SYNTHESIS OF 2-OXA AND 2-AZA ANALOGS OF PYRROLIZIDINE-3,5-DIONES (LUKES-SORM DILACTAM)

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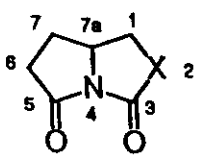
Abstract — The synthesis of 2-oxa and 2-aza analogs of pyrrolizidine-3,5-dione (Lukes-Sorm dilactam), which has amnesia reversal activity, is reported. Optically active (+)-2-oxa and (+)-2-aza analogs [(+)-2 and (+)-3] and racemic 2-aza analog and its 1-methoxycarbonyl derivatives [(±)-3 and (±)-13 and -14] were prepared from (-)-S-pyroglutamic acid and succinimide, respectively.

Pyrrolizidine-3,5-dione (Lukes-Sorm dilactam, 1) was first prepared from γ-oxopimelic acid by Lukes and Sorm[1] in 1947 and subsequently attracted the attention of many synthetic chemists.[2] This compound (1) serves as a key starting material for 5-substituted 2-pyrrolidinone and 3(and 5)-(di)substituted pyrrolizidine derivatives.[3] Recently, this compound was found to have amnesia reversal activity and has been named rolziracetam, which is said to presently be under a phase two clinical study in the interest of elderly patients with dementia.[4]



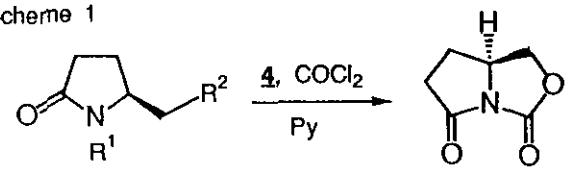
1 X = CH_2
2 X = O
3 X = NH

In the present study, attention was directed to the synthesis of 2-oxa and

2-aza analogs (2 and 3) of pyrrolizidine-3,5-dione (1) in consideration of potential biological applications. In the following is presented the synthesis of analogs [(+)-2, (+)-3, (±)-3, (±)-13 and (±)-14] of 1.

The reactions of S-5-hydroxymethyl-2-pyrrolidinone[5] (4) with phosgen or the phosgen dimer (trichloromethyl chloroformate)[6] in the presence of pyridine afforded (+)-S-dihydropyrrolo[1, 2-c]oxazole-3, 5(1H, 6H)-dione [(+)-2-oxarolziracetam, (+)-2] in moderate yields (35-50%) along with an array of many by-products. Reaction of N, O-bis-trimethylsilyl derivative (5) with phosgen in the presence of triethylamine also gave the same product [(+)-2] but in lesser yield (30%). Its separation, however, could be conducted more easily. The cyclization of O- or N-ethoxycarbonyl derivatives[7] (6 and 7, respectively) of 5-hydroxymethyl-2-pyrrolidinone (4) to the lactam [(+)-2] under various conditions was attempted with painstaking efforts but without success. (Scheme 1).

Scheme 1



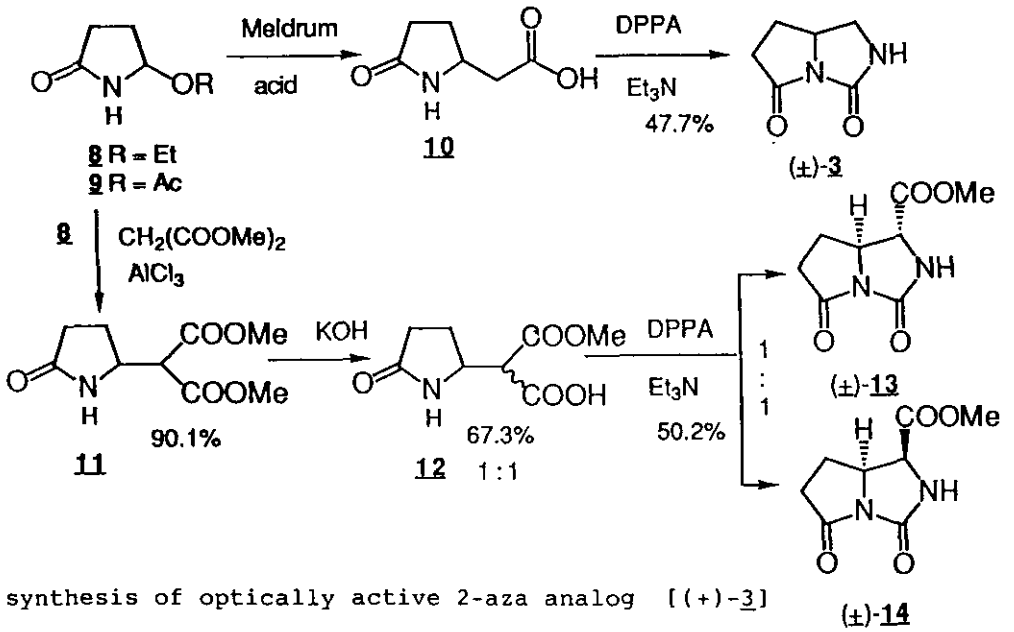
(+)-2

4 R^1 = H, R^2 = OH
5 R^1 = $SiMe_3$, R^2 = $OSiMe_3$
6 R1 = H, R^2 = OCOOEt
7 R^1 = COOEt, R^2 = OH
15 R^1 = H, R^2 = Br
16 R^1 = H, R^2 = CN

The racemic 2-aza analog [(±)-3] of 1 and its 1-methoxycarbonyl derivatives [(±)-13 and (±)-14] were prepared by the method in Scheme 2. The Curtius rearrangement using diphenyl phosphorazidate (DPPA)[8] of 2-oxopyrrolidinyl-5-acetic acid[9] (10), easily obtainable from succinimide via 5-acetoxy-2-pyrrolidinone (9), gave the desired lactam [(±)-3] in 48% yield. Hydrolysis in alkaline solution (1% KOH, MeOH-H_2O 4:1) of the diester (11) prepared from 5-ethoxy-2-pyrrolidinone (8) by the method of Klaus[10], gave the half-ester (12) in 67% yield as a 1:1 mixture of diastereomers. On this mixture, the Curtius reaction was carried out to afford a 1:1 mixture of 2-aza-1-methoxycarbonyl analogs (13 and 14) of 1 and the chromatographic separation of which gave 13 (1,7a-trans, less polar) and 14 (1,7a-cis, more polor), as

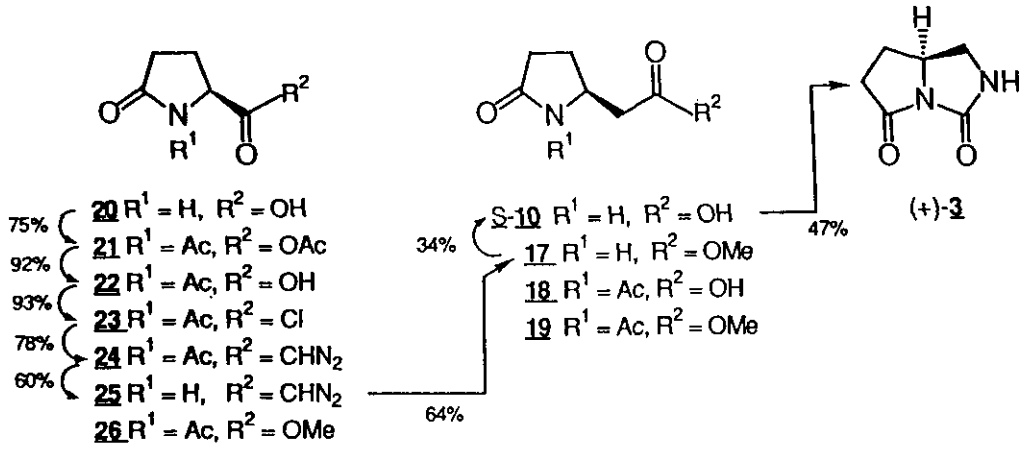
stereochemistry deduced from the results of an NOE experiment[11] on 13.

Scheme 2



The synthesis of optically active 2-aza analog [(+)-3] of 1 is presented in Scheme 3. According to Scheme 2, optically active 2-oxo-5-pyrrolidinylacetic acid (S-10)[12] is necessary for the synthesis of (+)-3. Hydrolysis of the optically active nitrile (16), prepared from the optically active alcohol (4) via the bromide (15) by the

Scheme 3



method of Silvermann,[5] was initially attempted to obtain the ester (17) or acid (10), but without success. The Arndt-Eistert reaction was subsequently carried out, which proceeds with retention[13] of stereochemistry, to bring about the homologation of S-pyroglutamic acid (20). The derivation of this acid to the diazoketone (25) has been reported by Wilk et al.,[14] but without specification as to its melting point and yield. The same or modified reactions were conducted several times and pyroglutamic acid (20) was concluded based on the results to be not suitable for obtaining its derivatives in view of its insolubility in various organic solvents. Consequently S-1-acetylpyroglutamic acid (22) was prepared via diacetate (21), as a material more suited to the purpose. The diazoketone (24) was prepared by reaction of the chloride (23) with diazomethane. Hydrolysis of 24 with ammonia gave 25, which was converted to the methyl acetate (17) by the action of silver oxide in hot methanol. Hydrolysis of the ester (17) gave an optically active acid (10), which showed mp 99-101°C and $[\alpha]_D^{26}$+19.35° (c=1.04, EtOH) (lit.,[12] mp 103-105°C and $[\alpha]_D^{26}$+17.6°). The Arndt-Eistert reaction of 24 afforded 19 which could not be subsequently converted to the 1-acetyl acid (18) or the acid (10). Reaction of the optically active acid (S-10) with DPPA gave the optically active (+)-3 in 47% yield.

The compounds discussed above were found capable reversing electroconvulsive shock (ECS)-induced amnesia in mice. The biological features of these compounds will be reported in near future.

EXPERIMENTAL

All melting points were determined by micro-melting point apparatus (Yanagimoto) without correction. Ir and mass spectra were measured on a Hitachi 200-10 spectrophotometer and a Hitachi M-80 spectrometer, respectively. ^{1}H-Nmr spectra were recorded on Varian EM-390 and/or Brucker M-400 instrument. Chemical shifts were recorded in ppm downfield from an internal standard

(tetramethylsilane). Thin layer chromatography (tlc) was carried out with precoated silica gel plates (Kiesel 60 F-254, Merck).

S-1-Trimethylsilyl-5-trimethylsilyloxymethyl-2-pyrrolidinone (5) -- A mixture of S-5-hydroxymethyl-2-pyrrolidinone[5] (4, 575 mg, 5 mmol), hexamethyldisilazane (HMDS, 5 ml) and a catalytic amount of Me_3SiCl was refluxed overnight. Excess HMDS was removed under reduced pressure and distillation of the residue gave 1263 mg (97.5%) of pure 5 as a colorless oil, bp 123-124°C (6 mmHg). Ir (KBr) 1685, 1250 cm^{-1}. ^{1}H-Nmr (90MHz, $CDCl_3$) δ 0.10 (9H, s, $SiMe_3$), 0.27 (9H, s, $SiMe_3$), 1.57-2.57 (4H, m, 3,4-H), 3.33-3.53 (2H, m, CH_2OTMS), 3.36-3.80 (1H, m, 5-H).

(+)-Dihydropyrrolo[1,2-c]oxazole-3,5(1H, 6H)dione [(+)-S-2-oxarolziracetam, (+)-2] -- Method A: A solution of phosgen (3.88 g, 39 mmol) in benzene (34 ml) was added dropwise at 0°C to a solution of pyridine (4.1 g, 52 mmol) and 4 (3.0 g, 26 mmol) in CH_2Cl_2 (60 ml) followed by stirring at room temperature for 1 day. The reaction mixture was evaporated under reduced pressure to give a brown oil, which was then extracted with $CHCl_3$. The $CHCl_3$ extract was concentrated under reduced pressure to a brown semi-solid (8.92 g) which, by chromatographic separation on silica gel with elution of $CHCl_3$, gave 1.83 g (49.8%) of (+)-2 as colorless prisms, mp 140-142°C. $[\alpha]_D$ +128.89° (c=0.47, $CHCl_3$). Ir (KBr) 1800, 1730, 1710 cm^{-1}. ^{1}H-Nmr (400 MHz, $CDCl_3$) δ 1.97-2.10 (1H, m, 7β-H), 2.39-2.49 (1H, m, 7α-H), 2.73 (1H, ddd, J=1, 9, 18 Hz, 6-H), 2.80-2.90 (1H, m, 6-H), 4.18 (1H, dd, J=8.5 Hz, 1-H), 4.63 (1H, dd, J=8.5 Hz, 1-H), 4.65-4.86 (1H, m, 7α-H). Ms m/z 141 (M^+). Anal. Calcd for $C_6H_7NO_3$: C, 51.03; H, 5.00; N, 9.93. Found: C, 51.22; H, 5.02; N, 9.90.

Method B: A solution of phosgen (380 mg, 3.8 mmol) in benzene (4 ml) was added dropwise at near 0°C to a solution of 5 (572 mg, 2.2 mmol) in benzene (20 ml) followed by stirring in an ice bath for 30 min and then at room temperature for 1 h. Triethylamine (558 mg, 5.5 mmol) was added dropwise to this reaction mixture. By the same work-up as in method A, pure prisms

(93 mg, 30.0%) of (+)-2 was obtained.

(±)-Dihydropyrrolo[1,2-c]imidazole-3,5(1H,6H)-dione [(±)-2-Azarolziracetam, (±)-3] -- A mixture of the acid (10, 428 mg, 3.0 mmol), diphenyl phosphorazidate (DPPA, 826 mg, 3.0 mmol) and triethylamine (304 mg, 3.0 mmol) in toluene (50 ml) was refluxed under an argon atmosphere for 20 h. A brown precipitate (221 mg) was collected by filtration and recrystallized from ethanol to give pale yellow needles (200 mg, 47.7%) of (±)-3, mp 186-190°C. Ir (KBr) 3280, 2870, 1770, 1750, 1685 cm^{-1}. ^{1}H-Nmr (400 MHz, $CDCl_3$) δ 1.97 (1H, dddd, J=9, 10, 13, 13Hz, 7-H), 2.37-2.43 (1H, m, 7-H), 2.62 (1H, dd, J=8, 17 Hz, 6-H), 2.75 (1H, ddd, J=8, 13, 17 Hz, 6-H), 3.33 (1H, dd, J=9.9 Hz, 1-H), 3.67 (1H, dd, J=9.9 Hz, 1-H), 4.57 (1H, ddd, J=6, 9, 18 Hz, 7a-H). Ms m/z 140 (M^+). Anal. Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.35; H, 5.76; N, 20.02.

(2-Oxo-5-pyrrolidinyl)malonic Acid Monomethyl Ester (12) -- A solution of the diester[10] (11, 108 mg, 0.5 mmol) in 1% KOH/MeOH-H_2O (4:1, 8.4 ml) was stirred at room temperature for 1 h followed by being concentrated in a water bath at 30°C under reduced pressure and acidification with 10% HCl to pH 4. The reaction mixture was evaporated under reduced pressure to give a solid which was extracted with hot benzene several times. Colorless prisms (68 mg, 67.3%) of monoester (12), obtained by evaporation of the benzene extract, were found to be a mixture of diastereomers (1:1) by spectral analysis, which were not separable. Physical data of this mixture are as follows: mp 142-143°C. Ir (KBr) 3220, 1750, 1720, 1705, 1635 cm^{-1}. ^{1}H-Nmr (400 MHz, $CDCl_3$) δ 1.90-2.09(1H, m, 4-H), 2.35-2.48 (3H, m, 3-H, 4-H), 3.44 (0.5H, d, J=9 Hz, C<u>H</u>(COOH)COOMe), 3.53 (0.5H, d, J=7 Hz, C<u>H</u>(COOH)COOMe), 3.79 (1.5H, s, $COOCH_3$), 3.80 (1.5H, s, $COOCH_3$), 4.24-4.32 (1H, m, 5-H). Ms m/z 157 (M^+-COOH). Anal. Calcd for $C_8H_{11}NO_5$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.85; H, 5.61; N, 6.83.

(±)-1,7a-trans- and (±)-1,7a-cis-1-Methoxycarbonyldihydropyrrolo[2,1-c]imidazole-3,5(1H,6H)-diones [(±)-trans- and (±)-cis-2-Aza-1-methoxycarbonyl-

rolziracetams, 13 and 14] -- A solution of DPPA (333 mg, 1.21 mmol) and triethylamine (122 mg, 1.21 mmol) in THF (5 ml) was added dropwise at room temperature to a solution of 12 (222 mg, 1.1 mmol) of THF (5 ml) under an argon atmosphere. The reaction mixture was refluxed for 5 h and evaporated under reduced pressure to give a solid (435 mg) which, by chromatographic separation on silica gel by elution with $CHCl_3$-MeOH (30:1), gave 55 mg of 13 as less polar, colorless needles and 55 mg of 14 as more polor, colorless needles. 13: mp 170-172°C. Ir (KBr) 3300, 1765, 1740, 1690 cm^{-1}. ^{1}H-Nmr (400 MHz, $CDCl_3$) δ 2.04-2.18 (1H, m, 7-H), 2.40-2.51 (1H, m, 7-H), 2.64 (1H, dd, J=9, 17 Hz, 6-H), 2.70-2.80 (1H, m, 6-H), 3.84 (3H, s, $COOCH_3$), 4.24 (1H, d, J=8 Hz, 1-H), 4.29-4.56 (1H, m, 7a-H), 5.58 (1H, br, NH). Ms (CI) m/z 199 (M^++1). Anal. Calcd for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.02; H, 5.01; N, 13.86. 14: mp 195-197°C. Ir (KBr) 3290, 1785, 1760, 1730, 1695 cm^{-1}. ^{1}H-Nmr (400 MHz, $CDCl_3$) δ 1.70-1.88 (1H, m, 7-H), 2.29-2.41 (1H, m, 7-H), 2.52-2.68 (1H, dd, J=9, 17 Hz, 6-H), 2.70-2.82 (1H, m, 6-H), 3.82 (3H, s, $COOCH_3$), 4.36 (1H, d, J=9Hz, 1-H), 4.78 (1H, ddd, J=6, 9, 10Hz, 7a-H), 5.76 (1H, br, NH). Ms (CI) m/z 199 (M^++1).

S-1-Acetylpyroglutamyldiazomethane [S-1-Acetyl-5-diazoacetyl-2-pyrrolidinone, (24)] -- A mixture of S-pyroglutamic acid (20, 500 mg, 3.9 mmol) and acetic anhydride (20 ml) was refluxed for 6 h and concentrated under reduced pressure to give an oil which, by dilution with benzene, yielded a small amount of precipitate. The precipitate (64 mg, 14.8%) was the diketopiperazine of 20 [mp>290°C, pale yellow prisms. Ir (KBr) 3380, 1760. 1690 cm^{-1}. ^{1}H-Nmr (90 MHz, D_2O) δ 2.17-2.83 (2H, m, CONCH), 4.80-5.10 (8H, m, $COCH_2CH_2$ x 2). Ms m/z 222 (M^+)]. The precipitate was removed by filtration and the filtrate was purified by distillation to give a yellow oil (619 mg, 75%) of acetic S-1-acetylpyroglutamic anhydride (21), bp 250 °C (2 mmHg). Ir ($CHCl_3$) 1820, 1750, 1690 cm^{-1}. ^{1}H-Nmr (90 MHz, $CDCl_3$) δ 2.10-2.37 (1H, m, 4-H), 2.43-2.90 (3H, m, 3-H, 4-H), 2.27 (3H, s, $COCH_3$), 2.50 (3H, s, $COCH_3$), 4.63-4.88 (1H, m, 5-H). Ms m/z 171 (M^+-$COCH_2$). A mixture of the

above oil (21, 619 mg, 2.91 mmol) and H_2O (5 ml) was stirred at room temperature for 2 h and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated under reduced pressure to give a brown oil which, on distillation, gave 457 mg (92%) of S-1-acetylpyroglutamic acid (22) as an oil, bp 183-195°C (0.3 mmHg). Ir (neat) 3024, 1752, 1703 cm^{-1}. ^{1}H-Nmr (400 MHz, $CDCl_3$) δ 2.14-2.23 (1H, m, 4-H), 2.32-2.44 (1H, m, 4-H), 2.54 (3H, s, $COCH_3$), 2.60 (1H, ddd, J=3, 9, 18 Hz, 3-H), 2.71-2.81 (1H, m, 3-H), 4.78 (1H, dd, J=3, 10 Hz, 5-H), 5.15 (1H, br, COOH). Ms m/z 171 (M^+). The above acid (22, 457 mg, 2.67 mmol) was converted to the corresponding acid chloride (23, 470 mg, 92.9%) by stirring in thionyl chloride (2 ml) at room temperature for 20 min and then at the refluxing temperature for 5 min followed by evaporation of excess thionyl chloride under reduced pressure. A solution of the above chloride (23) in CH_2Cl_2 (7 ml) was added to a solution of excess CH_2N_2 in ether (when a solid appeared, CH_2Cl_2 was added to dissolve it) and the reaction mixture was stirred overnight. After adding a small amount of AcOH to consume excess CH_2N_2, the solvent was removed to give a brown oil (458 mg) which, by chromatography on silica gel with elution of $CHCl_3$-MeOH (50:1) and recrystallization from ethanol, gave 376 mg (77.6%) of 24 as yellow prisms, mp 99-101°C. Ir (KBr) 2150, 2110, 1730, 1615 cm^{-1}. ^{1}H-Nmr (400 MHz, $CDCl_3$) δ 2.07 (1H, dddd, J=3, 3, 10, 13 Hz, 4-H), 2.23 (1H, ddd, J=9, 10, 13 Hz, 4-H), 2.53 (3H, s, $COCH_3$), 2.57 (1H, ddd, J=3, 9, 18 Hz, 3-H), 2.80 (1H, ddd, J=10, 10, 18 Hz, 3-H), 4.69 (1H, br, 5-H), 5.43 (1H, br, $COCHN_2$). Ms m/z 196 (M^++1). Anal. Calcd for $C_8H_9N_3O_3$: C, 49.23; H, 4.65; N, 21.53. Found: C, 49.28; H, 4.73; N, 21.57.

Methyl S-1-Acetylpyroglutamate (26) -- The reaction of 21 (2476 mg, 11.6 mmol) instead of acid chloride (23) with excess CH_2N_2 gave 998 mg (44%) of 24 as yellow prisms and 1180 mg (55.0%) of 26 as a colorless oil, bp 105-120°C (5 mmHg). Ir (neat) 1740, 1695 cm^{-1}. ^{1}H-Nmr (90 MHz, $CDCl_3$) δ 1.90-2.83 (4H, m, 4-H, 3-H), 2.55 (3H, s, $COCH_3$), 3.79 (3H, s, $COOCH_3$), 4.70-4.87 (1H, m, 5-H). Ms m/z 185 (M^+). Anal. Calcd for $C_8H_{11}NO_4$: C, 51.88;

H, 5.99; N, 7.56. Found: C, 50.03; H, 5.99; N, 7.39.

S-Pyroglutamyldiazomethane (S-5-Diazoacetyl-2-pyrolidinone) (25) -- A mixture of 24 (200 mg, 1.0 mmol) and 10% NH_4OH solution (9 ml) was stirred at room temperature for 30 min and extracted with $CHCl_3$. The extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a yellow oil which, on chromatography on silica gel with elution of $CHCl_3$-MeOH (30:1), gave 93 mg (59.5%) of pure 25 as yellow prisms, mp 115-117°C. Ir (KBr) 3130, 3070, 2110, 1710, 1700, 1650, 1625 cm^{-1}. ^{1}H-Nmr (400 MHz, $CDCl_3$) δ 2.11-2.21 (1H, m, 4-H), 2.29-2.54 (3H, m, 3-H, 4-H), 4.18 (1H, br, 5-H), 5.56 (1H, s, $COC\underline{H}N_2$), 6.73 (1H, br, NH). Ms (CI) m/z 154 (M^++1). Anal. Calcd for $C_6H_7N_3O_2$: C, 47.05; H, 4.61; N, 27.44. Found: C, 46.92; H, 4.60; N, 27.27.

Methyl S-2-Oxo-5-pyrrolidinylacetate (17) -- Silver oxide (70 mg, 0.3 mmol) was added to a solution of 25 (91 mg, 0.6 mmol) in methanol (5 ml) and the reaction mixture was refluxed for 2 h. Following removal of silver oxide by filtration, the filtrate was concentrated to the brown oil (91 mg) which, on chromatographic separation on silica gel by elution with $CHCl_3$, gave 60 mg (64.3%) of 17 as colorless oil. Ir (neat) 3250, 1735, 1690 cm^{-1}. ^{1}H-Nmr (400 MHz, $CDCl_3$) δ 1.65-1.78 (1H, m, 4-H), 2.25-2.35 (3H, m, 3-H, 4-H), 2.47 (1H, dd, J=9, 16 Hz, $C\underline{H}_2COOMe$), 2.54 (1H, dd, J=5, 16 Hz, $C\underline{H}_2COOMe$), 3.67 (3H, s, $CH_2COOC\underline{H}_3$), 3.93-4.02 (1H, m, 5-H), 6.52 (1H, br, NH). Ms (CI) m/z 158 (M^++1).

S-2-Oxo-5-pyrrolidinylacetic Acid (S-10) -- A mixture of 17 (521 mg, 3.32 mmol) and 1% KOH/MeOH-H_2O (4:1) solution (2 ml) was stirred at room temperature for 30 min followed by acidification with 10% HCl solution to pH 4. The solvent was removed under reduced pressure to give a brown residue (486 mg) which was extracted by hot benzene several times. The benzene extract was filtered to remove impurities and evaporated under reduced pressure to give a solid. Recrystallization of this solid from benzene gave 163 mg (34.4%) of pure S-10 as colorless prisms, mp 99-101°C, $[\alpha]_D^{26}$+19.35° (c=

1.04, EtOH) (lit.,[12] $[\alpha]_D^{26}$+17.6°). Ir (KBr) 3375, 3270, 1710, 1660 cm^{-1}. ^{1}H-Nmr (400 MHz, $CDCl_3$) δ 1.70-1.79 (1H, m, 4β-H), 2.31-2.39 (1H, m, 4α-H), 2.40-2.45 (2H, m, 3-H), 2.46 (1H, dd, J=11, 17 Hz, CH_2COOH), 2.67 (1H, dd, J=3, 17 Hz, CH_2COOH), 4.06-4.11 (1H, m, 5-H), 7.91 (1H, br, NH). Ms m/z 144 (M^++1).

(+)-S-Dihydropyrrolo[1,2-c]imidazole-3,5(1H,6H)-dione [(+)-3] -- In the same manner for preparing (±)-3 from (±)-10, 48 mg (46.7%) of optically active (+)-3 were obtained from 105 mg (0.73 mmol) of S-10. mp 193-195°C. $[\alpha]_D^{26}$ +71.56° (c=1.04, H_2O). Ir (KBr) 3280, 2870, 1770, 1750, 1685 cm^{-1}. ^{1}H-Nmr (400 MHz, $CDCl_3$) δ 1.97 (1H, dddd, J=9, 10, 13, 13 Hz, 7 -H), 2.37-2.43 (1H, m, 7α-H), 2.62 (1H, dd, J=6, 17 Hz, 6-H), 2.75 (1H, ddd, J=8, 13, 17 Hz, 6-H), 3.33 (1H, dd, J=9, 9 Hz, 1-H), 3.67 (1H, dd, J=9, 9 Hz, 1-H), 4.57 (1H, ddd, J=6, 9, 18 Hz, 7a-H), 5.97 (1H, br, NH). Ms m/z 140 (M^+). Anal. Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.44; H, 5.78; N, 19.95.

Methyl S-1-Acetyl-2-oxo-5-pyrrolidinylacetate (19) -- Following the same method as for preparing 17 from 25, 179 mg (60.9%) of 19 were obtained from 24 (288 mg, 1.48 mmol) as a colorless oil, bp 133-134°C (0.35 mmHg). Ir (neat) 1730, 1700, 1600 cm^{-1}. ^{1}H-Nmr (400 MHz, $CDCl_3$) δ 1.88-1.96 (1H, m, 4β-H), 2.20-2.31 (1H, m, 4α-H), 2.50 (3H, s, $COCH_3$), 2.53-2.60 (2H, m, 3-H), 2.65-2.76 (1H, m, CH_2COOMe), 2.81 (1H, dd, J=7, 16 Hz, CH_2COOMe), 3.70 (3H, s, CH_2COOCH_3), 4.66-4.72 (1H, m, 5-H). Ms m/z 199 (M^+). Anal. Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03. Found: C, 53.92; H, 6.75; N, 6.87.

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6. Hodogaya Chem. Co. Ltd. is gratefully acknowledged for supplying the phosgen dimer.

7. S-5-Ethoxycarbonyloxymethyl-2-pyrrolidinone (6): bp 120°C (4 mmHg). Ir ($CHCl_3$) 3350, 3250, 1745, 1690 cm^{-1}. ^{1}H-Nmr (90 MHz, $CDCl_3$) δ 1.30 (3H, t, J=7 Hz, OCH_2CH_3), 1.58-2.01 (1H, m, 4-H), 2.01-2.55 (3H, m, 3-H, 4-H), 3.88-4.55 (3H, m, $CH_2OCOOEt$, 5-H), 4.22 (2H, q, J= 7Hz, OCH_2Me), 6.27 (1H, br, NH). Ms (CI) m/z 188 (M^++1).

S-1-Ethoxycarbonyl-5-hydroxymethyl-2-pyrrolidinone (7): This compound was obtained in 78.4% yield by the hydrolysis of S-1-ethoxycarbonyl-5-trityloxymethyl-2-pyrrolidinone in 80% AcOH, which was obtained in 75% yield by reaction of S-5-trityloxy-2-pyrrolidinone[15] with ethyl chloroformate using n-BuLi as a base. mp 72-74°C. Ir (KBr) 3430, 1775, 1735, 1705 cm^{-1}. ^{1}H-Nmr (400 MHz, $CDCl_3$) δ 1.37 (3H, t, J=7 Hz, $COOCH_2CH_3$), 1.96-2.03 (1H, m, 4-H), 2.11-2.24 (1H, m, 4-H), 2.46 (1H, ddd, J=3, 10, 18 Hz, 3-H), 2.71 (1H, ddd, J=10, 10, 18 Hz, 3-H), 3.74-3.79 (1H, m, CH_2OH), 3.88-3.93 (1H, m, CH_2OH), 4.27-4.31 (1H, m, 5-H), 4.34 (2H, q, J=7 Hz, $COOCH_2Me$). Ms m/z 188 (M^++1). High ms calcd for $C_8H_{13}NO_4$: 187.0843. Found: 187.0826.

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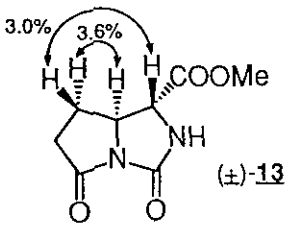

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