2R)-**6**. Yield: 25%; $[\alpha]_D^{25} = -16$ (*c* 4.3, $CHCl_3$), ee = 23%.
- *Rhodotorula glutinis*. Incubation time: 24 h. Yield: 70%; $[\alpha]_D^{25} = +53$ (*c* 2.05, $CHCl_3$), ee = 82%.
- *Cunninghamella elegans*. Incubation time: 24 h. Yield: 63%; $[\alpha]_D^{25} = +34$ (*c* 3.67, $CHCl_3$), ee = 52%.
- *Beauveria bassiana*. Incubation time: 48 h. Yield: 90%; $[\alpha]_D^{25} = -6$ (*c* 2.8, $CHCl_3$), ee = 9%.
- *Yamadazyma farinosa*. Incubation time: 6 h (anaerobic conditions). Yield: 30%; $[\alpha]_D^{25} = -68$ (*c* 4.6, $CHCl_3$), ee $\geqslant$ 98%.

4.4. Synthesis of (2R)-2-(2-aminopropyl)-2-methyl-1,3-dioxane **1**

4.4.1. Synthesis of (2S)-4,4-dimethoxy-2-pentanol 7

To a stirred solution of 270 mg (2.6 mmol) of (4*S*)-4-hydroxypentan-2-one **6** (obtained by microbiological reduction with baker's yeast) in 15 mL of dry methanol, placed under argon, was added 100 mg of amberlyst and then dropwise 3 g (3.1 mL, 28 mmol) of trimethyl orthoformate. After 1 h of reaction, when the reaction was complete (checked by GC), the mixture was filtered and the pH of the filtrate was immediately adjusted to 8 (with a pH meter apparatus) by adding triethylamine. The solvent was then removed. Compound **7** was further used without any purification. Retention time: 750 s (P2). ^{1}H NMR (400.13 MHz) δ: 1.18 (d, 3H, J = 5.7 Hz), 1.38 (s, 3H), 1.52 (dd, 1H, J = 2.5, 13.7 Hz), 1.95 (dd, 1H, J = 10.3, 13.7 Hz), 3.20 (s, 3H), 3.24 (s, 3H), 3.65 (s, 1H, exchangeable with D_2O), 4.02 (sex, 1H, J = 4.6 Hz). ^{13}C NMR (100.61 MHz) δ: 20.7 (CH_3), 23.1 (CH_3), 44.0 (CH_2), 47.0 (CH_3O), 47.2 (CH_3O), 63.3 (CH), 100.9 (Cq).

4.4.2. Synthesis of (–)-(2R)-4,4-dimethoxy-2-phthalimidopentane **8**

To a solution of **7** (2.6 mmol) in 20 mL of dry THF were added 0.8 g (5.2 mmol) of phthalimide and 1.4 g (5.2 mmol) of triphenylphosphine. This solution was cooled with an ice bath and placed

under argon. To this mixture was then added dropwise a solution of DEAD (910 mg, 820 μL, 5.2 mmol) in 10 mL of dry THF. After the end of the addition, the mixture was left under stirring overnight at room temperature. The solvent was then removed under vacuum, and the residue was filtered through a silica pad (3×5 cm) (eluent: hexane:ethyl acetate, 5:1). The filtrate was evaporated and the residue was purified on a silica gel column (eluent: pentane:ether, 60:40). A mixture of (+)-(2*R*)-4,4-dimethoxy-2-phthalimidopentane **8** and (–)-(4*R*)-4-phthalimido-2-pentanone **9** was obtained. Overall yield from **6**: 71%.

Compound (+)-(2*R*)-**8**. ^{1}H NMR (400.13 MHz) δ: 1.33 (s, 3H), 1.50 (d, 3H, J = 6.5 Hz), 1.78 (dd, 1H, J = 2.5, 13.5 Hz), 2.70 (dd, 1H, J = 10.4, 13.5 Hz), 2.95 (s, 3H), 3.15 (s, 3H), 4.50–4.63 (m, 1H), 7.65–7.74 (m, 2H), 7.78–7.85 (m, 2H). ^{13}C NMR (100.61 MHz) δ: 19.4 (CH_3), 20.5 (CH_3), 39.2 (CH), 43.1 (CH_2), 47.2 (CH_3O), 47.4 (CH_3O), 100.7 (Cq), 122.6 (CH_2 aromatic), 132.2 (Cq aromatic): 134.0 (CH_2 aromatic), 168.0 (CO phthalimide); $[\alpha]_D^{25} = +18$ (*c* 3.14, $CHCl_3$).

Compound (–)-(4*R*)-**9**. Same physical properties and NMR spectra as those previously reported;[5] $[\alpha]_D^{25} = -2.2$ (*c* 3.93, $CHCl_3$).

*4.4.3. Synthesis of (–)-(2*R*)-1-(2-methyl-1,3-dioxan-2-yl)-2-phthalimidopropane **5***

In a round-bottomed flask, fitted with a Dean–Stark apparatus, was added, to a solution of **8** and **9** (0.47 g) in 15 mL of toluene, 615 μL of freshly distilled propane-1,3-diol (5 equiv., 8 mmol) and 10 mg of *p*-TSA. The mixture was refluxed for 5 h, then cooled to room temperature and treated with a saturated $NaHCO_3$ solution. The two layers were separated, and the aqueous one was extracted several times with dichloromethane. The combined organic layers were washed with a brine solution and then dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel chromatography (eluent: pentane:ether, 60:40). Yield: 78%. Same physical constants and NMR spectra as those described previously.[5] $[\alpha]_D^{25} = -2.2$ (*c* 6.06, $CHCl_3$).

*4.4.4. Synthesis of (–)-(2*R*)-2-(2-aminopropyl)-2-methyl-1,3-dioxane **1***

To a solution of **5** (0.7 g, 2.42 mmol) in 7 mL of methanol was added 2.7 mL (21.1 equiv., 0.05 mol) of hydrazine monohydrate. The mixture was refluxed overnight. After cooling the reaction mixture to room temperature, 11 mL of a 2.6N KOH solution was added. The aqueous layer was extracted three times with dichloromethane (3×10 mL). The combined organic layers were washed with a saturated brine solution and dried over $MgSO_4$. After evaporation of the solvent under reduced pressure (without heating), a yellow oil of **1** was obtained in a 98% yield. Same physical constants and NMR spectra as those described previously.[5] $[\alpha]_D^{25} = -17.5$ (*c* 3.18, $CHCl_3$).

- Determination of the enantiomeric excess of **1**. In a NMR tube was placed 9.6 mg of (+)-mandelic acid. To this solid was added a solution of racemic, or enantiomerically pure **1** (10 mg, 1 equiv.) in $CDCl_3$. The mixture was stirred vigorously and the NMR spectrum was recorded. ^{1}H NMR (400.13 MHz) δ: Racemic **1**: 3.43 (m, 1H), 3.53 (m, 1H); (R)-**1**: 3.53 (m, 1H), ee $\geqslant$ 98%.

*4.5. Synthesis of (2*S*)-**1** from (2*R*)-4,4-dimethoxy-2-pentanol obtained with* A. niger

The same methods were used as those described above, starting from (2*R*)-**7** obtained by microbiological reduction with *A. niger*. (2*S*)-**1** was then obtained; $[\alpha]_D^{25} = +17.5$ (*c* 2.65, $CHCl_3$).

Acknowledgements

We greatfully acknowledge Martine Sancelme for her technical assistance in microbiology and for scientific discussions.

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