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(R)- and (S)-3-Hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone by Lipase-Catalyzed Resolution of the Racemic Mixture: New Chiral Auxiliaries Related to Pantolactone.

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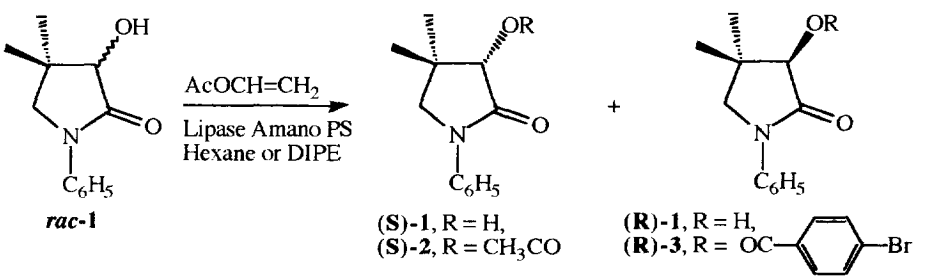
Abstract: (*R*)- and (*S*)-3-Hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone (***R*)-** and (***S*)-1** have been prepared by lipase-catalyzed enantioselective acetylation of (***S*)-1** from rac-1 with vinyl acetate. Controlled hydrolysis of the acetate (***S*)-2** gave (***S*)-1**. The configuration of (***R*)-1** and its *p*-bromobenzoate (***R*)-3** were established by X-ray diffraction analysis.

Recently, the use of D-pantolactone and other chiral alcohols, such as ethyl L-lactate, as chiral auxiliaries for the asymmetric synthesis of α-arylpropanoic acids from the corresponding racemic mixtures was described.[1] Moreover, D-pantolactone has been used as a chiral auxiliary for the asymmetric synthesis of methyl (S)-3-mercapto-2-methylpropionate[2], a precursor of captopril, paraconic acid,[2] (S)-α-aminoesters[3], (S)-2-aryloxy and (S)-2-hydroxy acids[4]. Esters of D-pantolactone have been also used in the asymmetric Diels-Alder[5] and Baylis-Hillman reactions.[6]

The use of D- or L-pantolactone as a chiral auxiliary in these syntheses present a general drawback: Due to their hygroscopic nature, D- or L-pantolactone are not easily recovered after the hydrolysis step necessary to separate the product from the chiral auxiliary. With other homochiral alcohols, such as ethyl L-lactate, diastereoselectivity is lower[1]. Moreover, for the synthesis of the more active (S)-enantiomers of the antiinflammatory α-arylpropanoic acids, the less easily available L-pantolactone is required.

In continuing our interest on the asymmetric synthesis of (S)-α-arylpropanoic acids[7], we were interested on a chiral auxiliary of the pantolactone type having the following characteristics: 1) non-hygroscopic solid more lipophilic than pantolactone, in order to be recovered in good yield, and 2) easily available in both enantiomeric forms. On these basis, 3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone ***rac*-1**, easily obtainable from *rac*-pantolactone by reaction with aniline[8], was chosen.



***rac*-1**

(S)-1, R = H,
(S)-2, R = CH_3CO

(R)-1, R = H,
(R)-3, R = OC–C6H4–Br

Scheme 1

Resolution of ***rac*-1** was carried out following standard procedures (Scheme 1)[9,10]. First, acetylation of ***rac*-1** with vinyl acetate catalyzed by different enzymes (Lipase Amano PS, Lipase MAP 10, Lipase Boehringer PS, Lipase Fluka PS, Lipase Amano AY, Lypozime 10,000 L and PPL Sigma) under different reaction conditions [Conditions A: 1 equiv of vinyl acetate in hexane; Conditions B: 1 equiv of vinyl acetate in diisopropyl ether (DIPE); Conditions C: excess of vinyl acetate as reactive and solvent; Conditions D: excess of vinyl acetate (4 ml / mmol ***rac*-1**) in hexane; Conditions E: excess of vinyl acetate (4 ml / mmol ***rac*-1**) in DIPE] was followed by high performance liquid-liquid chromatography (HPLC) using a reverse phase column. Only Lipase Amano PS under conditions D and E gave satisfactory conversion after 48 h (56.4 and 43.4%, respectively. Then, the enantioselectivity of the esterification with this enzyme under conditions D and E was controlled by HPLC using the chiral column CHIRALCEL OD-H. Under optimized conditions E (reaction time 72 h), **(R)-1** (92% yield, 99% ee) and (S)-3-acetoxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone, **(*S*)-2** (92% yield, 88% ee) were isolated from the esterification mixture by column chromatography (silica gel / mixtures of hexane, CH_2Cl_2 and methanol). Similarly, **(*S*)-2** (82% yield, 95% ee) was obtained from a reaction under conditions D for 64 h. In this case, the lower degree of esterification is responsible for the lower ee (58%) of the **(*R*)-1** isolated. Hydrolysis of **(*S*)-2** (95% ee) with a mixture of 2N HCl / AcOH in a ratio of 2 / 5 under reflux for 2.5 h afforded **(*S*)-1** (78% yield, 99% ee) after crystallization from ethanol.

All new compounds have been fully characterized through their spectroscopic data and elemental analysis. The NMR spectra have been assigned on the basis of COSY $^1H/^1H$ and $^1H/^{13}C$ experiments. The pairs of protons 4α-CH_3 / 4β-CH_3 and 5α-H / 5β-H have been assigned taking into account the presence of small long-range couplings (*W*) between 3-H and 4α-CH_3 and 5β-H, which makes the signals of the last protons to be wider as compared with 4β-CH_3 and 5α-H, respectively. To establish the configuration of **(*R*)-1**, its *p*-bromobenzoyl derivative **(*R*)-3** was prepared. X-ray diffraction analysis of both compounds clearly showed their (*R*)-configuration (Figures 1 and 2).

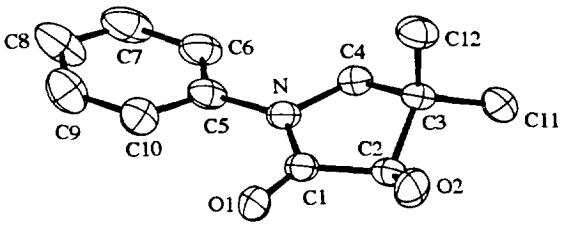


Figure 1. Perspective drawing (ORTEP) of **(*R*)-1**. The numbering is that used for the X-ray analysis.

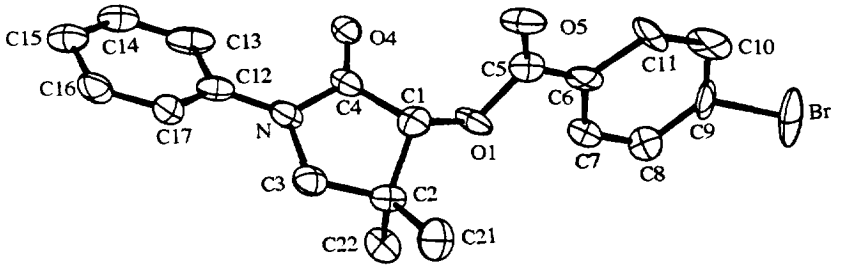


Figure 2. Perspective drawing (ORTEP) of **(*R*)-3**. The numbering is that used for the X-ray analysis.

In conclusion, an easy access to both enantiomers of 3-hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone, which can be worked on a multigram scale, have been developed. These new chiral auxiliaries are non-hygroscopic solids which can be easily purified by crystallization, which facilitates their recovery. The following paper describes their application for the enantioselective synthesis of α-arylpropanoic acids.

EXPERIMENTAL

Melting points were determined on a MFB 595010 M Gallenkamp melting point apparatus. 500 MHz ^1H NMR spectra were recorded on a Varian VXR 500 MHz spectrometer, 300 MHz ^1H and 75.5 MHz ^{13}C NMR spectra on a Varian Gemini 300 and 200 MHz ^1H and 50.3 MHz ^{13}C NMR spectra on a Varian Gemini 200. Chemical shifts (δ) are reported in ppm related to the tetramethylsilane. Optical rotations were measured on a Perkin Elmer 241 polarimeter. HPLC analyses were performed on a Hewlet-Packard apparatus, with UV detection at λ = 249 nm using conditions A for the non-stereospecific analyses and conditions B for the stereospecific HPLC analyses. Conditions A: Tracer Analytical column ODS-2, 25 x 0.45 cm, 10 μm silica gel, H_2O / acetonitrile in a ratio of 60 / 40 as eluent, flow 0.9 ml / min; Conditions B: CHIRALCEL OD-H column (25 x 0.46 cm) containing the chiral stationary phase cellulose tris-(3,5-dimethylphenylcarbamate), a mixture of hexane / isopropanol in the ratio of 93 / 7 as eluent, flow 0.8 ml / min). Solvents were of analytical grade. Lipases: Lipase Amano PS, Lipase MAP 10, Lipase Boehringer PS, Lipase Fluka PS, Lipase Amano AY, Lypozime 10,000 L and PPL Sigma

rac-3-Hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone ***rac*-1**. This compound was obtained in 82% yield by reaction of DL-pantolactone with aniline following the method described by Marieva et al.[8], m.p. 118-119°C. IR (KBr) ν = 3347 (OH st), 1683 (C=O st) cm^{-1}. $C_{12}H_{15}NO_2$ (205.26), calcd. C 70.22% H 7.37% N 6.82%. Found: C 70.29% H 7.48% N 6.82%.

rac-3-Acetoxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone ***rac*-2.** A mixture of ***rac*-1** (205 mg, 1.00 mmol), acetyl chloride (240 mg, 3.0 mmol) and anhydrous triethylamine (0.4 ml, 3.0 mmol) in anhydrous CH_2Cl_2 (5 ml) was stirred at room temperature for 18 h. Water (10 ml) was added and the mixture was washed with N HCl (2 x 5 ml), saturated aqueous solution of $NaHCO_3$ (3 x 5 ml), dried with Na_2SO_4, and concentrated *in vacuo* to give a residue (285 mg), which on column chromatography [silica gel (15 g), mixtures hexane / diethyl ether as eluent] gave ***rac*-2** (216 mg, 87% yield), m.p. 87-88 °C. IR (NaCl) ν = 1745 and 1713 (C=O st) cm^{-1}. The ^1H and ^{13}C NMR coincide with those of **(*S*)-2**. $C_{14}H_{17}NO_3$ (247.29), calcd. C 67.99% H 6.93% N 5.66%. Found: C 68.21% H 7.03% N 5.38%.

(S)-3-Acetoxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone **(*S*)-2**. Lipase Amano PS (8.00 g) was added to a solution of ***rac*-1** (4.00 g, 19.5 mmol) and vinyl acetate (80 ml) in hexane (240 ml). The mixture was stirred at 27 °C for 64 h, untill nearly 50% conversion was achieved (HPLC, conditions A, ***rac*-1**, r.t. 4.16 min, ***rac*-2**, r.t. 9.39 min). The enzyme was removed by filtration, the filtrate was dried with Na_2SO_4, the solvent was evaporated from the filtrate at reduced pressure and the residue was submitted to column chromatography [silica gel (230 g), mixtures hexane / CH_2Cl_2 / methanol]. **(*S*)-2** (1.97 g, 82% yield, 95% ee) was isolated on elution with CH_2Cl_2, while **(*R*)-1** (2.00 g, 58% ee) was obtained on elution with a mixture CH_2Cl_2 / methanol in a ratio of 99.5 / 0.5. The enantiomeric excesses of **(*S*)-2** and **(*R*)-1** were established by HPLC using conditions B: **(*S*)-2**, r.t. 20.93 min; **(*R*)-2**, r.t. 30.58 min; **(*R*)-1**, r.t. 18.28 min; **(*S*)-1**, r.t. 16.77 min.

Physical and spectroscopic data of (*S*)-**2**: Oil, b.p. 180 °C / 2 Torr. $[\alpha]_D^{22}$ ($CHCl_3$, c = 1.00) = -42.1 . ^1H NMR (500 MHz, $CDCl_3$) δ = 1.13 (s, 3 H, 4α-CH_3), 1.30 (s, 3 H, 4β-CH_3), 2.22 (s, 3 H, $COCH_3$), 3.51 (d, J = 9.5 Hz, 1 H, 5α-H), 3.61 (d, J = 9.5 Hz, 1 H, 5β-H), 5.40 (s, 1 H, 3-H), 7.17 (tt, J = 7.4 Hz, J = 1.2 Hz, 1 H, H*para*), 7.37 (m, 2 H, H*meta*), 7.62 (dm, J = 8.4 Hz, 2 H, H*ortho*). ^{13}C NMR (75.5 MHz) δ = 20.6 (CH_3, $COCH_3$), 21.0 (CH_3, 4α-CH_3), 24.7 (CH_3, 4β-CH_3), 37.2 (C, C4), 57.6 (CH_2, C5), 78.1 (CH, C3), 119.3 (CH, C*ortho*), 124.8 (CH, C*para*), 128.8 (CH, C-*meta*), 138.9 (C, C*ipso*), 168.8 (C, C2), 170.1 (C, $COCH_3$). IR (NaCl) ν = 1748 and 1715 (C=O st) cm^{-1}. $C_{14}H_{17}NO_3$ (247.29), calcd. C 68.00% H 6.93% N 5.66%. Found: C 68.04% H 6.99% N 5.54%.

(R)-3-Hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone (***R***)-**1**. Lipase Amano PS (18 g) was added to a solution of ***rac***-**1** (9.00 g, 43.9 mmol) and vinyl acetate (180 ml) in DIPE (540 ml). The mixture was stirred at 27 °C untill nearly 50% conversion was achieved (72 hours). The enzyme was removed by filtration and the solvent was evaporated from the filtrate at reduced pressure. The enantiomeric excesses of the unreacted alcohol (***R***)-**1** (99%) and of the acetyl ester (***S***)-**2** (89%) were established by HPLC using conditions B. *Physical and spectroscopic and data of* (***R***)-**1**: M. p. 144 -147 °C. $[\alpha]_D^{20}$ ($CHCl_3$, c = 1.00) = + 44.1 . ^1H NMR (500 MHz, $CDCl_3$) δ = 1.08 (s, 3 H, 4α-CH_3), 1.31 (s, 3 H, 4β-CH_3), 3.26 (d, J = 3.0 Hz, 1 H, OH), 3.44 (d, J = 9.5 Hz, 1 H, 5α-H), 3.53 (d, J = 9.5 Hz, 1 H, 5β-H), 4.09 (d, J = 3.0 Hz, 1 H, 3-H), 7.15 (broad t, J = 7.0 Hz, 1 H, H*para*), 7.36 (m, 2 H, H*meta*), 7.60 (dm, J = 8.2 Hz, 2 H, H*ortho*). ^{13}C NMR (75.5 MHz) δ = 20.0 (CH_3, 4α-CH_3), 24.5 (CH_3, 4β-CH_3), 38.3 (C, C4), 57.7 (CH_2, C5), 78.4 (CH, C3), 119.5 (CH, C*ortho*), 124.8 (CH, C*para*), 128.9 (CH, C*meta*), 139.1 (C, C*ipso*), 174.2 (C, C2); IR (KBr) ν = 3362 (OH st), 1691 (C=O st). $C_{12}H_{15}NO_2$ (205.26), calcd. C 70.22% H 7.37% N 6.82%. Found: C 70.34% H 7.40% N 6.76%.

(S)-3-Hydroxy-4,4-dimethyl-1-phenyl-2-pyrrolidinone (***S***)-**1**. A solution of (***S***)-**2**, (4.80 g), acetic acid (100 ml), and 2N HCl (40 ml) was stirred at 120°C (external temperature) for 2.5 hours. The mixture was allowed to cool to room temperature and was extracted with CH_2Cl_2 (3 x 40 ml). The combined organic extracts were washed with saturated aqueous solution of $NaHCO_3$ (3 x 20 ml), dried with Na_2SO_4 and concentrated *in vacuo* to give a solid residue (3.90 g) which on crystallization from ethanol gave (***S***)-**1** (3.10 g, 78% yield, 99% ee), m.p. 145 - 147 °C. $[\alpha]_D^{20}$ ($CHCl_3$, c = 1.00) = - 44.5 . The IR, ^1H and ^{13}C NMR spectra coincide with those of (***S***)-**1**. $C_{12}H_{15}NO_2$ (205.26), calcd. C 70.22% H 7.37% N 6.82%. Found: C 70.38% H 7.40% N 6.73%.

(R)-3-(4-bromobenzoyloxy)-4,4-dimethyl-1-phenyl-2-pyrrolidinone (***R***)-**3**[4]. A solution of (***R***)-**1** (200 mg, 0.97 mmol) in CH_2Cl_2 (1.0 ml) was added to a mixture of 4-(dimethylamino)pyridine (245 mg, 2.0 mmol) and 4-bromobenzoyl chloride (220 mg, 1.0 mmol) in CH_2Cl_2 (2.0 ml), and the mixture was stirred for 3 hours at room temperature. The solution was submitted to column chromatography [silica gel (20 g), CH_2Cl_2 as eluent] and the fractions containing the product were combined and concentrated at reduced pressure to give (***R***)-**3** (361 mg, 95% yield), m. p. 112-113 °C (ethanol). $[\alpha]_D^{20}$ ($CHCl_3$, c = 1.00) = - 8.6 . ^1H NMR (500 MHz, $CDCl_3$) δ = 1.21 (s, 3 H, 4α-CH_3), 1.35 (s, 3 H, 4β-CH_3), 3.56 (d, J = 9.5 Hz, 1 H, 5α-H), 3.66 (d, J = 9.5 Hz, 1 H, 5β-H), 5.61 (s, 1 H, 3-H), 7.16 (tt, J = 7.5 Hz, J' = 1.0 Hz, 1 H, H*para* phenyl), 7.37 (m, 2 H, H*meta* phenyl), 7.59 (dm, J = 8.5 Hz, H*meta* *p*-bromobenzoate), 7.63 (dm, J = 8.5 Hz, 2 H, H*ortho* phenyl), 7.97 (dm, J = 8.5 Hz, H*ortho* *p*-bromobenzoate). ^{13}C NMR (75.5 MHz) δ = 21.2 (CH_3, 4α-CH_3), 24.8 (CH_3, 4β-CH_3), 37.6 (C, C4), 57.6 (CH_2, C5), 78.8 (CH, C3), 119.3 (CH, C*ortho* phenyl), 124.9 (CH, C*para* phenyl), 128.2 (C) and 128.5 (C) (C*para* and C*ipso* *p*-bromobenzoate), 128.9 (CH, C*meta* phenyl), 131.4 (CH) and 131.7 (CH) (C*ortho* and C*meta* *p*-bromobenzoate), 139.0 (C, C*ipso* phenyl), 165.0 (C, COO *p*-bromobenzoate), 168.6 (C, C2). IR (KBr)

ν = 1732 and 1706 (C=O st) cm^{-1}. $C_{19}H_{18}BrNO_3$ (388.20), calcd. C 58.78% H 4.67% N 3.61% Br 20.58%. Found: C 58.71% H 4.60% N 3.59% Br 20.65%.

Table 1. Experimental data of the X-ray crystal structure determination of **(R)-1** and **(R)-3**.

Compound	**(*R*)-1**	**(*R*)-3**
Molecular formula	$C_9H_{15}NO_2$	$C_{19}H_{17}NO_3$
Molecular mass	205.25	387.25
Crystal system	orthorhombic	orthorhombic
Space grup	$P2_12_12_1$	$P2_12_12_1$
Cell parameters	[a]	[a]
a [Å]	20.358(4)	19.693(4)
b [Å]	6.179(2)	9.761(2)
c [Å]	8.905(2)	9.194(2)
V [$Å^3$]	1120.2(5)	1767.3(6)
Z	4	4
F(000)	440	756
d(calcd) [Mg m^{-3}]	1.217	1.395
Size of crystal [mm]	0.4 x 0.2 x 0.2	0.1 x 0.1 x 0.2
Measured reflections	3717	2919
Independent reflections	3278	2919
Observed reflections	1648	1125
μ(Mo-*K*α) [mm^{-1}][b]	0.083	2.334
R	0.0629	0.0996
*R*w	0.1510	0.2261
Absolute structure parameter	-5(3)	-0.08(4)
Diff. Four. $\Delta\rho_{max}$[c]	0.176	1.145
$\Delta\rho_{min}$[d]	-0.180	-1.060
Refined parameters	183	273
Max. shift / e.s.d.	0.44	2.7

[a] Determined by automatic centering of 25 reflections ($8 \leq \theta \leq 12°$). [b] μ(Mo-*K*α), Linear absorption coefficient. Radiation Mo-*K*α (λ = 0.71069Å). [c] Maximum and [d] minimum peaks in final difference synthesis.

X-ray Crystal-Structure Determinations of **(*R*)-1** *and* **(*R*)-3** (Table 1): A prismatic crystal was selected and mounted on a Philips PW-1100 four-circle diffractometer. Unit cell parameters were determined by automatic centering of 25 reflections and refined by the least-squares method. Intensities were collected with graphite-monochromatized Mo-*K*α radiation, using w/2θ scan technique. Reflections were measured in the range $2.00 \leq \theta \leq 30.04$ for **(*R*)-1**, and $2.07 \leq \theta \leq 30.00$ for **(*R*)-3**, and were assumed as observed by applying the condition $I \geq 2\,\sigma(I)$. Three reflections were measured every two hours as orientation and intensity control; significant intensity

decay was not observed. Lorentz polarization and absorption corrections were made for (***R***)-**3**, but no absorption corrections were made for (***R***)-**1**. The structure was solved by Direct methods [(***R***)-**1**] or by Patterson synthesis [(***R***)-**3**], using the SHELXS computer program[11] and refined by the full-matrix least-squares method with the SHELX-93 computer program[12]. The function minimized was Σ w $[|F_o|^2 - |F_c|^2]^2$, where w = $[\sigma^2(I) + (0.0978\ P)^2 + 0.0682\ P]^{-1}$ for (***R***)-**1** and w = $[\sigma^2(I) + (0.1752\ P)^2]^{-1}$ for (***R***)-**3**, being P = $(|F_o|^2 + 2|F_c|^2) / 3$ in both cases. f, f' and f" were taken from International Tables of X-ray Crystallography[13]. The extinction coefficient was 0.099(14) for (***R***)-**1** and 0.000(3) for (***R***)-**3**. The chirality of the structure was defined from the Flack coefficient, which is -5(3) for (***R***)-**1** and -0.08(4) for (***R***)-**3**[14]. The positions of all hydrogen atoms were computed and refined with an overall isotropic temperature factor by using a riding model for (***R***)-**3** or from a difference synthesis for (***R***)-**1**.

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