Pergamon

Tetrahedron Vol. 50, No. 48, pp. 13671-13686, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00890-6

Cycloaddition Reactions of Carbohydrate Derivatives. Part V[1]. A Hetero Diels-Alder Approach to Swainsonine Analogs

Pál Herczegh*[a], Imre Kovács[a], László Szilágyi[b], Ferenc Sztaricskai[a]

[a]Research Group for Antibiotics of the Hungarian Academy of Sciences, H-4010 Debrecen, P.O. Box 70, Hungary
[b]Department of Organic Chemistry, Kossuth University, H-4010, P.O. Box 20, Hungary.

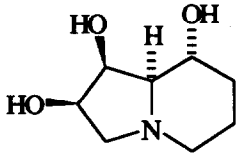
Amaya Berecibar, Claude Riche, Angèle Chiaroni
Alain Olesker and Gabor Lukacs

Institut de Chimie des Substances Naturelles du CNRS, 91198
Gif sur Yvette, France.

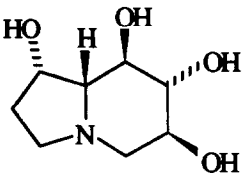
Abstract: Diastereoselective hetero Diels-Alder reactions of sugar derived azomethines **4a-4g** have been used for the construction of chiral piperidones **6** and **7**. Configuration of the major products was 6,1'-*threo* in every case. The enone system of **6** and **7** was reduced diastereoselectively and subsequently swainsonine-analog hydroxyindolizidines **28- 32** were prepared by an intramolecular reductive amination.

INTRODUCTION

Polyhydroxylated pyrrolidines, piperidines, indolizidines and quinolizidines can act as sugar mimics in various biological systems.[2-4] Many compounds of this type show potent specific, competitive glycosidase inhibitory activities, too. Hydroxylated indolizidine alkaloids swainsonine **1** and castanospermine **2** have potential medicinal applications as antimetastatic[5], antitumor[6], immunoregulatory[7] and anti-HIV[8,9] agents. A recent surge of activity into the synthetic chemistry of **1** and **2** and their analogs is also indicative of the importance of this area.[10-13] Recently we have devised a new synthetic route to hydroxylated indolizidines *via* cyclocondensation of sugar azomethines with Danishefsky's diene.[14] In the present paper we describe a more detailed study on that topic.



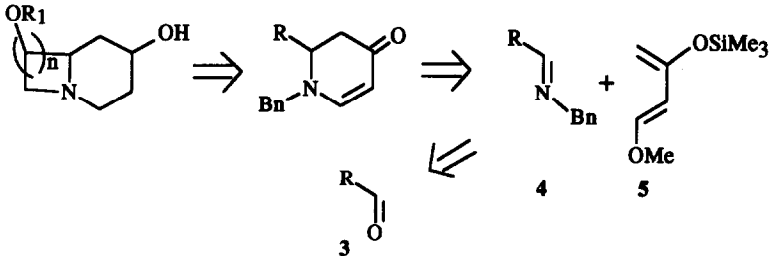
1



2

METHODS AND RESULTS

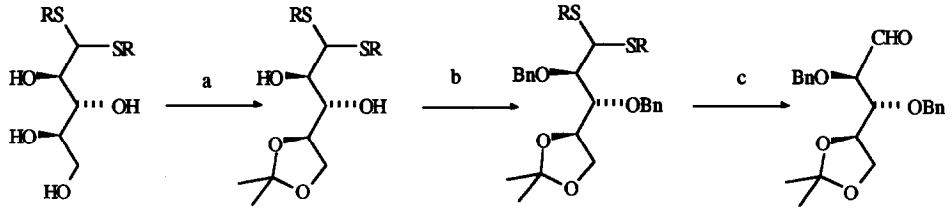
Our approach is based on the construction of a piperidine ring in a hetero Diels-Alder reaction of an azomethine **4**, prepared from a chiral aldehyde **3** (preferably made from sugars), with the activated diene **5** (Scheme 1). The configuration of the newly generated chiral center is determined by the aldehyde. Subsequently, a second, four to seven membered ring can be attached to the piperidine, bearing hydroxy substituents.



Scheme 1

Since the pioneering work of Danishefsky and Kerwin[15] numerous examples have appeared in the literature[16-33] of hetero Diels-Alder reactions of azomethines with activated dienes. In recent years chiral versions of this reaction have also been studied using asymmetric esters[22], amino acids[23-30], α-alkoxy-aldehydes[31,32], or a chiral catalyst.[33] This reaction is usually denoted as a [4+2] cycloaddition but Kunz and Pfrengle[24,25] postulated a tandem Mannich and Michael reactions sequence.

Chiral alkoxy aldehydes **3a-3g** served as starting compounds for the present study. They were prepared using literature methods (See Table 1) except **3e** which was synthesized from D-ribose mercaptals **8a**[39] or **8b**[40] using two alternative methods (Scheme 2). Kinetic monoisopropylidenation of **8a** with 2,2-dimethoxypropane, using pyridinium-*p*-toluenesulfonate catalyst[41] gave **9a**. Similar transformation of **8b** using 2-methoxypropene afforded **9b**.[42] Benzylation (**10a**, **10b**) and demercaptalization led to **3e**.



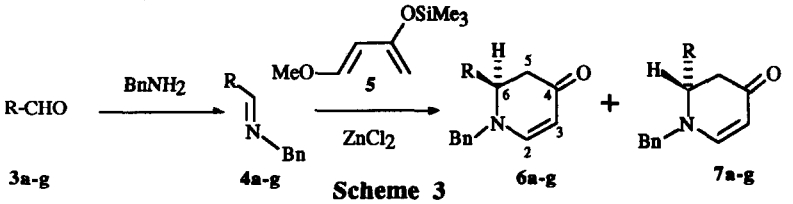
R = n-Pr **8a** **9a** **10a** **3e**

R = Et **8b** **9b** **10b**

a) DMP, Py-TsOH, acetone, rt, quant. (for **8a**); or 2-methoxypropene, TsOH, acetone, rt, 70% (for **8b**); b) NaH, BnBr, THF, $Bu_4N^+ I^-$, O°C to rt, 95-99%; c) HgO, H_2O/THF, $BF_3{\cdot}OEt_2$, rt, 64-70%.

Scheme 2

Aldehydes **3a-3g**, prepared according to the literature[34-38], were treated with benzylamine and the intermediate azomethines **4a-4g** were allowed to react with **5** in the presence of zinc chloride to give mixtures of diastereomeric pyridones **6** and **7** (Scheme 3, Table 1).



Scheme 3

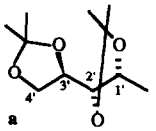
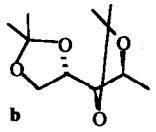
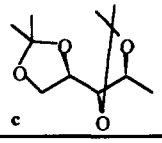
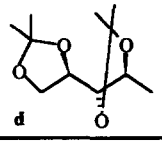
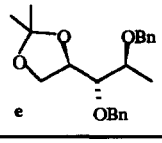
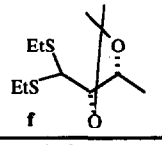
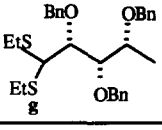
R	Literature	Solvent	Ratio of diast. 6/7	Yield (%)
 a	34	THF	06/94	79
		dioxane	17/83	79
 b	34	THF	94/06	80
 c	35	dioxane	67/33	65
 d	36	THF	90/10	61
 e		THF	65/35	62
		MeCN	95/05	76
 f	37	dioxane	14/86	77
 g	38	THF	20/80	65

Table 1

The configuration of the newly generated chiral center in the products could not be deduced from the NMR spectra because of free rotation around C-C bonds in the sugar side-chain. The stereostructure of the major product **7a** from **4a** and **5** could be determined as *S* using X-ray crystallography (Fig. 1).

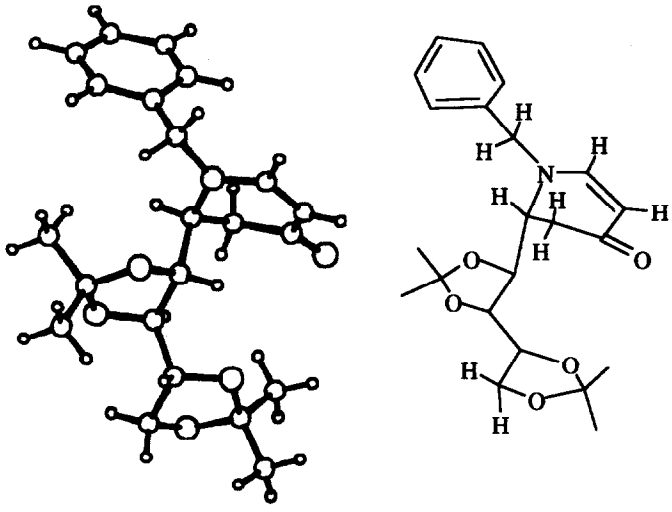


Figure 1

The CD-spectrum of **7a** exhibited a strong negative Cotton effect at 300 nm ($n \rightarrow \pi^*$ transition of the ketone). This is in good agreement with the theoretical work of Snatzke[46] and with a similar result for the piperidone type alkaloid multiflorin[47]. According to these data the configuration at the 6-position of our cycloadducts could be determined on the basis of the sign of the Cotton effect of their spectra : if it is negative the configuration at C-6 must be *S* (series **7**), if positive, the configuration must be *R* (series **6**).

Cyclocondensations of **4a-4g** proceeded with high diastereoselectivity. The configuration of the major products being 6,1'-*threo*. In the case of **4e** the selectivity was increased when using acetonitrile instead of THF. The stereoselectivity of the cycloadditions can be rationalized by assuming chelate stabilization by Lewis acid used (Fig. 2).

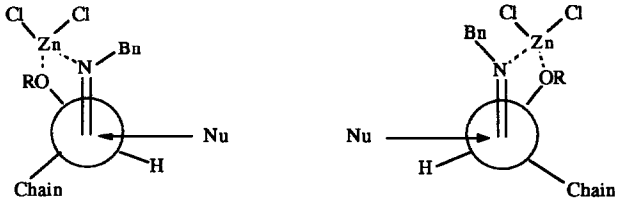


Figure 2

Next, **7a**, **6b**, **6d**, **6e** and **7e** were allowed to react with sodium borohydride in ethanol (Scheme 4). In all these cases fully diastereoselective reduction of the ring carbonyl was observed together with concomitant saturation of the double bond.

The configuration at C-4 in **12** was determined by an X-ray analysis (Fig. 3). For other derivatives this information could be deduced from the NMR spectra of the respective bicyclic end-products. The reason for the high diastereoselectivity observed in these reactions is under investigation.

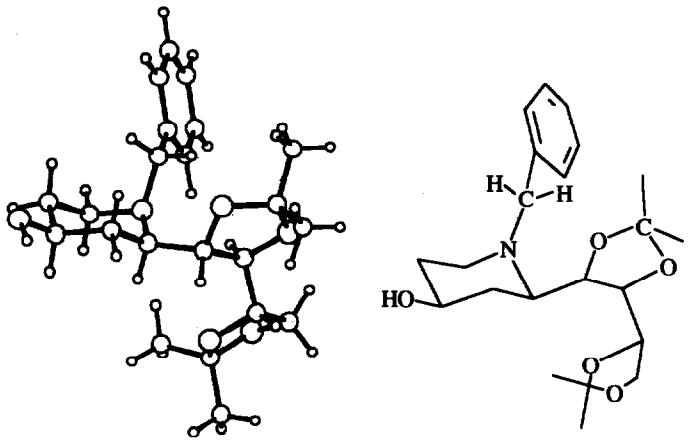
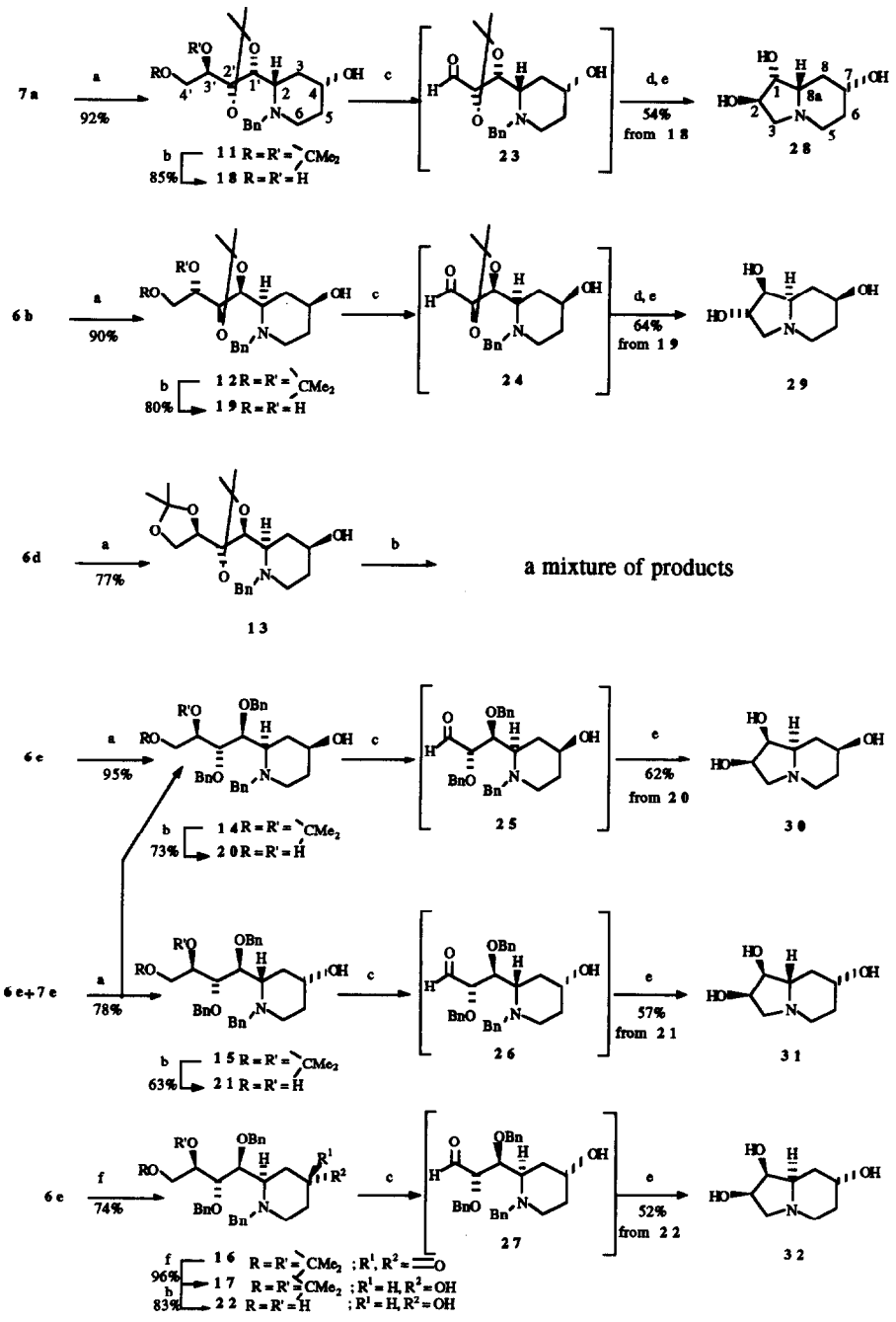


Figure 3

6e, upon treatment with L-selectride gave rise to the saturated ketone **16**[24], subsequent reaction of the latter with the same reagent resulted in **17**, the 4-epimer of **14**.

In order to construct the five-membered ring part of indolozidine, shortening of the tetraoxybutyl side-chains of **11**-**17** was necessary. Partial hydrolysis of the terminal isopropylidene groups in **11** and **12** was performed under mild, acidic conditions to give **18** and **19** respectively. Application of the same method to the *ribo* compound **13** resulted in the formation of a mixture of several products. Buchanan et al.[36] observed that D-ribose mercaptal gave on isopropylidination a 2,5:3,4-substituted product together with the expected 2,3:4,5-substituted compound. The former compound was formed under thermodynamic control. A similar rearrangement and subsequent partial hydrolysis can be assumed for **13**, too. Hydrolytic removal of the 4',5'-dioxolane group from **14**, **15** and **17** gave **20**, **21** and **22** respectively. Shortening of the side chains in **18**-**22** was achieved by glycol cleavage with lead(IV) acetate to give **23**-**27**. The latter compounds were used for the next step without purification.

Ring closure reactions in **25**-**27** were effected during catalytic hydrogenolysis. Ring closure reactions in the case of **23** and **24** were preceded by hydrolysis of the isopropylidene group followed by hydrogenolysis. Removal of the N- and O- protective groups had also taken place accompanied by intramolecular reductive amination of the aldehyde function, giving rise to the expected swainsonine analogs **28**-**32**.



a) $NaBH_4$, EtOH, rt, 16h ; b) H_2O/AcOH, 50-55°C, 12h ; c) $Pb(OAc)_4$, PhMe, 30 min. ; d) H_2O/CF_3CO_2H, r.t., 10 h ; e) H_2/Pd(C), AcOH, 16h ; f) L-Selectride, THF, -78°C, 1h → r.t.

Scheme 4

The structures of **28-32** have been ascertained by NMR spectroscopy including NOE experiments. NOE results, determined by using 1D or 2D (NOESY) measurements, relevant to the structures and conformations of the end-products are portrayed in Figure 4.

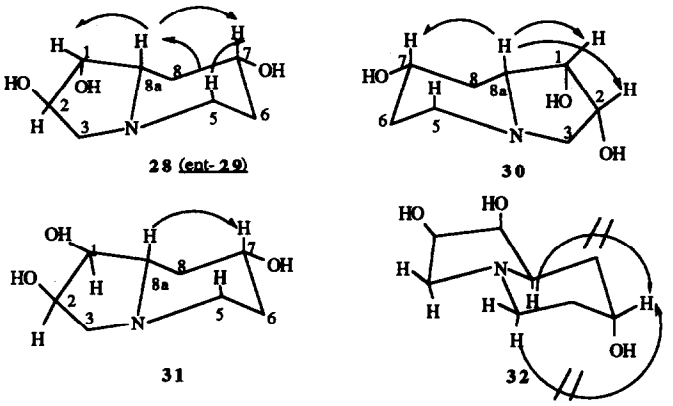


Figure 4

In the swainsonine analogs the hydroxy substituent of the six-membered ring is located at the C-7 position. Our derivatives **28** and **29** are the first representatives of this class of swainsonine analogs. Following our preliminary report[14] two papers appeared on the synthesis of **30**[13c] and **31**[13d]. **28** proved to be a moderate inhibitor of *Lupinus luteus* α-mannosidase ($K_i = 4.75 \times 10^{-4}$ M), while **29** inhibits β-glucosidase ($K_i = 1.6 \times 10^{-4}$ M). In their early work Colegate et al.[43] supposed that the 8-hydroxyl group is essential for biological activity. Our finding are in contradiction with that postulate. Cenci di Bello et al.[44] and Winkler and Holan[45] made attempts to find structure-activity relationships among swainsonine analogs. The latter authors summarize the configurational requirements for a potent mannosidase inhibitor. They assume that topographical equivalents of the 2- and 3- hydroxyl groups in the D-mannose molecule have the greatest influence on inhibitor efficiency. According to this theory **30** would be a potent α-mannosidase inhibitor because its C-1 and C-2 configurations are equivalent to the configurations at C-2 and C-3 of D-mannose. **30** is very similar also to swainsonine, configurations at C-1, C-2 and C-8a being the same in **1** and **30**. Rather surprisingly, we did not observe any α-mannosidase inhibitory activity of **30** against Jack bean or *Lupinus luteus* enzymes. Testing of other biological activities of our end-products is in progress.

EXPERIMENTAL

General methods. Adsorption chromatography was carried out using Kieselgel 60 for TLC, precoated aluminium-packed plates (Kieselgel 60 F_{203}, Merck) were used. Melting points were determined on a Kofler electric hot stage and were not corrected. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. I.R. spectra were recorded on a Perkin Elmer 283 D spectrometer in KBr pellets. ^1H and ^{13}C NMR spectra were obtained with Bruker WP200SY, WP250, WP300 and WP400 instruments. CI-MS spectra were recorded with a AEI SM-9 spectrometer using isobutane at 220°C, FAB spectra were obtained with an SM-80 instrument. X-Ray crystal Structure Determination : Data were collected on a CAD-4 Nonius

X-ray diffractometer, using graphite monochromated Cu Kα radiation and the θ - 2θ scan technique up to θ= 65°. Reflections having I> 3σ(I), σ(I) from counting statistics, were considered as observed , and kept in refinement calculations. The structures were solved by direct methods[48] and refined by full matrix least - squares, minimizing the function $\Sigma w(Fo - Fc)^2$ [49] with $w= 1/\sigma^2(Fo)+ 0.002070\ Fo2$ and $R_w= \{\Sigma w(Fo-Fc)^2/\Sigma wFo^2\}^{1/2}$. Difference Fourier maps showed all the hydrogen atoms. They were idealized (d C-H = 1.00 Å) and affected an isotropic thermal factor equivalent to that one of the bonded atom, plus 10%.

4,5-*Q*-Isopropylidene-D-ribose di-*n*-propyl-dithioacetal (9a). To a suspension of 8a (17.0 g, 60 mmol) in acetone (600 ml) 2,2-dimethoxypropane (14.7 mL, 120 mmol) and pyridinium *p*-toluenesulfonate (0.75 g, 3 mmol) were added under stirring. The agitation was continued for 1h until all of the starting material was dissolved. The reaction mixture was neutralized by the addition of saturated $NaHCO_3$ solution (20 mL) and evaporated to dryness. The residue was extracted with CH_2Cl_2 (400 mL), the organic phase was washed with $NaHCO_3$ and evaporated affording 9a as a syrup (21 g), pure enough for the next reaction step. A small sample was purified by chromatography (hexane-ethyl acetate 8 : 2). Oil, $[\alpha]_D$ +16.6 (c 2.12, $CHCl_3$), mass spectrum (E.I.): m/z 324 (M^+), ^1H NMR (200 MHz, $CDCl_3$) δ 4.43-3.65 (m, 6H, H-1 to H-5a,5b), 2.75-2.50 (m, 4H, 2 SCH_2), 1.45 and 1.37 [2s, 6H, $C(CH_3)_2$], Anal. Calcd for $C_{14}H_{28}O_4S_2$: C, 51.82; H, 8.70; S, 19.76. Found : C, 51.60; H, 8.67; S, 19.88.

4,5-*Q*-Isopropylidene-D-ribose diethyl-dithioacetal (9b). A solution of 8a (13.0 g, 50.7 mmol) in acetone (350 mL) was treated with 2-dimethoxypropene (15 mL, 157 mmol) and *p*-toluenesulfonic acid (96 mg) for 1.5h. After neutralizing with triethylamine, the mixture was evaporated and the residue was chromatographed using CH_2Cl_2 as eluent affording 10.5g (70%) of 9b. Oil, $[\alpha]_D$ +13.8 (c 1.0, $CHCl_3$), mass spectrum (C.I.): m/z 297 ($M^+ + H$), ^1H NMR (200 MHz, $CDCl_3$) δ 4.45-3.65 (m, 6H, H-1 to H-5a,5b), 2.80-2.60 (m, 4H, 2 SCH_2), 1.43 and 1.38 [2s, 6H, $C(CH_3)_2$]. Anal. Calcd for $C_{12}H_{24}O_4S_2$: C, 48.62; H, 8.16; S, 21.63. Found : C, 48.52; H, 8.18; S, 21.78.

2,3-di-*Q*-Benzyl-4,5-*Q*-isopropylidene-D-ribose di-*n*-propyl-dithioacetal (10a). 9a (20.14 g, 62 mmol) was benzylated at 0°C with benzyl bromide (15.5 mL, 130.3 mmol), sodium hydride (7.2 g 50% in oil, 150 mmol) and tetrabutylammonium iodide (1.16 g) in THF (130 mL) for 2h. Methanol (8 mL) was added then CH_2Cl_2 (100 mL); the mixture was filtered, evaporated, the residue was extracted with CH_2Cl_2. This organic solution was washed with water and the product was purified by chromatography giving rise to 10a (30.5g , 98.4%). Oil, $[\alpha]_D$ +32.8 (c 1.1, $CHCl_3$), mass spectrum (E.I.): m/z 504 (M^+), ^1H NMR (200 MHz, $CDCl_3$) δ 7.3 (m, 10H, 2 Ph), 4.77 and 4.76 (2 q, 4H, OCH_2Ph), 4.53-3.57 (m, 6H, H-1 to H-5a,5b), 2.6 (m, 4H, 2 SCH_2), 1.42 and 1.33 [2s, 6H, $C(CH_3)_2$]. Anal. Calcd for $C_{28}H_{40}O_4S_2$: C, 66.63; H, 7.99; S, 12.70. Found : C, 66.61; H, 8.03; S, 12.69.

2,3-di-*Q*-Benzyl-4,5-*Q*-isopropylidene-D-ribose diethyl-dithioacetal (10b). 9b was treated as just described. Yield: 95%, Oil, $[\alpha]_D$ +43.6 (c 1.1, $CHCl_3$), mass spectrum (C.I.): m/z 477 ($M^+ + H$), ^1H NMR (250 MHz, $CDCl_3$) δ 7.3 (m, 10H, 2 Ph), 4.9-4.6 (2q, 4H, OCH_2Ph), 4.45 (td, 1H, $J_{4,5}$ = 9 Hz, $J_{3,4}$ = 4 Hz, H-4), 4.20 (dd, 1H, $J_{2,3}$ = 6.6 Hz, H-3), 4.11 (d, 1H, $J_{1,2}$ = 6.6 Hz, H-1), 3.95 (t, 1H, $J_{4,5} = J_{5,5'}$ = 9 Hz, H-5), 3.80 (t, 1H, $J_{4,5} = J_{5,5'}$ = 9 Hz, H-5'), 3.72 (t, 1H, $J_{1,2} = J_{2,3}$ = 6.6

Hz, H-2), 2.65 (m, 4H, 2-SC$\underline{H}_2$-), 1.41 (2s, 6H, isopropylidene), 1.2 (m, 6H, 2-SCH$_2$C$\underline{H}_3$). Anal. Calcd for $C_{26}H_{36}O_4S_2$: C, 65.50; H, 7.61; S, 13.41. Found : C, 65.25; H, 7.73; S, 13.60.

2,3-di-*O*-Benzyl-4,5-*O*-isopropylidene-D-ribose (3e). Boron trifluoride diethyl etherate (14.2 mL, 115.5 mmol) was added to a stirred suspension of red mercury (II) oxide (25.1 g, 115.6 mmol) in a mixture of tetrahydrofuran (119 mL) and water (21 mL). Subsequently, a solution of 10a (26.5 g, 52.6 mmol) in THF (65 mL) was dropped in 20 min. and the stirring maintained for another 10 min. The reaction mixture was poured in ether (800 mL), dried with $MgSO_4$, filtered, washed with saturated $NaHCO_3$, affording, after chromatography (hexane-EtOAc 9 : 1) the syrupy product (13 g, 66.8%). $[\alpha]_D$ +33.9 (c 1.0, $CHCl_3$), mass spectrum (C.I.): m/z 371 (M^+ + H), ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.7 (s, 1H, H-1), 4.35 (m, 1H, H-4), 7.31 (m, 10H, 2Ph), 4.80-4.40 (2dd, 4H, $J_{A,B}$ = 10 Hz, 2-OC$\underline{H}_2$Ph), 4.35 (m, 1H, H-4), 4.11 (m, 2H, H-2, H-5), 3.83 (dd, 1H, $J_{4,5}$ = 4.5 Hz, H-5), 3.71 (m, 1H, H-3), 1.3 (s, 6H, 2 CH_3). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found : C, 71.48; H, 7.18.

General procedure for the preparation of (6) and (7). A solution of the aldehyde 3 (4 mmol) and benzylamine (4 mmol) in an appropriate solvent (40 mL, see Table 1) was stirred for 1-2 h with 3 Å molecular sieves (5 g). The mixture was filtered, 14-16 mmol of 5 was added, followed by an equimolar amount (4 mmol) of anhydrous zinc chloride. At the end of the reaction (2-3h, t.l.c.) saturated $NaHCO_3$ was added and the solvent evaporated in vacuum. The residue was extracted with ethyl acetate and products were isolated by column chromatography using hexane-ether-acetone 2 : 2 : 1 mixture as eluant.

***N*-Benzyl-(6*R*,1'*R*,2'*S*,3'*R*)-6-(1',2':3',4'-di-*O*-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-2,3-didehydropiperidine-4-one (6a).** $[\alpha]_D$ +37 (c 1.3, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4 (m, 5H, Ph), 7.1 (d, 1H, $J_{2,3}$ = 8 Hz, H-2), 5.0 (d, 1H, $J_{2,3}$ = 8 Hz, H-3), 4.45 (dd, 2H, $J_{A,B}$ = 10 Hz, CH_2Ph), 4.35 (m, 1H, H-1'), 3.5 (m, 1H, H-6), 2.60 (m, 2H, 5-CH_2), 1.3-1.0 (4s, 12H, 4 CH_3). ^{13}C NMR (50.33 MHz, $CDCl_3$) δ 190.2 (C-4), 153.1 (C-2), 97.5 (C-3), 80.9, 78.1, 77.8 (C-1', 2', 3'), 67.9 (C-4'), 56.1 (C-6), 34.9 (C-5). Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.19; H, 7.54; N, 3.62; O, 20.64. Found : C, 68.23; H, 7.58; N, 3.58; O, 21.01.

***N*-Benzyl-(6*S*,1'*R*,2'*S*,3'*R*)-6-(1',2':3',4'-di-*O*-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-2,3-didehydropiperidine-4-one (7a).** m.p. 75-78°C, $[\alpha]_D$ -215 (c 1.30, $CHCl_3$), mass spectrum (C.I.): m/z 388 (M^+ + H), ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.40 (m, 5H, phenyl), 7.1 (d, 1H, $J_{2,3}$ = 7 Hz, H-2), 5.1 (d, 1H, $J_{2,3}$ = 7 Hz, H-3), 4.71 (dd, 2H, $J_{A,B}$ = 10 Hz, -C$\underline{H}_2$Ph), 4.55 (t, 1H, $J_{1',2'} = J_{2',3'}$ = 6 Hz, H-2'), 4.11 (m, 2H, H-3', H-4'), 3.90 (m, 1H, H-4'), 3.75 (t, 1H, $J_{1',2'} = J_{2',3'}$ = 6 Hz, H-2'), 3.50 (m, 1H, H-6), 2.7-2.5 (m, 2H, 5-CH_2). Crystal data : C_{22} H_{29} N O_5 , Mw = 387, monoclinic, P 21, a= 10.593 (6), b= 5.841 (2), c= 17.440 (7) Å, β= 104.30 (2) °, V= 1045,6 $Å^3$, dc= 1.23 g cm^{-3}, Z= 2, λ (Cu Kα)= 1.5418 Å, F(000)= 416, μ= 6.7cm^{-1} (absorption ignored). 2034 (hkl and -hkl) measured reflections, 1965 unique, 1864 observed. R= 0.059, Rw= 0.071, w= $1/\sigma^2$(Fo)+ 0.01033 Fo^2. No residual higher than 0.26 e$Å^{-3}$ in the final difference map.

***N*-Benzyl-(6*R*,1'*S*,2'*R*,3'*S*)-6-(1',2':3',4'-di-*O*-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-2,3-didehydropiperidine-4-one (6b).** m.p. 77-78°C, $[\alpha]_D$ +218.7 (c 1.26,

$CHCl_3$), mass spectrum (C.I.): m/z 388 ($M^+ + H$). The ^1H and ^{13}C NMR spectra are superposable with those of 7a. Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.19; H, 7.54; N, 3.62; O, 20.64. Found : C, 68.25; H, 7.66; N, 3.62; O, 20.58.

N-Benzyl-(6S,1'S,2'R,3'S)-6-(1',2':3',4'-di-O-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-2,3-didehydropiperidine-4-one (7b). $[\alpha]_D$ -40.1 (c 1.2, $CHCl_3$). The ^1H and ^{13}C NMR spectra are superposable with those of 6a.

N-Benzyl-(6R,1'S,2'R,3'R)-6-(1',2':3',4'-di-O-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-2,3-didehydropiperidine-4-one (6c). A mixture of 6c and 7c was crystallized from hexane-ether to give 6c. m.p. 80-84°C. $[\alpha]_D$ +163.7 (c 1.58, $CHCl_3$), mass spectrum (C.I.): m/z 388 ($M^+ + H$), ^1H NMR (200 MHz, $CDCl_3$) δ 7.3 (m, 5H, phenyl), 7.12 (d, 1H, $J_{2,3}$ = 7 Hz, H-2), 4.98 (d, 1H, $J_{2,3}$ = 7 Hz, H-3), 4.66 (m, 1H, H-6). Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.19; H, 7.54; N, 3.62. Found : C, 68.12; H, 7.62; N, 3.90. 7c is not available in a pure form.

N-Benzyl-(6R,1'S,2'S,3'R)-6-(1',2':3',4'-di-O-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-2,3-didehydropiperidine-4-one (6d). m.p. 151-152°C, $[\alpha]_D$ +268.1 (c 0.88, $CHCl_3$), mass spectrum (E.I.): m/z 387 (M^+). ^1H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 5H, Ph), 7.0 (d, 1H, $J_{2,3}$ = 7.5 Hz, H-2), 4.95 (d, $J_{2,3}$ = 7.5 Hz, 1H, H-3), 4.90 (m, 1H, H-1'), 4.80-4.50 (dd, 2H, $J_{A,B}$ = 10 Hz,-CH_2Ph), 4.11 (m, 1H, H-4'), 3.95 (m, 2H, H-2', H-3'), 3.85 (m, 2H, H-2, H-4'), 2.80 (m, 1H, H-5ax), 2.40 (m, 1H, H-5eq). ^{13}C NMR (65 MHz, $CDCl_3$) δ 190.7 (C-4), 152.7 (C-2), 96.6 (C-3), 78.2 (C-2'), 74.3 (C-1'), 72.8 (C-3'), 68.1 (C-4'), 54.5 (C-6), 38.2 (C-5). Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.19; H, 7.54; N, 3.62; O, 20.64. Found : C,68.34; H, 7.71; N, 3.65; O, 20.48.

N-Benzyl-(6S,1'S,2'S,3'R)-6-(1',2':3',4'-di-O-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-2,3-didehydropiperidine-4-one (7d). $[\alpha]_D$ -87 (c 0.86, $CHCl_3$), ^1H NMR (250 MHz, $CDCl_3$) δ 7.4 (m, 5H, Ph), 7.0 (d, 1H, $J_{2,3}$ = 8 Hz, H-2), 5.0 (d, 1H, $J_{2,3}$ = 8 Hz, H-3), 4.45 (m, 1H, H-1'), 2.70 (m, 1H, H-5ax), 2.50 (m, 1H, H-5eq). ^{13}C NMR (65 MHz, $CDCl_3$) δ 190 (C-4), 152.8 (C-2), 97.2 (C-3), 78.9, 77.4, (C-2', C-1'), 73.3 (C-3'), 68.6 (C-4'), 54.3 (C-6), 37.0 (C-5). Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.19; H, 7.54; N, 3.62; O, 20.64. Found : C, 68.33; H, 7.85; N, 3.56; O, 20.79.

N-Benzyl-(6R,1'S,2'S,3'R)-6-(1',2'-di-O-benzyl-3',4'-O-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-2,3-didehydropiperidine-4-one (6e). $[\alpha]_D$ +129.4 (c 1.50, $CHCl_3$), mass spectrum (FAB): m/z 534 ($M^+ + Li$). ^1H NMR (200 MHz, $CDCl_3$) δ 7.3 (m, 15H, 3 Ph), 6.90 (d, 1H, $J_{2,3}$ = 7 Hz, H-2), 4.90 (d, 1H, $J_{2,3}$ = 7 Hz, H-3), 3.53 (m, 1H, H-6), 2.68 (m, 1H, H-5eq), 2.25 (m, 1H, H-5ax), 1.29 and 1.23 [2s, 6H, $C(CH_3)_2$]. Anal. Calcd for $C_{33}H_{37}NO_5$: C, 75.11; H, 7.07; N, 2.65. Found : C, 75.08; H, 7.12; N, 2.55.

N-Benzyl-(6S,1'S,2'S,3'R)-6-(1',2'-di-O-benzyl-3',4'-O-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-2,3-didehydropiperidine-4-one (7e). The 6*S* isomer could not be isolated in pure form. The ratio of diastereoisomers 6e and 7e could be deduced from the NMR spectrum of their mixture : (6.99, d, 1H, $J_{2,3}$ = 7 Hz, H-2).

***N*-Benzyl-(6*R*,1'*R*,2'*S*)-6-(1',2'-dihydroxy-3,3'-bis-ethylthio-1',2'-*O*-isopropylidene-1'-propyl)-2,3-didehydropiperidine-4-one (6f).** $[\alpha]_D$ +99.2 (c 0.93, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 7.4 (m, 5H, Ph), 7.17 (d, 1H, $J_{2,3}$ = 7 Hz, H-2), 4.97 (d, 1H, $J_{2,3}$ = 7 Hz, H-3), 3.80 (d, 1H, $J_{2',3'}$ = 6 Hz, H-3'), 1.46 and 1.45 [2s, 6H, $C(CH_3)_2$]. Anal. Calcd for $C_{22}H_{31}NO_3S_2$: C, 62.67; H, 7.41; N, 3.32. Found : C, 62.52; H, 7.29; N, 3.29.

***N*-Benzyl-(6*S*,1'*R*,2'*S*)-6-(1',2'-dihydroxy-3,3'-bis-ethylthio-1',2'-*O*-isopropylidene-1'-propyl)-2,3-didehydropiperidine-4-one (7f).** $[\alpha]_D$ -96.0 (c 1.23, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$) δ 7.4 (m, 5H, Ph), 7.11 (d, 1H, $J_{2,3}$ = 7 Hz, H-2), 4.97 (d, 1H, $J_{2,3}$ = 7 Hz, H-3), 3.83 (d, 1H, $J_{2',3'}$ = 6 Hz, H-3'), 1.42 and 1.51 [2s, 6H, $C(CH_3)_2$]. Anal. Calcd for $C_{22}H_{31}NO_3S_2$: C, 62.67; H, 7.41; N, 3.32. Found : C, 62.65; H, 7.37; N, 3.25.

***N*-Benzyl-(6*R*,1'*R*,2'*S*,3'*R*)-6-(1',2',3'-tri-*O*-benzyl-4',4'-bis-ethylthio-1',2',3'-trihydroxy-1'-butyl)-2,3-didehydropiperidine-4-one (6g).** $[\alpha]_D$ +40 (c 0.80, $CHCl_3$). mass spectrum (FAB): m/z 682 (M^+ + H). ^1H NMR (200 MHz, $CDCl_3$) δ 7.3 (m, 20H, 4 Ph), 6.80 (d, 1H, $J_{2,3}$ = 7 Hz, H-2), 5.0 (d, 1H, $J_{2,3}$ = 7 Hz, H-3), 2.15 (m, 1H, H-5ax), 2.0 (m, 1H, H-5eq). Anal. Calcd for $C_{41}H_{46}NO_4S_2$: C, 72.31; H, 6.82; N, 2.06. Found : C, 72.35; H, 6.88; N, 2.15.

***N*-Benzyl-(6*S*,1'*R*,2'*S*,3'*R*)-6-(1',2',3'-tri-*O*-benzyl-4',4'-bis-ethylthio-1',2',3'-trihydroxy-1'-butyl)-2,3-didehydropiperidine-4-one (7g).** $[\alpha]_D$ -205 (c 0.95, $CHCl_3$). mass spectrum (FAB): m/z 682 (M^+ + H). ^1H NMR (200 MHz, $CDCl_3$) δ 7.3 (m, 20H, 4 Ph), 6.90 (d, 1H, $J_{2,3}$ = 7 Hz, H-2), 4.90 (d, 1H, $J_{2,3}$ = 7 Hz, H-3), 3.90 (m, 2H, H-2', H-3'), 3.71 (d, 1H, $J_{3',4'}$ = 3 Hz, H-4'), 3.42 (m, 1H, H-2), 2.84 (m, 4H, 2-$SCH_2CH_2CH_3$), 2.20 (m, 1H, H-5eq), 2.0 (m, 1H, H-5ax). . Anal. Calcd for $C_{41}H_{46}NO_4S_2$: C, 72.31; H, 6.82; N, 2.06. Found : C, 72.18; H, 6.89; N, 2.10.

General procedure for sodium borohydride reduction of (6) and (7). A stirred solution of 6 or 7 (1mmol) in abs. ethanol (10 mL) was treated with 10 mmol of $NaBH_4$ for 16 h. Saturated $NaHCO_3$ was then added (2 mL) and the mixture was evaporated to dryness. The residue was extracted with CH_2Cl_2, washed with water and dried ($MgSO_4$). The extract was purified by column chromatography using hexane-ethyl acetate as eluant.

***N*-Benzyl-(2*S*,4*R*,1'*R*,2'*S*,3'*R*)-2-(1',2':3',4'-di-*O*-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-4-hydroxypiperidine (11).** Yield 92%, m.p. 95-97°. $[\alpha]_D$ +35 (c 1.20, $CHCl_3$), mass spectrum (C.I.): m/z 392 (M^+ + H), ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 5H, Ph), 4.5 (t, 1H, $J_{1',2'}$ = 6 Hz, H-1'), 3.2 (m, 1H, H-6ax), 2.85 (m, 1H, H-2), 2.45 (m, 1H, H-6eq), 2.1 (m, 1H, H-6ax), 1.82 (m, 1H, H-5ax), 1.7 (m, 1H, H-3eq). ^{13}C NMR (65 MHz, $CDCl_3$) δ 82.3, 79.3, 77.8 (C-1', 2', 3'), 68.0 (C-4), 66.1 (C-4'), 58.7 (C-2), 43.8 (C-6), 32.0, 29.2 (C-3, 5). Anal. Calcd for $C_{22}H_{33}NO_5$: C, 67.49; H, 8.49; N, 3.59; O, 20.43. Found : C, 67.75; H, 8.56; N, 3.57; O, 20.17.

***N*-Benzyl-(2*R*,4*S*,1'*S*,2'*R*,3'*S*)-2-(1',2':3',4'-di-*O*-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-4-hydroxypiperidine (12).** Yield 90%, $[\alpha]_D$ -40.2 (c 0.98, $CHCl_3$), mass

spectrum (C.I.): m/z 392 (M^+ + H); The NMR spectra of 12 are the same as for 11. Anal. Calcd for $C_{22}H_{33}NO_5$: C, 67.49; H, 8.49; N, 3.59; O, 20.43. Found : C, 67.45; H, 8.47; N, 3.63 N, 3.59;; O, 20.42. Crystal data : C_{22} H_{33} NO_5, Mw = 391.51, triclinic, P 1, a= 7.893 (6), b= 9.032 (5), c= 9.254(6) Å,α= 109.26(4), β= 100.74(4), γ= 109.55(4) °, V= 553.3(8) Å3, dc= 1.175 g cm^{-3}, Z= 1, λ (Cu Kα)= 1.5418 Å, F(000)= 208, μ= 5.9cm^{-1} (absorption ignored). 1875 measured reflections, 1582 observed. R= 0.040, Rw= 0.056, w= $1/\sigma^2$(Fo)+ 0.00207 Fo^2. No residual higher than 0.36 e$Å^{-3}$ in the final difference map.

***N*-Benzyl-(2*R*,4*S*,1'*S*,2'*S*,3'*R*)-2-(1',2':3',4'-di-*O*-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-4-hydroxypiperidine (13).** Yield 77%, $[\alpha]_D$ +15.8 (c 0.93, $CHCl_3$), mass spectrum (C.I.): m/z 392 (M^+ + H), ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (m, 5H, Ph), 4.55 (m 1H, H-1'), 3.30 (m, 1H, H-6ax), 3.00 (m, 1H, H-2), 2.55 (m, 1H, H-5ax) .^{13}C NMR (50 MHz, $CDCl_3$) δ 79.2, 78.4, 73.0 (C-1', 2', 3'), 68.3 (C-4), 68.1 (C-4'), 57.1 (C-2), 47.0 (C-6), 33.1, 29.6 (C-3, 5). Anal. Calcd for $C_{22}H_{33}NO_5$: C, 67.49; H, 8.49; N, 3.59; O, 20.43. Found : C, 67.35; H, 8.29; N, 3.69; O, 20.47.

***N*-Benzyl-(2*R*,4*S*,1'*S*,2'*S*,3'*R*)-2-(1',2'-di-*O*-benzyl-3',4'-*O*-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-4-hydroxypiperidine (14).** Yield 95%, $[\alpha]_D$ +11.7 (c 1.91, $CHCl_3$), mass spectrum (FAB): m/z 532 (M^+ + H), ^1H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 15H, 3 Ph), 4.42 (m, 1H, H-3'), 4.25 (m, 1H, H-2'), 4.10 (m, 1H, H-4'a), 3.85 (m, 2H, H-1', H-4'b), 3.6 (m, 1H, H-4), 2.80 (m, 1H, H-6eq), 2.63 (m, 1H, H-2), 2.1 (m, 2H, H-5, H-6ax). ^{13}C NMR (50 MHz, $CDCl_3$) δ 81.5 (C-1'), 78.5 (C-2'), 77 (C-3'), 69 (C-4), 64.7 (C-4'), 60.2 (C-2), 48.7 (C-6), 34.2 (C-3), 31.9 (C-5). Anal. Calcd for $C_{33}H_{41}NO_5$: C, 74.55; H, 7.77; N, 2.63. Found : C, 74.67; H, 7.87; N, 2.68.

***N*-Benzyl-(2*S*,4*R*,1'*S*,2'*S*,3'*R*)-2-(1',2'-di-*O*-benzyl-3',4'-*O*-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-4-hydroxypiperidine (15).** Isolated after reduction of the 65 : 35 mixture of 6e + 7e obtained in THF (see Table 1). $[\alpha]_D$ +0.7 (c 0.88, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 15H, 3 Ph), 4.90-4.61 (m, 4H, 2-OCH_2Ph), 4.25 (m, 1H, H-2'), 4.00 (t, 1H, $J_{2',3'}$ = $J_{3',4'}$ = 3.5 Hz, H-3'), 3.60 (m, 1H, H-4), 2.9 (m, 1H, H-6ax), 2.6 (m, 1H, H-2), 2.1 (m, 2H, H-5, H-6eq), 1.9 (m, 1H, H-3), 1.6 (m, 2H, H-3, H-5). ^{13}C NMR (50 MHz, $CDCl_3$) δ 68.8 (C-4), 65.7 (C-4'), 60.3 (C-2), 48.7 (C-6), 32.5 and 31.1 (C-3, C-5). Anal. Calcd for $C_{33}H_{41}NO_5$: C, 74.55; H, 7.77; N, 2.63. Found : C, 74.65; H, 7.88; N, 2.53.

***N*-Benzyl-(2*R*,1'*S*,2'*S*,3'*R*)-2-(1',2'-di-*O*-benzyl-3',4'-*O*-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-piperidine-4-one (16).** A solution of 6e (1.84g, 3.5 mmol) in 35 mL of dry THF under argon was cooled to -78°C and L-Selectride (4.0 mL of a 1.0 M solution, 4.0 mmol) was added in 5 min. The reaction mixture was stirred at that temperature for 1h, and was allowed to warm up to room temperature. The solution was quenched by slow addition of 2 mL of water. Ethanol (15 mL) and KOH (250 mg, 4.5 mmol) were added, the mixture was cooled to 0°C, and 30% H_2O_2 (1.6 mL, 15.5 mmol) was slowly added (30 min). The reaction was stirred at ambient temperature for 3h, the volatile components were removed at reduced pressure and the residue was dissolved in 200 mL of ether and the ether phase was washed thoroughly with 4% of aqueous triethanolamine solution (50 mL) and brine (2 x 30

mL), dried (K_2CO_3) and purified by column chromatography (hexane-ethyl acetate 4 : 1→3 : 2) to give 1.36 g (74%) of 16. $[\alpha]_D$ +21.5 (c 0.92, $CHCl_3$), mass spectrum (C.I.): m/z 530 ($M^+ + H$). ^1H NMR (300 MHz, $CDCl_3$) δ 4.56 (m, 1H, H-3'), 4.76 and 4.53 (2q, 4H, $J_{A,B}$ = 10 Hz, OCH_2Ph), 4.17-3.92 (m, 3H, H-2', H-4'a,4'b), 3.54 (m, 2H, H-2, H-1'), 3.34 (m, 1H, H-6), 2.86 (m, 1H, H-6), 2.69 (m, 1H, H-3), 2.46 (m, 1H, H-5), 2.34 (d, 1H, H-3), 2.17 (m, 1H, H-5). ^{13}C NMR (65 MHz, $CDCl_3$) δ 208.4 (C-4), 83.6 (C-1'), 79.4 (C-2'), 76.5 (C-3'), 65.3 (C-4'), 62.3 (C-2), 46.4 (C-6), 40.8 (C-3), 36.9 (C-5). Anal. Calcd for $C_{33}H_{39}NO_5$: C, 74.83; H, 7.42; N, 2.64. Found : C, 74.51; H, 7.41; N, 2.60.

N-Benzyl-(2R,4R,1'S,2'S,3'R)-2-(1',2'-di-O-benzyl-3',4'-O-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-4-hydroxypiperidine (17). The ketone 16 (1.36 g, 2.6 mmol) was treated with L-Selectride as describe above. Yield : 1.32 g (96%), $[\alpha]_D$ +16.4 (c 0.83, $CHCl_3$), mass spectrum (C.I.): m/z 532 ($M^+ + H$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.3 (m, 15H, 3 Ph), 4.36 (m, 1H, H-3'), 4.17-3.97 (m, 3H, H-2', H-4'a,4'b), 3.92-3.68 (m, 4H, H-4, H-1', NCH_2Ph), 3.12 (m, 1H, H-2), 2.63 (m, 2H, H-6), 1.73 (m, 2H, H-3eq,3ax), 1.66 (m, 1H, H-5), 1.50 (m, 1H, H-5). ^{13}C NMR (75 MHz, $CDCl_3$) δ 80.5 (C-1'), 79.9 (C-2'), 76.5 (C-3'), 65.7 (C-4'), 65.5 (C-4), 59.2 (C-2), 44.5 (C-6), 33.6 (C-3), 31.5 (C-5). Anal. Calcd for $C_{33}H_{41}NO_5$: C, 74.55; H, 7.77; N, 2.63. Found : C, 74.72; H, 7.83; N, 2.70.

General method for the partial hydrolysis of the 3',4'-O-isopropylidene group in (11)-(15) and (17). 1 g of products 11-15 and 17 was dissolved in acetic acid (42 mL), 14 mL of water was added and the mixture was kept at 50°C. The reaction was followed by T.L.C. When all of the starting material had disappeared it was evaporated to dryness. The residue was dissolved in methanol and was treated with Serdolit Blue anion exchange resin (OH^- form). After filtration, the methanol was evaporated and the product was purified by column chromatography using a CH_2Cl_2-MeOH mixture as eluent.

N-Benzyl-(2S,4R,1'R,2'S,3'R)-2-(1',2'-O-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-4-hydroxypiperidine (18). Yield 85%, m.p. 38-41°C. $[\alpha]_D$ -41 (c 1.20, $CHCl_3$), ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 5H, Ph), 4.45 (t, 1H, $J_{1',2'} = J_{2',3'}$ = 7Hz, H-1'), 4.30 (m, 1H, H-4'), 4.05 (t, 1H, $J_{1',2'} = J_{2',3'}$ = 7Hz, H-2'), 3.81 (m, 1H, H-4'), 3.72 (m, 3H, $-NCH_2Ph$, H-4), 3.61 (m, 1H, H-3'), 3.40 (m, 1H, H-5eq), 3.5 (m, 1H, H-2), 2.80 (m, 1H, H-6eq), 2.36 (m, 1H, H-3eq), 2.1 (m, 1H, H-5ax), 1.4 (s, 6H, 2 CH_3). Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.93; H, 8.32; N, 3.99. Found : C, 65.11; H, 8.47; N, 3.78.

N-Benzyl-(2R,4S,1'S,2'R,3'S)-2-(1',2'-O-isopropylidene-1',2',3',4'-tetrahydroxy-1'-butyl)-4-hydroxypiperidine (19). Yield 80%, m.p. 38-40°C. $[\alpha]_D$ +33.2 (c 1.07, $CHCl_3$), mass spectrum (C.I.): m/z 352 ($M^+ + H$). The NMR spectra were the same as for 18. Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.93; H, 8.32; N, 3.99. Found : C, 64.83; H, 8.52; N, 3.89.

N-Benzyl-(2R,4S,1'S,2'S,3'R)-2-(1',2'-di-O-benzyl-1',2',3',4'-tetrahydroxy-1'-butyl)-4-hydroxypiperidine (20). Yield 73%, $[\alpha]_D$ -4.3 (c 0.86, $CHCl_3$), mass spectrum (C.I.): m/z 492 ($M^+ + H$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 15H, 3 Ph), 4.90-4.30 (m, 4H, 2-OCH_2Ph), 4.01 (m, 1H, H-3'), 3.80-3.60 (m, 6H, H-1', H-4, 2H-4', $-NCH_2Ph$), 3.32 (m, 1H, H-2'), 3.10 (t, 1H, H-6ax), 2.83 (s, 1H, H-2), 2.55 (m, 1H, H-6eq), 2.03 (m, 1H, H-3ax), 1.73 (m, 1H, H-5ax), 1.60 (m, 1H,

H-3eq), 1.40 (m, 1H, H-5eq). ^{13}C NMR (50 MHz, $CDCl_3$) δ 84.2, 82.0 (C-1', C-2'), 69.2 (C-3'), 64.9, 63.6 (C-4, C-4'), 57.9 (C-2), 45.2 (C-6), 30.9 (C-3), 26.7 (C-5). Anal. Calcd for $C_{30}H_{37}NO_5$: C, 73.29; H, 7.59; N, 2.85. Found : C, 73.19; H, 7.48; N, 2.75.

***N*-Benzyl-(2*S*,4*R*,1'*S*,2'*S*,3'*R*)-2-(1',2'-di-*O*-benzyl-1',2',3',4'-tetrahydroxy-1'-butyl)-4-hydroxypiperidine (21).** Yield 63%, $[\alpha]_D$ -1.4 (c 0.79, $CHCl_3$), mass spectrum (C.I.): m/z 492 ($M^+ + H$). ^1H NMR (200 MHz, $CDCl_3$) δ 7.30 (m, 15H, 3 Ph), 4.90-4.60 (m, 4H, $J_{A,B}$ = 10 Hz, 2-OCH_2Ph), 4.10 (d, 1H, $J_{A,B}$ = 10 Hz, -NCH_2Ph), 3.31 (d, 1H, $J_{A,B}$ = 10 Hz, -NCH_2Ph), 2.92 (m 2H, H-2, H-6ax), 2.20 (m, 1H, H-6eq), 2.05 (m, 1H, H-3), 1.70 (m, 2H, H-3, H-5), 1.55 (m, 1H, H-5). Anal. Calcd for $C_{30}H_{37}NO_5$: C, 73.29; H, 7.59; N, 2.85. Found : C, 73.19; H, 7.48; N, 2.88.

***N*-Benzyl-(2*R*,4*R*,1'*S*,2'*S*,3'*R*)-2-(1',2'-di-*O*-benzyl1',2',3',4'-tetrahydroxy-1'-butyl)-4-hydroxypiperidine (22).** Yield 83%, $[\alpha]_D$ -15.1 (c 0.77, $CHCl_3$), mass spectrum (C.I.): m/z 492 ($M^+ + H$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 15H, 3 Ph), 4.20 (m, 1H, H-4), 3.90 (m, 1H, H-3'), 3.85-3.60 (m, 5H, H-1', H-4', NCH_2Ph), 3.35 (m, 1H, H-6), 3.10 (m, 1H, H-2'), 2.78 (m, 1H, H-6), 1.80-1.40 (m, 4H, H-3, H-5eq,5ax). ^{13}C NMR (75 MHz, $CDCl_3$) δ 86.1, 83.4 (C-1', C-2'), 68.5 (C-3'), 65.4, 64.1 (C-4, C-4'), 58.1 (C-2), 47.5 (C-6), 32.7 (C-3), 28.2 (C-5). Anal. Calcd for $C_{30}H_{37}NO_5$: C, 73.29; H, 7.59; N, 2.85. Found : C, 72.95; H, 7.65; N, 2.89.

General method for obtaining indolizidines (28)-(32). A stirred solution of compounds 18-22 (1.8 mmol) in dry toluene (50 mL) was treated with lead (IV) acetate (2.0 mmol) for 30 min. The mixture was washed with 0.5 M NaOH solution and brine, successively. After drying with $MgSO_4$, the products 23-27 were used for next operation without purification. The isopropylidene group of 23 and 24 was then removed by dissolving the compounds in 80% aqueous trifluoroacetic acid and keeping at room temperature for 10 hours. After evaporation these hydrolysates and the intermediates 25-27 were transformed into the end-products 28-32 by hydrogenolysis in acetic acid (15 mL) using equal amounts of palladium on carbon (10%) as catalyst for 16 hours. At the end of the reactions, the mixtures were filtered through a celite pad, evaporated to dryness. The residue was dissolved in methanol and the solution was treated with Serdolit Blue resin (OH^- form). After evaporation the product was purified by column chromatography using toluene-MeOH or CH_2Cl_2-MeOH-NH_3 aq. as eluent.

(1*R*,2*R*,7*R*,8a*S*)-1,2,7-Trihydroxy-octahydroindolizine (28). Yield 54%, $[\alpha]_D$ +11 (c 0.86, MeOH), mass spectrum (C.I.): m/z 174 ($M^+ + H$). ^1H NMR (200 MHz, D_2O+DCl, pH 2) δ 4.38 (dd, 1H, $J_{2,3ax}$ = 6.5 Hz, $J_{2,3eq}$ = 3.2 Hz, H-2), 4.2 (d, 1H, $J_{1,8a}$ = 2.9 Hz, H-1), 4.09 (m, 1H, H-7), 4.04 (dd, 1H, $J_{3ax,3eq}$ = 13 Hz, H-3ax), 3.7 (ddd, 1H, $J_{5ax,5eq}$ = 12.9 Hz, $J_{5eq,6ax}$ = 4.7 Hz, $J_{5eq,6eq}$ = 2.1 Hz, H-5eq), 3.51 (td, 1H, $J_{8ax,8a}$ = 12.5 Hz, $J_{8a\ ax,8eq}$ = 2.7 Hz, H-8a), 3.17 (m, 1H, $J_{5ax,6ax}$ = 13 Hz, H-5ax), 2.91 (m, 1H, H-3), 2.34 (m, 1H, H-8eq), 2.24 (m, 1H, H-6eq), 1.79 (m, 1H, H-6ax), 1.67 (m, 1H, H-8ax). Anal. Calcd for $C_8H_{15}NO_3$: C, 55.45; H, 8.73; N, 8.09. Found : C, 55.37; H, 8.53; N, 8.15.

(1*S*,2*S*,7*S*,8a*R*)-1,2,7-Trihydroxy-octahydroindolizine (29). Yield 64%, $[\alpha]_D$ -10.3 (c 1.04, MeOH), mass spectrum (E.I.): m/z 173 (M^+). The NMR spectra are superposable with those of 28 Anal. Calcd for $C_8H_{15}NO_3$: C, 55.45; H, 8.73; N, 8.09. Found : C, 55.27; H, 8.43; N, 8.16.

(1*S*,2*R*,7*S*,8a*R*)-1,2,7-Trihydroxy-octahydroindolizine (30). Yield 62%, m.p. 169-70°C (HCl salt), $[\alpha]_D$ -16.3 (c 1.1, MeOH), [lit [13c] $[\alpha]_D$ -20.3 (c 0.38, MeOH)], ^{1}H NMR (200 MHz, D_2O) δ 4.32 (m, 1H, $J_{1,2}$ = 6.1 Hz, H-2), 4.01 (dd, 1H, $J_{1,8a}$ = 4.0 Hz, H-1), 3.69 (m, 1H, $J_{7,8ax}$ = 11.5 Hz, $J_{7,8eq}$ = 4.5 Hz, $J_{7,6ax}$ = 11.1 Hz, $J_{7,6eq}$ = 2.5 Hz, H-7), 2.95 (m, 1H, H-5_{eq}), 2.78 (dd, 1H, H-3_{eq}), 2.41 (dd, 1H, H-3_{ax}), 2.10 (m, 1H, $J_{8a,8eq}$ = 2.3 Hz, $J_{8a,8ax}$ = 11.6 Hz, H-8a), 2.04 (m, 1H, H-5_{ax}), 1.95 (m, 1H, H-8_{eq}), 1.88 (m, 1H, H-6_{eq}), 1.46 (m, 1H, H-6_{ax}), 1.43 (q, 1H, H-8_{ax}). ^{13}C NMR (65 MHz, CD_3OD) δ 72.8 (C-1), 70.9 (C-2), 69.6 (C-7), 68.2 (C-8a), 61.9 (C-3), 51.2 (C-5), 34.7 (C-6, C-8). Anal. Calcd for $C_8H_{15}NO_3$: C, 55.45; H, 8.73; N, 8.09. Found : C, 55.30; H, 8.74; N, 8.10.

(1*S*,2*R*,7*R*,8a*S*)-1,2,7-Trihydroxy-octahydroindolizine (31). Yield 57%, $[\alpha]_D$ -21.5 (c 1.5, MeOH), mass spectrum (E.I.): m/z 173 (M^+). ^{1}H NMR (400 MHz, CD_3OD) δ 4.10 (dd, 1H, $J_{1,2}$ = 13 Hz, $J_{2,3}$ = 7 Hz, H-2), 3.62 (m, 2H, H-1, H-7), 2.20 (ddd, 1H, $J_{1,8a}$ = 2.5 Hz, $J_{7,8}$ = 4.5 Hz, H-8), 2.05 (m, 2H, H-3, H-5ax), 1.90 (ddd, 1H, $J_{8eq,8a}$ = 8 Hz, $J_{8ax,8a}$ = 12 Hz, H-8a), 1.85 (m, 1H, H-6), 1.40 (m, 1H, H-6), 1.1 (m, 1H, H-8ax), ^{13}C NMR (50 MHz, CD_3OD) δ 75.8 (C-1), 69.7 (C-2), 69.2 (C-7), 67.4 (C-8a), 62.0 (C-3), 51.3 (C-5), 38.6), 35.2 (C-8). Anal. Calcd for $C_8H_{15}NO_3$: C, 55.45; H, 8.73; N, 8.09. Found : C, 55.35; H, 8.80; N, 8.18.

(1*S*,2*R*,7*R*,8a*R*)-1,2,7-Trihydroxy-octahydroindolizine (32). Yield 52%, $[\alpha]_D$ -14.1 (c 0.66, MeOH), mass spectrum (C.I.): m/z 174 (M^+ + H). ^{1}H NMR (200 MHz, D_2O) δ 3.49 (m, 1H, $J_{1,2}$ = 6.0 Hz, $J_{2,3}$ = 7.7 Hz, $J_{2,3'}$ = 2.5 Hz, H-2), 3.34 (m, 1H, H-7), 3.17 (m, 1H, H-8a), 2.90 (m, 2H, H-3, H-5), 2.70-2.30 (m, 2H, H-3', H-5'), 1.90-1.60 (m, 4H, H-6eq,6ax, H-8eq,8ax). Calcd for $C_8H_{15}NO_3$: C, 55.45; H, 8.73; N, 8.09. Found : C, 55.17; H, 8.82; N, 8.05.

Acknowledgment. The work of the Hungarian group was supported by grants of National Science Fundation of Hungary (OTKA 1181, OTKA T 14402 and OTKA T4023). One of us (I.K.) expresses his sincere thanks to the "Fundation for the Hungarian Science" of the Hungarian Credit Bank and to the project of the European Community for Cooperation in Science and Technology with Central and Eastern European Countries for grants.

REFERENCES

(1) Part IV : Herczegh, P.; Kovács, I.; Szilágyi, L.; Varga, T.; Dinya, Z.; Sztaricskai, F. *Tetrahedron Lett.*, **1993**, *34*, 1211-1214.
(2) Fellows, L. E.; Fleet, G. W. J.; in Wagman, G. H.; Cooper, R. : *Natural Products Isolation,* Elsevier Eds, Amsterdam, **1988**.
(3) Fellows, L. E.; Kite, G. C.; Nash, R. J.; Simmonds, M. S. J.; Scofield, A. M. *Recent Adv. Phytochem.*, **1989**, *23*, 395-427.
(4) Elbein, A. ; Molineux, R. J. in Pelletier, S. W. *Alkaloids : Chemical and Biological Perspectives,* Vol 5. Wiley Ed. **1987**, 27, 1-54.
(5) Humphries, M. J. ; Matsumoto, K. ; White, S. L. ; Molineux, R. J. ; Olden, K. *Cancer Res.* **1988**, *48*, 1410-1415.
(6) Dennis, J. W. *Cancer Res.* **1986**, *46*, 5131-5136.
(7) Kino, T.; Inamura, N.; Nakahara, K.; Kiyoto, S.; Goto, T.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.*, **1985**, *38*, 936-940.
(8) Karpas, A.; Fleet, G. W. J.; Dwek, R. A.; Petursson, S.; Namgoong, S.K.; Ramsden, N. G.; Jacob, G. S.; Rademacher, T. W.; *Proc. Natl. Acad. Sci. USA*, **1988**, *85*, 9229-9233.

(9) Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature,* **1987**, *330*, 74-77.
(10) Howard, A. S.; Michael, J. P.; in Brossi A. *Alkaloids*, vol. 26, Academic Press New York **1986**, 275-308.
(11) A review on the synthesis of castanospermine : Burgess, K.; Henderson, I. *Tetrahedron*, **1992**, *48*, 4045-4066.
(12) A recent review on the synthesis of swainsonine, castanospermine, slaframine and their analogs: Herczegh, P.; Kovács, I.; Sztaricskai, F. in Lukacs, G. *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*, vol 2. Springer-Verlag, Berlin, **1993**, 751-828.
(13) Some synthesis of hydroxylated indolizidines published very recently: (a) Siriwardena, A. H.; Chiaroni, A.; Riche, C.; Grierson, D. S. *J. Org. Chem.*, **1992**, *57*, 5661-5666. (b) Lee, C. K.; ; Sim, K. Y.; Zhu, J. *Tetrahedron*, **1992**, *48*, 8541-8544. (c) Maggini, M.; Prato, M.; Ranelli, M.; Scorrano, G. *Tetrahedron Lett.*, **1992**, *33*, 6537-6540. (d) McCaig, A. E.; Wightman, R. H. *Tetrahedron Lett.*, **1993**, *34*, 3939-3942. (e) Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L.; Ulgheri, T. *J. Org. Chem.*, **1993**, *58*, 3397-3400.
(14) Herczegh, P.; Kovács, I.; Szilágyi, L.; Zsély, M.; Sztaricskai, F.; Berecibar, A.; Olesker, A.; Lukacs, G. *Tetrahedron Lett.*, **1992**, *33*, 3133-3136.
(15) Kerwin, J. F.; Danishefsky, S. J. *Tetrahedron Lett.*, **1982**, *23*, 3739-3742.
(16) Boger, D. L.; Weinreb, S. N. *Hetero Diels-Alder Methodology in Organic Synthesis,* Academic Press New York **1987**.
(17) Veyrat, C.; Wartski, L.; Seyden-Penne, J. *Tetrahedron Lett.*, **1986**, *27*, 2981-2984.
(18) Le Coz, L.; Wartski, L.; Seyden-Penne, J.; Charpin, P.; Nierlich, M. *Tetrahedron Lett.*, **1989**, *30*, 2795-2796.
(19) Le Coz, L.; Veyrat,-Martin C.; Wartski, L.; Seyden-Penne, J.; Bois, C.; Philoche-Levisalles, M. *J. Org. Chem.*, **1990**, *55*, 4870-4879.
(20) Nogue, D.; Paugam, R.; Wartski, L. *Tetrahedron Lett.*, **1992**, *33*, 1265-1268.
(21) Barluenga, J.; Aznar, F.; Valdes, C.; Cabal, M-P. *J. Org. Chem.*, **1993**, *58*, 3391-3396.
(22) Hamley, P.; Helmchen, G.; Holmes, A. B.; Marshall, D. R.; MacKinnon, J. W. M.; Smith, D. F.; Ziller, J. W. *J. Chem. Soc, Chem. Commun.*, **1992**, 786-788.
(23) McFarlane, A. K.; Thomas, G.; Whiting, A. *Tetrahedron Lett.*, **1993**, *34*, 2379-2382.
(24) Kunz, H.; Pfrengle, W. *Angew. Chem.*, **1989**, *101*, 1041-1042.
(25) Pfrengle, W.; Kunz, H. Waldmann, H.; Braun, M. *J. Org. Chem.*, **1989**, *54*, 4262-4263.
(26) Waldmann, H.; Braun, M.; Drager, M. *Angew. Chem.*, **1990**, *102*, 1445-1447.
(27) Waldmann, H.; Braun, M.; Drager, M. *Tetrahedron Asymmetry,* **1991**, *2*, 1231-1245.
(28) Waldmann, H.; Braun, M. *Liebigs Ann. Chem.*, **1991**, 1045-1048.
(29) Waldmann, H.; Braun, M. *Gazz. Chim. Italiana,* **1991**, *121*, 277-284.
(30) Waldmann, H.; Braun, M. *J. Org. Chem.*, **1992**, *57*, 4444-4451.
(31) Midland, M.; McLoughlin, J. I.; *Tetrahedron Lett.*, **1988**, *29*, 4653-4656.
(32) Midland, M.; Koops, R. W. *J. Org. Chem.*, **1992**, *57*, 1158-1161.
(33) Hattori, K.; Yamamoto, H. *J. Org. Chem.*, **1992**, *57*, 3264-3265.
(34) Zinner, H.; Kristen, H. *Chem. Ber.*, **1964**, *97*, 1654-1658.
(35) Kochetkov, N. K.; Dmitriev, B. A. *Tetrahedron*, **1965**, *21*, 803-815.
(36) Aslani-Shotorbani, G.; Buchanan, J. G.; Egdar, A. R.; Shashidi, P. K. *Carbohydr. Res.*, **1985**, *136*, 37-52.
(37) Herczegh, P.; Kovács, I.;Sztaricskai, F. *Tetrahedron*, **1991**, *47*, 1541-1546.
(38) Herczegh, P.; Zsély, M.; Szilágyi, L.; Batta, G.; Bajza, I.; Bognár, R. *Tetrahedron*, **1989**, *45*, 2793-2802.
(39) Zinner, H. *Chem. Ber.*, **1950**, *83*, 275-277.
(40) Hardegger, E.; Schreier, E.; El Heweihi, Z. *Helv. Chim. Acta*, **1950**, *33*, 1159-1164.
(41) Just, G.; Potvin, P. *Can. J. Chem.*, **1980**, *58*, 2173-2177.
(42) Grindley, T. B.; Cote, C. J. P.; Wickramage, C. *Carbohydr. Res.*, **1985**, *140*, 215-238.
(43) Colegate, S. M.; Dorling, P. R.; Huxtable, C. R. *Aust. J. Chem.*, **1984**, *37*, 1503-1509.
(44) Cenci di Bello, I.; Fleet, G.; Namgoong, S. K.; Tadano, K.; Winchester, B. *Biochem; J.*, **1989**, *259*, 855-861.
(45) Winkler, D. A.; Holan, G. *J. Med. Chem.*, **1989**, *32*, 2084-2089.
(46) Snatzke, G. *Tetrahedron*, **1965**, *21*, 413-422.
(47) Goldberg, S.; Moates, R. F. *J. Org. Chem.*, **1967**, *32*, 1832-1837.
(48) Sheldrick, G. M. A Program for Solution of Crystal Structure from Diffraction Data, University of Göttingen, Germany. SHELXS86. **1986**.
(49) Sheldrick, G. M. Program for Crystal Structure determination, University of Cambridge, United Kingdom. SHELX76. **1976**.

(*Received in Belgium* 5 *May* 1994; *accepted* 10 *October* 1994)