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CHEMOENZYMATIC SYNTHESIS OF ACETYL (R)-(+)- AND (S)-(-)-CYCLOSERINE

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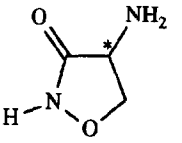
Abstract: The two enantiomers of acetyl cycloserine **8**, the immediate precursors of the chiral forms of cycloserine **1**, were prepared in enantiomeric excess higher than 98% by means of lipase-catalyzed hydrolysis of 3-benzyloxy-4-hydroxy-Δ^2-isoxazoline butyrate (±)-**5**. Among the five lipases tested, lipase from *Chromobacterium viscosum* was by far the most selective catalyst. Since the enantiomeric ratio (E) of the reaction was higher than 100, the hydrolysis spontaneously stopped at 50% conversion to yield (R)-3-benzyloxy-4-hydroxy-Δ^2-isoxazoline [(R)-(+)-**4**] and (S)-3-benzyloxy-4-hydroxy-Δ^2-isoxazoline butyrate [(S)-(-)-**5**] in almost enantiomerically pure form. Intermediates (R)-(+)-**4** and (S)-(-)-**5** were transformed into the enantiomers of acetyl cycloserine through a four step sequence. This strategy constitutes a valid alternative to the previously reported procedures.

D-cycloserine [(R)-4-aminoisoxazolidin-3-one, (+)-1], a natural broad-spectrum antibiotic isolated from the fermentation broths of *Streptomyces orchidaceus*, *Streptomyces garyphalus* and *Streptomyces lavendulus*, inhibits the synthesis of the bacterial cell wall when D-alanine is involved. It is clinically used as a tuberculostatic agent in combination with first choice antituberculous drugs.[1,2]



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The "unnatural" enantiomer (S)-(-)-**1** retains, at least in part, the *in vitro* activity of the natural isomer.[3] Comparative studies on (R)-(+)-**1** and (S)-(-)-**1** led to the conclusion that the two enantiomers display the antibacterial activity through a different mechanism of action.[3,4]

Quite recent reports evidenced that (R)-(+)-**1** also behaves as a partial agonist at the glycine modulatory site of the NMDA-receptor complex, a subclass of the glutaminergic receptors.[5-8] This positive modulation might be of interest in the treatment of cognitive impairments, i.e. the Alzheimer's disease.[8] On the contrary, (S)-(-)-**1** did not show any appreciable affinity for the same receptor-complex.[8]

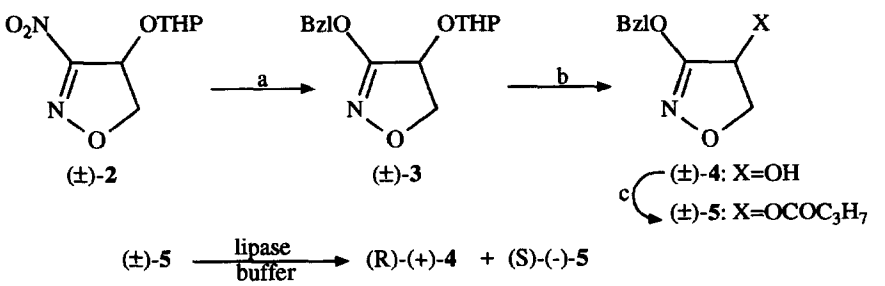
After assignment of the R configuration to the natural dextrorotatory antipode,[9] the two enantiomers of cycloserine were prepared via fractional crystallization of the diastereomeric salts of (±)-**1** with D- or L-tartaric acid[10] and by total synthesis.[11,12]

As an extension of our ongoing interest in the chemoenzymatic synthesis of biologically active compounds,[13] we now report the preparation of the two enantiomers of acetyl cycloserine, the immediate precursors of the chiral forms of cycloserine, via lipase-catalyzed resolution of a suitable intermediate.

RESULTS AND DISCUSSION

We approached the synthesis of the two enantiomers of acetyl cycloserine by selecting butyrate (±)-**5** (Scheme I) as a suitable substrate to attempt enzyme-catalyzed kinetic resolution. Ester (±)-**5** was synthesized from the known 3-nitro-4-hydroxy-Δ^2-isoxazoline tetrahydropyranyl ether (±)-**2**,[14] according to the reaction sequence reported in Scheme I. 3-Nitroisoxazoline (±)-**2** was reacted with a DMSO suspension of lithium benzylate to yield 3-benzyloxy-derivative (±)-**3** as a mixture of partially separable diastereomers (see Experimental). Removal of the THP group under standard conditions followed by esterification with butyryl chloride gave the desired ester (±)-**5**; this intermediate was prepared in multigram quantity.

SCHEME I



a:$PhCH_2OLi$/DMSO; b:IR-120/MeOH; c:C_3H_7COCl/Py.

Butyrate (±)-**5** was hydrolysed at pH 7 in the presence of one of the lipases listed in Table I. The degree of conversion and the enantiomeric excess (e.e.) were determined by chiral HPLC analysis (Chiralcel OJ) which gave base-line separations of the enantiomers of both alcohol **4** and ester **5**. Enantiomeric ratio (E) values were calculated according to literature.[15] The configuration of the produced alcohol as well as the residual ester was assigned by chemical correlation with the enantiomers of acetyl cycloserine, whose

structure was previously attributed.[16] All the lipases tested by us yielded invariably alcohol (R)-(+)-**4**. The configuration of the fast-hydrolyzed enantiomer (R) is predictable by the rules suggested by Kazlauskas et al. for lipase PS-catalyzed processes[17] and extended by us to primary alcohols carrying a heterocyclic nucleus.[18] Among the five lipases we took into account, the best result in terms of enantiopreference values was obtained with lipase from *Chromobacterium viscosum* (lipase CV) which recognized almost exclusively the R form of butyrate **5** (E >100). A drastic reduction in the enantiomer discrimination was observed in the

Table I. Hydrolysis of butyrate (±)-**5** catalyzed by lipases.

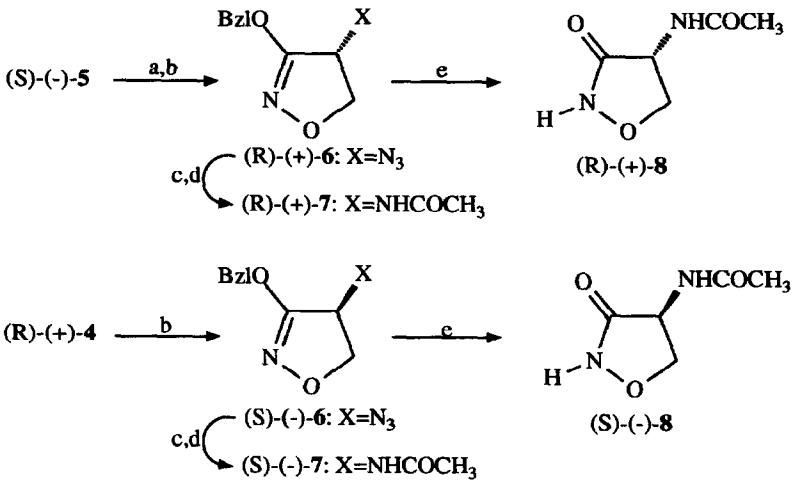
Enzyme	Degree of conv.(%)	Config. of the alcohol	e.e.(%) alcohol	e.e.(%) ester	E
Lipase PS	50	R	70	71	12
Lipase CV	50	R	>99	>99	>100
P.P.L.	15	R	68	11	6
M.M.L.	21	R	61	16	5
C.R.L.	13	R	50	8	3

remaining four cases (E =12-3). As a consequence, for preparative purposes we used the enantioselective hydrolysis of butyrate (±)-**5** mediated by lipase CV. The reaction spontaneously stopped at 50% conversion to yield alcohol (R)-(+)-**4** and ester (S)-(-)-**5** in enantiomeric excess higher than 99%. Intermediate (S)-(-)-**5** was hydrolyzed to (S)-(-)-**4** under standard conditions. By treating enantiomers (S)-(-)-**4** [(R)-(+)-**4**] with diphenylphosphoryl azide (DPPA), triphenylphosphine (TPP) and diethylazodicarboxylate (DEAD),[19] azide (R)-(+)-**6** [(S)-(-)-**6**] was obtained in 73% yield and complete inversion of configuration (e.e.=99%) (Scheme II).

The enantiomers of 3-benzyloxy-4-acetylamino-Δ^2-isoxazolines [(R)-(+)-**7** and (S)-(-)-**7**] (Scheme II) were prepared by treating (R)-(+)-**6** and (S)-(-)-**6** with TPP-water[20] followed by esterification of the primary amine group with acetyl chloride. Finally, N-acetyl cycloserines (R)-(+)-**8** and (S)-(-)-**8**[16] were obtained by catalytic hydrogenation (Pd/C, 5%) of the corresponding benzyloxy derivatives. As previously reported,[21] natural (R)-(+)-**1** and "unnatural" (S)-(-)-**1** cycloserine can be prepared by alkaline hydrolysis of acetyl derivatives (R)-(+)-**8** and (S)-(-)-**8**.

In summary, the synthesis of the enantiomers of acetyl cycloserine has been accomplished via an enantiospecific lipase CV-catalyzed hydrolysis of a suitable intermediate ester. The results of this study further evidence the versatility of the chemoenzymatic approach to the synthesis of biologically active chiral compounds.

SCHEME II



a:K_2CO_3/MeOH-H_2O; b:TPP-DEAD-DPPA/THF; c:TPP-H_2O/THF; d:AcCl/NEt_3; e:H_2-Pd/C,5

EXPERIMENTAL SECTION

Materials and Methods. Lipase from *Pseudomonas cepacia* (lipase PS) was purchased from Amano; lipase from *Chromobacterium viscosum* (lipase CV) was obtained from Finnsugar Biochemicals,Inc.; *Mucor miehei* lipase (M.M.L.) was bought from Biochemicals,LTD; porcine pancreatic lipase (P.P.L.) and *Candida rugosa* lipase (C.R.L.) were purchased from Sigma. Organic solvents were reagent grade. ^1H NMR spectra were recorded at 200 MHz in $CDCl_3$ solution (unless otherwise stated); chemical shifts (δ) are expressed in ppm and coupling constants (J) in hertz. Chiral HPLC analyses were performed with a Chiralcel OJ column (4.6x250 mm) and a wavelength of 254 nm at a flow rate of 1 mL/min with n.hexane/ethanol (9:1) as the mobile phase. TLC analyses were carried out on commercial silica gel GF_{254} plates. Melting points were determined on a Büchi apparatus and are uncorrected. Liquids were characterized by the oven temperature for bulb to bulb distillations. Rotary power determinations were performed with a Perkin Elmer 241 polarimeter coupled with a Haake N3-B thermostat. Mass spectra were recorded on a Hewlett Packard 5970 GC/MS system equipped with a wide bore silica gel column coated with methylsilicone gum.

Synthesis of (R,S)-3-benzyloxy-4-hydroxy-Δ^2-isoxazoline tetrahydropyranyl ether [(±)-3]. To a cold (5°C) and stirred solution of benzyl alcohol (30 mL, 0.29 mol) in anhydrous DMSO (200 mL), a hexane solution of butyllithium (87 mL, 1.6M) was added dropwise in 20 min. The mixture was stirred at room temperature for further 30 min, then a solution of (±)-**2**[14] (10 g, 46.3 mmol as a mixture of stereoisomers) in anhydrous DMSO (150 mL) was added portionwise. The resulting brown solution was stirred overnight, then treated with water (300 mL). The crude reaction mixture was extracted with diethyl ether (6x100 mL). The pooled organic phases were washed with water (3x100 mL) and dried over anhydrous sodium sulfate. After evaporation of volatiles, excess benzyl alcohol and residual DMSO were removed by distillation at 120 °C/1 mmHg. The residue was purified by silica gel column chromatography (eluent: cyclohexane-ethyl acetate 4:1) to yield 8.85 g (69%) of a mixture of diastereomers (±)-**3a** and (±)-**3b**.

(±)-**3a**: colorless prisms from n.hexane/ethyl acetate, mp 88-89 °C; R_f 0.35 (cyclohexane/ethyl acetate 4:1); ^{1}H NMR: 1.42-1.90 (m, 6); 3.52 (m, 1); 3.81 (m, 1); 4.38 (dd, 1, H-5; J=4.6 and 10.4); 4.45 (dd, 1, H-5'; J=7.7 and 10.4); 4.88 (m, 1); 4.98 (dd, 1, H-4; J=4.6 and 7.7); 5.20 (s, 2, CH_2Ph); 7.30-7.43 (m, 5, arom.). *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.81; H, 6.77; N, 5.02.

(±)-**3b**: colorless viscous oil, bp 200-205 °C/0.5 mmHg; R_f 0.31 (cyclohexane/ethyl acetate 4:1); ^{1}H NMR: 1.42-1.88 (m, 6); 3.49 (m, 1); 3.92 (m, 1); 4.36 (m, 2, H-5 and H-5'); 4.74 (m, 1); 5.06 (dd, 1, H-4; ($J_{4,5}$+$J_{4,5'}$ =11); 5.23 (s, 2, CH_2Ph); 7.30-7.43 (m, 5, arom.). *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.63; H, 6.71; N, 4.82.

Synthesis of (R,S)-3-benzyloxy-4-hydroxy-Δ^2-isoxazoline butyrate [(±)-5].

A. The mixture of isomers (±)-**3** (8.31 g, 30 mmol) was dissolved in methanol (100 mL) and treated at room temperature under stirring with 2.8 g of Amberlite IR-120. The disappearance of the starting material (4 h) was checked by TLC. After filtration and evaporation of the solvent at reduced pressure, the residue was column chromatographed (eluent: cyclohexane/ethyl acetate 3:2) to yield 4.98 g (86 %) of (±)-**4** as a thick pale yellow oil.

(±)-**4**: R_f 0.64 (cyclohexane/ethyl acetate 3:2); ^{1}H NMR: 2.87 (bs, 1, OH); 4.27 (dd, 1, H-5 J=4.2 and 10.3); 4.41 (dd, 1, H-5' J=7.4 and 10.3); 4.98 (m, 1, H-4); 5.17 (s, 2, CH_2Ph); 7.39 (m, 5, arom.). *Anal.* Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.89; H, 5.86; N, 7.06.

B. To an ice cooled solution of (±)-**4** (4.5 g, 23.3 mmol) and dry pyridine (3.2 mL, 40 mmol) in anhydrous dichloromethane (70 mL) was added dropwise a dichloromethane solution (10 mL) of butyryl chloride (4.15 mL, 40 mmol). The disappearance of the starting material (30 min) was monitored by TLC. The mixture was washed with a 20% aqueous solution of $CuSO_4$ (3x25 mL), then the organic phase was dried and concentrated. The residue was purified by column chromatography (eluent: cyclohexane/ethyl acetate 4:1) to yield 4.97 g (81 %) of the desired ester.

(±)-**5**: colorless liquid, bp 125-130 °C/1 mmHg; R_f 0.45 (cyclohexane/ethyl acetate 4:1); ^{1}H NMR: 0.94, 3, Me; J=7.3); 1.66 (m, 2, CH_2CH$_3$); 2.35 (t, 2, OCOCH_2; J=7.3); 4.29 (dd, 1, H-5; J=3.8 and 11.4); 4.55 (dd, 1, H-5'; J=7.7 and 11.4); 5.21 (s, 2, CH_2Ph); 5.85 (dd, 1, H-4; J=3.8 and 7.7); 7.39 (m, 5, arom.). *Anal.* Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.47; H, 6.22; N, 5.12.

Standard procedure for the lipase-catalyzed hydrolyses of (±)-5. The following procedure is representative. A 500 mL Erlenmeyer flask was charged with (±)-**5** (2.63 g, 10 mmol), lipase CV (13 mg), 0.1M potassium phosphate buffer, pH 7 (180 mL) and acetone (20 mL). The mixture was stirred at room temperature for about 1 h (50 % conversion), then it was lyophilized. The residue was extracted with acetone (3x20 mL) and column chromatographed on silica gel (eluent: cyclohexane/ethyl acetate 3:2) to yield 1.28 g (4.87 mmol) of (S)-(-)-**5** and 0.92 g (4.77 mmol) of (R)-(+)-**4**.

(S)-(-)-**5**: $[\alpha]_D^{20}$ -34.65 (c1.07, $CHCl_3$); e.e. >99%. *Anal.* Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.63; H, 6.27; N, 5.04.

(R)-(+)-**4**: colorless leaflets from n.hexane/ethyl acetate, mp 60-61 °C; $[\alpha]_D^{20}$ +72.46 (c1.1, $CHCl_3$); e.e. >99%. *Anal.* Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.31; H, 5.63; N, 7.01.

Chiral HPLC, retention times (min): (S)-(-)-**4**, 38.1; (R)-(+)-**4**, 42.8; (S)-(-)-**5**, 22.5; (R)-(+)-**5**, 24.5.

The same protocol was applied, on an analytical scale (100 mg substrate), to the hydrolyses catalyzed by lipase PS, P.P.L., M.M.L. and C.R.L.. The results are reported in Table I.

Chemical hydrolysis of butyrate (S)-(-)-5. A methanolic solution (25 mL) of (S)-(-)-**5** (1.18 g, 4.49 mmol) was treated with a 20% aqueous solution of potassium carbonate (10 mL). The mixture was stirred at room temperature until disappearance of the starting material (2 h). After evaporation of the solvent at reduced pressure, the aqueous phase was thoroughly extracted with ethyl acetate (5x10 mL). (S)-(-)-**4** (0.78 g, 90%) was obtained as a crystalline compound, mp 60-61 °C; $[\alpha]_D^{20}$ -73.35 (c1.0, $CHCl_3$). *Anal.* Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.43; H, 5.78; N, 7.13.

Synthesis of 4-acetylaminoisoxazolidin-3-ones (R)-(+)-8 and (S)-(-)-8.

A. A solution of (S)-(-)-**4** (0.720 g, 3.73 mmol) and triphenylphosphine (1.47 g, 5.6 mmol) in dry THF (30 mL) was cooled at 0 °C and stirred under nitrogen during the dropwise sequential addition of diethylazodicarboxylate (882 µL, 5.6 mmol) and diphenylphosphoryl azide (1.2 mL, 5.6 mmol). The reaction mixture was stirred at 0 °C for further 15 min, then was concentrated and flash chromatographed on silica gel (eluent: ligroin/ethyl acetate 15:1) to give 0.595 g (73 %) of (R)-(+)-**6** as a pale yellow oil.

(R)-3-Benzyloxy-4-azido-Δ^2-isoxazoline [(R)-(+)-**6**]: R_f 0.34 (cyclohexane/ethyl acetate 4:1); $[\alpha]_D^{20}$ +194.20 (c1.0, $CHCl_3$); IR: ν 2100 cm^{-1}. ^1H NMR: 4.29 (dd, 1, H-5; J=4.4 and 10.3); 4.48 (dd, 1, H-5'; J=8.2 and 10.3); 4.72 (dd, 1, H-4; J=4.4 and 8.2); 5.24 (s, 2, CH_2Ph); 7.41 (m, 5, arom.). MS (E.I.)= m/e 218 (M^+, 1%), 132 (M-86, 1), 92 (M-126, 7), 91 (M-127, 100), 77 (M-141, 4).

(S)-3-Benzyloxy-4-azido-Δ^2-isoxazoline [(S)-(-)-**6**] was similarly obtained (70 % yield) from (R)-(+)-**4**.

(S)-(-)-**6**: $[\alpha]_D^{20}$ -193.33 (c1.17, $CHCl_3$).

Chiral HPLC, retention times (min): (S)-(-)-**6**, 23.1; (R)-(+)-**6**, 32.2. The e.e. values were 99% for both the enantiomers.

B. To a stirred solution of (R)-(+)-**6** (0.545 g, 2.5 mmol) in 20 mL dry THF was added triphenylphosphine (0.787 g, 3 mmol) portionwise at room temperature. The resulting solution was stirred for

additional 3 h, then water (0.2 mL) was added. The mixture was stirred at room temperature overnight. The solvent was evaporated under vacuum and the residue was acidified with 2N HCl (15 mL). The solution was extracted with diethyl ether (5x5 mL); the aqueous phase was made alkaline (pH 10) with potassium carbonate then extracted with dichloromethane (5x5 mL). After the usual workup, the residue of the organic extracts was purified by column chromatography (eluent: ethyl acetate) to yield 0.293 g (61 %) of the amine as a yellow oil, bp 180-185 °C/0.5 mmHg.

(R)-3-Benzyloxy-4-amino-Δ^2-isoxazoline: R_f 0.25 (ethyl acetate); ^{1}H NMR: 1.70 (bs, 2, NH_2); 4.07 (dd, 1, H-5; J=8.4 and 8.6); 4.18 (m, 1, H-4); 4.32 (dd, 1, H-5'; J=8.4 and 8.2); 5.18 (s, 2, CH_2Ph); 7.40 (m, 5, arom.).

(S)-3-Benzyloxy-4-amino-Δ^2-isoxazoline was obtained in comparable yield (55%) starting from (S)-(-)-**6**.

C. To an ice cooled and stirred solution of (R)-3-benzyloxy-4-amino-Δ^2-isoxazoline (0.269 g, 1.4 mmol) and triethylamine (293 µL, 2.1 mmol) in anhydrous diethyl ether (20 mL) was added dropwise acetyl chloride (150 µL, 2.1 mmol). The reaction mixture was stirred for additional 30 min at 0 °C, then 10 mL of 2N HCl was added. The aqueous phase was separated and extracted with diethyl ether (3x10 mL). The organic extracts were worked up as usual and the residue was column chromatographed (eluent: ethyl acetate) to yield 0.305 g (93 %) of the expected amide.

(R)-3-Benzyloxy-4-acetylamino-Δ^2-isoxazoline [(R)-(+)-**7**]: colorless needles from n.hexane-ethyl acetate, mp 144-145 °C; $[\alpha]_D^{20}$ +47.82 (c1.05, $CHCl_3$); ^{1}H NMR: 2.00 (s, 3, Me); 4.13 (dd, 1, H-5; J=5.9 and 9.6); 4.59 (dd, 1, H-5'; J=9.2 and 9.6); 5.15 5.19 (dd, 2, CH_2Ph; J=11.8); 5.25-5.38 (m, 1, H-4); 6.16(bd, 1, NH; J=6.8); 7.38 (m, 5, arom.). *Anal.* Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.32; H, 5.84; N, 12.18.

(S)-3-Benzyloxy-4-acetylamino-Δ^2-isoxazoline [(S)-(-)-**7**]: mp 144-145 °C; $[\alpha]_D^{20}$ -47.43 (c1.12, $CHCl_3$). *Anal.* Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.45; H, 5.79; N, 12.09.

D. A solution of (R)-(+)-**7** [(S)-(-)-**7**] (0.270 g, 1.15 mmol) in methanol (20 mL) was submitted to catalytic hydrogenation at atmospheric pressure over 5% Pd/C (50 mg). After absorption of one equivalent of hydrogen, the catalyst was removed and the solvent was evaporated under vacuum to leave 0.144 g (88 %) of (R)-(+)-**8** as a crystalline compound.

(R)-(+)-**8**: colorless prisms from abs. ethanol, mp 177-178 °C, dec; R_f 0.23 (ethyl acetate/methanol 9:1); $[\alpha]_D^{20}$ +72.85 (c1.0, H_2O) [lit.^{20} +73.1 (H_2O)].

(S)-(-)-**8**: mp 177-178 °C, dec; $[\alpha]_D^{20}$ -72.23 (c1.0, H_2O) [lit.^{20} -70.1 (H_2O)]. ^{1}H NMR (acetone d_6): 1.96 (s, 3, Me); 3.99 (dd, 1, H-5; J=8.2 and 10.0); 4.64 (dd, 1, H-5'; J=8.2 and 8.2); 4.73-4.91 (m, 1, H-4); 7.55 (bs, 1, NH isoxazolidine).

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