Tetrahedron Vol. 49, No. 30, pp. 6627-6636, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Efficient Total Syntheses of (1*R*, 2*R*, 3*R*, 9*R*, 9a*R*)-1,2,3,9-Tetrahydroxyquinolizidine and Its Enantiomer

Gloria Rassu,* Giovanni Casiraghi,* Luigi Pinna, Pietro Spanu, and Fausta Ulgheri

Dipartimento di Chimica dell'Università and Istituto per l'Applicazione delle Tecniche Chimiche Avanzate del CNR, Via Vienna 2, I-07100 Sassari, Italy.

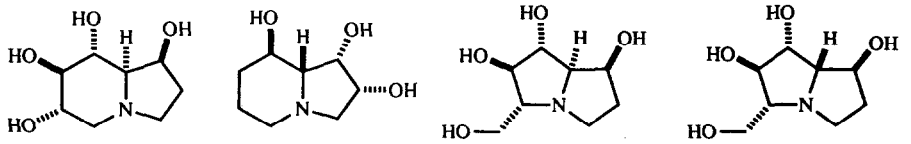
Mara Cornia and Franca Zanardi

Istituto di Chimica Organica dell'Università, Viale delle Scienze, I-43100 Parma, Italy

(*Received in UK* 19 *May* 1993)

Abstract: *Concise syntheses of two enantiomeric tetrahydroxyquinolizidines,* ***10*** *and ent-****10****, have been achieved from D-arabinose and L-arabinose, respectively. Highly diastereoselective homologation of imine* ***5*** *(or ent-****5****) using 2-(trimethylsiloxy)furan provided the nine-carbon butenolide* ***6*** *(or ent-****6****) which was elaborated into the quinolizidine* ***10*** *(or ent-****10****) via a clean sequence involving, as key operations, DBU-promoted γ-lactone to δ-lactam ring expansion (e.g.* ***7*** *to* ***8****) and cyclodehydration of a fully-deprotected hydroxypiperidine employing Ph3P, CCl4, Et3N (e.g.* ***9*** *to* ***10****). The procedure comprises five steps from* ***5*** *or ent-****5*** *and provides the title quinolizidine* ***10*** *or its enantiomer ent-****10*** *in 36-37% overall yields.*

Development of methods for the synthesis of pyranoses and furanoses in which the ring oxygen is replaced by nitrogen (azasugars) is currently an area of intense investigation.[1-3] Such skeletons form the basic structures of several biologically active alkaloids[4] such as castanospermine (**1**),[5] swainsonine (**2**),[6] australine (**3**),[7] and alexine (**4**).[8]

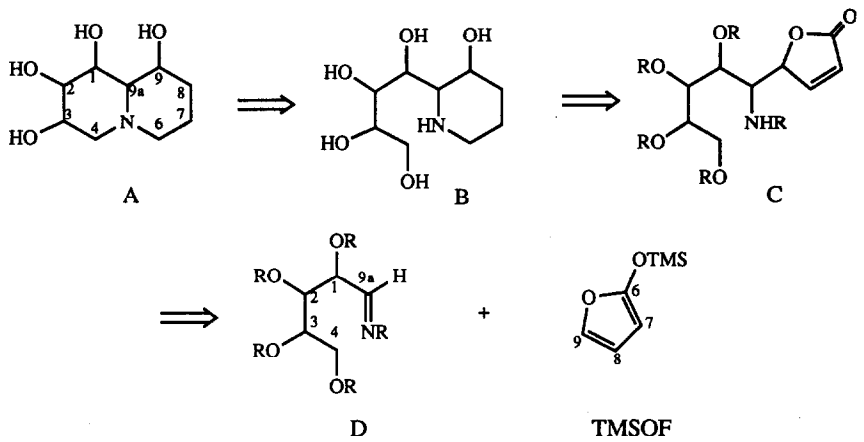


1 **2** **3** **4**

Compound **1** is a potent competitive and reversible inhibitor of various glucosidases, exhibiting anticancer, antiviral, and antiretroviral activities;[9] **2** displays remarkable physiological effects such as an α-D-mannosidase activity and immunoregulating capability;[10] **3** and **4**, ring-contracted congeners of

castanospermine, have recently been reported to act as potent glucosidase inhibitors, showing promise for application in anti-HIV chemotherapy.[11]

In the continuation of a research program to develop synthetically efficient approaches to azasugars and hydroxylated alkaloids, [12] we wish now to report a concise diastereoselective entry to (1*R*, 2*R*, 3*R*, 9*R*, 9a*R*)-1,2,3,9-tetrahydroxyquinolizidine (**10**) and its enantiomer *ent*-**10** which can be regarded as analogues of D- and L-1,6-diepicastanospermine.[13] The methodology utilises condensation of 2-(trimethylsiloxy)furan (TMSOF) with D- and L-arabinose-derived imines **5** and *ent*-**5** to generate the nine-carbon skeleton and chirality of the targets. A retrosynthetic plan for these alkaloids is depicted in Scheme 1.



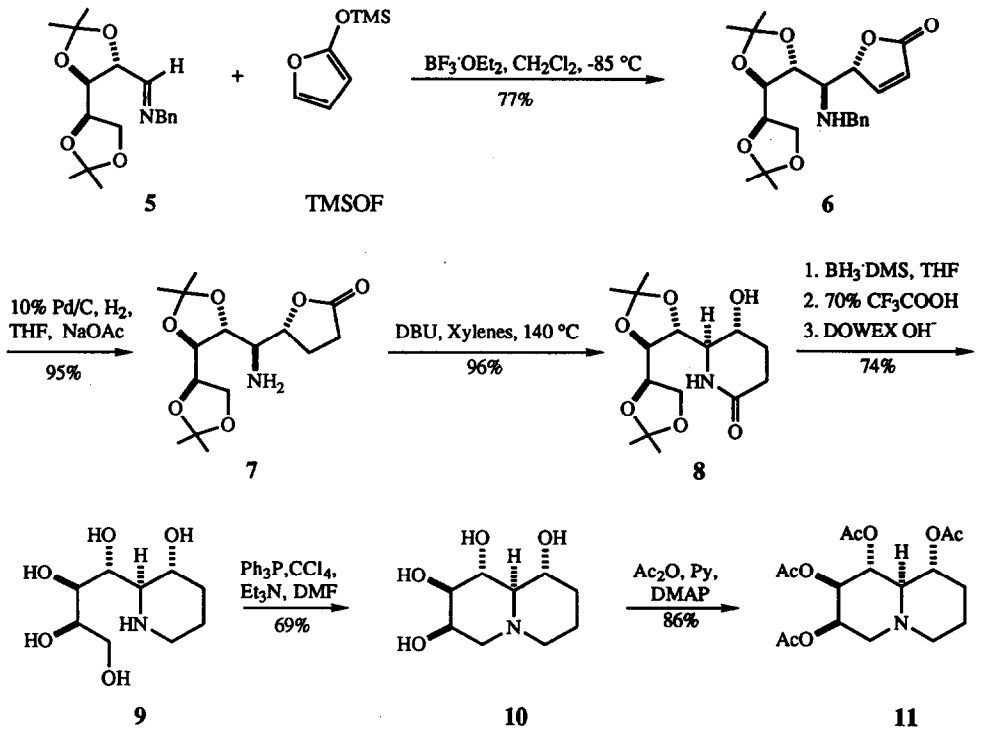
Scheme 1

The analysis shows that a disconnection of the C(4)-N bond of the quinolizidine molecule A would lead to monocyclic piperidine B which could be obtained from unsaturated γ-lactone C by hydrogenation, ring-enlargement, and subsequent carbonyl reduction. Nine-carbon lactone C could arise from pentose imine D via homologation by four carbon atoms using TMSOF.

Enantiomeric N-benzylimines **5** and *ent*-**5** were prepared from the corresponding sugars in ca 60% overall yields via a four steps sequence involving dithioacetalization (EtSH, HCl, $ZnCl_2$), protection (Me_2CO, H_2SO_4), aldehyde deblocking (HgO, $HgCl_2$, aq Me_2CO), and imine formation ($BnNH_2$, Et_2O, anhyd. $MgSO_4$).[14] Condensation of **5** with TMSOF was performed in CH_2Cl_2 at -85 °C in the presence of 1.0 equiv. of BF_3 etherate. This provided butenolide **6** as a single diastereomer in 77% isolated yield (Scheme 2).[15] Catalytic hydrogenation of **6** over palladium on carbon in NaOAc-buffered THF resulted in double bond saturation with concomitant removal of the nitrogen protecting group leading to crystalline amine **7** in 95% yield. Almost quantitative γ-lactone to δ-lactam ring expansion was obtained by exposing **7** to 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in xylenes at 140 °C. There was obtained crystalline lactam **8** (96%) whose stereochemistry was supported by the large coupling constant ($J_{4,5}$= 8.1 Hz) between the C(4) and C(5) protons in trans-diaxial disposition.

Reduction of the lactam **8** with borane-dimethyl sulfide complex in THF afforded an amine-borane adduct (not isolated) which was directly deprotected by treatment with 70% aqueous trifluoroacetic acid at

room temperature. Application of the crude reaction mixture to a Dowex OH^- column, elution with water, and lyophilization provided the pentahydroxypiperidine **9** in 74% yield from **8**. Finally, the aminoalcohol **9** was exposed at room temperature to Ph_3P, CCl_4, Et_3N in anhydrous dimethylformamide.[16] This led cleanly to intramolecular dehydration, resulting in formation of the quinolizidine **10** in 69% yield (36% from **5**).



Scheme 2

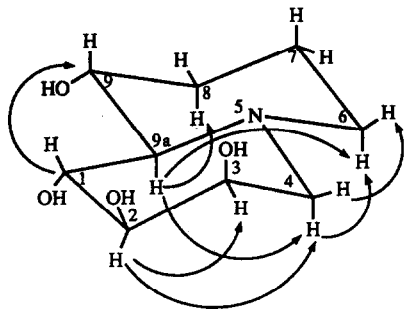
Paralleling exactly the above five steps protocol (enantiomeric series not shown in Scheme 2), (1*S*, 2*S*, 3*S*, 9*S* 9a*S*)-1,2,3,9-tetrahydroxyquinolizidine (*ent*-**10**) was constructed in 37% overall yield by starting with *ent*-**5**, via *ent*-**6**, *ent*-**7**, *ent*-**8**, and *ent*-**9** intermediates. As expected, *ent*-**10** displayed ^1H and ^{13}C NMR spectral characteristics identical to those observed for **10**, while the rotation value showed reverted sign.

Crystalline 1,2,3,9-tetra-*O*-acetyl derivative **11** was prepared from **10** in 86% yield via peracetylation by a standard method (Ac_2O, pyridine, DMAP). The stereochemistry of **11** was inferred from the 400 MHz ^1H NMR spectrum in $CDCl_3$ solution. Examination of the vicinal ^1H-^1H coupling constants (Figure 1) revealed that the less substituted ring exists in a perfect chair conformation with the C(9)OH in equatorial disposition, while the more substituted ring adopts a half-chair conformation.

The angular proton C(9a)H, anti relative to the lone pair on N(5), has an axial orientation relative to both the piperidine rings resulting in the observation of axial-axial couplings (J=9.3 and 6.3 Hz) with protons C(9)H and C(1)H. In addition, the vicinal coupling constant values observed for the coupling of C(2)H with the cis-disposed proton C(3)H and the trans-disposed proton C(1)H (J =7.8 and 3.9 Hz) are in agreement

with the dihedral angles of about 10° and 110° estimated from inspection of a molecular model. The results of a 2D NOESY experiment clearly established the trans nature of the bicyclic ring. Particularly diagnostic were the observed NOE's between the angular methine proton at the ring fusion (9a-H) and 4-H_{ax}, 6-H_{ax}, and 8-H_{ax}, as well as the NOE's between 1-H and 9-H, 2-H and 4-H_{ax}, 4-H_{ax} and 6-H_{ax}, and 4-H_{eq} and 6-H_{eq}. The distance between the aforementioned protons is within the limit for observing NOE's only in the case of the trans junction of the rings. [17]

The enantiomeric quinolizidines **10** and *ent*-**10** were preliminary tested against various glycosidases. Compound **10** is a competitive inhibitor of human acidic α-D-mannosidase with a value of K_i of 8.5 μM at ph = 4.5. This compound is also a weak inhibitor of β-D-mannosidase (IC_{50} ca 6 mM), but does not show activity against α-D-glucosidase. In contrast, *ent*-**10** does not inhibit any glycosidase.



$J_{1,2}$ = 3.9	$J_{4ax,4eq}$ = -12.2
$J_{1,9a}$ = 6.3	$J_{6ax,7ax}$ = 11.4
$J_{2,3}$ = 7.8	$J_{7ax,8ax}$ = 12.0
$J_{3,4ax}$ = 4.5	$J_{8ax,9}$ = 12.0
$J_{3,4eq}$ = 3.9	$J_{9,9a}$ = 9.3

Figure 1. ^{1}H NMR analysis of **11**: the results of NOESY experiment (arrows) and selected couplings constants (Hz).

In conclusion, the homologation of protected arabinose imines using 2-(trimethylsiloxy)furan allowed us to open a synthetically efficient route to certain tetrahydroxylated quinolizidines, a scantly studied class of bioactive alkaloids. Remarkably, the key ring-closure reaction was performed on a polyhydroxylated intermediate (*e.g.* **9**) without recourse to functional groups manipulation. Overall, the synthesis encompasses five steps (>35% overall yield) from **5** or *ent*-**5** and conveniently provides **10** or *ent*-**10** by adopting clean and simple chemistry. Exploitation of this technique en route to quinolizidine, indolizidine, and pyrrolizidine alkaloids bearing different substitution and stereochemistry will be the subject of future work.[18]

EXPERIMENTAL SECTION

General. NMR spectra were recorded on a Varian XL 300 and Bruker AMX-400 instruments operating at 300.13 and 400.13 MHz, respectively. Chemical shifts (δ) are given in ppm, coupling constants (*J*) in Hz. Optical rotations ($[\alpha]_D$) were measured on a Perkin-Elmer 241 instrument and are recorded in units of 10^{-1} deg cm^2 g^{-1}. The m.p.s. (Tottoli) are uncorrected. Column chromatography was invariably performed on Merck silica gel 70-230 Mesh. Kieselgel 60 F_{254} (from Merck) was used for TLC. All the solvents were distilled before use: THF over Na/benzophenone; Et_2O over $LiAlH_4$; CH_2Cl_2 over CaH_2. Elemental analyses were performed by the Microanalytical Laboratory of University of Sassari.

2-(Trimethylsiloxy)furan (TMSOF). This was prepared from 2-furaldehyde via 2(5H)furanone, according to the Brimble procedure.[19]

2,3;4,5-Di-*O*-isopropylidene-D- and L-arabinose. These protected derivatives were prepared from the corresponding sugars via dithioacetal formation, acetonidation, and deprotection of the aldehyde function, by following the procedures of Zinner.[14]

2,3;4,5-Di-*O*-isopropylidene-D- and L-arabinose *N*-benzylimine (5 and *ent*-5). These imines were prepared by reacting the above protected arabinose derivatives with benzylamine (1.0 equiv.) in anhydrous diethyl ether at room temperature (3h) in the presence of anhydrous $MgSO_4$. After filtration and removal of the ether, imines 5 and *ent*-5 were obtained quantitatively. These were used as such in the next reactions.

5-*N*-Benzylamino-6,7;8,9-di-*O*-isopropylidene-2,3,5-trideoxy-D-*glycero*-D-*talo*-non-2-enono-1,4-lactone (6). To a solution of imine 5 (3.02 g, 9.45 mmol) in anhydrous CH_2Cl_2 (60 mL), TMSOF (1.87 mL, 11.34 mmol) and $BF_3{\cdot}OEt_2$ (1.16 mL, 9.45 mmol) were added under argon at -85 °C. The mixture was stirred at this temperature for 30 min, then a saturated aqueous $NaHCO_3$ solution was added at -85 °C. After ambient temperature was reached, the slurry was extracted with diethyl ether (3x50 mL) and, after drying ($MgSO_4$), the solvent was evaporated under vacuum to give an oily residue. Flash chromatography over silica gel (hexane:EtOAc 6:4) furnished pure 6 (2.94 g, 77%) as a colorless oil (Found: C, 65.57; H, 7.40; N, 3.39. $C_{22}H_{29}NO_6$ requires C, 65.49; H, 7.24; N, 3.47 %); $[\alpha]_D^{22}$ -95.6 (c 0.91 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 1.32 (3H, s, Me), 1.35 (6H, s, Me_2), 1.38 (3H, s, Me), 3.19 (1H, bd, *J* 6.3, NH), 3.8-4.2 (8H, m), 5.15 (1H, dt, *J* 6.0 and 1.8, 4-H), 6.13 (1H, dd, *J* 5.7 and 1.8, 2-H), 7.28 (5H, m, CH_2Ph), 7.58 (1H, dd, *J* 5.7 and 1.5, 3-H); δ_C (75.2 MHz, $CDCl_3$) 25.07, 26.58, 26.98 (2C), 53.66, 58.66, 68.06, 77.04, 77.81, 80.65, 85.76, 109.61, 109.84, 122.25, 127.20, 128.08 (2C), 128.44 (2C), 140.11, 155.64, 173.06.

5-Amino-6,7;8,9-di-*O*-isopropylidene-2,3,5-trideoxy-D-*glycero*-D-*talo*-nonono-1,4-lactone (7). To a solution of 6 (2.50 g, 6.18 mmol) in anhydrous THF (100 mL), 10% Pd on carbon (0.25 g) and NaOAc (0.1 g) were added and the mixture was subjected to hydrogenation at ambient temperature and pressure for 8 h. Filtration, evaporation of the solvent, and flash chromatography over silica gel (AcOEt) afforded pure amine 7 (1.85 g, 95%), m.p. 64-66 °C (Found: C, 57.29; H, 8.14; N, 4.66. $C_{15}H_{25}NO_6$ requires C, 57.13; H, 7.99; N, 4.44 %); $[\alpha]_D^{22}$ +27.9 (c 1.4 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 1.33, 1.35, 1.39, 1.40 (each 3H, s, 4xMe), 1.45 (2H, bs, NH_2), 2.19 (1H, m, 3-H), 2.35 (1H, m, 3-H'), 2.57 (2H, m, 2-H_2), 3.12 (1H, dd, *J* 7.6 and 2.1, 5-H), 3.8-4.2 (5H, m, 6-H, 7-H, 8-H and 9-H_2), 4.48 (1H, q, *J* 7.4, 4-H); δ_C (75.2 MHz, $CDCl_3$) 24.35, 25.06, 26.61, 26.84, 26.96, 28.76, 53.63, 67.83, 77.08, 77.36, 79.70, 81.80, 109.31, 109.56, 177.12.

6,7;8,9-Di-*O*-isopropylidene-2,3-dideoxy-D-*glycero*-D-*talo*-nonono-δ-lactone (8). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, 1.2 mL, 8 mmol) was added to a stirred solution of amine 7

(1.25 g, 4 mmol) in xylenes (1 mL) and the mixture was heated at 140 °C for 6 h. The resulting syrup was concentrated under vacuum to leave mainly the title compound **8** which was purified by flash chromatography over silica gel (AcOEt). Crystallization of the purified product from chloroform-hexanes gave pure **8** (1.20 g, 96%) as colorless needles, m.p. 127-127 °C (Found: C, 56.99; H, 8.04; N, 4.56. $C_{15}H_{25}NO_6$ requires C, 57.13; H, 7.99; N, 4.44 %); $[\alpha]_D^{22}$ +45.3 (c 2.1 in $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 1.37, 1.38, 1.40, 1.45 (each 3H, s, 4xMe), 1.90 (1H, m, 3-H), 2.08 (1H, m, 3'-H), 2.38 (1H, ddd, *J* 18.3, 11.1, and 6.3, 2-H_{ax}), 2.51 (1H, ddd, *J* 18.3, 6.6, 4.2, 2-H_{eq}), 3.41 (1H, t, *J* 8.1, 5-H), 3.81 (1H, ddd, *J* 11.4, 7.8, and 3.9, 4-H), 3.90 (1H, dd, *J* 8.4 and 6.6, 6-H), 3.99 (1H, dd, *J* 9.0 and 5.7, 9-H), 4.07 (1H, dd, *J* 9.0 and 6.3, 7-H), 4.12 (1H, ddd, *J* 8.7, 5.5 and 5.7, 8-H), 4.24 (1H, dd, *J* 8.7 and 5.7, 9'-H), 4.39 (1H, bd, *J* 4.2, OH), 6.19 (1H, s, NH); δ_C (75.2 MHz, $CDCl_3$) 25.14, 25.92, 26.26 (2C), 28.02, 28.81, 61.82, 66.47, 68.39, 77.39, 78.76, 82.93, 109.47, 110.48, 171.07.

1,2,3,5-Tetradeoxy-1,5-imino-D-*glycero*-D-*talo*-nonitol (9). To a solution of lactam **8** (0.95 g, 3.0 mmol) in anhydrous THF (30 mL), borane-dimethyl sulfide complex (2.85 mL, 30 mmol) was added dropwise at room temperarure under stirring. After the mixture was allowed to react for 24 h under argon, methanol (20 mL) was carefully added and the mixture concentrated in vacuo to give a residue which was directly chromatographed on silica gel eluting with ethyl acetate. This gave rise to a single semisolid product, presumably an amine-borane complex, which was not characterized. This material was dissolved in 70% aqueous trifluoroacetic acid (5 mL) and allowed to stir at ambient temperatrure overnight. The solvent was removed and the glassy residue dissolved in distilled water (5 mL) and passed through a column charged with ca 2 g of DOWEX 1X8 resin in OH^- form, eluting with water. Evaporation of the solvent under vaccum and lyophilization afforded the free base **9** (0.49 g, 74%) as a white powder. A very pure sample was obtained by flash chromatography over silica gel eluting with MeOH:AcOEt:30% NH_4OH 5:5:2 mixture (Found: C, 48.92; H, 8.52; N, 6.01. $C_9H_{19}NO_5$ requires C, 48.86; H, 8.66; N, 6.33 %); $[\alpha]_D^{22}$ +37.8 (c 1.48 in MeOH); δ_H (300 MHz, D_2O) 1.38 (1H, qm, *J* ~12, 3-H_{ax}), 1.53 (1H, qm, *J* ~12, 2-H_{ax}), 1.76 (1H, dm, *J* ~13, H-2$_{eq}$), 1.94 (1H, dm, *J* ~13, H-3$_{eq}$), 2.80 (1H, td, *J* 12.3, 12.3, 3.3, 1-H_{ax}), 2.96 (1H, dd, *J* 9.0 and 2.7, 5-H), 3.12 (1H, bd, *J* ~12, 1-H_{eq}), 3.4-3.7 (5H, m), 4.22 (1H, bs); δ_C (75.2 MHz, D_2O) 22.00, 32.17, 45.34, 64.64, 65.60, 65.65, 66.64, 72.65, 75.30.

(1*R*, 2*R*, 3 *R*, 9 *R*, 9$_a$ *R*)-1,2,3,9-Tetrahydroxyquinolizidine (10). To a solution of piperidine **9** (0.35 g, 1.6 mmol) in anhydrous DMF (5 mL), triphenylphosphine (0.83 g, 3.2 mmol), CCl_4 (307 µL, 3.2 mmol), and triethylamine (435 µL, 3.14 mmol) were added under stirring at room temperature in the dark. The mixture was allowed to react for 12 h, then methanol (3 mL)was slowly added and the solution stirred for 30 min. The solvent was removed under vacuum and the brown oily residue chromatographed over SiO_2 eluting with a EtOAc:MeOH 1:1 solvent mixture. This afforded the title quinolizidine **10** (0.22 g, 69 %) as a white foam (Found: C, 53.25; H, 8.17; N, 6.95. $C_9H_{17}NO_4$ requires C, 53.19; H, 8.43; N, 6.89 %); $[\alpha]_D^{22}$ +35.0 (c 0.8 in MeOH); $[\alpha]_{578}^{22}$ +36.2; $[\alpha]_{546}^{22}$ +38.7;$[\alpha]_{436}^{22}$ +67.5;$[\alpha]_{365}^{22}$ +102.5; δ_H (300 MHz, CD_3OD) 1.46 (1H, qd, *J* 11.4 and 4.2, 8-H_{ax}), 1.73 (1H, m, 7-H_{ax}), 1.84 (1H, m, 7-H_{eq}), 2.12 (1H, dq, *J* 12.3 and 4.2, 8-H_{eq}), 2.66 (1H, m, 6-H_{ax}), 2.78 (1H, dd, *J* 9.3 and 5.7, 9$_a$-H), 2.99 (1H, dt, *J* 11.7 and 3.0, 6-H_{eq}), 3.70 (2H, m, 3-H and 9-H), 3.74 (1H, dd, *J* 11.7 and 4.2, 4-H_{eq}), 3.84 (1H, dd, *J* 11.7

and 4.5, H-4_{ax}), 4.17 (1H, dd, *J* 5.1 and 3.6, 1-H), 4.27 (1H, dd, *J* 7.2 and 3.6, 2-H); δ_C (75.2 MHz, CD_3OD) 23.40, 33.77, 47.58, 60.31, 64.75, 67.75, 68.67, 79.35, 79.46.

(1*R*, 2*R*, 3 *R*, 9 *R*, 9_a *R*)-1,2,3,9-Tetraacetoxyquinolizidine (11). A stirred solution of quinolizidine **10** (100 mg, 0.5 mmol), dry pyridine (1 mL), Ac_2O (500 μL), and DMAP (10 mg) was left under argon for 14 h. Evaporation of the solvent and subjection of the residue to silica gel column chromatography (hexanes:AcOEt 1:1 as eluant) gave a solid which was crystallized from hexanes:diethyl ether 1:1 to furnish pure tetraacetate **11** (160 mg, 86%) as colorless needles, m.p. 66-67.5 °C (Found: C, 54.69; H, 6.49; N, 3.70. $C_{17}H_{25}NO_8$ requires C, 54.98; H, 6.79; N, 3.77 %); $[\alpha]_D^{22}$ -3.5 (c 3.75 in $CHCl_3$) δ_H (400 MHz, $CDCl_3$) 1.25 (1H, qd, *J* 12.0 and 5.2, 8-H_{ax}), 1.61 (1H, m, 7-H_{ax}), 1.68 (1H, m, 7-H_{eq}), 1.98, 2.04, 2.06, 2.09 (each 3H, s, 4xOAc), 2.12 (1H, dq, *J* 12.0 and 4.2, 8-H_{eq}), 2.50 (1H, td, *J* 11.4 and 3.3, 6-H_{ax}), 2.94 (1H, dt, *J* 10.5 and 3.0, 6-H_{eq}), 3.12 (1H, dd, *J* 9.3 and 6.3, 9_a-H), 3.75 (1H, apparent quint., *J* 7.8, 4.2 and 4.2, 3-H), 4.07 (1H, dd, *J* 12.0 and 3.9, 4-H_{eq}), 4.25 (1H, dd, *J*12.3 and 4.5, 4-H_{ax}), 4.75 (1H, ddd, *J* 10.8, 9.6 and 4.5, 9-H), 5.26 (1H, dd, *J* 7.8 and 3.9, 2-H), 5.45 (1H, dd, *J* 6.3 and 3.3, 1-H); δ_C (100.13 MHz, $CDCl_3$) 20.70 (CH_3), 20.76 (CH_3), 21.08 (CH_3), 21.13 (CH_3), 22.75 (7-CH_2), 30.00 (8-CH_2), 46.47 (6-CH_2), 59.58 (4-CH_2), 60.70 (9a-CH), 63.43 (9-CH), 68.83 (3-CH), 76.03 (1-CH), 77.30 (2-CH), 169.51 (CO), 169.83 (CO), 169.94 (CO), 170.11 (CO).

5-*N*-Benzylamino-6,7;8,9-di-*O*-isopropylidene-2,3,5-trideoxy-L-*glycero*-L-*talo*-non-2-enono-1,4-lactone (*ent*-6). The title compound was prepared by starting with L-arabinose imine *ent*-**5** (1.05 g, 3.0 mmol) following the procedure described for its enantiomer **6**. Yield 1.18 g (80%), colorless foam; $[\alpha]_D^{22}$+96.3 (*c* 1.2 in $CHCl_3$). ^1H and ^{13}C NMR, see compound **6** (Found: C, 65.39; H, 7.36; N, 3.39. $C_{22}H_{29}NO_6$ requires C, 65.49; H, 7.24; N, 3.47 %).

5-Amino-6,7;8,9-di-*O*-isopropylidene-2,3,5-trideoxy-L-*glycero*-L-*talo*-nonono-1,4-lactone (*ent*-7). The title compound was prepared by starting with *ent*-**6** (0.95 g, 2.35 mmol) following the procedure described for its enantiomer **7**. Yield 675 mg (92 %), m.p. 68-69°C; $[\alpha]_D^{22}$ -27.7 (*c* 1.8 in $CHCl_3$). ^1H and ^{13}C NMR, see compound **7** (Found: C, 57.19; H, 7.77; N, 4.56. $C_{15}H_{25}NO_6$ requires C, 57.13; H, 7.99; N, 4.44%).

6,7;8,9-Di-*O*-isopropylidene-2,3-dideoxy-L-*glycero*-L-*talo*-nonono-δ-lactam (*ent*-8). The title lactam was prepared by starting with *ent*-**7** (500 mg, 1.58 mmol) following the procedure described for its enantiomer **8**. Yield 470 mg (94 %), m.p. 126-128.5 °C; $[\alpha]_D^{22}$ -45.7 (*c* 1.6 in $CHCl_3$). ^1H snd ^{13}C NMR, see compound **8** (Found: C, 56.98; H, 7.88; N, 4.61. $C_{15}H_{25}NO_6$ requires C, 57.13; H, 7.99; N, 4.44 %).

1,2,3,5-Tetradeoxy-1,5-imino-L-*glycero*-L-*talo*-nonitol (*ent*-9). The title piperidine was prepared by starting with *ent*-**8** (350 mg, 1.11 mmol) following the procedure described for its enantiomer **9**. Yield 184 mg (75%), white foam; $[\alpha]_D^{22}$ -38.0 (c 1.2 in MeOH). ^1H and ^{13}C NMR, see compound **9** (Found: C, 48.89; H, 8.67; N, 6.15. $C_9H_{19}NO_5$ requires C, 48.86; H, 8.66; N, 6.33 %).

(1*S*, 2*S*, 3 *S*, 9 *S*, 9$_a$ *S*)-1,2,3,9-Tetrahydroxyquinolizidine (*ent*-10). The title quinolizidine was prepared by starting with *ent*-**9** (150 mg, 0.68 mmol) following the procedure described for its enantiomer **10**. Yield 98 mg (71%, 37% from *ent*-**5**) lyophilized powder; $[\alpha]_D^{22}$ -35.4 (c 0.6 in MeOH); $[\alpha]_{365}^{22}$ -100.9. Tetraacetate: colorless needles (acetone:hexanes), m.p. 67-69 °C; $[\alpha]_D^{22}$ +4.5 (c 0.3 in $CHCl_3$) (Found: C, 54.77; H, 6.84; N, 3.59. $C_{17}H_{25}NO_8$ requires C, 54.98; H, 6.79; N, 3.77%).

ACKNOWLEDGEMENT

Support for this work was provided by Consiglio Nazionale delle Ricerche, Italy. We would like to thank Prof. Pierre Vogel for useful suggestions about the direct cyclodehydration procedure using Ph_3P, CCl_4, Et_3N.

REFERENCES AND NOTES

1. *Monocyclic derivatives*: Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337. Auberson, Y.; Vogel, P. *Angew. Chem. Int. Ed. Engl* . **1989**, *28*, 1498. Fleet, G. W. J.; Ramsden, N. G.; Witty, D. R. *Tetrahedron* **1989**, *45*, 327. Bruce, I.; Fleet, G. W. J.; Cenci di Bello, I.; Winchester, B. *Tetrahedron Lett.* **1989**, *30*, 7257. Fleet, G. W. J.; Ramsden, N. G.; Witty, R. R. *Tetrahedron* **1989**, *45*, 319. Anzeveno, P. B.; Creemer, L. J. *Tetrahedron Lett.* **1990**, *31*, 2085. Aoyagi, S.; Fujimaki, S.; Kibayashi, C. *J. Chem. Soc , Chem. Commun.* **1990**, 1457. Straub, A.; Effemberger, F.; Fisher, P. *J. Org. Chem.* **1990**, *55*, 3926. Fleet, G. W. J.; Carpenter, N. M.; Peturson, S.; Ramsden, N. G. *Tetrahedron Lett.* **1990**, *31*, 409. Aoyagi, S.; Fujimaki, S.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1991**, *56*, 815. Liotta, L. J.; Lee, J.; Ganem, B. *Tetrahedron* **1991**, *47*, 2433. Robina, I.; Gearing, R. P.; Buchanan, J. G.; Wightman, R. H. *J. Chem. Soc, Perkin Trans. I* **1990**, 2622. Buchanan, J. G.; Lumbard, K. W.; Sturgeon, R. J.; Thompson, D. K.; Wightman, R. H. *J. Chem. Soc, Perkin Trans. I* **1990**, 699. Wehner, V.; Jäger, V. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1169. Jäger, V.; Hümmer, W. *Angew Chem. Int. Ed. Engl.* **1990**, *29*, 1171. Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294. Somfai, P.; He, H. M.; Tanner, D. *Tetrahedron Lett.* **1991**, *32*, 283. Hung, R. R.; Straub, J. A.; Whitesides, G. M. *J. Org. Chem.* **1991**, *56*, 3849. Barret, A. G. M.; Pilipauskas, D. *J. Org. Chem.***1991**, *56*, 2787. Liu, K. K.; Kajimoto, T.; Chen, L.; Zhong, Z.; Ichikawa, Y.; Wong, C. H. *J. Org. Chem.* **1991**, *56*, 6280. Kajimoto, T.; Chen. L.; Liu, K. K.; Wong, C. H. *J. Am. Chem. Soc.* **1991**, *113*, 6678. Kajimoto, T.; Liu, K. K.; Pederson, R. L.; Zhong, Z.; Ichikawa, Y.; Porco, Jr., J. A.; Wong, C. H. *J. Am. Chem. Soc.* **1991**, *113*, 6187. Wang, Y. F.; Dumas, D. P.; Wong, C. H. *Tetrahedron Lett.* **1993**, *34*, 403. Chen, L.; Dumas, D. P.; Wong, C. H. *J. Am. Chem. Soc.* **1992**, *114*, 741. Myerscough, P. M.; Fairbanks, A. J.; Jones, A. H.; Bruce, I.; Choi, S. S.; Fleet, G. W. J.; Al-Daher, S. S.; Cenci di Bello, I.; Winchester, B. *Tetrahedron* **1992**, *48*, 10177. Bruce, I.; Fleet, G. W. J.; Cenci di Bello, I.; Winchester, B. *Tetrahedron* **1992**, *48*, 10191. Reitz, A. B.; Baxter, E. W. *Tetrahedron Lett.* **1990**, *31*, 6777. Rajanikanth, J. B.; Szarek, W. A. *J. Chem. Soc., Perkin Trans. I* **1992**, 2151. Moss, S. F.; Vallance,

S. L. *J. Chem. Soc., Perkin Trans. I* **1992**, 1959. Takano, S.; Moriya, M.; Ogasawara, K. *Tetrahedron: Asymmetry* **1992**, *3*, 681.

2. *Pyrrolizidine and indolizidine derivatives*: Miller, S. A.; Chamberlin, A. R. *J. Am. Chem. Soc.* **1990**, *112*, 8100. Burgess, K.; Henderson, I. *Tetrahedron Lett.* **1990**, *31*, 6949. Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513. Reymond, J.-L; Pinkerton, A. A.; Vogel, P. *J. Org. Chem.* **1991**, *56*, 2128. Pearson, W. H.; Bergmeier, S. C. *J. Org. Chem.* **1991**, *56*, 1976. Takata, H.; Bamba, Y.; Tajima, M.; Momose, T. *J. Org. Chem.* **1991**, *56*, 240. Buchanan, J. G.; Jigajinni, V. B.; Singh, G.; Wightmann, R. H. *J. Chem. Soc., Perkin Trans. I* **1987**, 2377. Tatsuta, K.; Takahashi, H.; Amemiya, Y.; Kinoshite, M. *J. Am. Chem. Soc.* **1983**, *105*, 4096. Carpenter, N. M.; Fleet, G. W. J.; Cenci di Bello, I.; Winchester, B.; Fellows, L. E.; Nash, R. J. *Tetrahedron Lett.* **1989**, *30*, 7261. Fairbanks, A. J.; Fleet, G. W. J.; Jones, A. H.; Bruce, I.; Al Daher, S.; Cenci di Bello, I.; Winchester, B. *Tetrahedron* **1991**, *47*, 131. Pearson, W. H.; Hines, J. V. *Tetrahedron Lett.* **1991**, *32*, 5513. Choi, S.; Bruce, I.; Fairbanks, A. J.; Fleet, G. W. J.; Jones, A. H.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1991**, *32*, 5517. Knight, D. W.; Share, A. C.; Gallagher, P. T. *J. Chem. Soc., Perkin Trans. I* **1991**, 1615. Ikota, N. *Tetrahedron Lett.* **1992**, *33*, 2553. Hendry, D.; Hough, L.; Richardson, A. C. *Tetrahedron* **1988**, *44*, 6153. Idem, *Ibidem* **1988**, *44*, 6143. Takahata, H.; Banba, Y.; Momose, T. *Tetrahedron: Asymmetry* **1992**, *3*, 999. Herczegh, P.; Kovacs, I.; Szilagyi, L.; Zsely, M.; Sztaricskai, F. *Tetrahedron Lett.* **1992**, *33*, 3133. Lee, C. K.; Sim, K. Y.; Zhu, J. *Tetrahedron* **1992**, *48*, 8541. Maggini, M.; Prato, M.; Ranelli, M.; Scorrano, G. *Tetrahedron Lett.* **1992**, *33*, 6537. Burgess, K.; Chaplin, D. A. *Tetrahedron Lett* **1992**, *33*, 6077. Gallagher, T.; Giles, M.; Subramanian, R. S.; Hadley, M. S. *J. Chem. Soc., Chem. Commun.* **1992**, 166. St-Denis, Y.; Chan, T.-H. *J. Org. Chem.* **1992**, *57*, 3078. Burgess, K.; Chaplin, D. A.; Henderson, I. *J. Org. Chem.* **1992**, *57*, 1103. Zhou, P.; Salleh, H. M.; Honek, J. F. *J. Org. Chem.* **1993**, *58*, 264. Ina, H.; Kibayashi, C. *J. Org. Chem.* **1993**, *58*, 52. Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045. Kibayashi, C. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman Ed.; Elsevier, Amsterdam, 1992, p. 229. Michael, J. P. *Nat. Prod. Rep.* **1991**, *8*, 553. Robins, D. J. *Nat. Prod. Rep.* **1992**, *9*, 313.

3. *Polyhydroxylated Quinolizidine derivatives:* Liu, P. S.; Rogers, R. S.; Kang, M. S.; Sunkara, P. S. *Tetrahedron Lett.* **1991**, *32*, 5853. Gradnig, G.; Berger, A.; Grasberger, V.; Stutz, A. E.; Legler, G. *Tetrahedron Lett.* **1991**, *32*, 4889.

4. For recent reviews, see: Fellows, L. E.; Fleet, G. W. J. in *Natural Products Isolation* ; Wagman, G. H., Cooper, R., Eds.; Elsevier: Amsterdam, 1989; pp. 539-559. Elbein, A. D. *Crit. Rew. Biochem.* **1984**, *16*, 21.

5. Hohenschutz, L. D.; Bell, E. A.; Jewiss, P. J.; Leworthy, D. P.; Price, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811. Nash, R. J.; Fellows, L. E.; Dring, J. V.; Stirton, C. H.; Carter, D.; Hegarty, M. P.; Bell, E. A. *Phytochemistry* **1988**, *27*, 1403.

6. Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.* **1979**, *32*, 2257. Molyneux, R. J.; James, L. F. *Science* **1982**, *216*, 190.

7. Molyneux, R. J.; Benson, M.; Wong, R.; Tropea, J.; Elbein, A. D. *J. Nat. Prod.* **1988**, *51*, 1198.

8. Nash, R. J.; Fellows, L. E.; Bring, J. V.; Fleet, G. W. J.; Derome, A. E.; Hamor, T. A.; Scofield, A. M.; Watkin, D. J. *Tetrahedron Lett.* **1988**, *29*, 2487.

9. Saul, R.; Chambers, J. P.; Molyneux, R. J.; Elbein, A. D. *Arch. Biochem. Biophys.* **1983**, *221*, 593. Walker, B. O.; Kowalski, M.; Goh, W. C.; Kozarsky, K.; Krieger, M.; Rosen, C.; Rohrschneider, L.; Haseltine, W. A.; Sodroski, J. *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 8120. Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res.* **1986**, *46*, 5215.
10. Dorling, P. R.; Huxtable, G. R.; Colegate, S. M. *Biochem. J.* **1980**, *181*, 649. Dennis, J. W. *Cancer Res.* **1986**, *46*, 5131.
11. Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Girdhar, A.; Ramsden, N. G.; Peach, J. M.; Hegarty, M. P.; Scofield, A. M. *Phytochemistry* **1990**, *29*, 111. Elbein, A. D.; Tropea, J. E.; Molyneaux, R. J. *U. S. Pat. Appl.* US 289, 907. *Chem Abstr.* **1990**, *113*, P 91444p.
12. Rassu, G.; Pinna, L.; Spanu, P.; Culeddu, N.; Casiraghi, G.; Gasparri Fava, G.; Ferrari Belicchi, M.; Pelosi, G. *Tetrahedron* **1992**, *48*, 727. Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L. *J. Org. Chem.* **1992**, *57*, 3760.
13. Fleet, G. W. J.; Ramsden, N. G.; Nash, R. J.; Fellows, L. E.; Jacob, G. S.; Molyneux, R. J.; Cenci di Bello, I.; Winchester, B. *Carbohydrate Res.* **1990**, *205*, 269.
14. Zinner, H.; Brandner, H.; Rembarz, G. *Chem. Ber.* **1956**, *89*, 800. Zinner, H.; Wittenburg, E.; Rembarz, G. *Chem. Ber.* **1959**, *92*, 1614.
15. The 5,6-anti selectivity (*erythro*) observed in this case is consistent with the prediction based on nonchelate Felkin-Ahn model. See: Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Ahn, N. Y.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. Ahn, N. Y. *Top. Curr. Chem.* **1980**, *88*, 145. At the contrary, the 4,5-anti selectivity may be attributed to quantitative self-epimerization at C-4, owing to the basic nature of amine **6**.
16. Chen, Y.; Vogel, P. *Tetrahedron Lett.* **1992**, *33*, 4917. Siriwardena, A. H.; Chiaroni, A.; Riche, C.; Grierson, D. S. *J. Org. Chem.* **1992**, *57*, 5661. Paulvannan, K.; Schwarz, J. B.; Stille, J. R. *Tetrahedron Lett.* **1993**, *34*, 215.
17. The saturated quinolizidine **11** was inferred to have trans ring fusion on the basis of prominent Bohlmann bands between 2750 cm^{-1} and 2835 cm^{-1} in its infra-red spectrum. See: Bohlmann, F.; Schumann, D.; Schulz, M. *Tetrahedron Lett.* **1964**, 173. Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157.
18. By adapting the sinthetic protocol disclosed herein to *D*- and *L*-threose imine derivatives, expeditious syntheses of swainsonine analogs have been successfully achieved. Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L.; Ulgheri, F. *J. Org. Chem.* **1993**, *58*, in press.
19. Brimble, M.A.; Brimble, M.; Gibson, J. *J. Chem. Soc., Perkin Trans I* **1989**, 179.