Straightforward Synthesis of Pyrrolidine Glycosidase Inhibitors *via* Asymmetric Hetero-Diels-Alder Reaction

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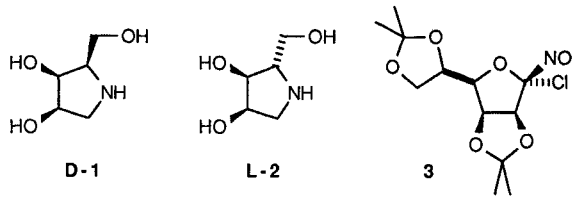
Received 9 September 1997

Abstract.- Base-catalysed rearrangement of the oxazine-carboxylate **8**, obtained from pentadienoic acid **4** by asymmetric hetero-Diels-Alder reaction followed by simple chemical transformations, led to the protected trihydroxy-proline **9**. Using various reduction conditions, the potent glycosidase inhibitors 1,4-dideoxy-1,4-imino-D-lyxitol **D-1** and 1,4-dideoxy-1,4-imino-L-ribitol **L-2** were obtained.

Introduction.- Some polyhydroxypyrrolidines are natural alkaloids which occur in *Leguminoseae* [1] or in Pteridophytes [2] and which possess glucosidase inhibitory [3] or immunostimulating properties [4] ; they show also some anti-HIV activity.[5]

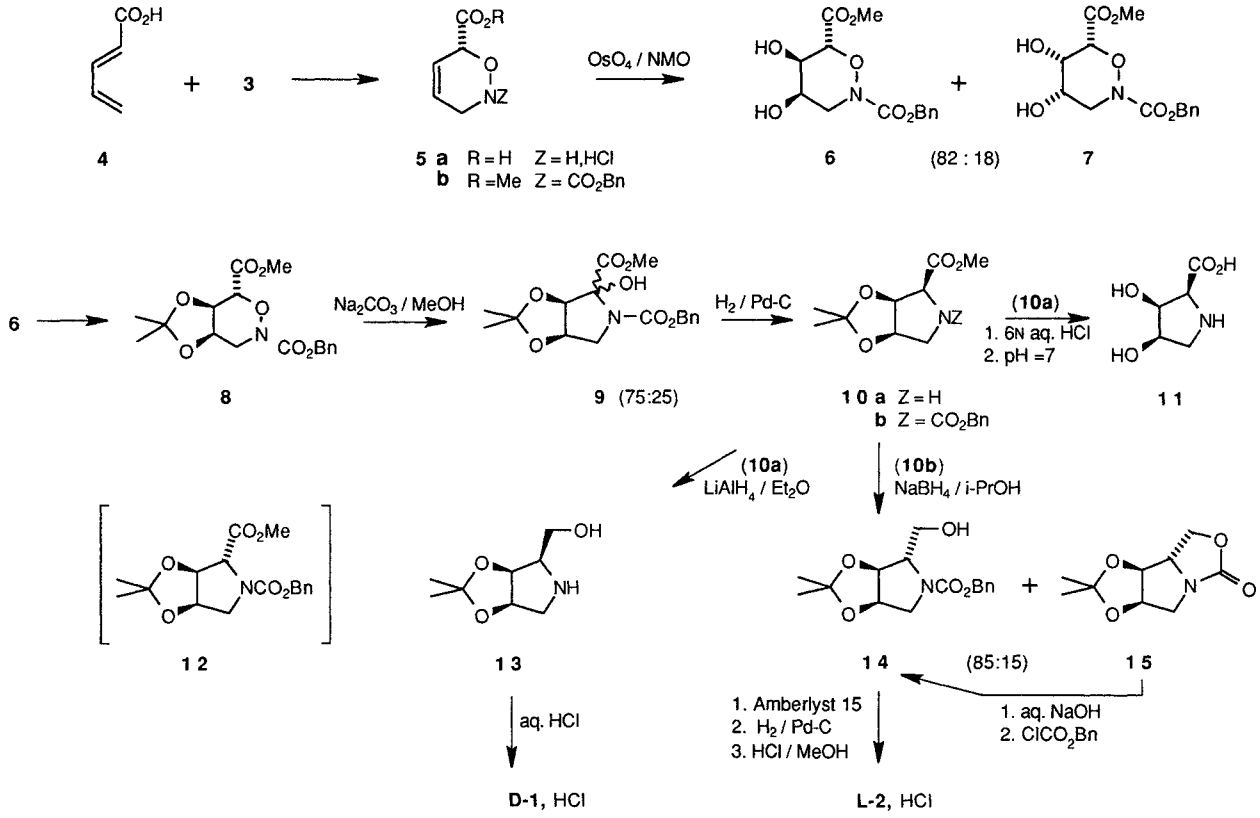
We describe herein the *de novo* synthesis of the two known 1,4-imino-1,4-deoxy-pentitols **D-1** and **L-2** in the D-lyxitol and L-ribitol series, respectively, starting from the easily available 1,3-pentadienoic acid [6] *via* hetero-Diels-Alder reaction with the chiral chloro-nitroso derivative **3** [7] that we had previously used for amino-sugar synthesis.[8,9] The key step is a base-induced rearrangement of the oxazane ring in γ-amino-ketone, which had already been studied by *Kresze*.[10]

The amino-D-lyxitol **D-1** is a glycosidase inhibitor and, in parti-cular, a powerful α-D-galactosidase inhibitor.[11] The amino-L-ribitol **L-2** possesses immunostimulating activities [4] whereas its enantiomer **D-2** is a glucosidase inhibitor.[12] Its pronounced biochemical properties account for the numerous syntheses of **D-1** [5,13,14,15], **D-2** [4,15,16] and **L-2**.[4,15,17]



Diels-Alder reaction.- Asymmetric Diels-Alder reaction of pentadienoic acid **4** with the chiral chloro-nitroso dienophile **3** (CH_2Cl_2/EtOH, overnight) gave in 75% yield the crystalline adduct **5a** as its hydrochloride, which was *N*-protected ($ClCO_2Bn$ / $NaHCO_3$) and esterified (HCl/MeOH) into **5b.** This reaction sequence was similar to the one we had followed for sorbic acid (1,4-hexadienoic acid) [9] and the absolute (6*R*) configuration for **5a** and **5b** was deduced by analogy.[7,9] According to ee-determination of **5b** by HPLC on chiral column [18], the enantioselectivity of this reaction was found to be 86% and rises to 95% after one recrystallisation of **5a.**

D-Lyxitol series.- Catalytic osmylation of **5b** (OsO_4, *N*-methylmorpholine (NMO), acetone/H_2O, 40°C, 5h) gave in 69% overall yield a 82:18 mixture of the two crystalline isomeric *cis*-diols **6** and **7**, which were separated by chromatography. Protection of the major *anti* diol **6** as the acetonide **8** (dimethoxypropane, Amberlyst-15, 1.5 h, rt, quant.)



Scheme

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followed by basic rearrangement with Na_2CO_3 in MeOH led to the γ-amino-ketone in its cyclic pyrrolidinic hemi-aminal form **9** as a 75:25 diastereoisomeric mixture, whose hydrogenolysis (Pd/C, MeOH, rt, 2.5 h) led to the crystalline dimethylacetal of *cis*-dihydroxy-L-proline methyl ester **10a**, which was characterised as the known *N*-protected **10b** [19,20,21] ($ClCO_2Bn$, $NaHCO_3$ in MeOH, rt) (94% yield from **6**). Deprotection of **10a** (aq. 6N HCl, 50°C, 1.5 d) gave in essentially quantitative yield the known (2*S*,3*S*,4*R*)-3,4-dihydroxy-L-proline **11**.[14,19]

Reduction of the methyl ester group of **10a** with $LiAlH_4$ in Et_2O[15] led without isomerisation to alcohol **13** and, after acidic deprotection (aq. HCl), to the 1,4-dideoxy-1,4-imino-D-lyxitol **D-1** in 85% yield from **10a** (30% from **4**), as a crystalline hydrochloride.[19]

L-Ribitol series.- It was reported that ester reduction of the *N*-protected all *cis* ester **10b** occurred much more slowly than with its 2-epimeric ester **12** [21] ; reduction of **10b** using $NaBH_4$ in *i*-PrOH (50°C, 6 h) led, *via* epimerisation to **12**, to reduction to the epimeric alcohol **14** as a mixture of this alcohol and its intramolecular cyclic urethane **15**. Opening of **15** by hydrolysis with aq. 2.5N NaOH and N-protection ($ClCO_2Bn$, $NaHCO_3$ in *i*-PrOH) again gave **14**, so that this reaction sequence when applied to the crude mixture of **14**, **15** led directly to the known epimeric alcohol **14** [4,20,21] in 69% overall yield from **10b**. Alcohol **14** was deprotected (Amberlyst-15 in EtOH, 80°C, 9 h ; then H_2/Pd-C, EtOH) and treated with HCl in MeOH to give the 1,4-dideoxy-1,4-imino-L-ribitol **L-2** in 85% yield from **14** (22% from **4**), as a crystalline hydrochloride.[19]

Pyrrolidines **10a** *and* **10b** : A soln of diol **6** (1.87 g, 6.0 mmol) in 2,2-dimethoxypropane (15 ml) was stirred at rt with Amberlyst-15 (0.24 g) for 1.5 h, then filtrated and evaporated to give crude **8** (2.8 g, quant.) which was reacted with stirring in MeOH (13 ml) with Na_2CO_3 (1.27 g, 12 mmol, 2 eq.) at rt for 1.5 h. After removing of the solids by centrifugation, the soln of **9** was hydrogenolysed over 5% Pd/C (0.15 g) at rt for 2.5 h. Removing of the catalyst by centrifugation led to a soln of **10a** (evaporation of the solvent give then quantitatively **10a**) which was protected by addition of $ClCO_2Bn$ (0.93 ml, 6.6 mmol, 1.1 eq.) and $NaHCO_3$ (1 g, 12 mmol, 2 eq.) and stirring for 15 mn. ; discarding of the solids, evaporation of the solvents and chromatography (CH_2Cl_2/Et_2O 6:4) gave pure **10b** (1.89 g, 94% yield from **6**).

Reduction of **10b** *to alcohol* **14** : To a soln of **10b** (0.53 g, 1.58 mmol) in *i*-PrOH (6ml) was added $NaBH_4$ (0.12 g, 3.17 mmol, 2 eq.). After stirring at 50°C for 6h, the soln was cooled at 0°C and water (0.7 ml) added. The partially formed cyclic urethane **15** was opened by addition under Ar of aq. 2.5N NaOH (0.65 ml, 1.62 mmol, 1 eq.) and stirring at 40°C for 6.5 h, then N-protected by addition of $NaHCO_3$ (0.53 g, 6.31mmol, 4 eq.) and $ClCO_2Bn$ (0.34 ml, 2.41 mmol, 1.5 eq.) and stirring at rt for 1h. The soln was diluted with water and extracted with CH_2Cl_2 (3x), the combined organic phases were dried over $MgSO_4$, and evaporated. Purification by chromatography (CH_2Cl_2/Et_2O 6:4) gave pure **14** (0.33 g, 69% yield from **10b**).

Acknowledgements: The support of the *Centre National de la Recherche Scientifique* (URA 135) and of the *Ministère de l'Enseignement Supérieur et de la Recherche* for a Ph. D. grant to Th. S. are gratefully acknowledged.

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(18) HPLC determination : Chiralpack AD Daicel column, UV detection: 254 nm, eluent : heptane/*i*-PrOH, 95/5 ; (±)-**5b** : Rt_1 for (6*R*) enantiomer = 26.4 mn, Rt_2 for (6*S*) enantiomer = 28.6 mn ; **5b** : Rt = 26.2 mn (k'_1=7.53, k'_2=7.95, k'_2/k'_1=1.095, res.=1.34, flow rate = 0.8 ml/mn, t°=26.7°C).

(19) **D-1**, HCl : mp= 157-9°C, $[\alpha]_D^{20}$=+21 (c=0.7, H_2O) ; lit.[11] : mp= 157-9°C, $[\alpha]_D^{20}$=+18.8 (c=0.16, H_2O) ; other physical data are in agreement with those of the lit.[13,14].
L-2, HCl : mp= 124-6°C, $[\alpha]_D^{15}$=–52 (c=0.6, H_2O) ; lit.[17] : mp= 126-131°C, $[\alpha]_D^{20}$=–59 (c=0.59, H_2O) ; other physical data are in agreement with those of the lit.[17].
6 : mp= 84-87°C (*i*-Pr_2O), $[\alpha]_D^{24}$=–40 (c=1, $CHCl_3$) ; IR ($CHCl_3$) : 3560, 1720, 1440, 1400, 1330, 1230, 1135, 1090 ; ^{1}H-NMR ($CDCl_3$): 7.34 (m, 5 arom.H), 5.25, 5.20 (2d, 2 benzyl. H, J=12.3), 4.66 (d, H-6), 4.30 (dd, Hb-3), 4.06 (m, H-4), 4.01 (m, H-5), 3.85 (s, OMe), 3.54 (dt, Ha-3), 3.44 (d, OH-5), 2.59 (t, OH-4),

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J(3a,3b)=14.5, *J*(3a,4)=1.8, *J*(3a,OH-4)=1.8, *J*(3b,4)=3.2, *J*(4,OH-4)=1.8, *J*(4,5)=3.1, *J*(5,OH-5)=3.4, *J*(5,6)=9.4. Anal. calc. for $C_{14}H_{17}NO_7$: C 54.02, H 5.51, N 4.50; found : C 53.8, H 5.3, N 4.4.

7 : mp= 132-4°C (*i*-PrOH), $[\alpha]_D^{23}$=–21 (c=1, $CHCl_3$) ; IR (KBr): 3460, 1710, 1700, 1440, 1410, 1340, 1300, 1220, 1085, 1070 ; ^{1}H-NMR ($CDCl_3$): 7.34 (m, 5 arom. H), 5.20 (s, 2 benzyl. H), 4.48 (d, H-6), 4.23 (m, H-5), 4.07 (dd, Hb-3), 3.81 (m, H-4), 3.81 (s, OMe), 3.45 (dd, Ha-3), 3.25 (d, OH-5), 3.14 (d, OH-4), *J*(3a,3b)=13.0, *J*(3a,4)=10.2, *J*(3b,4)=5.2, *J*(4,5)=3.2, *J*(4,OH-4)=8.0, *J*(5,OH-5)=5.5, *J*(5,6)=1.8. Anal. calc. for $C_{14}H_{17}NO_7$: C 54.02, H 5.51, N 4.50; found : C 53.7, H 5.5, N 4.4.

10b : resin, $[\alpha]_D^{20}$=–44 (c=1, $CHCl_3$) ; lit.[20] : $[\alpha]_D^{20}$=–46.5 (c=2.3, $CHCl_3$), identical ^{1}H- and ^{13}C-NMR data as in lit.[21].

11 : mp above 260°C (dec. and subl.), $[\alpha]_D^{18}$=–56 (c=0.6, H_2O) ; lit.[14] : mp dec. above 220°C, $[\alpha]_D^{20}$ =–56.8 (c=0.16, H_2O) ; other physical data are similar to those of the lit.[14].

14 : resin, $[\alpha]_D^{20}$=+40 (c=1, $CHCl_3$) ; for the D-enantiomer, lit.[20,21] : $[\alpha]_D^{20}$ =–46.0 (c=1, $CHCl_3$). Identical ^{1}H-NMR data as in lit.[4,21].

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