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Enantioselective Synthesis of Both Enantiomers of 3-Hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone

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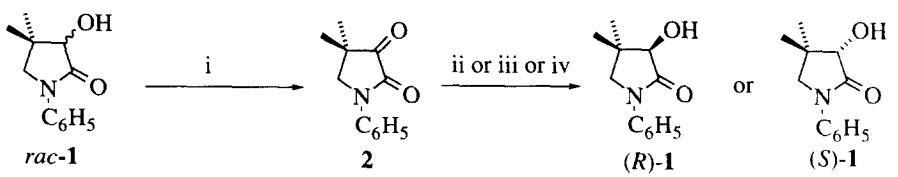
Abstract: The chiral auxiliaries (*R*)- and (*S*)-3-Hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone were obtained in good yield and e.e. by enantioselective reduction of 4,4-dimethyl-1-phenylpyrrolidine-2,3-dione with (-)- and (+)-*B*-chlorodiisopinocamphenylborane, (-)- and (+)-DIP-Chloride®, respectively. The (*R*)-enantiomer was also obtained by enantioselective hydrogenation of the same precursor using a complex of 1,5-cyclooctadiene Rh(I) and (2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-(diphenylphosphinomethyl)pyrrolidine, (*S*,*S*)-BPPM, as the chiral catalyst.

Keywords: Asymmetric synthesis; Hydrogenation; Reduction; Hydroxy acids and derivatives.

Some time ago we published a synthesis of both enantiomers of 3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone, (*R*)- and (*S*)-**1**, by enzymatic resolution of the racemic mixture.[1] These chiral auxiliaries were used in the formal deracemization of α-arylpropanoic acids,[2] α-substituted α-arylacetic acids,[3] α-chloro acids,[4] and α-amino acids,[5] and also in an enantioselective synthesis of α-hydroxy acids,[6] α-aryloxypropanoic acid herbicides,[6] and α-amino acids,[5] based on the dynamic kinetic resolution of α-bromo esters derived from these chiral auxiliaries on reaction with substituted phenoxides or dibenzylamine. These chiral auxiliaries are easily crystallizable non-hygroscopic solids more lipophilic than pantolactone, which greatly facilitates their recovery, while they are easily detectable by chiral HPLC under UV detection.

Future applications of these chiral auxiliaries were limited by their availability. Although the kinetic resolution of *rac*-**1** works well, globally it is a quite tedious process when carried out on a scale around 20 g. Consequently, we planned to develop a new process based on the enantioselective reduction of keto lactame **2**. Compound **2** is a new compound which was easily prepared in 94% yield by Swern oxidation of *rac*-**1**.[7,8]



rac-**1** **2** (*R*)-**1** (*S*)-**1**

i) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2, 94% yield, ii) (*S*,*S*)-BPPM, (1,5-cyclooctadiene)-Rh(I) chloride, THF, H_2, 40 atm, 50 °C, 72 h, 0.4 M concentration of **2**: quant. yield (76% e.e.) of crude (*R*)-**1**, 62% yield (>99% e.e.) after two recrystallizations from 2-propanol. iii) (-)-*B*-chlorodiisopinocamphenylborane [(-)-DIP-Chloride®], THF, 25 °C, 5 h, 1.36 M concentration of **2**: crude (*R*)-**1** (88% e.e.), 71% yield (>99% e.e.) of recrystallized product. iv) (+)-*B*-chlorodiisopinocamphenylborane [(+)-DIP-Chloride®], THF, 25 °C, 4 h, 1.70 M concentration of **2**: crude (*S*)-**1** (64% e.e.), 65% yield (>99% e.e.) of recrystallized product.

Scheme 1. Enantioselective synthesis of (*R*)- and (*S*)-**1**.

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Table 1. Reaction Conditions, Products, Yields and E.e.'s in the Enantioselective Hydrogenations of **2**.

Entry	Reaction conditions						Reaction product		
	Solvent	Subst. conc.	P (atm)	T (°C)	t (h)	catalyst[a]	Enant.	yield (%)	e.e.[b] (%)
1	THF	49 mM	35	20	72	A	(*R*)-**1**	quant.	19
2	MeOH	8.6 mM	65	50	48	B	(*R*)-**1**	97	30
3	THF	46 mM	35	50	72	C	(*R*)-**1**	quant. (68)[c]	54 (75)[c]
4	THF	400 mM	48	50	72	C	(*R*)-**1**	quant. (62)[d]	76 (>99)[d]

[a] In all cases the molar ratio substrate/catalyst was 100/1. Catalyst A: Complex formed from (*R*,*R*)-DIOP and (1,5-cyclooctadiene)-Rh(I) chloride; Catalyst B: [(*R*)-(+)-BINAP](*p*-cymene)-Ru(I) chloride; Catalyst C: complex formed from (*S*,*S*)-BPPM and (1,5-cyclooctadiene)-Rh(I) chloride. [b] Obtained by chiral HPLC using the chiral column Chiralcel OD-H.[1] [c] Yield or e.e. after one recrystallization from 2-propanol (2 mL solvent per g solute). [d] Yield or e.e. after two recrystallizations from 2-propanol (2 mL solvent per g solute).

The enantioselective reduction of keto lactam **2** was first carried out through a catalytic process using different chiral catalysts.[9] Although hydrogenation of **2** could be carried out in good yield by using a molar ratio substrate/catalyst of 100/1, enantioselectivities were usually low (Table 1). The best e.e. (76%) was obtained by using a complex formed from (2*S*,4*S*)-1-*tert*-butoxycarbonyl-4-(diphenylphosphino)-2-(diphenylphosphinomethyl)pyrrolidine, (*S*,*S*)-BPPM, and (1,5-cyclooctadiene)-Rh(I) chloride (Table 1, entry 4). After two recrystallizations from 2-propanol, (*R*)-**2** was obtained in 62% yield and >99% e.e.[10] Curiously, a similar reaction carried out at higher dilution (46 mM) took place with lower enantioselectivity (54% e.e.). Other catalysts, such as the complex formed from (1,5-cyclooctadiene)-Rh(I) chloride and (2*R*,3*R*)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, (*R*,*R*)-DIOP, or the commercially available [(*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphtyl](*p*-cymene)-Ru(I) chloride, [(*R*)-(+)-BINAP](*p*-cymene)-Ru(I) chloride, gave lower enantioselectivities, 19% and 30% e.e., respectively (Table 1, entries 1 and 2). The main enantiomer was always (*R*)-**1**.

Although the synthesis of (*R*)-**1** by enantioselective hydrogenation of **2**, according to the conditions of Table 1, entry 4, constitutes an improvement over the enzymatic resolution of *rac*-**1**,[1] the method is of limited value for the preparation of (*S*)-**1** because the (*R*,*R*)-BPPM diphosphine chiral ligand is not commercially available. Consequently, we studied other enantioselective reduction procedures. Among them, the use of the BH_3.THF complex in the presence of a catalytic amount of the commercially available (*R*)- or (*S*)-3a,4,5,6-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-c][1,3,2]oxazaborole,[11] (*R*)- or (*S*)-methyl-CBS-oxazaborolidine®, was considered. However, reduction of **2** (about 30 mM in THF) with BH_3.THF in the presence of the (*S*)-enantiomer of the above catalyst (1% molar) at room temperature took place very rapidly (about 10 min) giving *rac*-**1** in 95% yield. A similar reaction carried out at -78 °C was also completed in about 10 min and gave (*R*)-**1** (99% yield, 16% e.e.).

Then we tried the reduction of **2** in a non-catalytic way. (+)- and (-)-*B*-chlorodiisopinocamphenylborane, (+)- and (-)-DIP-chloride®, are easily available chiral reducing agents which can enantioselectively reduce hindered ketones.[12] Attempted reduction of **2** (0.1 M in THF) with (-)-DIP-chloride® left the starting compound essentially unchanged after 8 days. However, when this reaction was carried out at a higher concentration (1.36 M), reduction of **2** was completed in 5 h to give (*R*)-**1** (about 85% e.e.). Crystallization of the crude product from 2-propanol gave (*R*)-**1** (71% yield, >99% e.e.).[13] A similar reaction was carried out with **2**

(1.70 M in THF) and (+)-DIP-chloride® isolating, after one crystallization from 2-propanol, (*S*)-**1** (65% yield, >99% e.e.). Although some uncertainty may exist in the determination of the e.e. of (*R*)- or (*S*)-**1** on the crude reduction product, it seems clear that the enantioselectivity of the reduction of **2** with (+)-DIP-chloride® takes place with somewhat lower enantioselectivity, a fact that was not dependent on concentration and that might be due to a lower enantiopurity of the last reagent. Girard and Kagan[14] reported important non-linear effects in the reduction of acetophenone with (+)- or (-)-DIP Chloride® which allowed the obtention of 1-phenylethanol of higher e.e. than that of the (1*S*)-(-)- or (1*R*)-(+)-α-pinene, respectively, used to prepare the chloroborane reagent. However, this seems not to be the case in the reduction of **2**.

A related reagent, (*R*)-Alpine-borane[15] was unable to reduce **2** even at high molar concentration, in accord with its lower reactivity, especially towards hindered ketones.

In conclusion, multi-gram enantioselective syntheses of both enantiomers of 3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone, (*R*)- and (*S*)-**1**, have been developed, which are clearly superior to the previously reported procedure based on an enzymatic resolution of the racemic mixture. The required reagents (-)- or (+)-DIP-chloride® are easily available commercial compounds. Alternatively, (*R*)-**1** has been obtained by enantioselective hydrogenation using a Rh(I) complex derived from the (*S,S*)-BPPM diphosphine chiral ligand, under high pressure. The availability of (*R*)- and (*S*)-**1** through these new procedures makes these chiral auxiliaries good alternatives to the hygroscopic and difficult to recover (*R*)- and (*S*)-pantolactone.

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8. *4,4-Dimethyl-1-phenylpyrrolidine-2,3-dione, 2*. To a cooled (-60 °C) solution of oxalyl chloride (13.0 mL, 0.15 mol) in CH_2Cl_2 (50 mL), a solution of DMSO (21.0 mL, 0.30 mol) in CH_2Cl_2 (50 mL) and then, a solution of *rac*-**1** (10.3 g, 50 mmol) in CH_2Cl_2 (50 mL) were added dropwise, keeping the temperature under -50 °C. After 30 min at -50 °C, Et_3N (55.0 mL, 0.40 mol) was added dropwise, keeping the temperature under -50 °C. After 30 min at this temperature, the mixture was allowed to warm

to room temperature. The mixture was washed with aqueous 4 N HCl (3×100 mL), saturated aqueous solution of $NaHCO_3$ (3×100 mL). The dried solution (Na_2SO_4) was concentrated *in vacuo* and the residue (10.7 g) thus obtained was sublimed at 140 °C/1 Torr to give **2** as a white solid (9.50 g, 94% yield), m.p. 118-120 °C; IR (KBr) ν: 1760 and 1699 (C=O st) cm^{-1}; MS (EI), m/z (%): 203 ($M^{\cdot+}$, 25), 119 ($C_6H_5NCO^{\cdot+}$, 100), 104 (12), 91 (18), 77 (25), 56 (14), 51 (14). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.37 [s, 6 H, 4-$(CH_3)_2$], 3.88 (s, 2 H, 5-H_2), 7.31 (tm, J = 7.4 Hz, 1 H, H*para*), 7.47 (m, 2 H, H*meta*), 7.83 (dm, J = 8.7 Hz, 2 H, H*ortho*); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 23.8 [CH_3, 4-$(CH_3)_2$], 39.8 (C, C4), 56.6 (CH_2, C5), 119.2 (CH, C*ortho*), 126.7 (CH, C*para*), 129.2 (CH, C*meta*), 138.5 (C, C*ipso*), 157.8 (C, C2), 203.0 (C, C3). Anal. Calcd. for $C_{12}H_{13}NO_2$: C 70.91, H 6.45, N 6.89; found: C 70.94, H 6.51, N 6.87.

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10. *Enantioselective hydrogenation of* **2** *to* (R)-**1**. A solution of **2** (16.2 g, 80.0 mmol) and Et_3N (55.6 μL, 0.40 mmol) in degassed THF (100 mL) and a solution of (*S,S*)-BPPM (0.44 g, 0.80 mmol) and (1,5-cyclooctadiene)-Rh(I) chloride (0.20 g, 0.40 mmol) in degassed THF (100 mL) were stirred for 30 min in an Ar atmosphere. Both solutions were combined (approx. concentration of **2**, 0.4 M) and hydrogenated at 50 °C and 48 atm for 72 h. The mixture was filtered, the filtrate was concentrated *in vacuo* and the residue (17.0 g) containing (*R*)-**1** (76 e.e. by chiral HPLC) was recrystallized from 2-propanol (30 mL) to give (*R*)-**1** (11.8 g, 72% yield, 99 e.e.), which after another recrystallization from 2-propanol (25 mL) gave (*R*)-**1** (10.1 g, 62% yield, >99 e.e.).
A similar reaction carried out starting from **2** (470 mg, 2.32 mmol) in a total volume of 50 mL (approx. concentration of **2**, 46 mM) gave a crude (*R*)-**1** of only 54% e.e..

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13. *Enantioselective reduction of* **2** *to* (R)-**1** *with (-)-DIP-Chloride®*. A mixture of **2** (13.8 g, 68.0 mmol) and (-)-DIP-Chloride® (24.0 g, 74.8 mmol) in anhydrous THF (50 mL) was stirred at 25 °C for 5 h, following the reaction by TLC. Diethanolamine (15.8 g, 150 mmol) was added and the mixture was stirred at room temperature for 1 h. The precipitate was filtered and the filtrate was concentrated *in vacuo* to give a crude product (28.5 g) containing (*R*)-**1** (88% e.e. by HPLC), the excess of reagent and other products. This crude product was crystallized from 2-propanol (60 mL) to give (*R*)-**1** (9.87 g, 71% yield, > 99% e.e. by HPLC). The mother liquors were concentrated *in vacuo* and the residue (16.4 g) was crystallized from 2-propanol (30 mL) to give (*R*)-**1** (0.51 g, 97% e.e.). The mother liquors from this second crystallization were concentrated *in vacuo* and the residue (15.5 g) was submitted to column chromatography [silica gel (200 g), hexane/CH_2Cl_2] to give (*R*)-**1** (2.83 g, 40% e.e.). Global yield of alcohol **1**, 95%.

Enantioselective reduction of **2** *to* (S)-**1** *with (+)-DIP-Chloride®*. A mixture of **2** (13.8 g, 68.0 mmol) and (-)-DIP-Chloride® (24.0 g, 74.8 mmol) in anhydrous THF (40 mL) was stirred at 25 °C for 4 h, following the reaction by TLC. After a work-up similar to that described above, a crude product (30.8 g), containing (*S*)-**1** (64% e.e. by HPLC), was obtained. Crystallization from 2-propanol (60 mL) gave (*S*)-**1** (9.05 g, 65% yield, >99% e.e.). The mother liquors were concentrated *in vacuo* and the residue (20.1 g) was submitted to column chromatography [silica gel (200 g), hexane/CH_2Cl_2] to give (*S*)-**1** (3.76 g, 14% e.e.). Global yield of alcohol **1**, 92%.

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