Stereoselective Amination of 5-Substituted γ-Lactones and γ-Lactams – A Convenient Route for the Preparation of 5-Substituted (3*S*,5*S*)-3-Acetylaminotetrahydrofuran-2-ones and (3*S*,5*S*)-3-Acetylaminopyrrolidin-2-ones

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Keywords: Tetrahydrofuran-2-ones / Pyrrolidin-2-ones / Aminations / Nitrosations / Asymmetric synthesis

5-Substituted (*S*)-tetrahydrofuran-2-ones (**1a**,**b**) and (*S*)-pyrrolidin-2-ones (**1c**,**d**) were transformed in three steps, by treatment with *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent), followed by nitrosation and stereoselective catalytic hydrogenation, into the corresponding 5-substituted (3*S*,5*S*)-3-acetylaminotetrahydrofuran-2-ones (**4a**,**b**) and (3*S*,5*S*)-3-acetylaminopyrrolidin-2-ones (**4c**,**d**).

Nitrosation of "active" methylene groups followed by reduction of the resulting oxime is one of the most common methods for amination at the position adjacent to an electron-withdrawing group.[1] The advantage of this methodology is the use of cheap reagents and mild reaction conditions. The scope of this method, however, is usually limited to methylene groups bearing a strong electron-withdrawing substituent, e.g. nitroalkanes, ketones, 1,3-dicarbonyl compounds, and their analogs. Nitrosation of aliphatic carboxylic acid derivatives, such as lactones and lactams, is therefore hard to achieve. On the other hand, such compounds are sufficiently nucleophilic to react with *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent) to give the corresponding α-dimethylaminomethylene-substituted compounds.[2−5] 2-Substituted 3-dimethylaminopropenoates and their analogs react with various mono- and dinucleophiles and hence represent a useful synthetic tool for the preparation of a variety of heterocyclic systems.[6][7] 2-Substituted 3-dimethylaminopropenoates also react with electrophiles and, in this context, we have previously shown that nitrosation of α-dimethylaminomethylene-substituted carbonyl compounds leads to the formation of oximes and 1,2,4-oxadiazoles.[8][9] As a continuation of our work in this field, we report on the stereoselective amination of lactones **1a**,**b** and lactams **1c**,**d**. In this manner, 5-substituted (3*S*,5*S*)-3-acetylaminotetrahydrofuran-2-ones **4a**,**b** and (3*S*,5*S*)-3-acetylaminopyrrolidin-2-ones **4c**,**d** were prepared in 3 steps from easily accessible precursors. Since α-amino-γ-hydroxy and α,γ-diamino acid structural elements are both widely found in nature, a convenient stereoselective α-amination of lactones and lactams can serve as a useful synthetic tool in the synthesis of various biologically active compounds.[10]

Starting from (*S*)-2-oxotetrahydrofuran-5-carboxylic acid, (*S*)-5-hydroxymethyltetrahydrofuran-2-one, and (*S*)-5-methoxycarbonylpyrrolidin-2-one,[6] suitably protected lactones **1a**,**b** and lactams **1c**,**d** were prepared according to the procedures described in the literature.[11−13] Reactions of **1a**−**d** with *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent) gave 3-dimethylaminomethylene derivatives **2a**−**d**, which, after treatment with nitrous acid, afforded the corresponding oximes **3a**−**d**. Finally, catalytic hydrogenation of **3a**−**d** in the presence of acetic anhydride furnished 5-substituted (3*S*,5*S*)-3-acetylaminotetrahydrofuran-2-ones **4a**,**b**, (3*S*,5*S*)-3-acetylaminopyrrolidin-2-ones **4c**,**d** and their (3*R*,5*S*) epimers **5a**−**d**. Isomerically pure compounds **4a**−**d** were prepared either by crystallisation of crude isomeric mixtures (**4a**−**c**), or by chromatographic purification (**4d**). NMR spectra and elemental analyses for compounds **4a**−**d** are in agreement with the proposed structures (Scheme 1).

The stereoselectivity of the catalytic hydrogenation of oximes **3a**−**d** was generally high and was influenced by the substituent at position 5, as well as by the *N*-acyl group in the case of lactams **3c**,**d**. Hydrogenation of lactones **3a**,**b** and *N*-Boc-protected lactam **3d** proceeded with 82−86% d.e., thus indicating that the stereodirecting effect of the substituent at position 5 may not be particularly dependent on its bulkiness. On the other hand, when the stereoselectivities obtained in the hydrogenation of lactams **3c**,**d** are compared, it could be presumed that the choice of *N*-acyl group plays an important role, since d.e. values were significantly lower in the hydrogenation of *N*-benzoyl lactam **4c** with respect to *N*-Boc-lactam **4d** (Scheme 2).

The configurations of (3*S*,5*S*)-3-acetylamino-5-methoxycarbonyltetrahydrofuran-2-one (**4a**) and (3*S*,5*S*)-3-acetylamino-1-benzoyl-5-methoxycarbonylpyrrolidin-2-one (**4c**) were confirmed by NMR (NOE) experiments. A strong NOE effect was observed between 4-H_b and 3-H or 5-H, as

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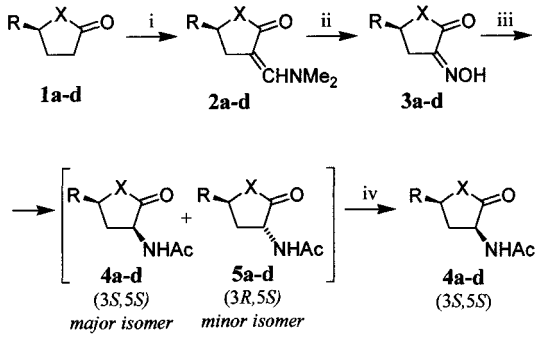
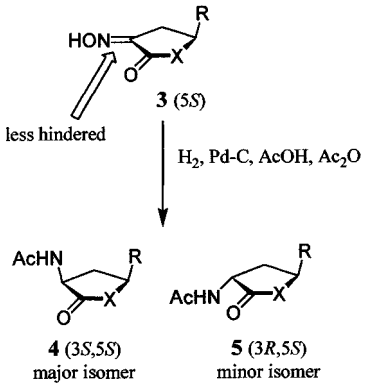


Compounds 1–4	R	X	Yield	2	3	4
a	CO_2Me	O		58	78	58
b	$PhCO_2CH_2$	O		43	81	56
c	CO_2Me	N–COPh		74	79	45
d	CO_2Me	N–Boc		87	79	44

Scheme 1. Reagents and conditions: i: *tert*-butoxybis(dimethylamino)methane (Bredereck's reagent), toluene, 90–100°C, 2 h; ii: HCl, $NaNO_2$, H_2O, 0°C, 2 h; iii: H_2, Pd/C, AcOH/Ac_2O, 20–60°C, 1 bar, 10 h; iv: crystallisation (**4a–c**) or chromatographic separation (**4d**)

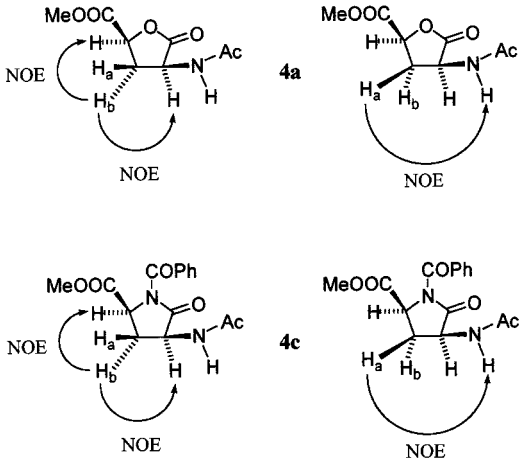


Compounds	R	X	d. r. **4** (3*S*,5*S*)/ **5** (3*R*,5*S*)	**4**, d.e. (%)
4a/5a	CO_2Me	O	91:9	82
4b/5b	$PhCO_2CH_2$	O	93:7	86
4c/5c	CO_2Me	N–COPh	75:25	50
4d/5d	CO_2Me	N–Boc	93:7	86

Scheme 2. Stereoselectivity of the catalytic hydrogenation of oximes **3a–d**

well as between NH and 4-H_a, while only a weak NOE effect was observed between 4-H_a and 3-H or 5-H. The structures of **4a** and **4c** are therefore in accordance with the proposed structures, indicating that hydrogenation of oximes **3a–d** takes place preferentially from the less hindered side of the C=N double bond (Scheme 3).

Since direct nitrosation of lactones and lactams is usually difficultly to achieve, these transformations represent a novel, convenient, and stereoselective introduction of the amino group to the position adjacent to the ring carbonyl



Scheme 3. Determination of the configurations of compounds **4a** and **4c** by NMR (NOE) experiments

group in the lactone and lactam moiety by 3-dimethylaminomethylene-substituted lactones and lactams as chiral 3-dimethylaminopropenoate analogs.

Experimental Section

General Remarks: Melting points were determined with a Kofler micro hot stage. – The ^{1}H-NMR spectra, ^{13}C-NMR spectra, and NOE measurements were obtained with a Bruker Avance DPX 300 (300 MHz) spectrometer with [D_6]DMSO and $CDCl_3$ as solvents and Me_4Si as internal standard. – The microanalyses for C, H, and N were obtained with a Perkin–Elmer CHN Analyser 2400. – The optical rotations were measured with a Perkin–Elmer 241 MC Polarimeter. – D.e. values were determined by examining the ^{1}H-NMR spectra of crude products. – TLC: Merck, Alufolien Kieselgel 60 F 254, 0.2 mm. – Flash chromatography (FC) was performed on a silica gel (FLUKA, Kieselgel 60, 0.04–0.063 mm). Crude products **4a–d** were obtained as mixtures of two isomers: major isomers **4a–d** and the corresponding minor isomers **5a–d**. Major isomers **4a–d** were isolated, purified and fully characterised, while minor isomers **5a–d** were detected and partially characterised by taking ^{1}H-NMR spectra of crude products.

Starting Materials: The following starting compounds were prepared according to the procedures described in the literature: (*S*)-5-methoxycarbonylpyrrolidin-2-one,[11] (*S*)-5-methoxycarbonyltetrahydrofuran-2-one (**1a**),[12] (*S*)-5-benzoyloxymethyltetrahydrofuran-2-one (**1b**),[13] and (*S*)-1-benzoyl-5-methoxycarbonylpyrrolidin-2-one (**1c**).[7f]

Methyl (*S*)-1-Benzoyl-2-oxopyrrolidine-5-carboxylate (1c):[7f] Benzoyl chloride (7.27 g, 52 mmol) was added to a solution of (*S*)-5-methoxycarbonylpyrrolidin-2-one (7.30 g, 50 mmol) in pyridine (75 mL) and the mixture was stirred at room temperature for 2 h. Volatile components were evaporated in vacuo, *n*-hexane (150 mL) was added to the residue, the precipitate collected by filtration, and washed with methanol (100 mL) to give **1c**. Yield: 10.39 g (84%), colorless crystals. – M.p. 150–152°C (methanol). – $[\alpha]_D^{23}$ = +30.1 (*c* = 1.1, CH_2Cl_2). – ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 2.00–2.04 (m, 1 H, 4-H_a), 2.41–2.47 (m, 1 H, 4-H_b), 2.57–2.62 (m, 2 H, 3-CH_2), 3.72 (s, 3 H, OMe), 4.84 (dd, 1 H, *J* = 3.9, 8.7 Hz, 5-H), 7.42–7.47 (m, 2 H, Ph), 7.54–7.61 (m, 3 H, Ph). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.2, 32.1, 53.1, 59.1, 128.3, 129.5,

132.7, 134.1, 170.8, 172.0, 173.8. − $C_{13}H_{13}NO_4$ (247.3): calcd. C 63.15, H 5.30, N 5.66; found C 62.96, H 5.20, N 5.58.

***1-tert*-Butyl 5-Methyl (*S*)-2-Oxopyrrolidine-1,5-dicarboxylate (1d):** Di-*tert*-butyl dicarbonate (29.5 g, 135 mmol) was added to a solution of (*S*)-5-methoxycarbonylpyrrolidin-2-one (10.0 g, 67 mmol) and 4-dimethylaminopyridine (0.56 g, 5 mmol) in acetonitrile (150 mL) and triethylamine (50 mL) and the mixture was stirred at room temperature for 3 h. Ethyl acetate (200 mL) was then added and the solution was washed with 3% hydrochloric acid (200 mL), aqueous sodium bicarbonate (200 mL), and brine (100 mL). The organic phase was dried with anhydrous sodium sulfate, filtered, and the filtrate concentrated in vacuo. The residue was triturated with *n*-hexane/ethyl acetate (1:1, 150 mL) and the precipitate collected by filtration to give **1d**. − Yield: 11.25 g (69%), colorless crystals. − M.p. 68−70°C (ethyl acetate/hexane). − $[\alpha]_D^{23} = -30.7$ (c = 1.16, CH_2Cl_2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 9 H, *t*Bu), 2.03 (ddt, 1 H, J = 3.6, 9.5, 13.2 Hz, 4-H_a), 2.32 (dq, 1 H, J = 9.4, 13.3 Hz, 4-H_b), 2.49 (ddd, 1 H, J = 3.7, 9.2, 17.4 Hz, 3-H_a), 2.64 (dt, 1 H, J = 9.8, 17.5 Hz, 3-H_b), 3.79 (s, 3 H, OMe), 4.62 (dd, 1 H, J = 3.1, 9.3 Hz, 5-H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 21.8, 28.2, 31.5, 52.9, 59.2, 83.9, 149.6, 172.2, 173.6. − $C_{11}H_{17}NO_5$ (243.3): calcd. C 54.31, H 7.04, N 5.76; found C 54.21, H 7.11, N 5.74.

General Procedure for the Preparation of 3-Dimethylaminomethylene-Substituted Tetrahydrofuran-2-ones and Pyrrolidin-2-ones 2a−d: A mixture of compound **1** (10 mmol), toluene (20 mL), and *tert*-butoxybis(dimethylamino)methane (2.61 g, 15 mmol) was heated at 90−100°C for 2 h, volatile components were evaporated in vacuo, and the solid residue crystallised from the appropriate solvent. The precipitate was collected by filtration to give **2**.

5-Methyl (*S*)-3-Dimethylaminomethylene-2-oxotetrahydrofuran-5-carboxylate (2a): Yield: 1.16 g (58%), colorless crystals. − M.p. 113−115°C (ethyl acetate). − $[\alpha]_D^{23} = +2.3$ (c = 1.10, CH_2Cl_2). − ^{1}H NMR (300 MHz, $CHCl_3$): δ = 3.04 (s, 6 H, NMe_2), 3.20 (ddd, 1 H, J = 1.3, 4.7, 14.3 Hz, 4-H_a), 3.43 (ddd, 1 H, J = 1.1, 10.0, 14.1 Hz, 4-H_b), 3.79 (s, 3 H, OMe), 4.86 (dd, 1 H, J = 5.0, 10.0 Hz, 5-H), 7.13 (t, 1 H, J = 1.5 Hz, 3′-H). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 30.2, 42.1, 52.8, 72.6, 84.8, 148.4, 171.8, 174.2. − $C_9H_{13}NO_4$ (199.2) calcd. C 54.26, H 6.58, N 7.03; found C 54.31, H 6.79, N 7.14.

(*S*)-5-Benzoyloxymethyl-3-dimethylaminomethylenetetrahydrofuran-2-one (2b): Yield: 1.18 g (43%), colorless crystals. − M.p. 109−111°C (ethyl acetate/cyclohexane). − $[\alpha]_D^{23} = +252.5$ (c = 1.00, ethanol). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.93 (ddd, 1 H, J = 1.3, 5.5, 14.3 Hz, 4-H_a), 3.03 (s, 6 H, NMe_2), 3.28 (ddd, 1 H, J = 1.4, 9.0, 14.3 Hz, 4-H_b), 4.41 (dd, 1 H, J = 5.8, 11.9 Hz, 5′-H_a), 4.47 (dd, 1 H, J = 4.0, 11.9 Hz, 5′-H_b), 4.77 (ddt, 1 H, J = 3.8, 5.7, 9.4 Hz, 5-H), 7.17 (t, 1 H, J = 1.7 Hz, 3′-H), 7.41−7.47 (m, 2 H, Ph), 7.54−7.60 (m, 1 H, Ph), 8.03−8.07 (m, 2 H, Ph). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 28.5, 41.7, 66.5, 73.3, 86.4, 128.4, 129.7, 129.8, 133.2, 147.6, 166.4, 174.7. − $C_{15}H_{17}NO_4$ (275.3): calcd. C 65.44, H 6.22, N 5.09; found C 65.06, H 6.05, N 5.08.

(*S*)-1-Benzoyl-3-dimethylaminomethylene-5-methoxycarbonylpyrrolidin-2-one (2c): Yield: 2.24 g (74%), colorless crystals. − M.p. 133−134°C (ethyl acetate). − $[\alpha]_D^{23} = -36.0$ (c = 1.25, $CHCl_3$). − ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 2.94 (dd, 1 H, J = 3.1, 14.8 Hz, 4-H_a), 3.02 (s, 6 H, NMe_2), 3.37 (dd, 1 H, J = 10.7, 14.6 Hz, 4-H_b), 3.69 (s, 3 H, OMe); 4.73 (dd, 1 H, J = 3.7, 10.2 Hz, 5-H), 7.02 (s, 1 H, 3′-H), 7.35−7.40 (m, 2 H, Ph), 7.45−7.51 (m, 3 H, Ph). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 27.3, 43.0, 53.3, 56.6, 91.7, 128.3, 129.5, 131.9, 136.1, 148.1, 170.2, 171.7, 172.8. − $C_{16}H_{18}N_2O_4$ (302.3): calcd. C 63.56, H 6.00, N 9.27; found C 63.34, H 6.35, N 9.13.

5-Methyl (*S*)-1-*tert*-Butoxycarbonyl-3-dimethylaminomethylene-2-oxopyrrolidine-5-carboxylate (2d): Yield: 2.60 g (87%), colorless crystals. − M.p. 131−133°C (ethyl acetate). − $[\alpha]_D^{23} = -55.9$ (c = 1.15, CH_2Cl_2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (s, 9 H, *t*Bu), 2.89 (ddd, 1 H, J = 1.5, 2.5, 14.8 Hz, 4-H_a), 3.01 (s, 6 H, NMe_2), 3.25 (ddd, 1 H, J = 1.5, 11.1, 14.8 Hz, 4-H_b), 3.75 (s, 3 H, OMe), 4.55 (dd, 1 H, J = 3.7, 10.6 Hz, 5-H), 7.13 (t, 1 H, J = 1.5 Hz, 3′-H). − ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 26.0, 28.5, 42.5, 53.0, 56.1, 81.7, 91.1, 146.8, 150.5, 169.1, 173.3. − $C_{14}H_{22}N_2O_5$ (298.3): calcd. C 56.36, H 7.43, N 9.39; found C 56.15, H 7.41, N 9.44

General Procedure for the Preparation of 3-Oximino-Substituted Tetrahydrofuran-2-ones and Pyrrolidin-2-ones 3a−d: A stirred suspension of 3-dimethylaminomethylene compound **2** (1 mmol) in water (3 mL) was cooled to 0°C, hydrochloric acid (4%, 2 mL, precooled to 0°C) was then added, followed by dropwise addition of aqueous sodium nitrite (a solution of 90 mg of $NaNO_2$ in 3 mL of water). Stirring at 0°C was continued for 2 h and the precipitate collected by filtration to give **3**.

5-Methyl (*S*)-3-Oximino-2-oxotetrahydrofuran-5-carboxylate (3a): 135 mg (78%), colorless crystals. − M.p. 106−109°C (ethyl acetate/cyclohexane). − $[\alpha]_D^{23} = +4.9$ (c = 0.92, CH_2Cl_2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.16 (dd, 1 H, J = 4.5, 19.6 Hz, 4-H_a), 3.36 (dd, 1 H, J = 9.4, 19.6 Hz, 4-H_b), 3.84 (s, 3 H, OMe), 5.15 (dd, 1 H, J = 4.5, 9.4 Hz, 5-H), 10.39 (br. s, 1 H, OH). − ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 28.6, 53.5, 73.3, 145.8, 165.6, 170.5. − $C_6H_7NO_5$ (173.1) calcd: C 41.63, H 4.08, N 8.09; found C 41.40, H 3.94, N 7.90.

(*S*)-5-Benzoyloxymethyl-3-oximinotetrahydrofuran-2-one (3b): Yield: 202 mg (81%), colorless crystals. − M.p. 166−168°C (ethanol/water). − $[\alpha]_D^{23} = +148.5$ (c = 0.96, CH_2Cl_2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.99 (dd, 1 H, J = 4.5, 19.2 Hz, 4-H_a), 3.22 (dd, 1 H, J = 8.7, 19.2 Hz, 4-H_b), 4.47 (dd, 1 H, J = 4.7, 12.3 Hz, 5′-H_a), 4.59 (dd, 1 H, J = 3.2, 12.2 Hz, 5′-H_b), 5.03−5.09 (ddt, 1 H, J = 3.0, 4.5, 8.7 Hz, 5-H), 7.41−7.46 (m, 2 H, Ph), 7.54−7.60 (m, 1 H, Ph), 7.96−8.00 (m, 2 H, Ph), 11.40 (br. s, 1 H, OH). − ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 27.4, 66.7, 75.3, 129.7, 129.9, 131.0, 134.5, 147.6, 166.2, 166.3. − $C_{12}H_{11}NO_5$ (249.2): calcd. C 57.83, H 4.45, N 5.62; found C 58.11, H 4.55, N 5.38.

5-Methyl (*S*)-1-Benzoyl-3-oximino-2-oxopyrrolidine-5-carboxylate (3c): Yield: 218 mg (79%), colorless crystals. − M.p. 170−173°C (water). − $[\alpha]_D^{25} = +7.35$ (c = 1.02, CH_2Cl_2). − ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 2.89 (dd, 1 H, J = 3.2, 19.0 Hz, 4-H_a), 3.21 (dd, 1 H, J = 9.9, 19.0 Hz, 4-H_b), 3.72 (s, 3 H, OMe), 4.96 (dd, 1 H, J = 3.2, 9.9 Hz, 5-H), 7.45−7.50 (m, 2 H, Ph), 7.58−7.66 (m, 3 H, Ph), 12.79 (s, 1 H, OH). − ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 25.7, 53.6, 55.1, 128.8, 129.7, 133.1, 134.5, 150.1, 162.8, 170.7, 171.9. − $C_{13}H_{12}N_2O_5$ (276.3): calcd. C 56.52, H 4.38, N 10.14; found C 56.44, H 4.37, N 10.16.

5-Methyl (*S*)-1-*tert*-Butoxycarbonyl-3-oximino-2-oxopyrrolidine-5-carboxylate (3d): Yield: 215 mg (79%), colorless crystals. − M.p. 145−147°C (methanol). − $[\alpha]_D^{25} = +6.6$ (c = 0.82, CH_2Cl_2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (s, 9 H, *t*Bu), 2.87 (dd, 1 H, J = 3.2, 19.8 Hz, 4-H_a), 3.16 (dd, 1 H, J = 10.0, 19.8 Hz, 4-H_b), 3.79 (s, 3 H, OMe), 4.74 (dd, 1 H, J = 3.2, 10.0 Hz, 5-H), 10.50 (br. s, 1 H, OH). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 24.9, 28.2, 53.3, 55.2, 85.1, 149.3, 149.6, 161.8, 171.4. − $C_{11}H_{16}N_2O_6$ (272.3): calcd. C 48.52, H 5.92, N 10.29; found C 48.24, H 5.84, N 10.24.

General Procedure for the Preparation of 5-Substituted (3*S*,5*S*)-3-Acetylaminotetrahydrofuran-2-ones 4a,b and (3*S*,5*S*)-3-Acetylaminopyrrolidin-2-ones 4c,d: A mixture of oxime **3** (1 mmol), acetic acid (5 mL), acetic anhydride (2 mL), and palladium on charcoal (10% Pd/C, 80 mg) was hydrogenated (1 bar, **3a**,**c**,**d**: 20°C, **3b**: 60°C) for 10 h. The catalyst was removed by filtration, washed with methanol, and the filtrate concentrated in vacuo. The residue was purified by flash chromatography (FC) using ethyl acetate/*n*-hexane (1:1) as eluant. Fractions containing the product were combined and evaporated in vacuo to give a mixture of **4** and its epimer **5**. Isomerically pure compounds **4a**−**d** were obtained either upon crystallisation (**4a**−**c**), or upon chromatographic separation (FC, **4d**).

5-Methyl (3*S*,5*S*)-3-Acetylamino-2-oxotetrahydrofuran-5-carboxylate (4a): Yield: 117 mg (58%), colorless crystals. − M.p. 122−124°C (ethyl acetate). − $[\alpha]_D^{23} = -5.7$ (c = 0.65, CH_2Cl_2). − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.85 (s, 3 H, MeCO), 2.16 (ddd, 1 H, J = 10.4, 11.1, 12.1 Hz, 4-H$_a$), 2.71 (ddd, 1 H, J = 7.0, 9.2, 12.1 Hz, 4-H$_b$), 3.73 (s, 3 H, COOMe), 4.67 (ddd, 1 H, J = 7.9, 9.0, 10.9 Hz, 3-H), 5.04 (dd, 1 H, J = 7.0, 10.4 Hz, 5-H), 8.42 (d, 1 H, J = 7.9 Hz, NH). − ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 23.1, 31.9, 49.0, 53.2, 73.3, 170.1, 170.2, 174.6. − $C_8H_{11}NO_5$ (201.2): calcd. C 47.76, H 5.51, N 6.96; found C 47.44, H 5.42, N 7.25.

Minor Isomer 5a: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.99 (s, 3 H, MeCO), 3.71 (s, 3 H, COOMe), 4.92 (dd, 1 H, J = 6.8, 10.5 Hz, 5-H).

(3*S*,5*S*)-3-Acetylamino-5-benzoyloxymethyltetrahydrofuran-2-one (4b): Yield: 155 mg (56%), colorless crystals. − M.p. 153−156°C (toluene). − $[\alpha]_D^{23} = +104.0$ (c = 1.16, CH_2Cl_2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.98 (dt, 1 H, J = 11.5, 12.4 Hz, 4-H$_a$), 2.05 (s, 3 H, MeCO), 2.96 (ddd, 1 H, J = 5.7, 8.7, 12.4 Hz, 4-H$_b$), 4.47 (dd, 1 H, J = 6.0, 12.4 Hz, 5′-H$_a$), 4.61 (dd, 1 H, J = 3.0, 12.4 Hz, 5′-H$_b$), 4.69 (ddd, 1 H, J = 6.0, 8.7, 11.7 Hz, 3-H), 4.82 (ddt, 1 H, J = 3.0, 5.8, 11.7 Hz, 5-H), 6.10 (d, 1 H, J = 5.6 Hz, NH), 7.43−7.48 (m, 2 H, Ph), 7.56−7.62 (m, 1 H, Ph), 8.03−8.06 (m, 2 H, Ph). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.8, 32.4, 50.1, 64.8, 75.4, 128.5, 129.2, 129.8, 133.5, 166.0, 170.5, 174.3. − $C_{14}H_{15}NO_5$ (277.3): calcd. C 60.64, H 5.45, N 5.05; found C 60.29, H 5.42, N 5.10.

Minor Isomer 5b: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.61−1.73 (m, 1 H, 4-H$_a$), 1.93 (s, 3 H, MeCO), 4.91−4.98 (m, 1 H, 5-H).

5-Methyl (3*S*,5*S*)-3-Acetylamino-1-benzoyl-2-oxopyrrolidine-5-carboxylate (4c): Yield: 137 mg (45%), colorless crystals. − M.p. 188−191°C (ethyl acetate). − $[\alpha]_D^{23} = -87.1$ (c = 0.76, CH_2Cl_2). − ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.86 (s, 3 H, MeCO), 1.99 (dd, 1 H, J = 10.7, 12.4 Hz, 4-H$_a$), 2.65 (ddd, 1 H, J = 7.3, 8.9, 11.9 Hz, 4-H$_b$), 3.68 (s, 3 H, OMe), 4.50 (dt, 1 H, J = 8.5, 10.9 Hz, 3-H), 4.78 (dd, 1 H, J = 7.2, 10.5 Hz, 5-H), 7.44−7.49 (m, 2 H, Ph), 7.56−7.62 (m, 1 H, Ph), 7.66−7.69 (m, 2 H, Ph), 8.46 (d, 1 H, J = 7.9 Hz, NH). − ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ = 22.2, 27.8, 50.7, 52.3, 54.9, 127.7, 129.2, 132.3, 133.6, 169.4, 170.1, 170.4, 171.4. − $C_{15}H_{16}N_2O_5$ (304.3): calcd. C 59.21, H 5.30, N 9.21; found C 59.07, H 5.37, N 9.17.

Minor Isomer 5c: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.88 (s, 3 H, MeCO), 3.75 (s, 3 H, OMe), 4.30−4.39 (m, 1 H, 3-H), 4.88 (dd, 1 H, J = 2.8, 8.1 Hz, 5-H), 8.52 (d, 1 H, J = 7.5 Hz, NH).

5-Methyl (3*S*,5*S*)-3-Acetylamino-1-*tert*-butoxycarbonyl-2-oxopyrrolidine-5-carboxylate Monohydrate (4d): Yield: 140 mg (44%), colorless solid. − M.p. 48−56°C (FC, ether/petroleum ether, 2:1). − $[\alpha]_D^{23} = -5.8$ (c = 1.00, CH_2Cl_2). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, *t*Bu), 1.82 (ddd, 1 H, J = 9.4, 10.1, 12.5 Hz, 4-H$_a$), 2.04 (s, 3 H, MeCO), 2.92 (ddd, 1 H, J = 7.5, 8.7, 12.8 Hz, 4-H$_b$), 3.79 (s, 3 H, OMe), 4.49 (dd, 1 H, J = 7.5, 9.0 Hz 5-H), 4.63 (ddd, 1 H, J = 6.4, 9.0, 10.2 Hz, 3-H), 6.79 (d, 1 H, J = 6.4 Hz, NH). − ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 22.8, 27.8, 29.8, 51.3, 52.7, 56.1, 84.5, 148.9, 170.9, 171.3, 171.5. − $C_{13}H_{22}N_2O_7$ (318.3): calcd. C 49.05, H 6.97, N 8.80; found C 49.16, H 6.88, N 8.43. − HRMS (FAB, MH^+); $C_{13}H_{21}N_2O_6$: calcd. 301.1400; found 301.1410.

Minor Isomer 5d: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.51 (s, 9 H, *t*Bu), 2.03 (s, 3 H, MeCO), 3.05−3.14 (m, 1 H, 4-H$_b$), 3.80 (s, 3 H, OMe), 4.26 (dd, 1 H, J = 7.2, 9.0 Hz, 5-H), 6.52 (d, 1 H, J = 7.5 Hz, NH).

Acknowledgments

The authors wish to express their gratitude to the Ministry of Science and Technology, Slovenia, for financial support.

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Received December 11, 1998
[O98553]