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Enantiopure aryl-[1,2,5,6-tetrahydro-pyridinyl] methanols and their use for heterogeneous hydrogenation of ethyl pyruvate

Khalid Azyat ^a, Arlette Solladié-Cavallo ^{a,*}, Arlette Klein ^a, Richard Welter ^b

^a *Laboratoire de stéréochimie organométallique associé au CNRS, ECPM/Université Louis-Pasteur, 25, rue Becquerel, 67087 Strasbourg, France*

^b *Laboratoire DECOMET, ILB, Université Louis-Pasteur, 4, rue Blaise-Pascal, 67000 Strasbourg, France*

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Abstract

Both enantiomers of two new chiral modifiers (naphthyl- and anthryl-[1,2,5,6-tetrahydro-pyridinyl] methanols, **4H** and **5H**) are obtained for the first time from inexpensive D-mannitol in 10 easy steps. Until now *erythro*-**4H** is the only synthetic chiral modifier available under both enantiomeric forms, which provide enantioselectivities almost as high as those obtained with natural cinchonidine, for which only one enantiomer is available. It is shown that the anthryl group may be less efficient than the naphthyl (the e.e.% drops from 75% with *erythro*-**4H** to 46% with *erythro*-**5H**) and that *N*-methyl substitution (trisubstituted nitrogen as in cinchonidine) leads also to a drop in the e.e.% (from 75% with **4H** to 39% with **4Me**). *To cite this article: K. Azyat et al., C. R. Chimie 10 (2007).*

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Résumé

Les deux énantiomères de deux nouveaux modifiants chiraux (le naphthyl- et l'anthryl-[1,2,5,6-tétrahydro-pyridinyl] méthanol, **4H** et **5H**) sont obtenus pour la première fois en 10 étapes à partir du D-mannitol. Jusqu'à présent, l'*érythro*-**4H** est le seul modifiant chiral de synthèse dont les deux énantiomères sont facilement accessibles et qui donne (lors de l'hydrogénation du pyruvate) des énantiosélectivités comparables à celles de la cinchonidine naturelle (un seul énantiomère disponible). Il a été montré que le groupe anthryl peut être moins efficace qu'un naphthyl (lactate d'éthyle ayant 46% e.e. avec *érythro*-**5H** contre 75% e.e. avec *érythro*-**4H**) et que la *N*-méthylation (pour obtenir un azote trisubstitué comme dans la cinchonidine) produit aussi un abaissement de l'énantiosélectivité (39% e.e. avec **4Me** au lieu de 75% e.e. avec **4H**). *Pour citer cet article : K. Azyat et al., C. R. Chimie 10 (2007).*

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Keywords: Naphthyl-[1,2,5,6-tetrahydro-pyridyl] methanol; Anthryl-[1,2,5,6-tetrahydro-pyridyl] methanol; Enantiopure aryl-tetrahydro methanols; Chiral modifiers; Asymmetric heterogeneous hydrogenation

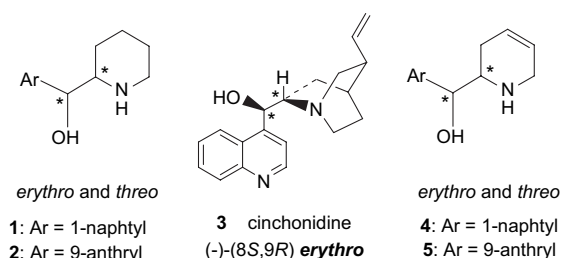
Mots-clés : Naphthyl-[1,2,5,6-tétrahydro-pyridyl] méthanol ; Anthryl-[1,2,5,6-pyridyl-tétrahydro] méthanol ; Aryl-tétrahydro méthanols énantiopurs ; Modifiants chiraux ; Hydrogénation hétérogène asymétrique

* Corresponding author.

E-mail address: cavallo@chimie.u-strasbg.fr (A. Solladié-Cavallo).

1. Introduction

During work on asymmetric catalytic and heterogeneous hydrogenation of α -ketoesters over Al_2O_3 -supported platinum using a chiral modifier (the Orito reaction [1], known for about 30 years [2]), we found [3] that *erythro*-piperidyl naphthyl alcohol **1** was, in such reactions, a chiral catalyst almost as efficient as natural *erythro*-cinchonidine **3**. Different routes toward enantiopure aryl piperidyl alcohol **1** were explored [4] but, until now, no efficient and short asymmetric synthesis have been found and resolution of the amino alcohol itself or of the precursor aryl-pyridyl methanol is still necessary.



An enantioselective synthesis from *D*-mannitol of enantio and diastereopure aryl-[1,2,5,6-tetrahydro-pyridinyl] methanols **4** and **5** [5], precursors of **1** and **2** [5], has thus been envisaged and is described here as well as the direct use of these modifiers for asymmetric heterogeneous hydrogenation of ethyl pyruvate.

2. Synthesis

The first five steps of the synthesis are presented in Scheme 1. The starting protected glyceraldehyde **6**, Scheme 1, obtained from *D*-mannitol [6], must be

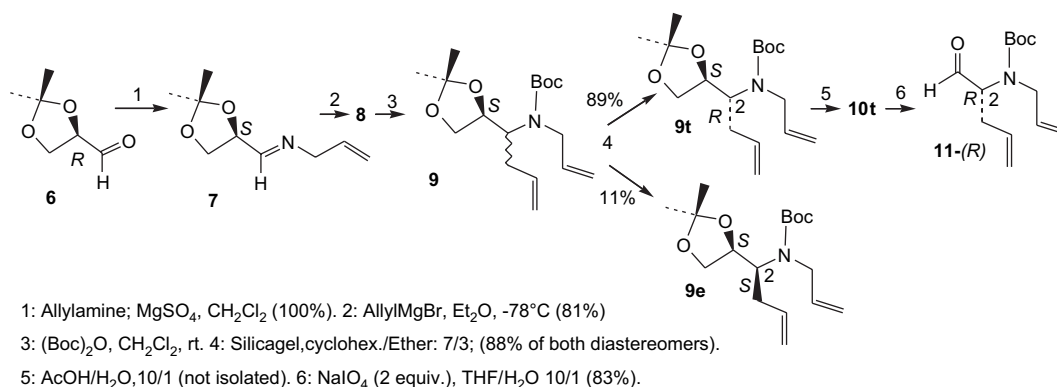
freshly prepared and immediately used to prepare the allyl imine **7** [7]. The addition of allyl Grignard reagent onto **7** proceeds smoothly to give, at -78°C , compound **8** as an 89/11 mixture of both diastereomers (according to ^1H NMR). After Boc protection, the major diastereomer of compounds **9** (**9t**) was separated by chromatography.

Compound **9t**-(1*S*,2*R*) was then transformed into aldehyde **11**-(*R*) in two steps and 41% overall yield from **6**, Scheme 1.

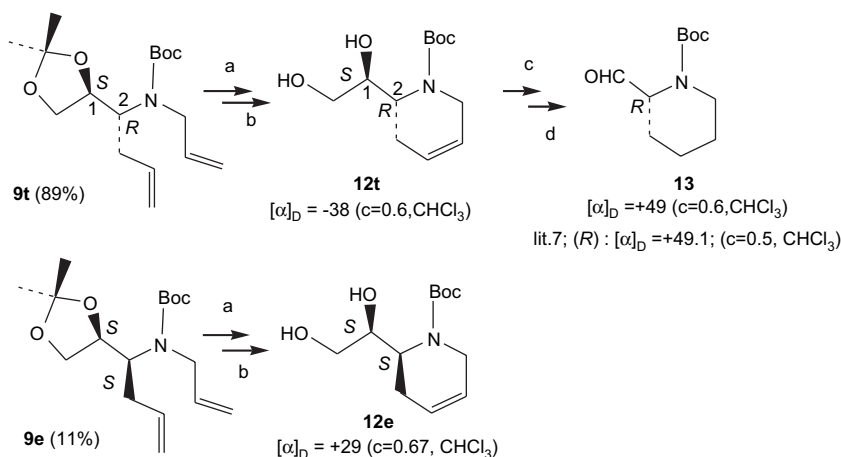
The (2*R*)-absolute configuration of compound **11** was assigned using **9t**. A single crystal of **12t**, obtained in two steps from **9t** (Scheme 2), was analyzed by X-ray diffraction and, as seen in Fig. 1, shown to be the *threo* isomer; therefore, the configuration at C1 (C14 or C2 in Fig. 1) being (1*S*), the configuration at C2 (C15 or C3 in Fig. 1) is (*R*). Moreover, **12t** (Scheme 2) was also transformed into the known (*R*)-(+)-aldehyde **13**.

The next three steps are given in Scheme 3. Addition of naphthyl Grignard reagent onto (*R*)-**11** provides higher yield (**14a** = 83%) than addition of the anthryl Grignard reagent (**14b** = 55%). Mixture of diastereomers was obtained and separated by chromatography. In both cases, the *erythro* isomer (**II**) is major (*cf.* below for assignment). Formation of the six-membered ring was performed using the Grubbs (1st generation) catalyst [8] and provided satisfying yields in both the cases (94% of **15a-II** and 85% of **15b-II**).

Finally, deprotection of **15a-II** and **15b-II** provided the desired diastereo and enantiopure amino alcohols **4H-II** and **5H-II** in good to satisfying yields (97% and 71%, respectively). LiAlH_4 reduction of **15a-II** provided diastereo and enantiopure **4Me-II** in good yield, but reduction of **15b-II** did not proceed under similar conditions and **5Me-II** was not obtained.



Scheme 1. Synthesis of **4H**, **5H** and **4Me**; steps 1–6.



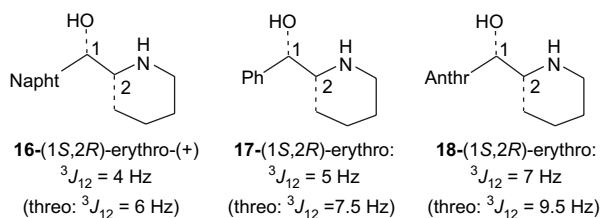
a: Grubb's 1st generation catalyst 5% mol. CH₂Cl₂, rt. b: AcOH/H₂O, 10/1
 c: Pd/C-H₂ (20 bar) in AcOEt. d: NaIO₄ (2 equiv.), THF/H₂O, 10/1, rt.

Scheme 2. Chemical correlation for assignment of the *R*-configuration at C2.

3. Determination of the *erythro* structure of **4H-II** and **5H-II**

The *erythro* structure of **4H-II** and **5H-II** has been determined using NMR. In previous studies concerning enantiopure *erythro* and *threo* amino alcohols **16**, some of us have shown by VCD [4a] that the diastereomer determined as being *erythro* by NMR (on the basis of the smaller value of the ³*J* coupling constant: 4 Hz compared to 6 Hz for the *threo* isomer) was indeed *erythro*. The known amino alcohols **17** [4a] exhibit also a smaller coupling constant for the *erythro* isomer than for the *threo* isomers (5 Hz versus 7.5 Hz) as well as **18** [4b] (7 Hz versus 9.5 Hz). Therefore, compared,

respectively, to **16**, **17** and **18**, **4H-II**, having a coupling constant of 3 Hz, and **5H-II**, having a coupling constant of 7 Hz, were assigned the *erythro* structure.



4. Heterogeneous hydrogenation of ethyl pyruvate

To test the amino alcohols **4H-II**, **5H-II** and **4Me-II**, we have chosen a well-defined catalysts from Engelhard: 5% Pt/Al₂O₃ – 4759 (E4759). The results are summarized in Table 1.

The enantiomeric excesses of the ethyl lactate produced were determined by gas chromatography on a Cyclodex-B capillary column (30 m) using a HP 5890 GC-FID instrument; the e.r. values were reproducible within 1% (for the same sample).

The most important feature of these hydrogenations is the high enantioselectivity obtained for the ethyl lactate with *erythro*-**4H** (75% e.e.), comparable to that obtained with the saturated homologue *erythro*-**1** (Table 1, compare row 2 with rows 5 and 6). It could be postulated that the double bond of **4H** is hydrogenated during the reaction (just as the vinyl group in cinchonidine) but without drastic consequence on the outcome of the reaction.

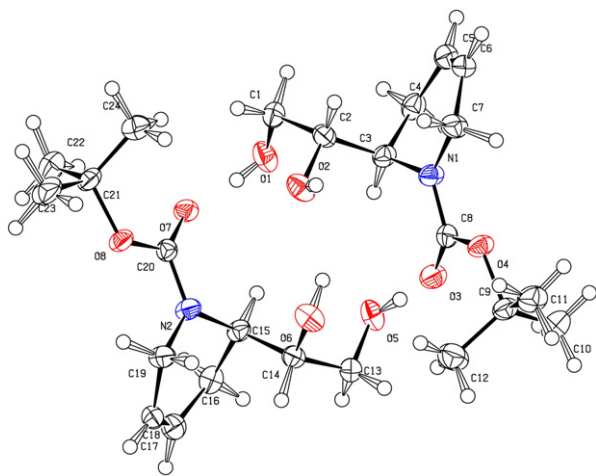
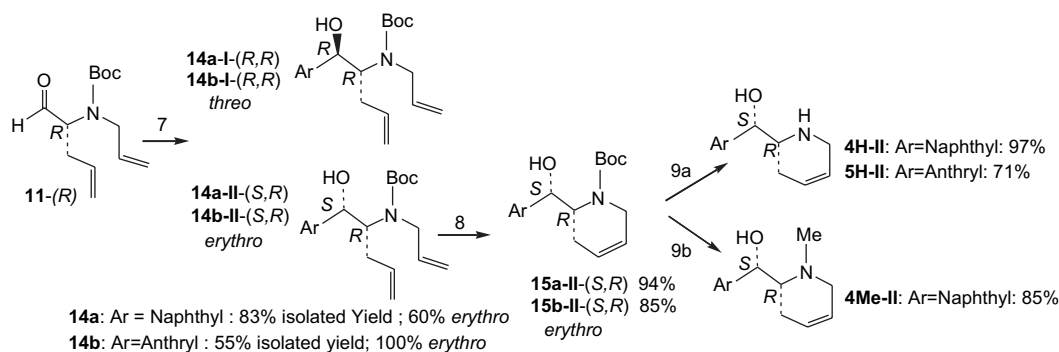


Fig. 1. Asymmetric unit of the crystal structure of **12t** with labelling scheme. The ellipsoids enclose 50% of the electronic density.



7: Aryl Grignard, THF, -78°C. Silicagel, cyclohex./ether: 7/3. 8: Grubb's 1st generation catalyst 5% mol. CH₂Cl₂, rt. 9a: HCl 2M/MeOH, rt, 2 days. 9b: LiAlH₄, THF, reflux.

Scheme 3. Synthesis of **4H**, **5H** and **4Me**; last three steps.

Therefore, compound **4H** can be used directly (no need of a preliminary hydrogenation into *erythro*-1).

Compound **5H** with an anthryl group instead of a naphthyl group (**4H**) provided lower enantioselectivity and lower yield under identical conditions (Table 1, compare rows 3 and 4).

It appears also that introduction of a methyl onto nitrogen¹ (**4Me**) decreases the enantioselectivity with 39% e.e. for the isolated ethyl lactate using **4Me** instead of 75% e.e. using **4H** (Table 1, compare rows 2 and 4).

It is worth noting that the enantioselectivities determined by NMR (e.e.%) and from the optical rotation of the lactate (o.p.%) are almost identical (Table 1, compare column 2 and 4).

It must be noted that the reproducibility from one operator to another is about ±0.5 (Table 1, compare rows 5 and 6).

5. Conclusion

The new modifier *erythro*-**4H** is as efficient as *erythro*-**1** (compared rows 1 and 5 in Table 1) and is obtained in enantiopure form from inexpensive D-mannitol in 10 easy steps. Moreover, both enantiomers of **4H** can be obtained from D-mannitol as it is possible, in running step 2 at room temperature, to obtain a 1/1 mixture and to isolate the *erythro* **9e** in satisfying yield, thus providing the (*S*)-aldehyde **11**. Until now, *erythro*-**4H** and *erythro*-**1** are the only two synthetic chiral modifiers available under both enantiomeric forms, which provide enantioselectivities almost as high as those obtained with natural cinchonidine [9], for which only one enantiomer is available.

¹ A methyl group was introduced to get closer to cinchonidine (CD) where the nitrogen atom is trisubstituted.

It must be noted that previous conclusions that the anthryl group should provide more efficient compound have to be reconsidered, as, obviously, in this case the anthryl group is less efficient than the naphthyl: the e.e.% drops from 75% with *erythro*-**4H** (naphthyl) to 46% with *erythro*-**5H** (anthryl). Moreover, *N*-methyl substitution (trisubstituted nitrogen as in cinchonidine) leads also to a drop in the e.e.% (from 75% with **4H** to 39% with **4Me**).

6. Experimental section

¹H (400 MHz and 300 MHz) and ¹³C (75.4 MHz) NMR spectra were recorded on a Bruker AC 400 and AC 300 spectrometers with CDCl₃ as solvent. Chemical shifts (δ) are given in ppm downfield from TMS as an internal standard and the coupling constants (*J*) are

Table 1
Hydrogenation of pyruvate in AcOH using E4759 (Engelhard) at room temperature, S/C^a = 100, S/M^b = 2650, of ethyl pyruvate concentration = 3 mol/L, 40 bar, 2 h

Modifier	Conversion, %	e.e., (%)	Lactate (<i>R/S</i>)	o.p. %	Absolute configuration
(-)-(9 <i>R</i> ,8 <i>S</i>)- CD ^c	100	87	93.5/6.5	87	<i>R</i>
(+)-(1 <i>S</i> ,2 <i>R</i>)- 4H	100	75	12.5/87.5	72	<i>S</i>
(+)-(1 <i>S</i> ,2 <i>R</i>)- 5H	88	46	27/73	45	<i>S</i>
(+)-(1 <i>S</i> ,2 <i>R</i>)- 4Me	80	39	30.5/69.5	40	<i>S</i>
(+)-(1 <i>S</i> ,2 <i>R</i>)- 1 ^d	100	72	14/86	—	<i>S</i>
(-)-(1 <i>R</i> ,2 <i>S</i>)- 1	100	73	86.5/13.5	73	<i>R</i>

^a S/C = substrate/catalyst.

^b S/M = substrate/modifier.

^c Numbering of atoms are different: the C9 in CD is called C1 in **4H**, **5H** and **4Me** idem: C8 in CD = C2 in **4H**, **5H** and **4Me**.

^d cf. Ref. 3c.

given in Hz. Optical rotation were determined on a PerkinElmer 241 MC polarimeter. TLC was performed on Merck's glass plates with silica gel 60 F₂₅₄. Silica gel Si 60 (40–60 μm) from Merck was used for the chromatographic purifications.

The selected crystal has been mounted on a Nonius Kappa-CCD area detector diffractometer (Mo Kα, λ = 0.71073 Å). The cell parameters were determined from reflections taken from one set of 10 frames (1.0° steps in ϕ angle), each at 20-s exposure. The structures were solved using direct methods (SIR97) and refined against F² using the SHELXL97 software. The absorption values were not corrected. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were found by Fourier differences.

Crystallographic data (excluding structure factors) have been deposited in the Cambridge Crystallographic Data Centre as supplementary publication. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

6.1. Crystal data and structure refinement details

Colourless crystal; crystal dimension: 0.1 × 0.15 × 0.20 mm³; C₁₂H₂₁NO₄; M = 243.30 g mol⁻¹; monoclinic; space group P2₁; a = 6.012(1) Å; b = 22.091(5) Å; c = 9.798(2) Å; β = 90.66(5)°; Z = 4; D_c = 1.242 g cm⁻³; μ(Mo Kα) = 0.092 mm⁻¹; a total of 6573 reflections; 2.27° < θ < 30.04°; 3894 independent reflections with 3122 having I > 2σ(I); 475 parameters; final results: R1 = 0.0404; wR2 = 0.0860, Goof = 1.055, maximum residual electronic density = 0.159 eÅ⁻³.

6.2. General procedure for the synthesis of **9t** and **9e** (steps 1–4)

To a solution of aldehyde **6** (7.310 g, 54.8 mmol) in anhydrous CH₂Cl₂ (250 mL) were added anhydrous MgSO₄ (25 g) and then, dropwise, allyl amine (10.3 mL, 137 mmol). After stirring for 1.5 h at room temperature, MgSO₄ was filtered out. The solvent was evaporated and imine **7** was obtained (9.32 g, yield = 99%). Imine **7**: [α]_D = +52.0 (c = 0.95, CHCl₃). ¹H NMR (CDCl₃, 300 MHz): δ 1.37 (s, 3H, CH₃), 1.42 (s, 3H, CH₃), 4.02 (dd, 1H, ²J = 9, ³J = 6), 4.05 (m, 2H), 4.17 (dd, 1H, ²J = 9, ³J = 5.5), 4.56 (ddd, 1H, OCH, ³J = 6, ³J = 5.5, ³J = 5), 5.18 (m, 2H, CH=CH₂), 5.93 (m, 1H, CH=CH₂), 7.65 (d, 1H, CH=N, ³J = 5). Anal.

for C₉H₁₅NO₂. Found: C, 63.51; H, 9.11. Calcd: C, 63.88; H, 8.93.

To a solution of imine **7** (6.8 g, 40 mmol) in anhydrous Et₂O (100 mL) was added dropwise and at -78 °C a solution of allyl MgBr (80 mL, 80 mmol) in anhydrous Et₂O (40 mL). The mixture was stirred for 1 h at -78 °C (a precipitate formed rapidly). After addition of a saturated solution of NH₄Cl (50 mL), the organic and aqueous phases were separated and the aqueous phase extracted with Et₂O (3 × 20 mL). The organic phases were joined, dried over Na₂SO₄, filtered and the solvent evaporated. Compound **9** was obtained as a diastereomeric mixture (6.92 g, yield = 82%, **8I/8II** = 89/11). Compound **8I** + **8II**: yellow oil. ¹H NMR (CDCl₃, 400 MHz) signals of **I** and **II** overlapped δ: 2.13 (m, 1H), 2.28 (m, 1H), 3.31 (m, 1H), 3.35 (m, 1H), 3.73 (m, 1H), 4.02 (m, 1H), 4.09 (m, 1H), 5.08–5.22 (m, 4H), 5.85 (m, 2H); signals not overlapped δ: 1.36 (s, 3H, CH₃, **II**), 1.35 (s, 3H, CH₃, **I**), 1.40 (s, 3H, CH₃, **I**), 1.41 (s, 3H, CH₃, **II**), 2.72 (q, 1H, **I**, ³J = ³J = 6), 2.78 (q, 1H, **II**, ³J = ³J = 6).

To a solution of **8(I+II)** (4.9 g, 23.5 mmol) in CH₂Cl₂ (90 mL) was added a solution of (Boc)₂O (6.15 g, 28 mmol) in CH₂Cl₂ (10 mL), stirring was maintained for 12 h at room temperature, then CH₂Cl₂ was evaporated and the crude product was purified by silica gel chromatography (pentane/ether = 8/2). The major diastereomer **9t** was isolated in 88% yield.

[α]_D = +36.0 (c = 0.69, CHCl₃). ¹H NMR (CDCl₃, 300 MHz): δ 1.33 (s, 3H, CH₃), 1.40 (s, 3H, CH₃), 1.48 (s, 9H, *t*-Bu), 2.28 (m, 1H), 2.45 (m, 1H), 2.70 (m, 1H), 3.60 (m, 1H), 3.83 (m, 1H), 3.99 (m, 1H), 4.20 (m, 2H), 5.06 (m, 4H, CH=CH₂), 5.74 (m, 2H, CH=CH₂). Anal. for C₁₇H₂₉NO₄. Found: C, 65.32; H, 9.52. Calcd: C, 65.56; H, 9.38.

6.3. General procedure for the synthesis of **11-(R)** (steps 5 and 6)

A solution of **9t** (2 g, 6.43 mmol, 1 equiv) in AcOH (30 mL) and H₂O (3 mL) was stirred for two days at room temperature. After extraction with CH₂Cl₂ (5 × 20 mL), the organic phases were joined, washed with a 15% NaOH solution (15 mL) and then with a saturated solution of NaCl (3 × 10 mL). The resulting organic phase was dried over Na₂SO₄, and, after filtration, the solvent was evaporated. After purification on a silica gel column (hexane/ether = 1/4), 1.62 g of **10t** was obtained (yield = 93%). [α]_D = +10.0 (c = 1.01, CHCl₃). ¹H NMR (CDCl₃, 300 MHz): δ 1.46 (s, 9H, *t*-Bu), 2.35 (m, 2H), 3.52 (m, 2H), 3.76

(m, 3H, OCH₂ + NCH), 4.13 (m, 1H, OCH), 5.13 (m, 4H, CH₂=), 5.77 (m, 2H, CH=).

To a solution of **10t** (1.33 g, 4.90 mmol) in a mixture THF (10 mL)/H₂O (1 mL) were added NaIO₄ (2 equiv) by portions for over 20 min. After stirring for 1 h at room temperature, the crude mixture was filtered over Celite and the solvent evaporated to give 0.96 g of **11-(R)** (yield 82%), which was used rapidly for the next step. ¹H NMR (CDCl₃, 300 MHz) of a sample purified over silica gel (hexane/ether = 7/3) δ : 1.43 (s, 9H, *t*-Bu), 2.50 (m, 1H), 2.78 (m, 1H), 3.57 (m, 2H), 4.15 (m, 1H), 5.10 (m, 4H), 5.80 (m, 2H), 9.55 (d, 1H, ³*J* = 9).

6.4. General procedure for the synthesis of **15a-II** and **15b-II** (steps 7 and 8)

To a suspension of Mg (5.4 mmol) in anhydrous THF (4 mL) were added dibromoethane (0.1 mL) and then, dropwise, a solution of the desired bromide (1-naphthyl or 9-anthryl) in anhydrous THF (5.4 mmol in 10 mL); after addition the mixture was stirred under reflux until Mg has totally disappeared. Then the mixture was cooled to room temperature (all under argon) and a solution of **11-(R)** in anhydrous THF (2.7 equiv in 6 mL) was added dropwise under stirring. The reaction was monitored by CCM and work-up was done when no aldehyde was detected. After addition of NH₄Cl (saturated solution), the THF was evaporated and the crude product extracted with Et₂O (5 × 15 mL). The combined organic phases were dried over Na₂SO₄, filtered out, the solvent evaporated and the crude products purified by chromatography over silica gel to give **14a-II** and **14b-II**.

Compound **14a-II**: hexane/ether = 1/1. ¹H NMR (CDCl₃, 300 MHz): δ 1.49 (s, 9H, *t*-Bu), 2.72 (m, 1H), 2.95 (m, 1H), 3.56 (m, 3H), 5.05 (m, 4H), 5.60 (m, 2H), 5.63 (m, 1H), 7.48 (m, 3H), 7.75 (m, 1H), 7.87 (m, 2H), 8.03 (m, 1H). Anal. for C₂₃H₂₉NO₃. Found: C, 75.19; H, 8.09. Calcd: C, 75.17; H, 7.95.

Compound **14b-II**: hexane/ether = 1/1. ¹H NMR (CDCl₃, 300 MHz): δ 1.40 (s, 9H, *t*-Bu), 2.58–3.56 (m, 3H), 4.47 (m, 1H), 4.63 (m, 1H), 5.08 (m, 4H), 5.78 (m, 2H), 6.68 (m, 1H), 7.47 (m, 4H), 7.98 (m, 2H), 8.40 (s, 1H), 8.75 (bm, 2H). Anal. for C₂₇H₃₁NO₃. Found: C, 77.50; H, 7.55. Calcd: C, 77.66; H, 7.48.

To a solution of first-generation Grubbs catalyst (0.079 g, 0.097 mmol) in anhydrous CH₂Cl₂ (5 mL) was added dropwise a solution of **14a-II** (or **14b-II**) in anhydrous CH₂Cl₂ (1.93 mmol in 40 mL). After stirring for 2 h at room temperature, the solvent was evaporated and the residue purified by chromatography (silica gel, hexane/ether = 1/1) to give **15a-II** (94% yield) or **15b-II** (85% yield) as colourless oils.

Compound **15a-II**: ¹H NMR (CDCl₃, 300 MHz): δ 1.43 (s, 9H, *t*-Bu), 2.32 (m, 2H), 2.66 (m, 2H), 4.13 (m, 1H), 4.80 (m, 1H), 5.78 (m, 1H), 5.89 (m, 1H), 7.50 (m, 4H), 7.83 (m, 1H), 7.86 (m, 1H), 8.39 (d, 1H, ³*J* = 8). Anal. for C₂₁H₂₅NO₃. Found: C, 74.14; H, 7.75. Calcd: C, 74.31; H, 7.42.

Compound **15b-II**: ¹H NMR (CDCl₃, 300 MHz): δ 1.44 (s, 9H, *t*-Bu), 2.46 (m, 2H), 3.03 (m, 1H), 3.78 (m, 1H), 5.33 (m, 1H), 5.73 (m, 1H), 5.99 (m, 1H), 6.23 (m, 1H), 7.50 (m, 4H), 7.99 (m, 2H), 8.41 (s, 1H), 8.70 (m, 2H). Anal. for C₂₅H₂₇NO₃. Found: C, 76.82; H, 7.05. Calcd: C, 77.09; H, 6.98.

6.5. Preparation of **4H-II**, **5H-II** and **4Me-II** (steps 9a and 9b)

A solution of **15a-II** or **15b-II** (0.6 mmol) in MeOH (20 mL) and 2 M HCl (20 mL) was stirred overnight at room temperature. After cooling at 0 °C, a 2 M NaOH solution was added until pH 8, then CH₂Cl₂ (50 mL) was added and the organic phase recovered. The aqueous phase was then further extracted with CH₂Cl₂ (10 × 15 mL), the combined organic phases were dried over Na₂SO₄, filtered and the solvent evaporated providing **4H-II** (97% yield) or **5H-II** (71% yield).

Compound **4H-II**: [α]_D = +29.4 (*c* = 0.36, CHCl₃). ¹H NMR (CDCl₃, 300 MHz): δ 1.55 (m, 1H), 2.34 (m, 1H), 3.38 (dt, 1H, ²*J* = 11, ³*J* = 3.5 and 3.5), 3.54 (b, 2H), 5.00 (bs, 2H, NH + OH), 5.63 (m, 1H), 5.67 (m, 1H), 5.90 (d, 1H, ³*J* = 3.5), 7.47 (m, 3H), 7.78 (m, 2H), 7.85 (m, 1H), 8.09 (d, 1H, ³*J* = 7). ¹³C NMR (CDCl₃, 75 MHz): δ 24.0, 44.5, 56.5, 71.0, 123.0, 123.9, 125.3, 125.6, 126.2, 127.9, 128.8, 130.2, 133.6, 136.5. Anal. for C₁₆H₁₇NO. Found: C, 80.03; H, 7.31. Calcd: C, 80.30; H, 7.16.

Compound **5H-II**: [α]_D = not determined because of too much light absorption. ¹H NMR (CDCl₃, 300 MHz): δ 1.30 (m, 1H), 2.54 (m, 3H), 3.21 (b, 2H, NH + OH), 3.78 (m, 1H), 5.66 (m, 1H), 5.84 (m, 1H), 6.22 (d, 1H, ³*J* = 7), 7.47 (m, 4H), 8.01 (m, 2H), 8.45 (s, 1H), 8.77 (b, 2H). ¹³C NMR (CDCl₃, 75 MHz): δ 23.5, 43.0, 55.6, 70.0, 124.2, 125.7, 128.3, 129.2, 130.2, 131.6, 132.5. Anal. for C₂₀H₁₉NO. Found: C, 82.81; H, 6.87. Calcd: C, 83.01; H, 6.62.

To a solution of **15a-II** (0.66 mmol) in anhydrous THF (10 mL) was added by portion LiAlH₄ powder (~0.1 g, 1.2 equiv), and the mixture was stirred under reflux for 24 h. The work-up was done through addition of H₂O (0.1 mL), NaOH 15% (0.1 mL) and H₂O (0.3 mL); after stirring until the precipitate formed becomes powdered and white (~2 h), the solution was filtered out and the precipitate carefully rinsed with Et₂O.

The organic phases were joined and the solvent evaporated to provide **4Me-II** (85% yield).

Compound **4Me-II**: $[\alpha]_D = +33.3$ ($c = 0.60$, CHCl_3). $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 2.35 (m, 2H), 2.76 (s, 3H, Me), 2.87 (m, 1H), 3.07 (m, 1H), 3.65 (b, 1H, OH), 3.78 (m, 1H), 5.59 (m, 2H), 6.09 (d, 1H, $^3J = 3$), 7.50 (m, 3H), 7.81 (m, 3H), 7.99 (m, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 75 MHz): δ 24.0, 41.8, 61.7, 65.4, 67.6, 122.5, 123.2, 124.1, 125.0, 125.2, 125.4, 125.8, 127.6, 129.0, 133.6, 136.0. Anal. for $\text{C}_{17}\text{H}_{19}\text{NO}$. Found: C, 80.38; H, 7.93. Calcd: C, 80.59; H, 7.56.

6.6. Synthesis of **12t** and **12e** (Scheme 2)

Deprotection of **9t** and cyclisation have been done using the procedures described above.

Compound **12t**: $[\alpha]_D = -38.0$ ($c = 0.6$, CHCl_3). $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 1.47 (s, 9H, *t*-Bu), 2.07 (m, 1H), 2.49 (m, 1H), 3.53–3.73 (m, 4H), 4.19 (m, 1H), 4.45 (m, 1H), 5.72 (m, 2H). Anal. for $\text{C}_{12}\text{H}_{21}\text{NO}_4$. Found: C, 59.03; H, 8.96. Calcd: C, 59.24; H, 8.70.

Compound **12e**: $[\alpha]_D = +29.0$ ($c = 0.67$, CHCl_3). $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 1.47 (s, 9H, *t*-Bu), 2.17 (m, 1H), 2.35 (m, 1H), 3.50–3.70 (m, 4H), 4.22 (m, 1H), 4.30 (m, 1H), 5.65 (m, 2H).

6.7. Synthesis of **13-(R)** (Scheme 2)

Hydrogenation of the double bond was done on **12t** using $\text{H}_2/\text{Pd/C}$: in a 100-mL autoclave were introduced **12t** (1.11 g, 4.57 mmol), AcOEt (25 mL) and the catalyst Pd/C (50 mg). After having purged three times (successive vacuum and H_2), the H_2 pressure was adjusted to 20 bar and the mixture was maintained under this H_2 pressure under stirring for 2 h. After filtration, the catalyst was rinsed with AcOEt , the solvents were joined and then evaporated to provide the desired hydrogenated compound (1.007 g, 90% yield), which was directly transformed into the desired known aldehyde **13** (90% yield), using the same conditions as for preparation of **11-(R)**.

Compound **13-(R)** (Ref. [10]): $[\alpha]_D = +49.0$ ($c = 0.6$, CHCl_3). $^1\text{H NMR}$ (CDCl_3 , 300 MHz): δ 1.27 (m, 2H), 1.47 (s, 9H, *t*-Bu), 1.62 (m, 3H), 2.11 (m, 1H), 2.89 (bm, 1H), 3.93 (m, 1H), 4.56 (m, 1H), 9.57 (s, 1H). Anal. for $\text{C}_{11}\text{H}_{17}\text{NO}_3$. Found: C, 62.28; H, 8.32. Calcd: C, 62.54; H, 8.11.

6.8. Heterogeneous hydrogenation of ethyl pyruvate

All heterogeneous hydrogenations have been conducted with a well-defined catalyst from Engelhard: 5% $\text{Pt}/\text{Al}_2\text{O}_3 - 4759$ (E4759). AcOH was used as

solvent, the reactions were run at room temperature and under 40 bar H_2 , stirring was maintained at ~ 500 rpm and the pyruvate, purchased from Aldrich, was distilled before use. Commercial cinchonidine (CD) was used as a reference.

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References

- [1] (a) Y. Orito, S. Imai, S. Niwa, *J. Chem. Soc. Jpn* (1979) 1118; (b) Y. Orito, S. Imai, S. Niwa, G.H. Nguyen, *J. Synth. Org. Chem. Jpn.* (1980) 670.
- [2] (a) T. Bürgi, A. Baiker, *Acc. Chem. Res.* 37 (2004) 909 and included references for previous reviews; (b) A. Baiker, *Catal. Today* 100 (2005) 159 and included references for previous reviews.
- [3] (a) C. Marsol, Ph.D., Strasbourg University, France, 2001 (started 1998); (b) A. Solladié-Cavallo, C. Marsol, F. Garin, Second European Catalysis Symposium, Pisa, Italy, 2001; (c) A. Solladié-Cavallo, C. Marsol, F. Garin, *Tetrahedron Lett.* 43 (2002) 4733–4735; (d) K. Azyat, Ph.D., Strasbourg University, France, 2005 (started 2002).
- [4] (a) A. Solladié-Cavallo, C. Marsol, M. Yaakoub, K. Azyat, M. Roje, A. Klein, C. Suteu, X. Cao, T.B. Freedmann, L. Nafié, *J. Org. Chem.* 68 (19) (2003) 7308; (b) A. Solladié-Cavallo, C. Marsol, K. Azyat, M. Roje, C. Welch, J. Chilenski, P. Taillason, H. D'Orchymont, *Eur. J. Org. Chem.* (2007) 826.
- [5] For comparison of anthryl and naphthyl groups cf.; (a) A. Solladié-Cavallo, C. Marsol, C. Suteu, F. Garin, *Enantiomer* (2001) 245; (b) S. Diezi, M. Hess, E. Orglmeister, T. Mallat, A. Baiker, *J. Mol. Catal. A: Chem.* 239 (2005) 49; (c) E. Orglmeister, T. Bürgi, T. Mallat, A. Baiker, *J. Catal.* 232 (2005) 137; (d) C. Exner, A. Pfaltz, M. Studer, H.U. Blaser, *Adv. Synth. Catal.* 345 (2003) 1253.
- [6] C.R. Schmid, J.D. Bryant, M. Dowlatzadah, J.L. Philips, D.E. Prather, R.D. Shantz, N.L. Seer, C.S. Vianco, *J. Org. Chem.* 56 (1991) 4056.
- [7] F. Unquera, F.L. Merchan, P. Merino, T. Tejero, *Tetrahedron* 52 (1996) 7045.
- [8] For the preparation of six-membered ring through ring-closing metathesis using Grubbs catalyst see: X. Ginesta, M.A. Pericàs, A. Riera, *Tetrahedron Lett.* (2002) 779.
- [9] Ethyl lactate having an enantiomeric excess up to 95% can be obtained with CD according to adjustment of the reactions conditions (H.U. Blaser, H.P. Jalett, M. Müller, M. Studer, *Catal. Today* 37 (1997) 441) one may thus expect that higher e.e.% could also be obtained with **1** and **4H** by optimizing the reaction conditions. See also: M. Besson, C. Pinel, *Topics Catal.* 5 (1998) 25. H.U. Blaser, *Chem. Commun.* (2003) 293 and Ref. 5d.
- [10] R. Alibés, M. Balbé, F. Busqué, P. De March, L. Elias, M. Figueredo, *J. Font, Org. Lett.* 6 (2004) 1813.