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Stereoselective synthesis and glycosidase inhibitory activity of 3,4-dihydroxy-pyrrolidin-2-one, 3,4-dihydroxy-piperidin-2-one and 1,2-dihydroxy-pyrrolizidin-3-one

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Abstract—3,4-Dihydroxy-pyrrolidin-2-one, 3,4-dihydroxy-piperidin-2-one and 1,2-dihydroxy-pyrrolizidin-3-one have been synthesized, using a simple strategy based on the asymmetric dihydroxylation of vinylogous aminoesters and subsequent mild intramolecular cyclization. All these compounds show a partial inhibition of α-glucosidase, but were inactive towards other glycosidases.

3,4-Dihydroxy-pyrrolidin-2-one, 3,4-dihydroxy-piperidin-2-one and 1,2-dihydroxy-pyrrolizidin-3-one constitute attractive synthetic targets as they are designed and developed as useful tools for promising biological applications including antifungal, AIDS agents and antitumour antibiotics.[1] These compounds also represent potent glycosidase inhibitors.[2] The potential tautomerisation of the carboxamide moiety was interesting to mimic the 2-hydroxyl of the natural substrates that lacks in the structure of most iminosugar inhibitors. Likewise, such optically active α,β-dihydroxy-γ-lactams have been shown to be versatile starting materials for the asymmetric synthesis of biologically active compounds.[3]

Consequently, the research of new methods for the preparation of these heterocycles or synthetic analogues and the study of their capacity to inhibit glycosidase are of increasing interest. Many syntheses have been reported, often in connection with a particular structure and with sophisticated methods including numerous steps.[1–4] We have previously investigated stereoselective methods for the synthesis of vinylogous aminoesters[5] and we have shown that the insertion of a *Z* ethenyl–CH=CR^1– group between the α-carbon and the ester moiety into an aminoester induced the formation of a very stable closed conformation.[6]

As a result, the ester group of such *Z* vinylogous aminoesters was found to be positioned near the amino moiety and an easy intramolecular cyclization into enantiopure unsaturated γ- or δ-lactams was clearly a favoured transformation.[7] In this letter, we describe a novel possibility that offers this strategy to obtain the newly substituted azasugar analogues 3,4-dihydroxy-pyrrolidin-2-one, 3,4-dihydroxy-piperidin-2-one and 1, 2-dihydroxy-pyrrolizidin-3-one **4**, via the asymmetric dihydroxylation of vinylogous aminoesters **1** and subsequent intramolecular cyclization (Scheme 1). The glycosidase inhibitory activity of the new iminosugar analogues **4** is also described.

Z or *E* vinylogous aminoesters **1** were prepared using a Horner reaction between suitable phosphonate anions and α- or β-*N*-*t*-butoxycarbonyl aminoaldehydes, as previously described by us.[5] The asymmetric dihydroxylation of vinylogous aminoesters **1** was investigated using either the achiral reagent osmium tetroxide-*N*-methyl-morpholine *N*-oxide (NMO/OsO_4) or osmium tetroxide in the presence of quinine and quinidine

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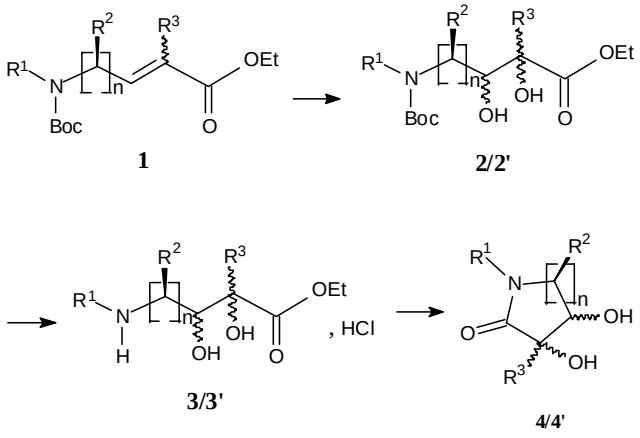

Scheme 1. Synthesis of dihydroxylactams **4/4′**.

ligands (AD-mix-α and AD-mix-β) under conditions of the Sharpless catalytic asymmetric dihydroxylation (AD)[8] (Table 1). When the C=C double bond was feebly hindered (**1a**, **1b** and **1f**), the Sharpless catalytic asymmetric dihydroxylation (AD) could be used to set the stereochemistry of the final two stereocentres into **4/4′**. With a bulky R^2, the AD led to lower reaction rates (**1c**, **1d** and **1e**) and the dihydroxylation with NMO/OsO_4 was then the most efficient system. Removal of the *N*-*t*-butoxycarbonyl-protecting group of α,β-dihydroxy-γ-aminoesters **2/2′** with HCl/ether yielded the corresponding hydrochlorides **3/3′** without affecting the diol group. Subsequent addition of triethylamine (2.5 equiv) for 2 h at 20 °C in dichloromethane provided a stereospecifically cyclic material **4/4′** in good yields. The strategy allowed the construction of dihydroxylactams **4/4′** with different substituents at the 3 or 5 positions and allowed the preparation of 3,4-dihydroxy-2-pyrrolidinone, 3,4-dihydroxy-2-piperidinone and 1,2-dihydroxy-3-pyrrolizidinone. No products of intermolecular reaction were detected, even in the case of $n = 2$. The mild cyclization conditions, and then the enhanced reactivity of α, β-dihydroxy-γ-aminoesters **3/3′** compared to those of vinylogous aminoesters[7] and corresponding hydrogenated aminoesters[9] could be explained by the α-hydroxy neighbouring-group participation.

It is known that the rate of asymmetric dihydroxylation of electron-deficient olefins can be very low.[7] However, in the present case, the AD of vinylogous aminoesters **1a**, **1f** and **1g** gave satisfactory results at room temperature under the standard conditions.[10] In these cases, an estimation of the enantiomeric excess of **2/2′** was obtained from the diastereomeric ratio of the Mosher ester derivatives of **2/2′** determined by ^{1}H NMR and ^{19}F NMR analyses. Interesting levels of enantioselectivity were thus obtained with AD-mix-β that could be compared favourably with recent reports in the literature relating the asymmetric dihydroxylation of 1,2-disubstituted γ-amino-α, β-unsaturated ester derivatives.[1a,e,3d,11] Particularly, *Z* and *E* vinylogous β-alanine derivatives **1f**(**Z**) and **1g**(**E**) gave the corresponding pairs of enantiomeric diols **2f/2′f** and **2g/2′g**, respectively (these two pairs being diastereomeric to each other), in good yields and with an excellent enantioselectivity (ee = 96). On the basis of the Sharpless 'mnemonic device,'[9] **1g**(**E**) would lead to the major diol (2*S*,3*R*) **2g**. However, in the absence of such a model in the case of (**Z**) olefin, it would be hazardous to propose the configuration of the major diol **2f**. In the context of matching and mismatching in the AD reaction, the vinylogous alanine **1a**(**Z**) and AD-mix-β (85% yield, ee = 60) and **1b**(**Z**) and AD-mix-β (70% yield, de = 56) represent the matched pairs, whereas the set **1a**(**Z**) and AD-mix-α (90% yield, ee = 38) and **1b**(**Z**) and AD-mix-α (30% yield, de = 22) that lead to lower stereoselectivity constitute the mismatching pairs.

Compounds **1c**, **1d** and **1e** only efficiently reacted with the classical achiral system NMO/OsO_4 (68–78%). In these cases, it appeared that the stereoselectivity depended on the degree of substitution of the double bond, the best diastereoselection being obtained with the trisubstituted olefins **1c** and **1d**. Similar results have been reported by Koskinen et al. in dihydroxylation of a cyclically protected vinylogous serine.[12] Moreover, in the case of **1d**, the dihydroxylation led to the diastereomers **2d/2′d**, which could be easily separated on a chromatographic silica gel column. Consequently, after removal of Boc of pure **2d** and further cyclization, pure **4d** was easily obtained.

The mechanism of osmylation is not well defined in the case of *Z*-trisubstituted γ-amino-α, β-unsaturated ester derivatives. Consequently, the factors determining the stereoselectivity are particularly difficult to evaluate. In

Table 1. Enantiomeric or diastereomeric excess and isolated yields of α, β-dihydroxy-γ-aminoesters **2/2′** and dihydroxylactams **4/4′**

1	R^1	R^2	R^3	*n*	Dihydroxylation conditions	2/2′	ee	de	Yield %	4/4′	Yield %
1a(**Z**)	H	H	Me	1	AD-mix β, 3days	**2a/2′a**80/20[a]	60		85	**4a/4′a**	82
1a(**Z**)	H	H	Me	1	AD-mixα, 3days	**2a/2′a**69/31[a]	38		90	—	—
1b(**Z**)	H	Me	Me	1	AD-mixβ, 15days	**2b/2′b**78/22[b]		56	70	**4b/4′b**70/30[b]	66
1b(**Z**)	H	Me	Me	1	AD-mixα, 15days	**2b/2′b**61/39[b]		22	30	—	—
1c(**Z**)	H	iPr	Me	1	OsO_4/NMO,1day	**2c/2′c** 75/25[b]		50	68	**4c/4′c** 79/21[b]	68
1d(**Z**)	–$(CH_2)_3$–		Me	1	OsO_4/NMO,15 days	**2d/2′d** 81/19[b]		62	78	**4d**100/0[c]	73
1e(**Z**)	–$(CH_2)_3$-		H	1	OsO_4/NMO,15 days	**2e/2′e** 59/41[b]		18	73	**4e/4′e** 59/41[b]	79
1f(**Z**)	H	H	Me	2	AD-mix β, 1day	**2f/2′f**98/2[a]	96		78	**4f/4′f**	75
1g(**E**)	H	H	Me	2	AD-mix β, 2days	**2g/2′g**98/2[a]	96		84	**4g/4′g**	72

[a] The enantiomeric ratio was determined by ^{1}H NMR and ^{19}F NMR of the Mosher ester derivatives.
[b] The diastereomeric ratio was determined by ^{1}H NMR of the crude product.
[c] Pure **4d** was obtained from pure **2d**.

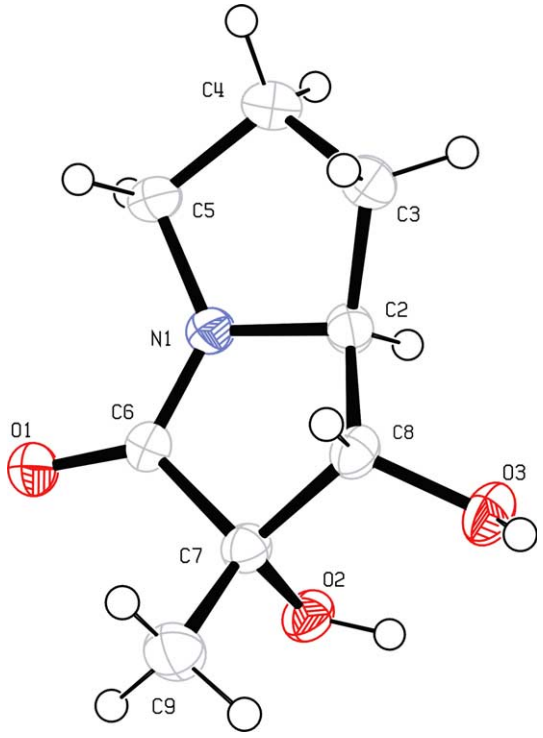

Figure 1. Ortep[16] view of one of the molecules of the asymmetric unit of the lactam **4d**. Ellipsoids are drawn at the 50% probability level.

accordance with the Vedejs' model[13a] and by analogy with the reported catalytic osmylation of 4-alkoxy-2-methyl Z-enoates[13b] and E-vinylogous leucine,[13c] the (2*S*, 3*S*, 4*S*)-configuration can be predicted for the major diols **2c**, **2d** and **2e**. The results accord also with the preferred approach of OsO_4 to the *Z*-4-alkenylazetidinones.[11c] In order to confirm the predictions of the Vedejs' model, the relative stereochemistry of the 1-hydroxyl and the methyl group into the cyclic product **4d** was tentatively established by ^{1}H NMR spectroscopy on the basis of a NOE study. A NOE between 1-H and Me confirmed the *syn* relation between these atoms and led to the (1*S*, 2*S*, 7a*S*)-configuration. In addition, the coupling constant values between 1-H and 7a-H ($^3J_{1,7a}$ = 6.6 Hz) were compatible with the antiperiplanar relationship between these hydrogens.[14] Definitive evidence for such assignment was provided by the determinations of the crystal structures of **2d** and **4d** and confirmed the (*S*, *S*, *S*)-configuration in the major diastereomer (Figure 1).[15] These NMR data and the crystal data confirmed the prediction of the Vedejs' model.[14,15]

The inhibitory activity of four α,β-dihydroxy γ-lactams **4b/4b′**, **4c/4c′**, **4d** and **4f/4f′** was tested towards 22 glycosidases.[17] They did not inhibit the following enzymes at 1 mM concentration: α-L-fucosidase from bovine kidney, α-galactosidase from coffee beans, α-galactosidase from *Escherichia coli*, β-galactosidase from *E. coli*, β-galactosidase from bovine liver, β-galactosidase from *Aspergillus oryzae*, α-glucosidase from rice, amyloglucosidase from *Aspergillus niger*, amyloglucosidase from *rhizopus* mold, β-glucosidase from almonds, α-mannosidase from jack beans, β-mannosidase from *Helix pomotia*, β-xylosidase from *A. niger*, β-*N*-acetylglucosaminidase from jack beans, β-*N*-acetylglucosaminidase from bovine kidney. In return, all the tested compounds revealed inhibition of α-glucosidase from yeast with a percentage near 50% (**4b/4b′**: 48%, **4c/4c′**: 51%, **4d**: 45%, **4f/4f′**: 46%).

In summary, a simple stereoselective access to dihydroxy lactams **4** via a facile sequence asymmetric dihydroxylation-cyclization of *Z* vinylogous aminoesters was described which provided a versatile route to the construction of five- and six-membered ring heterocycles and substituted pyrrolizidinones. The diastereoselectivity of the catalytic osmylation of vinylogous aminoesters **1** could be predicted with the Vedejs'model. Although these compounds only showed modest inhibition of α-glucosidase among many glycosidases tested, these dihydroxy lactams may offer an interesting framework for selective glucosidase inhibitors with further modification.

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14. All new compounds exhibited spectral data consistent with their structures. Selected spectral data, **4d**: colourless oil; $R_f = 0.59$ (ethyl acetate/hexane: 1:1); $[\alpha]_D = -32.4$ (*c* 0.5, $CHCl_3$); IR(KBr) 3635–3070, 1670, 1170, 1035 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ1.39 (s, 3 H, C(CH_3)); 1.37–1.54 (m, 1H, –CH–CH_2–CH_2), 1.90–2.31 (m, 2H, –CH–CH_2–CH_2; 1H, –CH–CH_2–CH_2), 3.05–3.16 (m, 1H, NCH_2); 3.37–3.52 (m, 1H, NC*H*2), 3.57 (dq, $^3J_{H-H} = 6.6$ Hz, $^3J_{H-H} = 8.8$ Hz, 1H, NC*H*); 3.74 (d, $^3J_{H-H} = 6.6$ Hz, 1H, C*H*(OH)); ^{13}C NMR (62.9 MHz, $CDCl_3$): 21.4 (C(*C*H_3)), 26.7, 29.7 (s, s, CH–*C*H_2–*C*H_2); 41.2 (–N–*C*H_2–), 66.6 (N–*C*H), 79.2 (–C(*C*H_3)–), 79.7 (*C*H(OH)); 172.7 (*C*(O)N); EIMS *m*/*z* 172.1 [MH^+]; Anal. Calcd for C_8 $H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.34; H, 7.40; N, 8.05; **2d**: isolated yield 62%, powder; $R_f = 0.40$ (ethyl acetate/hexane, 1:1); mp 117 °C; $[\alpha]_D = -42.1$ (*c* 0.3, $CHCl_3$), IR(KBr) 3595–3145, 1746, 1665, 1169, 1111 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.24 (t, $^3J_{H-H} = 7.0$ Hz, 3H, OCH_2CH_3), 1.39 (s, 3H, CH_3),1.43 (s, 9H, C(CH_3)$_3$), 1.70–2.80 (m, 4H, CH–CH_2–CH_2), 2.90–3.10 (m, 1H, N–C*H*–CH_2), 3.11–3.30 (m, 1H, N–C*H*–CH_2), 3.60–3.70 (m, 1H, C*H*OH), 3.70–3.82 (m, 1H, N–C*H*–CHOH), 4.08 (q, $^3J_{H-H} = 7.0$ Hz, 2 H, OCH_2CH_3), 5.25–5.50 (m, 2 H, O*H*); Anal. Calcd for $C_{15}H_{27}NO_6$: C, 56.77; H, 8.57; N, 4.41. Found: C, 56.53; H, 8.40; N, 4.62 **2′d** isolated yield 15%, yellow oil; $R_f = 0.59$ (ethyl acetate/hexane, 1:1); $[\alpha]_D = -15.0$ (*c* 1.8, $CHCl_3$), IR(KBr) 3595–3145, 1746, 1692, 1165, 1110 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ 1.22 (t, $^3J_{H-H} = 7.0$ Hz, 3 H, OCH_2CH_3), 1.37 (s, 9H, C(CH_3)$_3$), 1.39 (s, 3H, CH_3), 1.57–2.05 (m, 4H, CH–CH_2–CH_2), 3.13–3.25 (m, 1H, N–C*H*–CH_2),3.25–3.50 (m, 1H, N–C*H*–CH_2), 3.52–3.65 (m, 1H, C*H*–OH), 3.77–3.95 (m, 1H, N–C*H*–CHOH), 4.18 (q, $^3J_{H-H} = 7.0$ Hz, 2H, OCH_2CH_3), 4.70–4.80 (m, 2H, O*H*); ^{13}C NMR (62.9 MHz, $CDCl_3$): 14.3 (OCH_2CH_3), 23.1 (C(*C*H_3)), 24.3 (CH–CH_2–*C*H_2), 28.5 (C(*C*H_3)$_3$, 47.9 (–N–*C*H_2–), 58.4 (N–*C*H), 61.5 (OCH_2CH_3), 75.9 (*C*H(OH)); 77.1 (–*C*(CH_3)), 81.1 (*C*(CH_3)$_3$), 158.5 (*C*(O), Boc), 173.0 (*C*(O) OCH_2CH_3).
15. Crystal data for **2d**: Molecular formula $C_{15}H_{27}N_1O_6$, $M = 317.38$, orthorhombic, $P2_12_12_1$, $a = 6.6830(1)$ Å, $b = 15.4722(2)$ Å, $c = 16.6539(3)$ Å, $V = 1722.03(5)$ Å^3, $Z = 4$, $D_c = 1.224$ mg m^{-3}. X-ray diffraction data were collected at room temperature with MoKα radiation using the Bruker AXS Kappa CCD system. The structure was solved using direct methods and the model was refined by full-matrix least-squares procedures on F^2 to values of $R_1 = 0.0352$ and of $Rw_2 = 0.0867$ for 1966 reflections with $I > 2\sigma(I)$. Crystal data for **4d**: Molecular formula $C_8H_{13}N_1O_3$, $M = 171.19$, monoclinic, $P2_1$, $a = 8.5580(1)$ Å, $b = 11.7910(2)$ Å, $c = 9.2980(2)$ Å, $\beta = 116.836(1)°$, $V = 837.19(2)$ Å^3, $Z = 4$, $D_c = 1.358$ mg m^{-3}. X-ray diffraction data were collected at room temperature with MoKα radiation using the Bruker AXS Kappa CCD system. The structure was solved using direct methods and the model was refined by full-matrix least-squares procedures on F^2 to values of $R_1 = 0.0314$ and of $Rw_2 = 0.0722$ for 1681 reflections with $I > 2\sigma(I)$. Details of the crystal structure (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 277301 and CCDC 277302 for **2d** and **4d**, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk]. These data can be obtained free of charge via http://www.ccdc.cam.uk/conts/retrieving.html (or from the Cambridge Data centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).
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