Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 11, pp. 3327-3332, 1996

0957-4166/96 $15.00 + 0.00

PII: S0957-4166(96)00434-X

2,5-Dihydropyrrole Derivatives as Enantiomerically Enriched Building Blocks: Synthesis of the Geissman-Waiss Lactone and Polyhydroxylated Pyrrolidines.

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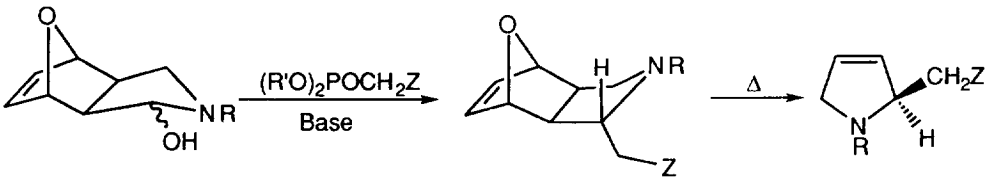
Abstract : Starting from enantiomerically pure 2,5-dihydropyrroles substituted at 2-position, efficient stereoselective syntheses of the (+)-Geissman-Waiss lactone and of (+)-1,4,5-trideoxy-1,4-imino-D-ribo-hexitol hydrochloride have been achieved. This work illustrates the high potential of 2,5-dihydropyrroles for the obtention of polyhydroxylated nitrogen heterocycles. Copyright © 1996 Elsevier Science Ltd

A number of polyhydroxylated monocyclic or bicyclic alkaloids have been attractive synthetic targets since they possess interesting biological activities as inhibitors of glycosidases.[1,2] We have recently shown that enantiomerically enriched 2,5-dihydropyrroles **3** substituted in 2-position by a functionalized chain could be easily obtained from the hydroxy amides or carbamates **1** by a Wittig Horner reaction followed by a highly stereoselective intramolecular Michael addition and a retro-Diels-Alder reaction.[3]

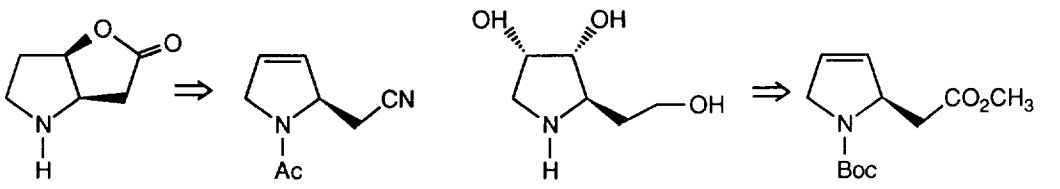


1 R = $COCH_3$
R = COOtBu
R = $COOCH_2Ph$

2 Z = $CN, CO_2CH_3, COCH_3$
$CON(OCH_3)CH_3$

3

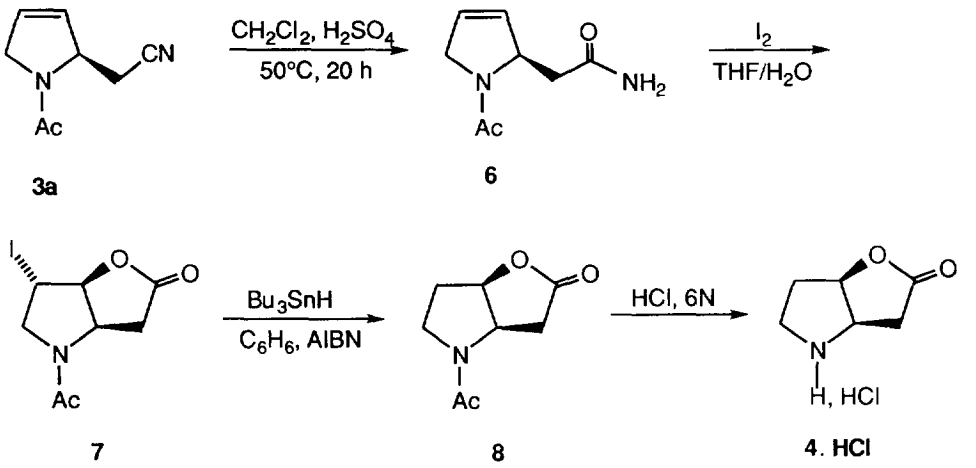
These synthons are useful intermediates for the synthesis of hydroxylated five-membered nitrogen rings and their synthetic potential is illustrated in this paper by efficient syntheses of the (+)-Geissman-Waiss lactone **4** and (+)-1,4,5-trideoxy-1,4-imino-D-*ribo*-hexitol **5**.



4 **3a** **5** **3b**

Synthesis of the Geissman-Waiss lactone 4

(+)-(1*R*,5*R*)-2-oxa-6-azabicyclo[3.3.0]octan-3-one **4** is a potentially versatile synthon for the synthesis of naturally occuring pyrrolizidine alkaloids of the necine family. This lactone was first prepared in racemic form during the original total synthesis of (±)-retronecine [4] and, since then, has been converted efficiently into a number of necines including (+)-retronecine, (+)-platynecine and (+)-croalbinecine. It is now reffered to as the Geissman-Waiss lactone and has been the subject of several synthetic studies aimed at preparing either the racemic [5] or the enantiomerically enriched [6] material. Our synthesis of the lactone **4** starts from the enantiomerically pure functionalized pyrroline **3a** [6] and is depicted in Scheme 1.



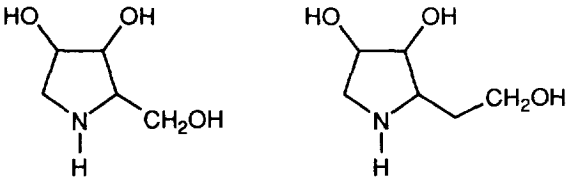
Scheme 1

The nitrile **3a** dissolved in dichloromethane is hydrolyzed by reaction with sulfuric acid at 5°C to give the corresponding amide **6** in 94% yield. Without purification, the amide **6** is treated with 3 equivalents of iodine in tetrahydrofuran-water (1:1) at 0°C for 2 hours to give in 86% yield the iodolactone **7** arising from hydrolysis of an iminium ion intermediate.[7] Deiodination of **7** by reduction with tributyltin hydride in refluxing benzene in the presence of a catalytic amount of AIBN (2,2'-aza-bisisobutyronitrile) afforded almost quantitatively the lactone **8**, $[\alpha]_D^{20}$ = -201 (c = 0.4, $CHCl_3$) ; litt.[6c] : $[\alpha]_D$ = -192 (c = 0.4, $CHCl_3$). Deacetylation of compound **8** in aqueous hydrochloric acid gave in 77% yield the Geissman-Waiss lactone as its crystalline hydrochloride (**4.HCl**) with physical properties (mp 187-188°C ; $[\alpha]_D^{20}$ = +44 (c = 0.4, MeOH) and spectra in good agreement with those reported.[6]

Synthesis of 1,4,5-trideoxy-1,4-imino-D-*ribo*-hexitol 5

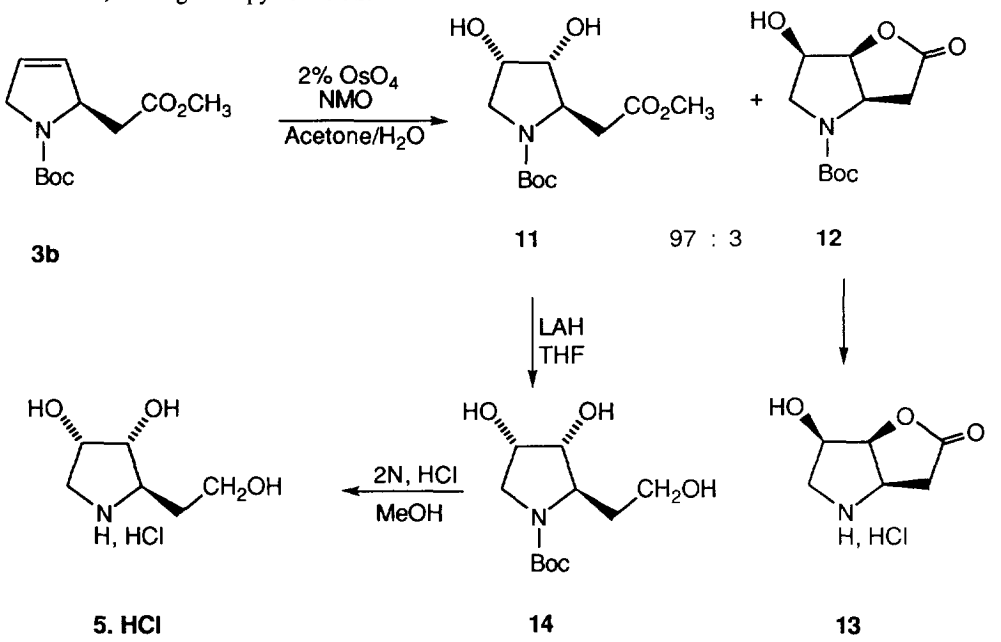
A number of polyhydroxypyrrolidines have been known to be selective inhibitors of glycosidases. Thus, these compounds, able to inhibit the biosynthetic pathway of glycoproteins, are potentially useful as antiviral, antibacterial, antitumoral or antidiabetic agents.[8] Therefore, in the last ten years, polyhydroxylated pyrrolidines have been the objects of considerable synthetic efforts.[2b] In particular all the stereoisomers of 1,4-dideoxy-1,4-iminopentitols **9** have already been described.[9] However, to our knowledge, only three

stereoisomers, with *lyxo* or *xylo* configuration, of the related iminohexitols derivatives **10** have been reported.[10-12]



9 **10**

As shown in Scheme 2, we describe herein an expeditious synthesis of 1,4,5-trideoxy-1,4-imino-D-*ribo*-hexitol **5**, starting from pyrroline **3b**.[3]



Scheme 2

Standard *cis*-dihydroxylation of the pyrroline **3b** gave quantitatively and with an excellent diastereoselectivity (97/3) the dihydroxypyrrolidine **11** together with a very small amount of lactone **12** arising from dihydroxylation on the more hindered face of **3b**. The configuration of **12** was confirmed by its transformation to the known hydrochloride **13**.[11c,14] The methyl ester **11** was then reduced with lithium aluminum hydride in refluxing THF to afford with an excellent yield (86%) the protected trihydroxypyrrolidine **14**. Finally, deprotection with 2N HCl in methanol gave the desired trihydroxylated pyrrolidine as its cristalline hydrochloride (**5.HCl**). This compound showed no significant activity as a glycosidase inhibitor when tested with 24 different glycosidases.[15]

In summary we have shown that 3-pyrrolines **3** are useful building blocks for the synthesis of polyhydroxylated alkaloids containing five-membered nitrogen heterocycles.

EXPERIMENTAL SECTION

General : IR spectra were recorded on a Perkin Elmer 682 spectrophotometer. NMR spectra were recorded on a Bruker AM 250 or AC 200 spectrometer with tetramethylsilane as an internal standard. Mass spectra were obtained with a GC/MS R.10-10 spectrometer. Optical rotations were measured on a Perkin Elmer 241 polarimeter. All reactions were carried out under an inert atmosphere of argon and monitored by thin-layer chromatography (TLC). TLC was performed on Merck silicagel 60F-254 precoated on glass.

(2*R*)-1-Acetyl-2-carbamoylmethyl-2,5-dihydropyrrole (6). To a solution of nitrile **3a** (158 mg, 1.05 mmol) in dichloromethane (12 mL) was added concentrated sulfuric acid (1.8 mL). The mixture was kept at 5°C for 20 hours and then cooled to 0°C. The pH was adjusted to pH 10 by careful addition of a 4N ammonia aqueous solution. After decantation, the aqueous layer was extracted with dichloromethane (4x40 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo to give 167 mg (94%) of the diamide **6** as a colorless solid which could not been obtained totally pure. ^1H NMR ($CDCl_3$, 200 MHz) δ 2.09 (s, 3H), 2.49 (dd, J = 14.0 Hz, 7.8 Hz, 1H), 2.93 (dd, J = 14.0, 3.3 Hz, 1H), 4.25 (m, 2H), 4.97 (m, 1H), 5.32 (bs, 1H), 5.92 (m, 2H), 6.29 (bs, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.7, 40.2, 54.5, 61.6, 124.4, 130.7, 169.6, 172.9; CIMS (NH_3) m/z (relative intensity) : 169 (MH^+, 100).

(1*S*,5*R*,8*S*)-6-Acetyl-8-iodo-2-oxa-6-azabicyclo[3.3.0]octan-3-one (7). To a stirred solution of amide **6** (112.4 mg, 0.67 mmol) in tetrahydrofuran/water (1/1, 5 mL), cooled at 0°C, was added iodine (509 mg, 2 mmol). The solution was stirred for 2 h and a saturated aqueous solution of sodium thiosulfate (5 mL) was then added. The reaction mixture was extracted with dichloromethane (3x20 mL) and the organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/EtOH : 95/5) to afford 170 mg (86%) of the iodolactone **7** as a colorless solid : mp 145°C (dec.); $[\alpha]_D^{20}$ = +105 (c 0.6, $CHCl_3$); IR (KBr) 1800, 1650 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.09 (s, 3H), 2.89 (d, J = 4 Hz, 2H), 3.91 (d, J = 13 Hz, 1H), 4.18 (dd, J = 13, 4.2 Hz, 1H), 4.51 (d, J = 4.2 Hz, 1H), 4.98 (ddd, J = 4.1, 4.0, 4.0 Hz, 1H), 5.19 (d, J = 4.1 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.7, 22.5, 35.0, 55.8, 56.4, 87.6, 169.3, 174.8; CIMS (NH_3) m/z (relative intensity) : 313 (MNH_4^+, 100), 296 (MH^+, 88). Anal. calcd for $C_8H_{10}INO_3$: C, 32.56; H, 3.42; N, 4.75. Found: C, 32.81; H, 3.46; N, 4.82.

(1*R*,5*R*)-6-Acetyl-2-oxa-6-azabicyclo[3.3.0]octan-3-one (8). To a stirred solution of iodide **7** (130 mg, 0.44 mmol) and AIBN (3 mg) in benzene (15 mL) was added freshly distilled tributyltin hydride (180 µL, 0.66 mmol). The solution was stirred for 20 min. at 80°C and was allowed to cool to rt. The solvent was removed in vacuo and tin derivatives were eliminated by heating for one hour at 50°C under 10^{-2} torr. The oily residue was purified by chromatography on silica gel (CH_2Cl_2/EtOH : 95/5) to give 66.8 mg (90%) of the lactone **8** as a pale yellow oil; $[\alpha]_D^{20}$ = -201 (c 0.4, $CHCl_3$); lit.[6c] $[\alpha]_D^{20}$ = -192 (c 0.4, $CHCl_3$); IR ($CDCl_3$) 1790, 1650 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 2.05 - 2.20 (m, 1H), 2.10 (s, 3H), 2.41 (dd, J = 14.1, 5.9 Hz, 1H), 2.87 (d, J = 4.1 Hz, 2H), 3.53 - 3.76 (m, 2H), 4.62 (ddd, J = 4.5, 4.5, 4.0 Hz, 1H), 5.10 (dd, J = 4.5, 4.5 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.9, 31.1, 35.5, 45.5, 57.9, 82.5, 169.2, 175.6; CIMS (NH_3) m/z (relative intensity) : 187 (MNH_4^+, 61), 170 (MH^+, 100), 169 (M^+, 12). Anal. calcd for $C_8H_{11}NO_3$: C, 56.81; H, 6.51; N, 8.30. Found: C, 56.63; H, 6.72; N, 8.15.

(1*R*,5*R*)-2-Oxa-6-azabicyclo[3.3.0]octan-3-one hydrochloride (4.HCl). A solution of lactone **8** (62 mg, 0.37 mmol) in 6N aqueous hydrochloric acid (1 mL) was refluxed for 20 h. The solvent was evaporated in vacuo and the water was removed from the residue by 3 azeotropic distillations with methanol. The solid residue was recrystallized from absolute ethanol to give 46 mg (77%) of the hydrochloride **4.HCl** as a colorless solid; mp : 187-188°C (dec); $[\alpha]_D^{20}$ = +44 (c 0.4, MeOH); lit.[6i] mp 185-186°C, $[\alpha]_D^{23}$ = +45.7 (c 0.555, MeOH). Spectral data were in good agreement with those reported in the literature.[6h,i]

(2*R*,3*R*,4*S*)-1-*tert*-Butoxycarbonyl-2-methoxycarbonylmethyl-3,4-dihydroxypyrrolidine (11). To a solution of 4-methylmorpholine-N-oxide (612 mg, 5.2 mmol) and osmium tetroxide (820 µl of a 4% aqueous solution, 0.13 mmol) in water (10 mL) was added a solution of the pyrroline **3b** (1.20 g, 5 mmol) in acetone (10 mL). The mixture was stirred for 12 h at rt and the solvents were removed in vacuo. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 97/3) to give 32.2 mg (2.7%) of lactone **12** and 1.32 g (96%) of the pyrrolidine **11** as a pale yellow oil.

Lactone **12**: IR ($CDCl_3$) 3580, 1795, 1690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 70°C) δ 1.49 (s, 9H), 2.17 (m, 1H), 2.80 (m, 2H), 3.30 (dd, J = 11.5, 7.1 Hz, 1H), 3.84 (dd, J = 11.5, 6.5 Hz, 1H), 4.36 (m, 1H), 4.48 (m, 1H), 4.90 (dd, J = 6.0, 4.5 Hz, 1H); CIMS (NH_3) m/z (relative intensity) : 261 (MNH_4^+, 100), 244 (MH^+, 63).

Pyrrolidine **11**: $[\alpha]_D^{20}$ = -24 (c 0.5, MeOH); IR (film) 3420, 1745, 1690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 70°C) δ 1.47 (s, 9H), 1.60 (bs, 1H), 2.45 (dd, J = 16.3, 9.5 Hz, 1H), 2.73 (bs, 1H), 3.18 (m, 1H), 3.43 (dd, J = 12.0, 4.6 Hz, 1H), 3.59 (dd, J = 12.0, 3.5 Hz, 1H), 3.70 (s, 3H), 3.90 (m, 1H), 4.09 (dd, J = 4.5, 4.5 Hz, 1H), 4.20 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 2 conformers are present: δ 28.3, 29.6 and 30.8, 36.5 and 37.0, 50.7 and 51.1, 51.9, 58.8, 69.3 and 69.7, 80.0, 154.6, 172.3 and 172.9; CIMS (NH_3) m/z (relative intensity) : 276 (MH^+, 92), 220 (100). Anal. calcd for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09. Found: C, 52.74; H,7.62; N, 5.21.

(1*S*,5*R*,8*R*)-8-Hydroxy-2-oxa-6-azabicyclo[3.3.0]octan-3-one hydrochloride (13). To a stirred solution of lactone **12** (32 mg, 0.13 mmol) in methanol (2.5 mL) cooled at 0°C was added concentrated hydrochloric acid (0.5 mL). The mixture was stirred for 1 h at 0°C and the solvents were removed in vacuo. The residue was recristallized from ethanol/diethylether to give 7 mg of **13** as a colorless solid; mp 160-162°C; $[\alpha]_D^{20}$ = +19 (c 0.1, MeOH); lit.[11c] mp 164-165°C, $[\alpha]_D^{20}$ = +19.7 (c 0.299, MeOH).

(2*R*,3*R*,4*S*)-1-*tert*-Butoxycarbonyl-2-(2-hydroxyethyl)-3,4-dihydroxypyrrolidine (14). To a suspension of lithium aluminum hydride (50 mg, 1.3 mmol) in anhydrous tetrahydrofuran (10 mL) was added a solution of the ester **11** (220 mg, 0.8 mmol) in anhydrous tetrahydrofuran (2 mL). The mixture was heated at 60°C for 2 h, allowed to cool to rt and hydrolyzed with a solution of potassium hydrogen sulfate (460 mg) in water (5 mL). The mixture was extracted with dichloromethane (5x10 mL) and chloroform (2x10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 95/5) to afford 170mg (86%) of triol **14** as a colorless oil; $[\alpha]_D^{20}$ = -25 (c 1, $CHCl_3$); IR (film) 3450, 1675 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, 70°C) δ 1.47 (s, 9H), 1.80 (m, 2H), 3.48 (d, J = 5.4 Hz, 2H), 3.70 (m, 2H), 3.84 (m, 1H), 3.96 (dd, J = 3.8, 3.8 Hz, 1H), 4.25 (ddd, J = 5.4, 5.4, 3.8 Hz, 1H); CIMS (NH_3) m/z (relative intensity) : 248 (MH^+, 97), 192 (100). Anal. calcd for $C_{11}H_{21}NO_5$: C, 53.44; H, 8.50; N, 5.67. Found: C, 53.15; H, 8.34; N, 5.82.

1,4,5-Trideoxy-1,4-imino-D-*ribo*-hexitol hydrochloride (5.HCl). To a stirred solution of pyrrolidine **14** (140 mg, 0.56 mmol) in methanol (3 mL) was added slowly at 0°C concentrated hydrochloric acid (1 mL). The mixture was stirred for 1 h at 0°C and the solvents were removed in vacuo. The solid residue was dried by two azeotropic distillations with methanol and recristallized from ethanol/diethyl ether to give 96 mg (92%) of hydrochloride **5.HCl** as a colorless solid: mp 120-122°C; $[\alpha]_D^{20}$ = +55 (c 0.35, H_2O); IR (KBr) 3420, 3320, 3260, 1050 cm^{-1}; ^1H NMR (250 MHz, D_2O) δ 1.8 (m, 2H), 3.1 (d, J = 13 Hz, 1H), 3.30 (m, 2H), 3.55 (m, 2H), 3.85 (dd, J = 9.0, 4.0 Hz, 1H), 4.1 (m, 1H); ^{13}C NMR (63 MHz, D_2O) δ 40.0, 51.7, 61.2, 66.4, 71.3, 77.2; CIMS (NH_3) m/z (relative intensity) : 148 (M^+-Cl, 100). Anal. calcd for $C_6H_{14}ClNO_3$: C, 39.23; H, 7.63; N, 7.63. Found: C, 39.51; H, 7.41; N, 7.25.

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15. Inhibition tests have been made by Sylviane Picasso in the laboratory of Professor P. Vogel in Lausanne. We thank them for their kind cooperation.

(*Received in UK* 10 *September* 1996)