New Route to Bicyclic Pyrazolidinones and Hydroxypyrrolidines from α,β-Unsaturated Sugar δ-Lactones

Joanna Rabiczko and Marek Chmielewski*

Institute of Organic Chemistry of the Polish Academy of Sciences, 01-224 Warsaw, Poland

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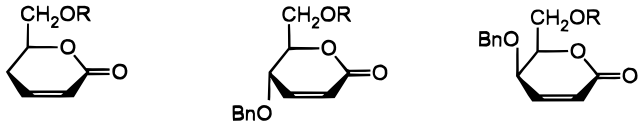
There is a considerable interest in the chemistry, synthesis, and biological activity of pyrazolidinones[1,2] and hydroxypyrrolidines.[3,4] The former represent a new class of antibacterial agents[1] or interesting intermediates for the synthesis of β-lactams,[2] whereas the latter[3] and their bicyclic derivatives[4] such as indolizines exhibit strong activity as inhibitors of glycosidases and have the potential for the treatment of a variety of diseases.[5]

Recently, we have reported on the conjugate addition−rearrangement of hydrazines and hydroxylamines to α,β-unsaturated sugar δ-lactones **1**, which proceeds *anti* to the terminal substituent of the enelactone to afford 5-substituted pyrazolidin-3-ones **2** or 3-substituted isoxazolidin-5-ones **3**, respectively (Scheme 1).[6,7]

The introduction of a sulfonyloxy substituent to the terminal carbon atom of the polyol side chain in **3** caused the migration of the nitrogen atom of the hydroxylamine fragment from C-3 to C-6 of the sugar chain and the formation of a bicyclic compound **5**. The direct reaction of sulfonate **4** with *N*-benzylhydroxylamine led to the double adduct **6** and low yield of **5** only (Scheme 1).[8]

It was of interest to investigate similar reactions involving hydrazine and α,β-unsaturated δ-lactones that have an sp^3 electrophilic center at C-6 of the sugar chain.

For the present studies, we selected the lactones D-glycero **7**, D-erythro **8**, and D-threo **9** having a free hydroxy group at the terminal C-6 carbon atom. Compounds **7**−**9** were subjected to reaction with tosyl chloride and pyridine to afford the corresponding sulfonates **10**−**12**.



7: R = H **8:** R = H **9:** R = H

10: R = Ts **11:** R = Ts **12:** R = Ts

13: R = Tf

The addition of hydrazine to lactones **10**, **11**, and **12** according to the known procedure yielded the bicyclic pyrazolidinones **14**, **15**, and **16** in 65%, 60%, and 55% yield, respectively.

Reaction of the triflate **13** with hydrazine led to a complicated mixture of products as a result of the coincident reaction of the nucleophile with the conjugated system and with the sp^3 electrophilic center and was not investigated further.

Configurations at C-5 of compounds **15** and **16** were proven by NOE experiments, whereas that of **14** was assigned on the assumption that the steric pathway of the hydrazine addition to all of the lactones **10**−**12** was the same. An NOE experiment on **15** did not show any interaction between H-5 (δ 4.02) and H-6 (δ 3.91) protons whereas the experiment on **16** showed the enhancement of the intensity of the signal H-6 (δ 3.90) by 14% when

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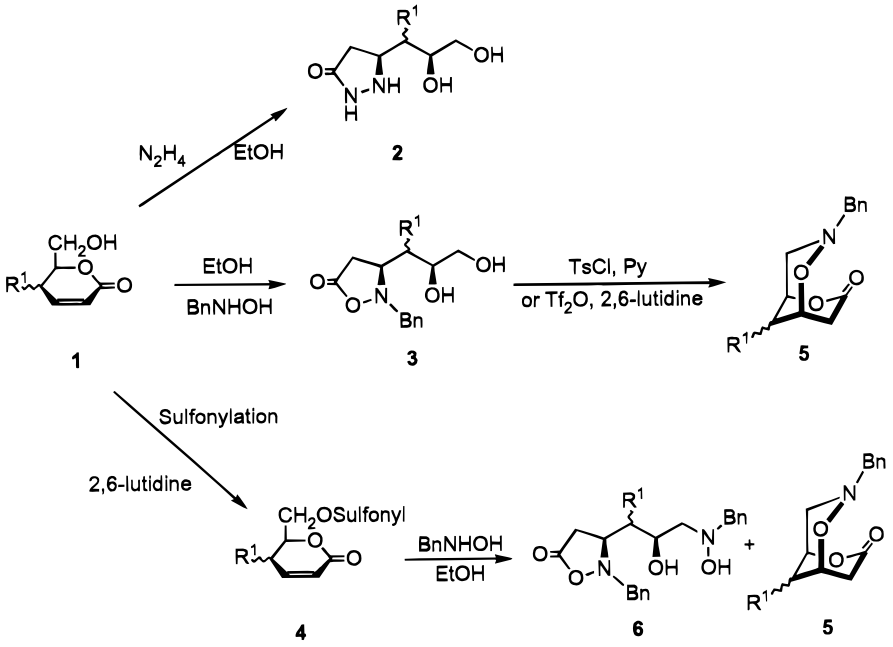
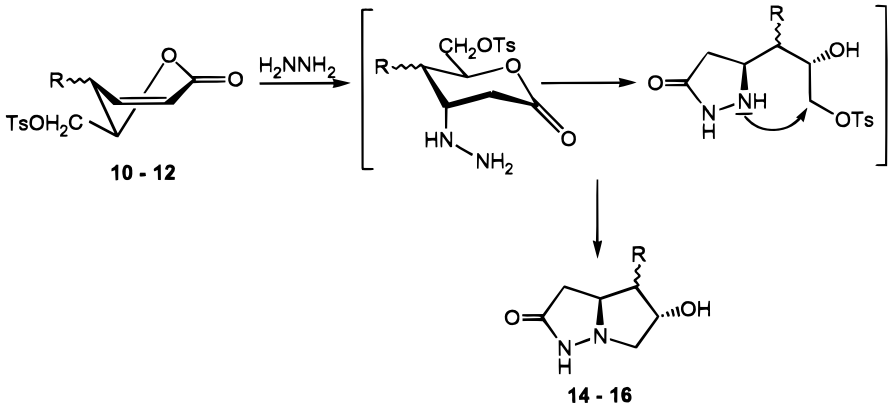
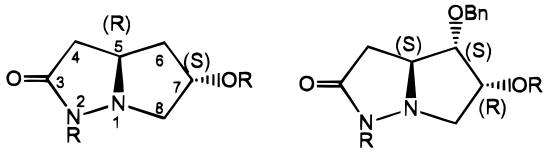
Scheme 1



Scheme 2



H-5 (δ 4.27) was irradiated. Consequently, a (5*R*) configuration was assigned to **14**, and (5*S*) to both **15** and

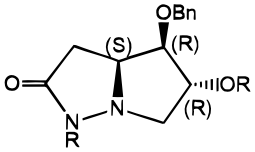


14: R = H

15: R = H

17: R = Ac

18: R = Ac



16: R = H

19: R = Ac

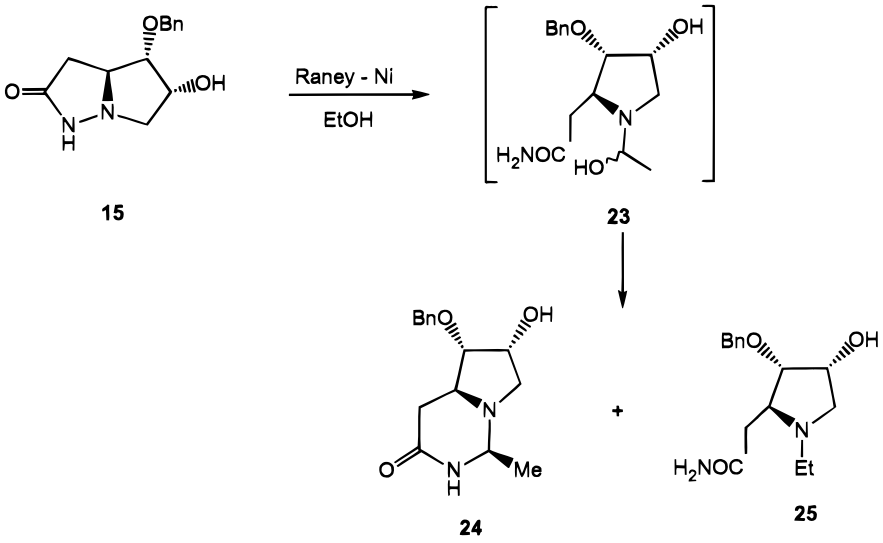
16. These findings testified to anti approach of the hydrazine molecule to the C-6 carbon atom of lactones **10**−**12**. Thus, it means that the stereochemical course of addition follows previous observations.[6,7,9] The conjugate addition−rearrangement leading to the pyrazolidin-3-one intermediate was followed by the simultaneous alkylation of the N-1 nitrogen atom by the terminal tosyloxymethyl group to afford bicyclic compounds **14**−**16** (Scheme 2). It is worth comparing the hydrazine addition to lactones **10** and **11** with the similar reaction in which both lactones reacted with *N*-benzylhydroxylamine to give preferentially the double adduct **6**.

Acetylation of compounds **14**−**16** gave respective diacetates **17**−**19**. Methanolysis of compounds **17**−**19** led to opening of the pyrazolidinone ring, yielding the corresponding methyl esters **20**−**22**.

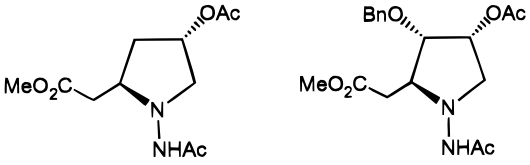
Hydrogenolysis of the N−N bond in the bicyclic pyrazolidinones **14**−**16** over Raney nickel proceeds with difficulty. In ethanol solution, compound **15** afforded mixture of products **24** and **25**. The preparation of ethylidene compound **24** and *N*-ethyl compound **25** varied, depending on the proportion of Raney nickel and reaction conditions. Obviously, the formation of compounds **24** and **25** was the result of hydrogenolysis at the N−N bond followed by reaction of the pyrrolidine

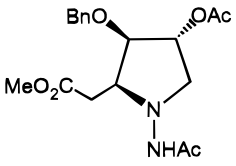
(9) Frelek, J.; Panfil, I.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. Submitted for publication.

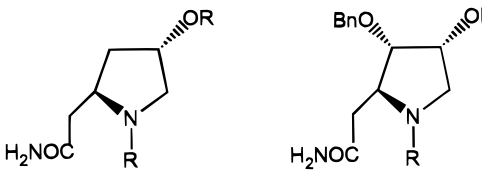
Scheme 3

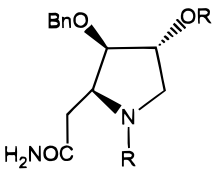


nitrogen atom with acetaldehyde that was formed by the dehydrogenation of ethanol over Raney nickel (Scheme 3). The intermediate aminal of acetaldehyde **23** was the precursor of both compounds **24** and **25**. Configuration at C-2 of **24** was proven by NOE experiment, which showed the enhancement of the intensity of the signal H-6 (δ 2.93) by 6.2% when H-2 (δ 3.98) was irradiated. Conversely, the signal due to H-2 was enhanced by 5.8% when H-6 was irradiated.









Hydrogenolysis of the bicyclic pyrazolidinones **14**−**16** in water solution over Raney nickel afforded amides **26**−**28**, respectively, which were characterized as di-acetates **29**−**31**.

In this paper, we demonstrated that conjugate addition−rearrangement of hydrazine to α,β-unsaturated sugar δ-lactones allowed a short and efficient synthesis of bicyclic pyrazolidinones and β-D-amino acid derivatives such as (2*R*,4*S*)-4-hydroxyhomoproline, (2*S*,3*S*,4*R*)-3,4-dihydroxyhomoproline, and (2*S*,3*R*,4*R*)-3,4-dihydroxyhomoproline.

Experimental Section

^{1}H NMR spectra were recorded at 200 and 500 MHz. Column chromatography was performed on Merck silica gel 230−400 mesh.

The lactones **8** and **9** were obtained from ethyl 2,3-dideoxy-α-D-erythro- and α-D-threohex-2-enopyranoside, respectively, by standard sequences of reactions which consisted of 6-*O*-silylation, followed by 4-*O*-benzylation, and anomeric oxidation to the lactone stage.[10,11] The lactone **10** was obtained according to the known procedure.[12]

4-*O*-Benzyl-2,3-dideoxy-D-erythrohex-2-eno-1,5-aldonolactone (8). 4-*O*-Benzyl-6-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-D-erythrohex-2-eno-1,5-aldonolactone (10.0 g, 0.02 mmol) in dry THF (100 mL) was treated with tetrabutylammonium fluoride hydrate (6.66 g, 0.021 mmol) and stirred at room temperature for 15 min. Subsequently, solvent was evaporated, and the crude product was purified on silica gel to give **8** (4.21 g, 0.018 mol, 85%) as a syrup: $[\alpha]_D = +83.11°$ (*c* 1.1, CH_2Cl_2); IR (film) 3427, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.40−7.31 (m, 5H), 6.89 (dd, 1H, J = 1.9, 10.0 Hz), 5.95 (dd, 1H, J = 2.0, 10.0 Hz), 4.74, 4.66 (2d, 2H, J = 11.6 Hz), 4.48 (ddd, 1H, J = 1.9, 2.0, 10.0 Hz), 4.35 (ddd, 1H, J = 2.7, 3.4, 10.0 Hz), 3.94 (dd, 1H, J = 2.7, 12.6 Hz), 3.84 (dd, 1H, J = 3.4, 12.6 Hz); MS (LSIMS, HR) *m*/*z* (M^+) calcd

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for $C_{13}H_{15}O_4$ 235.09703, found 235.09616. Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.68; H, 6.20.

4-*O*-Benzyl-2,3-dideoxy-D-threohex-2-eno-1,5-aldonolactone (9). Compound **9** was obtained from 4-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-2,3-dideoxy-D-threohex-2-eno-1,5-aldonolactone according to the procedure described above: mp 81−82 °C; $[\alpha]_D = -273.9$ (*c* 1.0, CH_2Cl_2); IR (film) 3271, 1729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42−7.30 (m, 5H), 6.94 (dd, 1H, J = 5.2, 9.8 Hz), 6.20 (d, 1H, J = 9.8 Hz), 4.67, 4.56 (2d, 2H, J = 11.8 Hz), 4.50 (m, 1H, J = 3.3, 5.3, 6.7 Hz), 4.12 (dd, 1H, J = 3.3, 5.2 Hz), 4.08 (dd, 1H, J = 6.7, 11.9 Hz), 3.91 (dd, 1H, J = 5.3, 11.9 Hz); MS (LSIMS, HR) *m*/*z* (M^+) calcd for $C_{13}H_{15}O_4$ 235.09703, found 235.09617. Anal. Calcd for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02. Found: C, 66.67; H, 6.03.

4-*O*-Benzyl-6-*O*-tosyl-2,3-dideoxy-D-erythrohex-2-eno-1,5-aldonolactone (11). Compound **11** was obtained from **8** using standard tosylation procedure: 85%, mp 75−76 °C; $[\alpha]_D = +32.1$ (*c* 0.4, CH_2Cl_2); IR (film) 1742 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.81−7.32 (m, 9H), 6.85 (d, 1H, J = 10.0 Hz), 5.95 (dd, 1H, J = 0.9, 10.0 Hz), 4.69, 4.63 (2d, 2H, J = 11.3 Hz), 4.48−4.36 (m, 3H, H-4,5,6), 4.19 (m, 1H), 2.45 (s, 3H); MS (LSIMS, HR) *m*/*z* (M^+) calcd for $C_{20}H_{21}O_6S$ 389.10590, found 389.10758. Anal. Calcd for $C_{20}H_{20}O_6S$: C, 61.84; H, 5.19. Found: C, 61.62; H, 5.24.

4-*O*-Benzyl-6-*O*-tosyl-2,3-dideoxy-D-threohex-2-eno-1,5-aldonolactone (12). Compound **12** was obtained from **9** using standard tosylation procedure: 87%; mp 101−102 °C; $[\alpha]_D = -162.8$ (*c* 1.0, CH_2Cl_2); IR (film) 1734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.85−7.23 (m, 9H), 6.87 (dd, 1H, J = 5.4, 9.8 Hz), 6.14 (d, 1H, J = 9.8 Hz), 4.64 (m, 1H, J = 3.1, 6.2, 6.8 Hz), 4.58, 4.54 (2d, 2H, J = 11.6 Hz), 4.42 (dd, 1H, J = 6.8, 10.3 Hz), 4.25 (dd, 1H, J = 6.2, 10.3 Hz), 4.07 (dd, 1H, J = 3.1, 5.4 Hz), 2.45 (s, 3H); MS (LSIMS, HR) *m*/*z* (M^+) calcd for $C_{20}H_{21}O_6S$ 389.10590, found 389.10883. Anal. Calcd for $C_{20}H_{20}O_6S$: C, 61.84; H, 5.19. Found: C, 61.67; H, 5.29.

Reaction of Lactones 10−12 with Hydrazine. General Procedure. The lactones **10**−**12** (0.13 g, 0.34 mmol) in anhydrous ethanol (10 mL) were treated with hydrazine (14 μL, 0.45 mmol) at room temperature. After 1 h, the mixture was evaporated and purified on a silica gel column using ethyl acetate−methanol 30:1 v/v as an eluent to afford compounds **14**−**16**, respectively.

(5*R*,7*S*)-1,2-Diaza-7-hydroxy-3-oxo-[3.3.0]bicyclooctane (14): 65%; mp 185−186 °C; $[\alpha]_D = +71.8$ (*c* 0.6, MeOH); IR (Nujol) 3346, 1665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.54 (m, 1H, J = 2.7, 3.3, 5.0, 5.6 Hz), 4.20 (m, 1H, J = 6.4, 7.3, 7.5, 9.3 Hz), 3.17 (ddd, 1H, J = 1.0, 2.7, 11.7 Hz), 3.01 (dd, 1H, J = 5.0, 11.7 Hz), 2.65 (dd, 1H, J = 9.3, 17.2 Hz), 2.47 (dd, 1H, J = 7.3, 17.2 Hz) 2.02−2.13 (m, 2H); MS (LSIMS) *m*/*z* $(M + H)^+$ 143. Anal. Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 50.6; H, 7.1; N, 19.8.

(5*R*,7S)-7-Acetoxy-2-acetyl-1,2-diaza-3-oxo-[3.3.0]bicyclooctane (17): mp 129−130 °C; $[\alpha]_D = -53.7$ (*c* 0.8, CH_2Cl_2); IR (film) 1741, 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.44 (m, 1H, J = 1.8, 3.0, 5.7, 6.6 Hz), 4.17 (m, 1H, J = 4.7, 7.6, 8.4, 9.9 Hz), 3.84 (ddd, 1H, J = 1.3, 1.8, 12.1 Hz), 2.96 (dd, 1H, J = 5.7, 12.1 Hz), 2.88 (dd, 1H, J = 8.4, 17.9 Hz), 2.65 (dd, 1H, J = 9.9, 17.9 Hz), 2.30 (dddd, 1H. J = 1.3, 3.0, 7.6, 14.6 Hz), 2.21 (ddd, 1H, J = 4.7, 6.6, 14.6 Hz,), 2.48 (s, 3H), 2.08 (s, 3H). Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.9; H, 6.4; N, 12.3.

(5*S*,6*S*,7*R*)-1,2-Diaza-6-benzyloxy-7-hydroxy-3-oxo-[3.3.0]-bicyclooctane (15): 60%; mp 102−103 °C; $[\alpha]_D = +5.8$ (*c* 0.6, CH_2Cl_2); IR (film) 3278, 1678 cm^{-1}; ^1H NMR (CD_3OD) δ 7.41−7.27 (m, 5H), 4.73, 4.59 (2d, 2H, J = 11.3 Hz), 4.46 (m, 1H, J = 4.4, 4.8, 5.1 Hz), 4.02 (m, 1H), 3.91 (dd, 1H, J = 4.4, 4.7 Hz), 3.27 (dd, 1H, J = 4.8, 11.8 Hz), 3.00 (dd, 1H, J = 5.1, 11.8 Hz), 2.65 (dd, 1H, J = 10.4, 17.6 Hz), 2.46 (dd, 1 H, J = 7.2, 17.6 Hz). Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 62.88; H, 6.50; N, 11.28. Found: C, 62.7; H, 6.5; N, 11.3.

(5*S*,6*S*,7*R*)-7-Acetoxy-2-acetyl-1,2-diaza-6-benzyloxy-3-oxo-[3.3.0]bicyclooctane (18): mp 76−77 °C; $[\alpha]_D = -91.5$ (*c* 0.5, CH_2Cl_2); IR (film) 1740, 1704 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39−7.29 (m, 5H), 5.53 (m, 1H, J = 1.9, 4.3, 4.6 Hz), 4.68, 4.47 (2d, 2H, J = 11.9 Hz), 3.97 (dd, 1H, J = 1.9, 12.9 Hz), 3.96 (m, 1H), 3.88 (dd, 1H, J = 4.7, 7.2 Hz), 3.00 (dd, 1H, J = 4.6, 12.9 Hz), 2.95 (dd, 1H, J = 10.0, 18.5 Hz), 2.62 (dd, 1H, J = 6.2, 18.5 Hz), 2.45 (s, 3H), 2.14 (s, 3H). Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.3; H, 6.1; N, 8.3.

(5*S*,6*R*,7*R*)-1,2-Diaza-6-benzyloxy-7-hydroxy-3-oxo-[3.3.0]-bicyclooctane (16): 55%; mp 132−133 °C; $[\alpha]_D = +41.9$ (*c* 1.6, MeOH); IR (Nujol) 3210, 1661 cm^{-1}; ^1H NMR (CD_3OD) δ 7.35−7.25 (m, 5H), 4.69, 4.56 (2d, 2H, J = 11.8 Hz), 4.41 (m, 1H, J = 2.6, 2.8, 5.0 Hz), 4.27 (m, 1H, J = 5.7, 6.6, 10.5 Hz), 3.90 (dd, 1H, J = 2.6, 5.7 Hz), 3.19 (dd, 1H, J = 2.8, 11.5 Hz), 3.03 (dd, 1H, J = 5.0, 11.5 Hz), 2.90 (dd, 1H, J = 6.6, 17.2 Hz), 2.46 (dd, 1H, J = 10.5, 17.2 Hz); MS (EI, HR) *m*/*z* (M^+) calcd for $C_{13}H_{16}N_2O_3$ 248.116093, found 248.115783. Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.6; H, 6.6; N, 11.1.

(5*S*,6*R*,7*R*)-7-Acetoxy-2-acetyl-1,2-diaza-6-benzyloxy-3-oxo-[3.3.0]bicyclooctane (19): mp 128−129 °C; $[\alpha]_D = -59.5$ (*c* 0.6, CH_2Cl_2); IR (film) 1744, 1703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39−7.29 (m, 5H), 5.34 (d, 1H, J = 5.2 Hz), 4.79, 4.57 (2d, 2H, J = 12.1 Hz), 4.15 (m, 1H, J = 5.4, 7.3, 9.9 Hz), 4.00 (d, 1H, J = 12.5 Hz), 3.17 (dd, 1H, J = 7.3, 18.2 Hz), 3.07 (dd, 1H, J = 5.2, 12.5 Hz), 2.66 (dd, 1H, J = 9.9, 18.2 Hz), 2.47 (s, 3H), 2.09 (s, 3H); MS (LSIMS, HR) *m*/*z* $(M + H)^+$ calcd for $C_{17}H_{20}N_2O_5$ 333.145043, found 333.146821. Anal. Calcd for $C_{17}H_{20}N_2O_5$: C, 61.44; H, 6.07; N, 8.43. Found: C, 61.2; H, 6.5; N, 8.2.

(2*R*,4*S*)-*N*-Acetylamino-4-acetoxy-2-methoxycarbonylmethyl-pyrrolidine (20). Compound **17** (0.01 g, 0.03 mmol) was dissolved in methanol (2 mL) and stirred for 48 h. Subsequently the solvent was evaporated, and the crude product was purified on a silica gel column using hexane−ethyl acetate 1:4 v/v as an eluent to give **20** (0.006 g, 50%): mp 83−84 °C; $[\alpha]_D = +26.0$ (*c* 0.6, CH_2Cl_2); IR (film) 3454, 3184, 1738, 1664 cm^{-1}; ^1H NMR ($CDCl_3$) signals due to the major rotamer (63%) δ 6.30 (bs, 1H), 5.12 (m, 1H), 3.72 (bm, 1H), 3.68 (s, 3H), 3.31 (m, 1H), 2.64 (bm, 1H), 2.62 (dd, 1H, J = 5.6, 15.4 Hz), 2.38 (dd, 1H, J = 7.4, 15.4 Hz), 1.7−2.2 (m, 2H), 2.06, 2.06 (2s, 6H); signals due to the minor rotamer (37%) δ 6.45 (bs, 1H), 5.12 (m, 1H), 3.84 (dd, 1H, J = 6.5, 10.9 Hz), 3.67 (s, 3H), 3.51 (m, 1H), 2.77 (dd, 1H, J = 4.1, 10.9 Hz), 2.67 (dd, 1H, J = 5.7, 16.1 Hz), 2.47 (dd, 1H, J = 7.0, 16.1 Hz), 1.7−2.2 (m, 2H), 2.05, 1.91 (2s, 6H); MS (EI, HR) *m*/*z* $(M + H)^+$ calcd for $C_{11}H_{19}N_2O_5$ 259.129393, found 259.128006. Anal. Calcd for $C_{11}H_{18}N_2O_5$: C, 51.15; H, 7.02; N, 10.85. Found: C, 51.2; H, 7.3; N, 10.8.

(2*S*,3*S*,4*R*)-*N*-Acetylamino-4-acetoxy-3-benzyloxy-2-methoxycarbonylmethyl-pyrrolidine (21). Compound **21** was obtained from **18** according to the procedure described for **20**: 50%; syrup; $[\alpha]_D = -31.3$ (*c* 0.5, CH_2Cl_2); IR (film) 3348, 1738, 1673 cm^{-1}; ^1H NMR ($CDCl_3$) 1:1 mixture of rotamers δ 7.42−7.29 (m, 5H), 6.87, 6.67 (2s, 1H), 5.36 (m, 1H), 4.66, 4.42 (2d, 1H, J = 11.1 Hz), 4.65, 4.39 (2d, 1H, J = 11.2 Hz), 3.93 (dd, 0.5H, J = 6.0, 12.0 Hz), 3.82 (dd, 0.5H, J = 4.9, 8.9 Hz), 3.74 (dd, 0.5H, J = 5.5, 12.2 Hz), 3.72 (dd, 0.5H, J = 5.0, 9.6 Hz), 3.65, 3.64 (2s, 3H), 3.47, 3.36 (2m, 1H), 2.87 (dd, 0.5H, J = 2.7, 12.0 Hz), 2.84 (dd, 0.5H, J = 2.0, 12.2 Hz), 2.59 (m, 2H), 2.49 (dd, 1H, J = 8.1, 16.3 Hz), 2.41 (dd, 1H, J = 6.8, 14.9 Hz), 2.17, 2.16, 2.05, 1.91 (4s, 6H). Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69. Found: C, 59.4; H, 6.8; N, 7.5.

(2*S*,3*R*,4*R*)-*N*-Acetylamino-4-acetoxy-3-benzyloxy-2-methoxycarbonylmethyl-pyrrolidine (22). Compound **22** was obtained from **19** according to the procedure described for **20**: 60%; mp 125−126 °C; $[\alpha]_D = +72.1$ (*c* 1.0, CH_2Cl_2); IR (film) 3226, 1732, 1662 cm^{-1}; ^1H NMR ($CDCl_3$) major component (66%) δ 7.42−7.29 (m, 5H), 6.18 (bs, 1H), 5.16 (m, 1H), 4.72, 4.48 (2d, 2H, J = 11.8 Hz), 3.99 (m, 1H), 3.72 (m, 1H), 3.61 (s, 3H), 3.34 (bs, 1H), 2.55−2.80 (m, 3H), 2.08, 1.64, (2s, 6H); minor component (34%) δ 7.42−7.29 (m,5H), 6.75 (s, 1H), 5.16 (m, 1H), 4.72, 4.49 (2d, 2H, J = 11.8 Hz), 3.99 (m, 1H), 3.65−3.85 (m, 2H), 3.60 (s, 3H), 3.15 (dd, 1H, J = 4.4, 11.7 Hz), 2.55−2.80 (m, 2H), 2.07, 1.87, (2s, 6H); MS (LSIMS, HR) *m*/*z*: $(M+H)^+$ calcd for $C_{18}H_{25}N_2O_6$: 365.171262. Found: 365.170873. Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.33; H, 6.64; N, 7.69. Found: C, 59.4; H, 6.7; N, 7.8.

(2*S*,6*S*,7*S*,*R*)-1,3-Diaza-7-benzyloxy-2-methyl-3-oxo-[4.3.0]-bicyclononane and (2S,3*S*,4*R*)-3-Benzyloxy-2-carbamoylmethyl-1-ethyl-4-hydroxy-pyrrolidine (24 and 25). Compound **15** (0.08 g, 0.32 mmol) was dissolved in anhydrous ethanol (1 mL) and treated with Raney nickel (0.5 g suspension in ethanol). The mixture was stirred for 1 h at room temperature until disappearance of the substrate. Subsequently, the mixture

was filtered through Celite and evaporated. The crude product was separated using ethyl acetate−methanol 20:1 v/v as an eluent to afford **24** (0.029 g, 33%) and **25** (0.041 g, 45%).

24: mp 105−106 °C; $[\alpha]_D = -58.5$ (*c* 1.3, CH_2Cl_2); IR (film) 3299, 1663 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40−7.32 (m, 5H), 6.01 (bs, 1H), 4.67, 4.59 (2d, 2H, $J = 11.7$ Hz), 4.27 (m, 1H), 3.98 (q, 1H, $J = 5.9$ Hz) 3.58 (dd, 1H, $J = 6.0, 7.5$ Hz), 3.40 (dd, 1H, $J = 6.8, 10.1$ Hz), 2.93 (ddd, 1H, $J = 4.7, 7.5, 9.8$ Hz), 2.73 (d, 1H, $J = 3.9$ Hz), 2.58 (dd, 1H, $J = 4.7, 16.7$ Hz), 2.44 (dd, 1H, $J = 3.8, 10.1$ Hz), 2.25 (dd, 1H, *J* 9.8, 16.7 Hz), 1.25 (d, 3H, $J = 5.9$ Hz); MS (LSIMS, HR) *m*/*z* $(M + H)^+$ calcd for $C_{15}H_{21}$ 277.15521, found 277.15414. Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found: C, 64.91; H, 7.41; N, 9.98.

25: mp 134−135 °C; $[\alpha]_D = +28.6$ (*c* 0.8, CH_2Cl_2); IR (film) 3364, 3177, 1653, 1632 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83, 5.46 (2bs, 2H), 7.39−7.30 (m, 5H), 4.66, 4.59 (2d, 2H, $J = 11.4$ Hz), 4.13 (q, 1H, $J = 5.5$ Hz, 3.77 (bt, 1H), 3.40 (dd, 1H, $J = 5.6, 10.6$ Hz), 2.94 (m, 1H), 2.89, 2.39 (2dq, 2H), 2.60 (dd, 1H, $J = 4.8, 16.3$ Hz), 2.52 (bs, 1H), 2.42−2.50 (m, 2H), 1.10 (t, $J = 7.2$ Hz); MS (LSIMS, HR) *m*/*z* $(M + H)^+$ calcd for $C_{15}H_{23}N_2O_3$ 279.17087, found 279.17460.

(2*R*,4*S*)-4-Acetoxy-*N*-acetyl-2-carbamoylmethyl-pyrrolidine (29). Compound **14** (0.10 g, 0.7 mmol) was dissolved in water (5 mL), treated with a suspension of Raney nickel in water (0.3 g, pH = 7), and stirred for 2 h until the disappearance of the substrate. Subsequently, the mixture was filtered through Celite which was washed with methanol. The solvents were evaporated to dryness, and the residue was acetylated with acetic anhydride−pyridine 1:1 mixture and stirred overnight. Subsequently, the mixture was evaporated to dryness and purified on a silica gel column using ethyl acetatea−methanol 40:1 v/v as an eluent to give **29** (0.092 g, 57%): syrup; $[\alpha]_D = +28.0$ (*c* 1.3, CH_2Cl_2); IR (film) 3358, 3200, 1737, 1670, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.11, 5.40 (2bs, 2H), 5.26 (m, 1H, $J = 2.1, 3.1, 4.6, 5.2$ Hz), 4.37 (m, 1H, $J = 3.2, 7.5, 7.7, 7.8$ Hz), 3.77 (dd, 1H, $J = 4.6, 11.9$ Hz), 3.54 (m, 1H, $J = 1.5, 2.1, 11.9$ Hz), 2.77 (dd, 1H, $J = 3.2, 14.3$ Hz), 2.65 (dd, 1H, $J = 7.5, 14.3$ Hz), 2.37 (ddd, 1H, $J = 5.2, 7.7, 14.1$ Hz), 2.31 (dddd, 1H, $J = 1.5, 3.1, 7.8, 14.1$ Hz), 2.05 (s, 6H); MS (EI, HR) *m*/*z* (M^+) calcd for $C_{10}H_{16}N_2O_4$ 228.11101, found 228.11020. Anal. Calcd for $C_{10}H_{16}N_2O_4$: C, 52.62; H, 7.07; N, 12.27. Found: C, 52.35; H, 6.87; N, 12.12.

(2*S*,3*S*,4*R*)-4-Acetoxy-*N*-acetyl-3-benzyloxy-2-carbamoylmethyl-pyrrolidine (30). Compound **30** was obtained from **15** according to the procedure described above: 63%; mp 118−119 °C; $[\alpha]_D = +20.9$ (*c* 0.6, CH_2Cl_2); IR (film) 3391, 3193, 1742, 1728, 1644 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.37−7.27 (m, 5H), 6.10, 5.32 (2bs, 2H), 5.31 (q, 1H), 4.64, 4.60 (2d, 2H, $J = 11.5$ Hz), 4.41 (dd, 1H, $J = 4.3, 4.9$ Hz), 4.16 (m, 1H, $J = 2.8, 4.9, 7.5$ Hz), 3.80 (dd, $J = 5.5, 11.0$ Hz), 3.58 (dd, 1H, $J = 4.7, 11.0$ Hz), 2.73 (dd, 1H, $J = 7.5, 14.6$ Hz), 2.63 (dd, 1H, $J = 2.8, 14.6$ Hz), 2.09, 2.04 (2s, 6H); MS (LSIMS, HR) *m*/*z* $(M + H)^+$ calcd for $C_{17}H_{23}N_2O_5$ 335.16071, found 335.16369. Anal. Calcd for $C_{17}H_{22}N_2O_5$: C, 61.07; H, 6.63; N, 8.38. Found: C, 60.75; H, 6.90; N, 8.21.

(2*S*,3*R*,4*R*)-4-Acetoxy-*N*-acetyl-3-benzyloxy-2-carbamoylmethyl-pyrrolidine (31). Compound **31** was obtained from **16** according to the procedure described above: 53%; syrup; $[\alpha]_D = +33.7$ (*c* 1.1, CH_3OH); IR (film) 3332, 3197, 1741, 1674, 1633 cm^{-1}; ^1H NMR ($CDCl_3$) major rotamer δ 7.38−7.29 (m, 5H), 6.00, 5.38 (2bs, 2H), 5.16 (m, 1H), 4.66, 4.59 (2d, 2H, $J = 11.3$ Hz), 4.50 (m, 1H), 4.22 (dd, 1H, $J = 1.9, 5.6$ Hz), 3.86 (dd, 1H, $J = 4.6, 11.9$ Hz), 3.44 (d, 1H, $J = 11.9$ Hz), 3.12 (dd, 1H, $J = 4.4, 15.6$ Hz), 2.58 (dd, 1H, $J = 8.9, 15.6$ Hz), 2.07, 2.02 (2s, 6H); minor rotamer δ 7.38−7.29 (m, 5H), 5.81, 5.46 (2bs, 2H), 4.63 (d, 1H, $J = 12.4$ Hz), 3.71 (dd, 1H, $J = 4.1, 13.2$ Hz); 3.65 (dd, 1H, $J = 6.3, 13.2$ Hz), 2.70 (dd, 1H, $J = 8.8, 15.1$ Hz), 2.42 (dd, 1H, $J = 4.8, 15.1$ Hz), 2.13, 2.04 (2s, 6H); MS (EI, HR) *m*/*z* $(M + H)^+$ calcd for $C_{17}H_{23}N_2O_5$ 335.16071, found 335.16039. Anal. Calcd $C_{17}H_{22}N_2O_5$: C, 61.07; H, 6.63; N, 8.38. Found: C, 60.81; H, 6.82; N, 8.48.

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