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Stereoselective chemoenzymatic synthesis of both enantiomers of protected 4-amino-2-pentanone

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Abstract

An acetal protected 4-amino-2-pentanone was synthesised by two different routes in 10 and seven steps, respectively, the key step being a microbiological reduction. Both enantiomers of the amine were obtained enantiomerically pure.

1. Introduction

Previously,[1] some of us have reported on a stereoselective synthesis of (2,4)-di- or (2,3,4)-trisubstituted piperidines, by an intramolecular cyclisation of chiral dienal iron tricarbonyl complexes and an achiral amine. The stereoselectivity of the reaction arose from the chirality of the organometallic complexes used and, consequently, chiral organometallic complexes had to be prepared. Another strategy to affect this cyclisation would consist of starting from a chiral amine and an achiral aldehyde to obtain substitutions at other positions (see following accompanying paper). For this purpose, enantiomerically pure substituted primary amines need to be prepared and used as starting materials (Scheme 1). This fashion of introducing chirality should be attractive since the synthesis of enantiomerically pure organoiron complexes is not always obvious.

The amine group is one of the fundamental structures in organic chemistry. Chiral amines are intermediates for many syntheses of drugs or natural products, and are also used as chiral auxiliaries and resolving agents.[2] Several methods have been developed for the preparation of chiral amines. Most of them correspond to the resolution of racemic amines either by chemical (fractional crystallisation of the diastereoisomeric salt of the amine with a chiral acid,[3] chromatographical (on a chiral stationary

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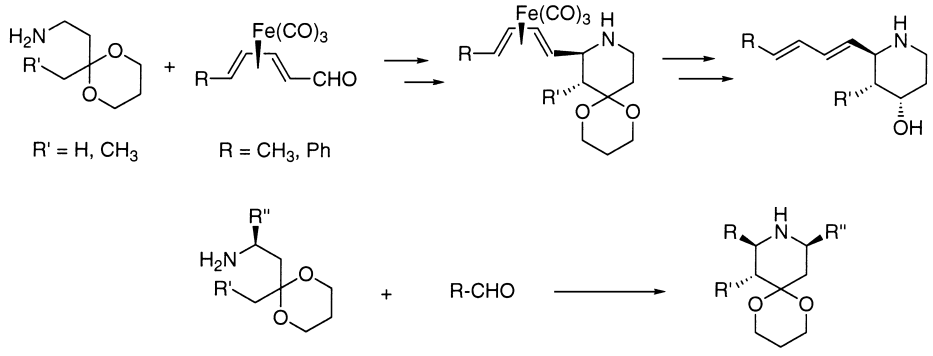
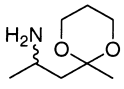


Scheme 1. Strategies for the synthesis of chiral substituted piperidines

phase[4]) or by enzymatic methods (use of lipases,[5] enzyme catalysed aminolysis in organic solvents[6]). The disadvantage of all these resolution procedures is the theoretical maximum yield limit of 50%. Other chemical methods, such as nucleophilic 1,2-addition of organometallic reagents[7] to imines or reduction by metal hydrides[8] of a CN double bond, or stereoselective Michael addition of a chiral amine to α,β-unsaturated esters,[9] have allowed the synthesis of enantiomerically enriched amines. Those strategies which use a chiral synthon as starting material are very elegant but the problem can then be, in some cases, obtaining the enantiomerically pure precursors.

For our own part, we have worked for several years on the microbiological reduction of various keto compounds[10] and have shown that in many cases, by choosing the appropriate microorganism, both enantiomers of the corresponding alcohol could be obtained with high enantiomeric excesses. So, we envisaged the preparation of chiral amines through chiral alcohols.

In this paper, the preparation of both enantiomers of protected 4-amino-2-pentanone **1** (Scheme 1, $R'=H$, $R''=CH_3$) is reported via a chemoenzymatic synthesis, the key step being a microbiological reduction of a prochiral keto compound.



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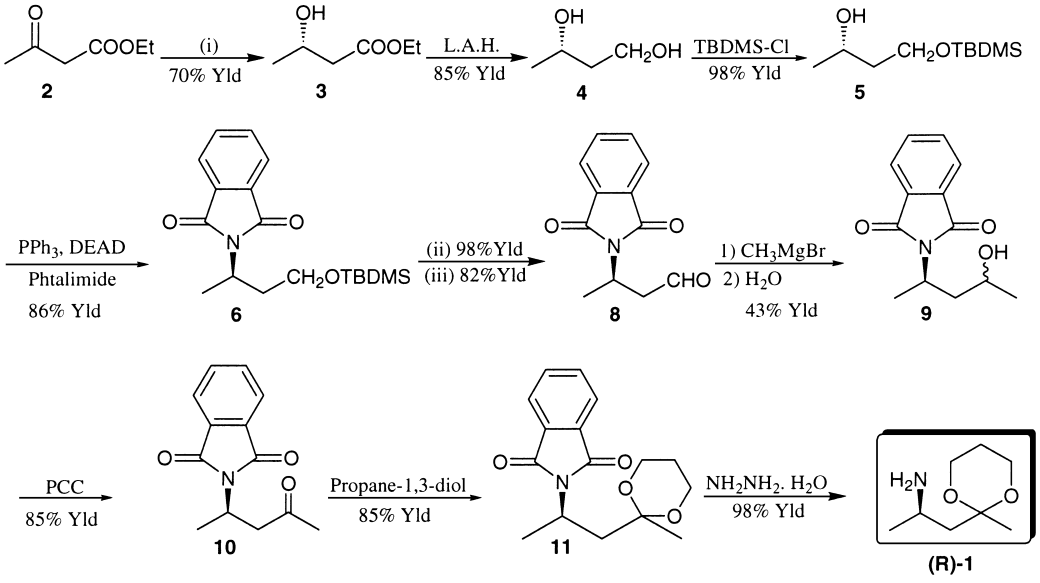
2. Results and discussion

*2.1. Synthesis of (*R*)-**1** by microbiological reduction of ethyl acetoacetate (Method A)*

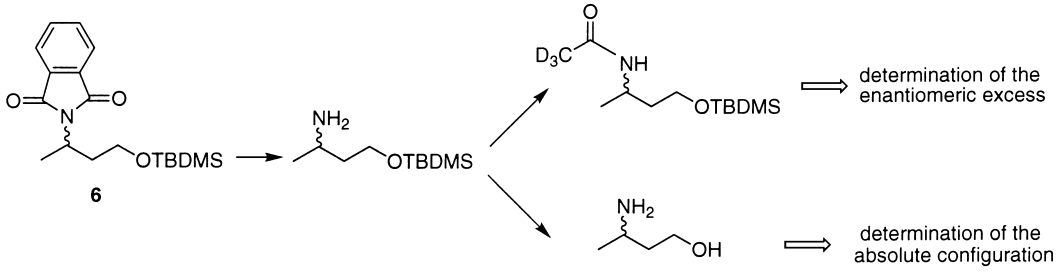
The first step of our proposed route (Scheme 2) consisted of the microbiological reduction of a β-ketoester, ethyl acetoacetate **2**. For this key step, corresponding to the introduction of the asymmetric carbon, obtaining the enantiomerically pure hydroxyester is necessary. The asymmetric reduction of ethyl acetoacetate by baker's yeast has long been known[11] and is now a well-established procedure for the synthesis of (3*S*)-ethyl 3-hydroxybutanoate of high but variable enantiomeric excess (ee 77–99%), according to the method of bioconversion used: fermentation or non-fermentation processes, control of substrate concentration,[12] immobilisation of baker's yeast,[13] or use of specific dehydrogenase inhibitor.[14] For our protocol, the following method was chosen: 40 g of freeze-dried baker's yeast in 500 mL of distilled water, addition of 1 g of **2**, incubation time: 1 h. The (3*S*)-ethyl 3-hydroxybutanoate **3** was obtained enantiomerically pure in 70% yield. The enantiomeric excess was determined on the basis of the corresponding MTPA-ester[15] by ^1H NMR and showed that **3** was obtained enantiomerically pure.

Since it has been reported by Buisson et al.[16] that reduction of **2** by the fungus *Geotrichum candidum* yielded (3*R*)-**3** in a 75% yield and with an ee≥98%, both enantiomers of the hydroxyester **3** could be obtained in an enantiomerically pure form by simply choosing the appropriate microorganism for the reduction step.



Scheme 2. Synthetic route for the preparation of **1** (Method A). (i) Microbiological reduction with baker's yeast, (ii) AcOH/H_2O/THF, (iii) PCC

The ester function of the β-hydroxyester was then reduced with $LiAlH_4$ to yield the (+)-(3*S*)-1,3-butanediol **4** in 85% yield. At this step, the optical purity of **4** was checked by comparing the value of the specific rotation of the product obtained with that given in the literature[17] ($[\alpha]_D^{25}$=+30.3 (*c* 1.5, MeOH); lit.[17] $[\alpha]_D$=+28.9 (*c* 0.96, MeOH); ee=97%). The primary alcohol function was then selectively and quantitatively protected as its *tert*-butyldimethylsilyl derivative **5**[18] and then transformed into phthalimide **6** through a Mitsunobu reaction[19] (86% yield). The Mitsunobu reaction is known to take place with an inversion of configuration, but in some cases, almost complete racemisation has been observed.[20] In order to confirm the stereochemical course of the reaction, we checked the enantiomeric excess and the absolute configuration of phthalimide **6** (Scheme 3). The first attempts to determine the enantiomeric excess by classical methods (GC or HPLC fitted out with chiral columns) failed. It was finally determined by deuterium NMR of its *N*-trideuteroacetyl derivative in a chiral solvent [dichloromethane solution of γ-benzyl L-glutamate (PBLG)] as described previously[21] and was found to be enantiomerically pure.



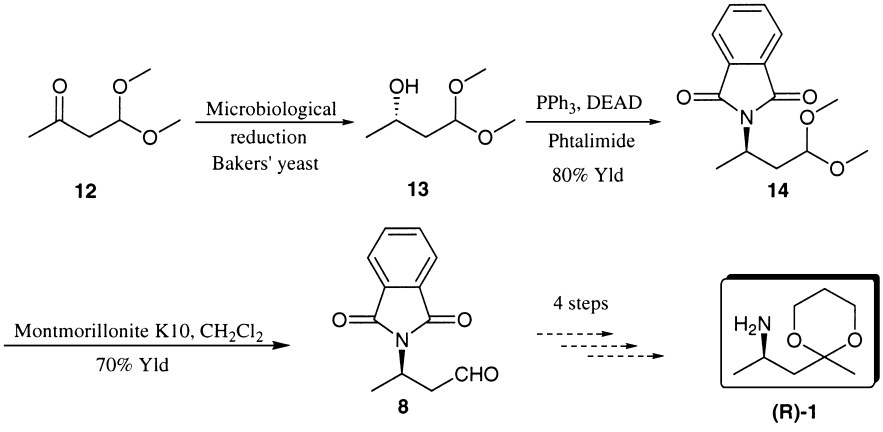
Scheme 3.

The absolute configuration of phthalimide **6** was assigned by chemical correlation (Scheme 3). After cleavage of the phthalimido group by hydrazinolysis and deprotection of the alcohol function, 3-aminobutanol was obtained. By comparing the sign of the optical rotation of 3-aminobutanol obtained with that described in the literature,[22] the absolute configuration was assigned to be (*R*). Compound **6** also had the (*R*) absolute configuration and was obtained enantiomerically pure. So in this case, the Mitsunobu reaction took place with a complete inversion of configuration.

The alcohol function of **6** was then quantitatively deprotected and oxidised with PCC, yielding the corresponding aldehyde **8**. Homologation of the carbon chain was realised with methylmagnesium bromide at room temperature. During this reaction, the formation of many by-products was observed, corresponding in particular to the attack of the alkylmagnesium on the C=O functions of the phthalimide, a phenomenon that has already been reported (even at 0°C).[23] In their case, the best results (in terms of yield) were obtained at −15°C with 1.1 equiv. of methylmagnesium bromide. A mixture of two diastereoisomers of **9** was obtained in a 70:30 ratio in an overall yield of 43%. They were not separated as the next step was the oxidation with PCC of the alcohol function (compound **10**). The last two steps consisted of the protection of the ketone with propane 1,3-diol (yield: 85%) and the deprotection of the amino function by cleavage of the phthalimido group with hydrazine (yield: 98%). By this route, the chiral synthon (*R*)-**1** was obtained in 10 steps with a 12% overall yield. The enantiomeric excess of **1** was checked again, even though no reaction had taken place directly on the asymmetric carbon since the Mitsunobu reaction. It was determined by ^{1}H NMR of **1** in the presence of (+)-mandelic acid as chiral solvating agent,[24] that amine **1** was enantiomerically pure.

*2.2. Synthesis of both enantiomers of **1** by microbiological reduction of 4,4-dimethoxy-2-butanone (Method B)*

Another route, containing fewer steps, was then envisaged (Scheme 4), the key step also being a microbiological reduction. The starting material was 4,4-dimethoxy-2-butanone **12**.



Scheme 4. Synthetic route for the preparation of (*R*)-**1** (Method B)

*2.2.1. Microbiological reduction of **12***

The microbiological reduction of **12** has not been fully studied previously. In the literature, Wong et al.[25] studied the enzymatic reduction of **12** by several alcohol dehydrogenases. In their case, **13** was not

Table 1
Microbiological reductions of **12**

	Incubation time (days)	Ratio ketone / alcohol	$[\alpha]_D^{.25}$	ee	Yield
Bakers' yeast	3	23 / 77	**- 11.7**	**≥ 98%**	**75%**
R. glutinis	3	70 / 30	- 11.7	≥ 98%	26%
Y. farinosa	2	10 / 90	**+ 11.7**	**≥ 98%**	**50%**
Z. rouxii	2	80 / 20	- 11.7	≥ 98%	18%
A. niger	3	77 / 23	- 8.1	70%	20%
L. kefir	4	90 /10	+ 5.1	45%	7%

characterised and was directly converted into the corresponding MTPA-ester. That is the reason why we decided to test several strains of microorganisms for the reduction of **12**. The results obtained with the most efficient ones are reported in Table 1.

Most of the microorganisms tested are not able to reduce **12** (data not shown). This compound is difficult to reduce microbiologically. Even after a long incubation time, the percentage of reduced ketone was not very high. Only the strains of yeast, and in particular baker's yeast and *Yamadazyma farinosa*, gave enantiomerically pure **13**, (*S*)-**13** and (*R*)-**13**, respectively, with good yields. In each case, the enantiomeric excess of the alcohol **13** obtained was determined after conversion into the corresponding MTPA-ester and analysis by ^{1}H NMR.

*2.2.2. Synthesis of both enantiomers of **1***

The strategy for the synthesis is similar to that described above: Mitsunobu reaction with both enantiomers of **13** and deprotection of the aldehyde function yielded **8**. For this last step (**14** → **8**), several reagents were used: wet silica,[26] formic acid[27] and montmorillonite K10.[28] Only the use of montmorillonite K10 gave **8** in good yield (70%). The value of the specific rotation of **8** obtained by this method was identical to that obtained by the previous synthesis (Method A). This shorter synthetic route allowed the preparation of both enantiomers of **1** in enantiomerically pure form, starting from the alcohol obtained by microbiological reduction either with baker's yeast ((*R*)-**1**) or with *Yamadazyma farinosa* ((*S*)-**1**). In the case of the reduction with baker's yeast, (*R*)-**1** was obtained in seven steps with a 13.5% overall yield and an ee≥98%.

The decrease in the number of steps (seven instead of 10) has not, to a great extent, improved the overall yield. This fact was a little disappointing but not very surprising, since this second synthesis does not avoid the critical step (in terms of yield) of addition of methylmagnesium bromide on the aldehyde.

A completely different synthetic route of **1**, avoiding this limitating step, needs to be envisaged to improve the overall yield and also to make this route more satisfactory. However, with these two syntheses, both enantiomers of **1** have been obtained enantiomerically pure. They have been used for the syntheses of several piperidines (see following paper). Moreover, these methods could be extended to the synthesis of other chiral amines by simply changing the structure of the alkylmagnesium or of the starting materials.

3. Experimental

3.1. General methods

Gas chromatography (GC) was performed using an instrument equipped with a flame ionisation detector and a 50 m×0.32 mm capillary column coated with Carbowax 20 M. The carrier gas was hydrogen at 65 kPa. Oven temperature: P1 (40°C for 5 min and then 40 to 200°C at 8°C/min) or P2 (80°C for 5 min and then 80 to 200°C at 5°C/min). For ^{1}H (400.13 MHz) and ^{13}C (100.61 MHz) NMR spectra, the chemical shifts were relative to chloroform. Microanalyses were performed by the Service Central d'Analyses du CNRS, Vernaison (France). High resolution mass spectrometry (HRMS) was performed by the Centre Régional de Mesures Physiques de l'Ouest, Université de Rennes (France).

3.2. 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 and for the bacterium *Lactobacillus kefir* DSM 20587 have already been described elsewhere.[29] The yeast *Zygosaccharomyces rouxii* ATCC 13356 was grown on a medium containing glucose, 20 g; malt extract, 6 g; yeast extract, 6 g; tryptone (Difco), 10 g and H_2O, 1 L; pH=6.0; preculture and culture: 48 h. The bioconversion was carried out as previously described.[29] The yeast *Yamadazyma farinosa* IFO 10896 was grown on a medium containing glucose, 50 g; tryptone (Difco), 7 g; yeast extract, 5 g; K_2HPO_4, 2 g; KH_2PO_4, 3 g and H_2O, 1 L; pH=6.5; preculture and culture: 48 h. In this last case, the bioconversion reaction was carried out under anaerobic conditions according to Ohta.[30]

3.3. Microbiological reductions

3.3.1. Microbiological reduction of ethyl 3-oxobutanoate *2*

In a 1 L Erlenmeyer flask, containing 40 g of baker's yeast in 500 mL of distilled water, was added, under stirring, 1 g of ethyl 3-oxobutanoate **2**. Incubation time: 1 h. Yield: 70% (700 mg). (+)-(3*S*)-**3**: ^{1}H NMR (400.13 MHz) δ: 1.20 (3H, t, *J*=7.2 Hz), 1.28 (3H, d, *J*=7.2 Hz), 2.40 (1H, dd, *J*=8.1 Hz, *J*=16.2 Hz), 2.48 (1H, dd, *J*=4.2 Hz, *J*=16.4 Hz), 3.15 (1H, s, exchangeable with D_2O), 4.19 (3H, m). $[\alpha]_D^{25}$=+39.5 (*c* 5.4, $CHCl_3$); ee=98%. Lit.[31] (+)-(3*S*)-**3**: $[\alpha]_D^{25}$=+41.5 (*c* 4.7, $CHCl_3$); ee=98%.

3.3.2. Determination of the enantiomeric excess of *3*

The enantiomeric excess was determined by ^{1}H NMR after converting an aliquot of racemic and optically active **3** into the corresponding MTPA-ester according to Mosher.[15] ^{1}H NMR (400.13 MHz) δ (for the *R* enantiomer): 1.19 (t, 3H, *J*=7.2 Hz), 1.42 (d, 3H, *J*=6.4 Hz), 2.50 (ABX spectrum, dd, 1H, *J*=4.2 Hz, *J*=17.5 Hz), 2.70 (ABX spectrum, dd, 1H, *J*=8.2 Hz, *J*=17.5 Hz), 3.55 (s, 3H), 4.06 (q, 2H, *J*=7.2 Hz), 5.50–5.63 (m, 1H), 7.35–7.45 (m, 3H), 7.49–7.56 (m, 2H). For the *S* enantiomer: 1.24 (t, 3H, *J*=7.2 Hz), 1.33 (d, 3H, *J*=6.4 Hz), 2.55 (ABX spectrum, dd, 1H, *J*=4.2 Hz, *J*=17.5 Hz), 2.74 (ABX spectrum, dd, 1H, *J*=8.2 Hz, *J*=17.5 Hz), 3.55 (s, 3H), 4.12 (q, 2H, *J*=7.2 Hz), 5.50–5.63 (m, 1H), 7.35–7.45 (m, 3H), 7.49–7.56 (m, 2H).

*3.3.3. Microbiological reductions of 4,4-dimethoxy-2-butanone **12***

Incubation times varied and 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.

Baker's yeast: incubation time: 3 days. The residue from 15 flasks consisted of 23% of **12** and 77% of (−)-(2*S*)-**13**. Yield: 75% (565 mg). (−)-(2*S*)-**13**: retention time: 850 s (P1). ^{1}H NMR (400.13 MHz) δ: 1.17 (d, 3H, *J*=5.2 Hz), 1.65–1.80 (m, 2H), 3.00 (s, 1H, exchangeable with D_2O), 3.33 (s, 3H), 3.38 (s, 3H), 3.90–4.00 (m, 1H), 4.55 (t, 1H, *J*=5.2 Hz). $[\alpha]_D^{25}$=−11.7 (*c* 1.5, $CHCl_3$); ee=98%. Lit.[32] (−)-(2*S*)-**13**: $[\alpha]_D^{20}$=−13.1 (*c* 1.1, $CHCl_3$); ee=98%.

*3.3.4. Determination of the enantiomeric excess of **13***

The enantiomeric excess was determined by ^{1}H NMR after converting an aliquot of racemic and optically active **13** into the corresponding MTPA-ester. ^{1}H NMR (400.13 MHz) δ (for the *S* enantiomer): 1.32 (d, 3H, *J*=7.2 Hz), 1.80–1.90 (m, 1H), 1.96–2.05 (m, 1H), 3.30 (s, 3H), 3.33 (s, 3H), 3.55 (s, 3H), 4.41 (dd, 1H, *J*=4.7 Hz, *J*=7.0 Hz), 5.18–5.30 (m, 1H), 7.37–7.45 (m, 3H), 7.50–7.58 (m, 2H). For the *R* enantiomer: 1.38 (d, 3H, *J*=7.2 Hz), 1.75–1.85 (m, 1H), 1.85–1.95 (m, 1H), 3.25 (s, 3H), 3.28 (s, 3H), 3.58 (s, 3H), 4.21 (dd, 1H, *J*=4.8 Hz, *J*=6.9 Hz), 5.18–5.30 (m, 1H), 7.37–7.45 (m, 3H), 7.50–7.58 (m, 2H).

Aspergillus niger: incubation time: 3 days. The residue from five flasks consisted of 77% of **12** and 23% of (−)-(2*S*)-**13**. Yield: 20% (50 mg). $[\alpha]_D^{25}$=−8.1 (*c* 2.34, $CHCl_3$); ee=70%.

Lactobacillus kefir: incubation time: 4 days. The residue from six flasks consisted of 90% of **12** and 10% of (+)-(2*R*)-**13**. Yield: 7% (20 mg). $[\alpha]_D^{25}$=+5.1 (*c* 1.68, $CHCl_3$); ee=45%.

Rhodotorula glutinis: incubation time: 3 days. The residue from eight flasks consisted of 70% of **12** and 30% of (−)-(2*S*)-**13**. Yield: 26% (105 mg). $[\alpha]_D^{25}$=−11.7 (*c* 2.05, $CHCl_3$); ee=98%.

Zygosaccharomyces rouxii: incubation time: 48 h. The residue from six flasks consisted of 80% of **12** and 20% of (−)-(2*S*)-**13**. Yield: 18% (58 mg). $[\alpha]_D^{25}$=−11.7 (*c* 0.67, $CHCl_3$); ee=98%.

Yamadazyma farinosa: incubation time: 48 h (anaerobic conditions[28]). The residue from 10 flasks consisted of 90% of (+)-(2*R*)-**13**. Yield: 50% (250 mg). $[\alpha]_D^{25}$=+11.7 (*c* 4.6, $CHCl_3$); ee=98%.

*3.4. Synthesis of (*R*)-**1** from the (*S*)-hydroxyester **3** obtained by reduction with baker's yeast (Method A)*

*3.4.1. (+)-(3*S*)-1,3-Butanediol **4***

To a suspension of $LiAlH_4$ (1.1 g, 29 mmol) in 30 mL of dry ether was added dropwise a solution of the (3*S*)-hydroxyester **3** (5.8 g, 44 mmol) in 20 mL of dry ether. After 6 h of reaction were added successively 1.1 mL of water, then 1.1 mL of a 30% NaOH solution and finally 2.2 mL of water. The mixture was filtered on a $MgSO_4$ pad. The filtrate was dried on $MgSO_4$. After evaporation of the solvent, the residue was purified on a silica gel column, eluent: pentane:ether, 20:80, and then 100% ether. Yield: 85% (3.4 g). Retention time: 840 s (P2). ^{1}H NMR (400.13 MHz) δ: 1.23 (d, 3H, *J*=7.1 Hz), 1.64–1.74 (m, 2H), 3.45 (s, 2H, exchangeable with D_2O), 3.75–3.92 (m, 2H), 4.00–4.11 (m, 1H). $[\alpha]_D^{25}$=+30.3 (*c* 1.5, MeOH). Lit.[17] (+)-(3*S*)-**4**: $[\alpha]_D$=+28.9 (*c* 0.969, MeOH), ee=97%.

*3.4.2. (−)-(3*S*)-1-(*tert*-Butyldimethylsilyloxy)-3-butanol **5***

To a solution of **4** (1.6 g, 17.8 mmol) and imidazole (3 g, 42.8 mmol) in 30 mL of dry THF, placed in an ice bath, was added dropwise a solution of 2.70 g (17.8 mmol, 1 equiv.) of TBDMS-Cl in 20 mL of dry THF. The mixture was stirred for 2 h at room temperature. The solvent was removed under vacuum. The residue obtained was dissolved in 75 mL of ether and washed three times with water (3×25 mL). The organic layer was dried on $MgSO_4$. The residue, obtained after evaporation of the solvent, was purified

by column chromatography, eluent: pentane:ether, 60:40. Yield: 98% (3.5 g). Retention time: 515 s (P2). ^{1}H NMR (400.13 MHz) δ: 0.05 (s, 3H), 0.09 (s, 3H), 0.87 (s, 9H), 1.17 (d, 3H, *J*=6.1 Hz), 1.54–1.71 (m, 2H), 3.48 (s, 1H, exchangeable with D_2O), 3.75–3.82 (m, 1H), 3.83–3.89 (m, 1H), 3.94–4.04 (m, 1H); ^{13}C NMR (100.61 MHz) δ: −5.6 (CH_3 TBDMS), −5.5 (CH_3 TBDMS), 18.1 (C TBDMS), 23.3 (CH_3), 25.9 (3×CH_3 TBDMS), 40.1 (CH_2), 62.6 (CH_2–OTBDMS), 68.1 (CH). HRMS analysis (LSIMS Cs^+, $C_{10}H_{25}O_2Si$=205.1624). Found: 205.1626. $[\alpha]_D^{25}$=−2.9 (*c* 4.43, $CHCl_3$).

*3.4.3. (−)-(3*R*)-1-(*tert*-Butyldimethylsilyloxy)-3-phthalimidobutane **6***

To a solution of **5** (2.2 g, 10.8 mmol) in 80 mL of dry THF were added 3.20 g (21.7 mmol) of phthalimide and 5.70 g (21.7 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 (3.8 g, 21.7 mmol) in 12.5 mL of dry THF. After the end of 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. Yield: 86% (3.1 g). ^{1}H NMR (400.13 MHz) δ: −0.10 (s, 6H), 0.80 (s, 9H), 1.45 (d, 3H, *J*=6.8 Hz), 1.85–1.98 (m, 1H), 2.23–2.37 (m, 1H), 3.50–3.68 (m, 2H), 4.45–4.60 (m, 1H), 7.62–7.73 (m, 2H), 7.75–7.85 (m, 2H); ^{13}C NMR (100.61 MHz) δ: −5.6 (CH_3 TBDMS), −5.5 (CH_3 TBDMS), 18.8 (C TBDMS), 18.8 (CH_3), 25.8 (3×CH_3 TBDMS), 36.3 (CH_2), 44.7 (CH), 60.6 (CH_2–OTBDMS), 123.0 (Ar), 132.2 (C Ar), 133.7 (Ar), 168.4 (CO). HRMS analysis (LSIMS Cs^+, $C_{18}H_{28}NO_3Si$=334.1838). Found: 334.1834. $[\alpha]_D^{25}$=−16.8 (*c* 4.0, $CHCl_3$).

*3.4.4. Determination of the enantiomeric excess of **6***

The enantiomeric excess was determined by ^{2}H NMR of the derivative obtained by reacting an aliquot of racemic and optically active **6**, after cleavage of the phthalimide function, with acetyl-d_3 chloride (CD_3COCl).

3.4.4.1. Cleavage of the phthalimide group. To a solution of **6** (155 mg, 0.46 mmol) in 1.5 mL of methanol was added 0.5 mL (21.1 equiv., 9.5 mmol) of hydrazine monohydrate. The mixture was refluxed overnight. After cooling the reaction mixture to room temperature, 1.4 mL of a 2.6N KOH solution was added. The aqueous layer was extracted three times with dichloromethane (3×5 mL). The combined organic layers were washed with a saturated brine solution and dried on $MgSO_4$. Yield: 97% (92 mg). ^{1}H NMR (400.13 MHz) δ: 0.05 (s, 6H), 0.90 (s, 9H), 1.10 (d, 3H, *J*=7.1 Hz), 1.45–1.60 (m, 2H), 2.02 (s, 2H, exchangeable with D_2O), 3.00–3.15 (m, 1H), 3.60–3.77 (m, 2H); ^{13}C NMR (100.61 MHz) δ: −5.6 (CH_3 TBDMS), −5.5 (CH_3 TBDMS), 18.3 (C TBDMS), 19.9 (CH_3), 26.0 (3×CH_3 TBDMS), 38.2 (CH_2), 45.8 (CH), 60.4 (CH_2–O).

3.4.4.2. Synthesis of the deuterated derivative. To a solution of amine (0.45 mmol, 92 mg) and dry triethylamine (1.2 equiv., 0.54 mmol, 55 mg, 75.5 μL) in 5 mL of dry ether, under argon and cooled at 0°C, was added acetyl-d_3 chloride (1.1 equiv., 0.50 mmol, 35.5 μL). The reaction mixture was stirred for 10 min at 0°C, and then 15 min at room temperature. A white precipitate (triethylamine hydrochloride) appeared. After filtration of this precipitate and evaporation of the solvent, the residue was purified by column chromatography, eluent: pentane:ether, 80:20, and then 100% ether. Yield: 57% (64 mg). ^{1}H NMR (400.13 MHz) δ: 0.05 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.15 (d, 3H, *J*=6.9 Hz), 1.50–1.62 (m, 1H), 1.68–1.83 (m, 1H), 3.61–3.72 (m, 1H), 3.72–3.85 (m, 1H), 3.98–4.15 (m, 1H), 6.45 (s, 1H,

exchangeable with D_2O). $[\alpha]_D^{25}=-11.7$ (*c* 0.6, $CHCl_3$); ee=98%; ^2H NMR (303 K): racemic: $\Delta\nu_1=148.5$ Hz, $\Delta\nu_2=108.2$ Hz, (3*R*)-deuterated compound: $\Delta\nu=150.0$ Hz.

3.4.5. Determination of the absolute configuration of ***6***

3.4.5.1. Cleavage of the phthalimide function of ***6****.* The same procedure as that described above was used. Yield: 97%.

*3.4.5.2. Synthesis of (3*R*)-3-aminobutanol.* To a solution of 1-(*tert*-butyldimethylsilyloxy)-3-aminobutane (100 mg, 0.49 mmol) in 3 mL of dry THF was added, under stirring, 4.5 mL of a 1 M solution of tetrabutylammonium fluoride in THF. The mixture was stirred for 1 h. Then an aqueous solution of ammonium chloride was added and the reaction mixture was extracted four times with ether. The organic layer was dried on $MgSO_4$. After evaporation of the solvent, the residue was purified on a silica gel column, eluent: ethyl acetate:MeOH, 70:30. Yield: 80% (35 mg). ^1H NMR (400.13 MHz) δ: 1.28 (d, 3H, *J*=6.6 Hz), 1.52–2.00 (m, 2H), 3.30–3.50 (m, 1H), 3.53–3.86 (m, 2H), 5.50 (s, 3H, exchangeable with D_2O). $[\alpha]_D^{25}=-25.0$ (*c* 1.25, EtOH). Lit.[22]: (+)-(3*S*)-3-aminobutanol: $[\alpha]_D^{20}=+16.3$ (*c* 4.5, EtOH).

*3.4.6. (−)-(3*R*)-3-Phthalimido-1-butanol* ***7***

A solution of **6** (2.2 g, 6.6 mmol) in a mixture of glacial acetic acid:water:THF, 3:1:1 (21.6 mL) was stirred overnight at room temperature. The mixture was concentrated under vacuum and the water and acetic acid traces were removed by co-distillation with toluene (2×20 mL) under reduced pressure. The white solid obtained was purified by column chromatography, eluent: pentane:ether, 50:50. Yield: 98% (1.4 g); mp=65–66°C. ^1H NMR (400.13 MHz) δ: 1.47 (d, 3H, *J*=7.0 Hz), 1.92–2.06 (m, 1H), 2.20–2.30 (m, 1H), 2.52 (s, 1H, exchangeable with D_2O), 3.50–3.57 (m, 1H), 3.61–3.68 (m, 1H), 4.51–4.62 (m, 1H), 7.62–7.70 (m, 2H), 7.72–7.80 (m, 2H); ^{13}C NMR (100.61 MHz) δ: 18.5 (CH_3), 36.3 (CH_2), 44.2 (CH), 59.5 (CH_2OH), 123.0 (Ar), 131.8 (C Ar), 133.9 (Ar), 168.7 (CO). Anal. calcd for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.94; N, 6.39. Found: C, 65.69; H, 6.01; N, 6.37. $[\alpha]_D^{25}=-26.6$ (*c* 13.3, $CHCl_3$).

*3.4.7. (−)-(3*R*)-3-Phthalimidobutanal* ***8***

To a suspension of 1.8 g (1.5 equiv., 8.25 mmol) of PCC in methylene chloride was added rapidly a solution of **7** (1.2 g, 5.5 mmol) in 12 mL of methylene chloride. The mixture was stirred for 3 h at room temperature. The black reaction mixture was diluted with 5 vol. of anhydrous ether, the solvent was decanted, and the black solid was washed twice with ether (causing it to be granular). Product was isolated simply by filtration of the organic extracts through Florisil and evaporation of the solvent at reduced pressure. The residue was then purified by column chromatography on silica gel, eluent: ethyl acetate:cyclohexane, 40:60. A white solid was isolated with an 82% yield (975 mg); mp=105–106°C. ^1H NMR (400.13 MHz) δ: 1.47 (d, 3H, *J*=6.9 Hz), 3.00 (ddd, 1H, *J*=1.0 Hz, *J*=5.9 Hz, *J*=17.2 Hz), 3.29 (ddd, 1H, *J*=1.0 Hz, *J*=8.4 Hz, *J*=17.2 Hz), 4.89 (m, 1H), 7.65–7.75 (m, 2H), 7.75–7.85 (m, 2H), 9.80 (s, 1H); ^{13}C NMR (100.61 MHz) δ: 18.8 (CH_3), 41.4 (CH_2), 47.3 (CH), 123.2 (Ar), 131.8 (C Ar), 134.0 (Ar), 168.1 (CO), 199.4 (CHO). Anal. calcd for $C_{12}H_{11}NO_3$: C, 66.36; H, 5.07; N, 6.45. Found: C, 66.34; H, 5.18; N, 6.37. $[\alpha]_D^{25}=-3.6$ (*c* 2.3, $CHCl_3$).

*3.4.8. (2*R*,4*R*)- and (2*S*,4*R*)-4-Phthalimido-2-pentanol* ***9***

In a round-bottom flask was stirred, under argon, 0.92 g (4.24 mmol) of **8** in 40 mL of dry THF. To this mixture cooled at −15°C, was added dropwise 1.55 mL (1.1 equiv.) of a 3 M solution of

methylmagnesium bromide in THF. The reaction mixture was stirred at −10°C for 5 h, and then hydrolysed by a mixture of water and THF. The aqueous layer was washed three times with ether. The combined organic layers were evaporated, and the residue was purified on a silica gel column, eluent: pentane:ether, 40:60. A mixture of both diastereoisomers (ratio: 70:30) was obtained. Yield: 43% (425 mg). ^{1}H NMR (400.13 MHz) δ: 1.10, *1.16* (d, 3H, J=6.3 Hz), *1.42*, 1.46 (d, 3H, *J*=7.0 Hz), 1.56–1.66, *1.80–1.89* (m, 1H), *2.06–2.16*, 2.15–2.24 (m, 1H), 2.36 (s, 1H, exchangeable with D_2O), 3.55–3.65, *3.75–3.90* (m, 1H), *4.48* (m, 1H), 4.51–4.60 (m, 1H), 7.65–7.75 (m, 2H), 7.75–7.85 (m, 2H); ^{13}C NMR (100.61 MHz) δ: *18.7*, 18.8 (CH_3); 23.1, *24.1* (CH_3); *42.6*, 43.1 (CH_2); 44.3, *45.0* (CH–N); 64.6, *66.2* (CH–O), *123.0*, 123.2 (Ar), 131.8, *132.0* (C Ar), *133.7*, 134.0 (Ar), *168.7*, 168.9 (CO).

*3.4.9. (−)-(4R)-4-Phthalimido-2-pentanone **10***

To a suspension of 1.4 g (1.5 equiv., 6.45 mmol) of PCC in 60 mL of methylene chloride was added rapidly a solution of **9** (1 g, 4.25 mmol) in 20 mL of methylene chloride. The mixture was stirred for 3 h at room temperature. The black reaction mixture was diluted with 5 volumes of anhydrous ether, the solvent was decanted, and the black solid was washed twice with ether (causing it to be granular). Product was isolated simply by filtration of the organic extracts through Florisil and evaporation of the solvent at reduced pressure. The residue was then purified by column chromatography on silica gel, eluent: pentane:ether, 50:50. A white solid was isolated with an 85% yield (845 mg); mp=60–62°C. ^{1}H NMR (400.13 MHz) δ: 1.42 (d, 3H, *J*=6.9 Hz), 2.13 (s, 3H), 3.00 (ABX spectrum, dd, 1H, *J*=6.4 Hz, *J*=17.8 Hz), 3.29 (ABX spectrum, dd, 1H, *J*=8.0 Hz, *J*=17.8 Hz), 4.82 (m, 1H), 7.65–7.71 (m, 2H), 7.76–7.82 (m, 2H); ^{13}C NMR (100.61 MHz) δ: 18.8 (CH_3), 30.1 (CH_3), 42.4 (CH–N), 46.9 (CH_2), 123.1 (Ar), 131.9 (C Ar), 133.9 (Ar), 168.2 (CO phthalimide), 205.8 (CO). Anal. calcd for $C_{13}H_{13}NO_3$: C, 67.53; H, 5.63; N, 6.06. Found: C, 67.52; H, 5.73; N, 6.13. $[\alpha]_D^{25}$=−2.2 (*c* 8.65, $CHCl_3$).

*3.4.10. (−)-(2R)-1-(2-methyl-1,3-dioxan-2-yl)-2-phthalimidopropane **11***

In a round bottomed flask, fitted with a Dean–Stark apparatus, was added, to a solution of **10** (0.87 g, 3.8 mmol) in 12 mL of toluene, 545 μL of freshly distilled propane-1,3-diol (2 equiv., 7.6 mmol, 535 mg) and 20 mg of APTS. 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 on $MgSO_4$. After evaporation of the solvent, the residue was purified by silica gel chromatography, eluent: pentane:ether, 60:40. Yield: 85% (925 mg); mp=78–79°C. ^{1}H NMR (400.13 MHz) δ: 1.23–1.34 (m, 1H), 1.36 (s, 3H), 1.47 (d, 3H, *J*=6.9 Hz), 1.65–1.80 (m, 1H), 1.80 (dd, 1H, *J*=3.0 Hz, *J*=15.4 Hz), 2.74 (dd, 1H, *J*=10.2 Hz, *J*=15.4 Hz), 3.40–3.50 (m, 1H), 3.69–3.86 (m, 3H), 4.73–4.85 (m, 1H), 7.61–7.71 (m, 2H), 7.75–7.85 (m, 2H); ^{13}C NMR (100.61 MHz) δ: 19.9 (CH_3), 20.0 (CH_3), 25.0 (CH_2 acetal), 42.2 (CH–N), 42.5 (CH_2), 59.7, 59.8 (CH_2 acetal), 98.4 (C acetal), 122.9 (Ar), 132.3 (C Ar), 133.5 (Ar), 168.7 (CO phthalimide). Anal. calcd for $C_{16}H_{19}NO_4$: C, 66.43; H, 6.57; N, 4.84. Found: C, 66.39; H, 6.67; N, 4.91. $[\alpha]_D^{25}$=−2.2 (*c* 8.65, $CHCl_3$).

*3.4.11. (−)-(2R)-1-(2-Methyl-1,3-dioxan-2-yl)-2-aminopropane **1***

To a solution of **11** (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 on $MgSO_4$. After evaporation of the solvent under reduced pressure (without heating), a yellow oil of **1** was obtained in a 97% yield (375 mg). ^{1}H NMR (400.13 MHz) δ: 0.96 (d,

3H, *J*=6.5 Hz), 1.26 (s, 3H), 1.30–1.38 (m, 1H), 1.40–1.50 (m, 1H), 1.60–1.80 (m, 2H), 3.10 (s, 2H, exchangeable with D_2O), 3.19–3.30 (m, 1H), 3.65–3.75 (m, 2H), 3.75–3.85 (m, 2H); ^{13}C NMR (100.61 MHz) δ: 19.9 (CH_3), 23.6 (CH_3), 25.2 (CH_2 acetal), 42.7 (CH_2), 47.8 (CH–N), 59.3, 59.5 (CH_2 acetal), 98.9 (C acetal). Anal. calcd for $C_8H_{17}NO_2$: C, 60.35; H, 10.76; N, 8.80. Found: C, 60.39; H, 10.69; N, 8.77. $[\alpha]_D^{25}$=−17.5 (*c* 2.03, $CHCl_3$).

*3.4.12. Determination of the enantiomeric excess of **1***

In an NMR tube was placed 9.6 mg of (+)-mandelic acid. To this solid was added a solution of racemic, or optically 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=98%.

*3.5. Synthesis of (*R*)-**1** from (*S*)-4,4-dimethoxy-2-butanol obtained by reduction with baker's yeast (Method B)*

*3.5.1. (−)-(3*R*)-4,4-Dimethoxy-3-phthalimidobutane **14***

To a solution of **13** (0.32 g, 2.4 mmol) in 18 mL of dry THF was added 0.70 g (4.8 mmol) of phthalimide and 1.30 g (4.8 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 (0.85 g, 4.8 mmol) in 2.5 mL of dry THF. Same work-up as that described previously for **6**. The residue was purified on a silica gel column, eluent: pentane:ether, 60:40. Yield: 80% (502 mg). ^{1}H NMR (400.13 MHz) δ: 1.46 (d, 3H, *J*=7.0 Hz), 1.85–2.00 (m, 1H), 2.35–2.50 (m, 1H), 3.15 (s, 3H), 3.25 (s, 3H), 4.32 (t, 1H, *J*=7.0 Hz), 4.43–4.55 (m, 1H), 7.61–7.71 (m, 2H), 7.75–7.85 (m, 2H); ^{13}C NMR (100.61 MHz) δ: 18.9 (CH_3), 36.1 (CH–N), 43.7 (CH_2), 52.7, 52.8 (OCH_3), 102.5 (CH), 122.9 (Ar), 131.9 (C Ar), 133.7 (Ar), 168.3 (CO phthalimide). HRMS analysis (LSIMS Cs^+, $C_{14}H_{16}NO_4$=262.1079). Found 262.1079. $[\alpha]_D^{25}$=−5.5 (*c* 10.85, $CHCl_3$).

*3.5.2. (−)-(3*R*)-3-Phthalimidobutanal **8***

Compound **14** (0.85 g, 3.25 mmol) was dissolved in 100 mL of dichloromethane and montmorillionite K10 (800 mg) was added. The mixture was stirred for 1 h at room temperature. Once the starting material has been consumed, the yellow solution was filtered through Celite to remove the K10. The Celite was washed with dichloromethane (3×30 mL) and the solvent removed under reduced pressure to give a white solid. Purification by column chromatography (eluent: ethyl acetate:cyclohexane, 20:80) gave **8** with a 70% yield (490 mg). Same NMR spectra and melting point as those described above. $[\alpha]_D^{25}$=−3.5 (*c* 2.20, $CHCl_3$).

*3.6. Synthesis of (*S*)-**1** from (2*R*)-4,4-dimethoxy-2-butanol obtained with* Y. farinosa *(Method B)*

The same methods were used as those described above, starting from (2*R*)-**13** obtained by microbiological reduction with *Y. farinosa*. (*S*)-**1** was then obtained. $[\alpha]_D^{25}$=+17.5 (*c* 2.45, $CHCl_3$).

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