JOC Article

Stereoselective Syntheses of 1,4-Dideoxy-1,4-imino-octitols and Novel Tetrahydroxyindolizidines

Ana T. Carmona, José Fuentes, and Inmaculada Robina*

Departamento de Química Orgánica, Facultad de Química, Universidad de Sevilla, Apartado 553, E-41071 Sevilla, Spain

Eliazar Rodríguez García, Raynald Demange, and Pierre Vogel

Institute of Molecular and Biological Chemistry, Swiss Federal Institute of Technology (EPFL), BCH, CH 1015 Lausanne-Dorigny, Switzerland

Ana L. Winters

Institute of Grasssland and Enviromental Research, Plas Gogesddan, Aberystwyth 5423 3EB, U.K.

robina@us.es

Received November 11, 2002

A new route for the preparation of four new indolizidines, (1*R*,2*S*,6*S*,7*S*,8a*S*)- and (1*R*,2*S*,6*R*,7*R*,-8a*S*)-1,2,6,7-tetrahydroxyindolizidine (**30** and **32**) and (1*S*,2*R*,7*S*,8*S*,8a*R*)- and (1*S*,2*R*,7*R*,8*R*,8a*R*)-1,2,7,8-tetrahydroxyindolizidine (**44** and **46**), is reported. The synthesis is based on Knoevenagel homologation of the readily available enantiomerically pure pyrrolidin-carbaldehydes **13** and **37** followed by asymmetric dihydroxylation of the subsequent alkenyl pyrrolidines and cyclization of the corresponding imino-octitols. The new indolizidines and their precursors (imino-octitols **20**, **25**, **26**) and indolizidinones **28a** and **28b** have been tested for inhibitory activities toward 26 glycosidases. The enzymatic inhibition of *trans*-7-hydroxy-D-(−)-swainsonine (**44**) toward α-mannosidases is similar to that described for *trans*-7-hydroxy-L-(+)-swainsonine (**11b**) toward naringinase (α-L-rhamnosidase from *Penicillium decumbens*).

Introduction

Glycosidases and glycosyltransferases belong to an important group of enzymes involved in the biosynthesis and processing of the glycoconjugate components of all organisms.[1] The discovery of specific inhibitors of these enzymes is allowing important advances in the control of cellular functions. Some inhibitors of glycosidases and glycosyltransferases have shown promising chemotherapeutic applications against diabetes,[2] cancer,[3] and viral infections including AIDS.[4] Many glycosidase inhibitors mimic the configuration, shape, and charge distribution of the cation liberated during the enzyme-catalyzed processes. Among the most powerful glycosidase inhibitors are 1,5-dideoxy-1,5-iminoalditols,[5] which are protonated under physiological conditions. 1,4-Dideoxy-1,4-iminoalditols are also an important class of glycosidase inhibitors, although their higher conformational flexibility reduces, in some instances, their selectivity. Imino-*C*-disaccharides have emerged as a possible solution to increase selectivity in enzyme inhibition because they contain not only the information of the glycosyl moiety that is cleaved during the enzymatic hydrolysis, but also that of the aglycon.[6] Several approaches have been made for the synthesis of these compounds[7] that generally imply a coupling reaction between a pyrrolidine or piperidine moiety and a sugar compound or a precursor. On the other hand, homochiral polyhydroxylated pyrrolidines and piperidines joined to polyolic chains through C−C links (iminoalditols) can be considered as acyclic imino-*C*-disaccharide analogues and, therefore, are po-

(1) (a) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300−2324. (b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683−720. (c) Petrescu, A. J.; Negroiu, G.; Dwek, R. A.; Petrescu, S. M. *Chem. Rev.* **2000**, *100*, 4697−4711.

(2) See, e.g.: (a) Rhinehart, B. L.; Robinson, K. M.; Liu, P. S.; Payne, A. J.; Wheatley, M. E.; Wagner, S. R. *J. Pharmacol. Exp. Ther.* **1987**, *241*, 915. (b) Leonhardt, M. W.; Hanefield, M.; Fischer, S.; Schulze, J. *Eur. J. Clin. Invest.* **1994**, *24*, 45. (c) Bisschoff, H. *Eur. J. Clin. Invest.* **1994**, *3*, 3. (d) Robinson, K. M.; Begovic, M. E.; Rhinehart, B. L.; Heinecke, E. W.; Ducep, J.-B.; Kastner, P. R.; Marshall, F. N.; Danzin, C. *Diabetes* **1991**, *40*, 825.

(3) (a) Dennis, J. W.; Koch, K.; Beckner, D. *J. Natl. Cancer Inst.* **1989**, *81*, 1028. (b) Gross, P. E.; Baker, M. A.; Carver, J. P.; Dennis, J. W. *Clin. Cancer Res.* **1995**, *1*, 935. (c) Goss, P. E.; Reid, C. L.; Baily, D.; Dennis, J. W. *Clin. Cancer Res.* **1999**, *21*, 412−421. (d) Dennis, J. W.; Granovsky, M.; Warren, C. E. *Biochim. Biophys. Acta* **1999**, *1473*, 21−34.

(4) (a) Karlsson, G. B.; Butters, T. D.; Dwek, R. A.; Platt, F. M. *J. Biol. Chem.* **1993**, *268*, 570−576. (b) Johnson, V. A.; Wolker, B. D.; Barlow, M. A.; Paradis, T. J.; Chon, T. C.; Hirsoh, M. S. *Antimicrob. Agents Chemother.* **1989**, *33*, 53−57. (c) Fisher, P. B.; Karlsson, G. B.; Dwek, R. A.; Platt, F. M. *J. Virol.* **1996**, *70*, 7153−7160. (d) Fenouillet, E.; Papandreou, M. J.; Jones, I. M. *Virology* **1997**, *231*, 89−95.

(5) Stütz, A. E. *Iminosugars as Glycosidase Inhibitors, Nojirimycin and Beyond*; Wiley-VCH: Weinheim, 1999.

(6) (a) Svenson, B.; Sierks, M. R. *Carbohydr. Res.* **1992**, *227*, 29−44. (b) Lee, S.-B.; Park, K.-H.; Robyt, J. F. *Carbohydr. Res.* **2001**, *331*, 13−18. (c) Aleshin, A. E.; Firsov, L. M.; Honzat, R. *J. Biol. Chem.* **1994**, *269*, 15631−15639. (d) McCarter, J. D.; Yeung, W.; Chow, J.; Dolphin, D.; Withers, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 5792−5797.

10.1021/jo026688a CCC: $25.00
Published on Web 04/24/2003

tential specific inhibitors of glycosidases. A number of iminoalditols with short-polyolic side chains have been described and shown to be inhibitors of glycosidases; e.g., iminohexitols such as 1,4-dideoxy-1,4-imino-D-mannitol[8] (**1**), -D-talitol[9] (**2**), and -L-allitol (**3**)[10] are inhibitors of α-mannosidases, and the related 1,4-dideoxy-1,4-imino-L-iditol (**4**) is a potent inhibitor of α-D-galactosidases. Iminoheptitols such as 1,4-imino-L-*glycero*-D-*ido* (**5**) and 1,4-imino-L-*glycero*-D-*gluco*heptitols (**6**)[11] or 2,5-imino-L-*glycero*-L-*gulo* (**7**) and -D-*glycero*-D-*manno*heptitols (**8**)[12] have proved to be good and specific inhibitors of α- and *β*-D-glucosidases. Several 1,5-dideoxy-1,5-iminoheptitols[13] and 1,5-dideoxy-1,5-imino-octitols[14] have been synthesized and evaluated as glycosidase inhibitors. Most of them showed weak or no inhibition toward glycosidases, except 1,5,7-trideoxy-1,5-imino-D-*glycero*-D-*gluco*-heptitol (**9**)[15] that was found to be a strong inhibitor ($K_i = 3\ \mu M$) of yeast α-glucosidase.

Long-chain iminoalditols present the additional advantage of being interesting intermediates in the synthesis of polyhydroxylated bicyclic alkaloids. Among them, indolizidines constitute an important group of compounds. In addition to the synthesis of naturally occurring lentiginosine,[16] swainsonine,[17] and castanospermine,[18] a number of stereoisomers and other analogues have been prepared and assayed as inhibitors of glycosidases. This has produced information on structure−activity relationships, and several reviews concerning their synthesis and their biological properties have been reported[19] (Figure 1).

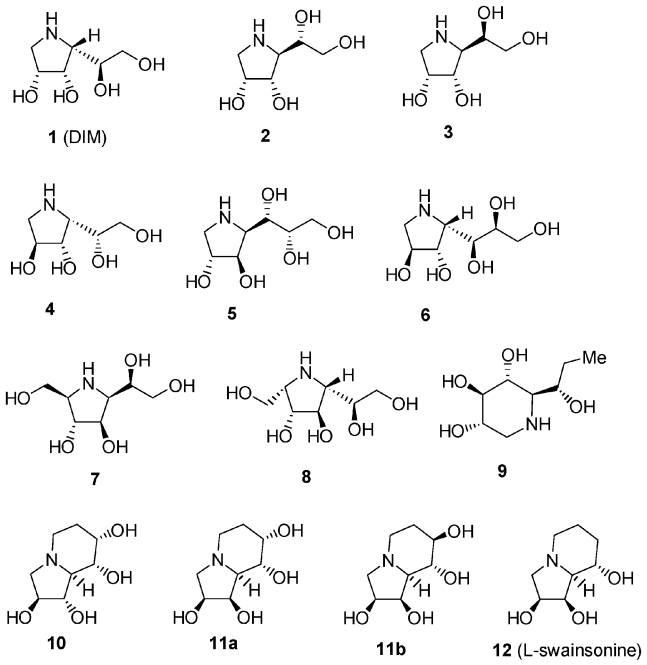


FIGURE 1.

1,6,7,8-Tetrahydroxyindolizidines have been prepared by internal nucleophilic displacement,[20] intramolecular conjugate addition,[21] intramolecular amide formation,[22] or double cyclization processes.[23] Lennarzt and co-workers[24] have reported the preparation of 1,2,6,7-tetrahydroxyindolizidine **10** via hexahydro-3-oxoindolizidine as a key intermediate, which was formed by ring closing

(7) (a) Johnson, C. R.; Miller, M. W.; Golebiowski, A.; Sundram, H.; Ksebati, M. B. *Tetrahedron Lett.* **1994**, *35*, 8991−8994. (b) Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 4856−4865. (c) Leewenburgh, M. A.; Picasso, S.; Overkleeft, H. S.; van der Marel, G. A.; Vogel, P.; van Boom, J. H. *Eur. J. Org. Chem.* **1999**, *1185*, 1185−1189. (d) Martin, O. R.; Liu, L.; Yang, F. *Tetrahedron Lett.* **1996**, *37*, 1991−1994. (e) Saavedra, O. M.; Martin, O. *J. Org. Chem.* **1996**, *61*, 6987−6993. (f) Baudat, A.; Vogel, P. *Tetrahedron Lett.* **1996**, *37*, 483−484. (g) Baudat, A.; Vogel, P. *J. Org. Chem.* **1997**, *62*, 6252−6260. (h) Frerot, E.; Marquis, C.; Vogel, P. *Tetrahedron Lett.* **1996**, *37*, 2023−2026. (i) Kraehenbuehl, K.; Picasso, S.; Vogel, P. *Helv. Chim. Acta* **1998**, *81*, 1439−1479. (j) Zhu, Y. H.; Vogel, P. *J. Org. Chem.* **1999**, *64*, 666−669. (k) Marquis, C.; Picasso, S.; Vogel, P. *Synthesis* **1999**, 1441−1452. (l) Marquis, C.; Cardona, F.; Robina, I.; Wurth, G.; Vogel, P. *Heterocycles* **2002**, *56*, 181−208. (m) Cardona, F.; Robina, I.; Vogel, P. *J. Carbohydr. Chem.* **2000**, *19*, 555−571. (n) Zhu, Y.-H.; Vogel, P. *J. Chem. Soc., Chem. Commun.* **1999**, 1873−1874. (o) Cardona, F.; Valenza, S.; Picasso, A.; Goti, A.; Brandi, A. *J. Org. Chem.* **1998**, *63*, 7311−7318. (p) Navarro, I.; Vogel, P. *Helv. Chim. Acta* **2002**, *85*, 152−160.

(8) (a) Fleet, G. W. J.; Shaw, A. N.; Evans, S. V.; Fellows, L. E. *J. Chem. Soc., Chem. Commun.* **1984**, 1240−1241. (b) Palamartczky, G.; Mitchell, M.; Smith, P. W.; Fleet, G. W. J.; Elbein, A. D. *Arch. Biochem. Biophys.* **1985**, *242*, 35.

(9) (a) Fleet, G. W. J.; Son, J. C.; Green, D. S.; Cenci di Bello, I.; Winchester, B. *Tetrahedron* **1988**, *44*, 2649−2655.

(10) (a) Al Dasher, S.; Fleet, G. W. J.; Namgoong, S. K.; Winchester, B. *Biochem. J.* **1989**, *258*, 613. (b) Fleet, G. W. J.; Son, J. C. *Tetrahedron* **1988**, *44*, 2637−2647.

(11) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319−384.

(12) (a) Takebayashi, M.; Hiranuma, S.; Kanie, Y.; Kajimoto, T.; Kanie, O.; Wong, C.-H. *J. Org. Chem.* **1999**, *64*, 5280−5291. (b) Saotome, C.; Kanie, Y.; Kanie, O.; Wong, C.-H. *Bioorg. Med. Chem.* **2000**, *8*, 2249−2261.

(13) Lundt, I.; Madsen, R. *Synthesis* **1995**, 787−794.

(14) (a) Picasso, S.; Chen, Y.; Vogel, P. *Carbohydr. Lett.* **1994**, *1*, 1−8. (b) Chen, Y.; Vogel, P. *J. Org. Chem.* **1994**, *59*, 2487−2496.

(15) Berger, A.; Dax, K.; Gradnig, G.; Grassberger, V.; Stutz, A. E.; Underank, M.; Legler, G.; Bause, E. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 27−32.

(16) (a) Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806−6812. (b) Cardona, F.; Goti, A.; Picasso, S.; Vogel, P.; Brandi, A. *J. Carbohydr. Chem.* **2000**, *19*, 585−601.

(17) Nemr, A. E. *Tetrahedron* **2000**, *56*, 8579−8629.

(18) For a review, see, e.g.: Cossy, J.; Vogel, P. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1993; Vol. 12, p 275. 1-Epicastanospermine: Denmark, S. E.; Herbert, B. *J. Org. Chem.* **2000**, *65*, 2887−2896. 5-Azacastanospermine: Søndergard, K.; Liang, X.; Bols, M. *Chem. Eur. J.* **2001**, *7*, 2324−2331.

(19) (a) Burgess, K.; Henderson, I. *Tetrahedron* **1992**, *48*, 4045−4066. (b) Jaeger, V.; Mueller, R.; Leibold, T.; Hein, M.; Schwartz, M.; Fengler, M.; Jaroskova, L.; Paetzel, M.; LeRoy, P.-Y. *Bull. Soc. Chim. Belg.* **1994**, *103*, 491−507. (c) Picasso, S. *Chimia* **1996**, *50*, 648−649. (d) Goti, A.; Cichi, S.; Cordero, F. M.; Fedi, V.; Brandi, A. *Molecules* **1999**, *4*, 1−12. (e) Asano, N.; Nash, R. J.; Molyneaux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645−1680. (f) El Ashry, E. S. H.; Rashed, N.; Shobier, A. H. S. *Pharmazie* **2000**, *5*, 331−348. (g) Despinoy, X. L. M.; McNab, H. *Tetrahedron* **2000**, *56*, 6359−6383.

(20) From 4-octuloses: Izquierdo, I.; Plaza, M. T.; Robles, R.; Mota, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 1015−1027. From octitols and derivatives: (a) Izquierdo, I.; Plaza, M. T.; Robles, R.; Rodríguez, C.; Ramírez, A.; Mota, A. J. *Eur. J. Org. Chem.* **1999**, 1269−1274. (b) Chen Y.; Vogel, P. *J. Org. Chem.* **1994**, *59*, 2487−2496. From D-glucono-*δ*-lactone: Gerspacher, M.; Rapoport, H. *J. Org. Chem.* **1991**, *56*, 3700−3706. From D-xylose: Mulzer, J.; Demhlow, H.; Bushman, J.; Luger, P. *J. Org. Chem.* **1992**, *57*, 3194−3202. From D-treose: Casiraghi, G.; Ulgheri, F.; Spanu, P.; Rassu, G.; Pinna, L.; Fava, G. G.; Ferrari, M. B.; Pelosi, G. *J. Chem. Soc., Perkin Trans 1* **1993**, 2991−2997.

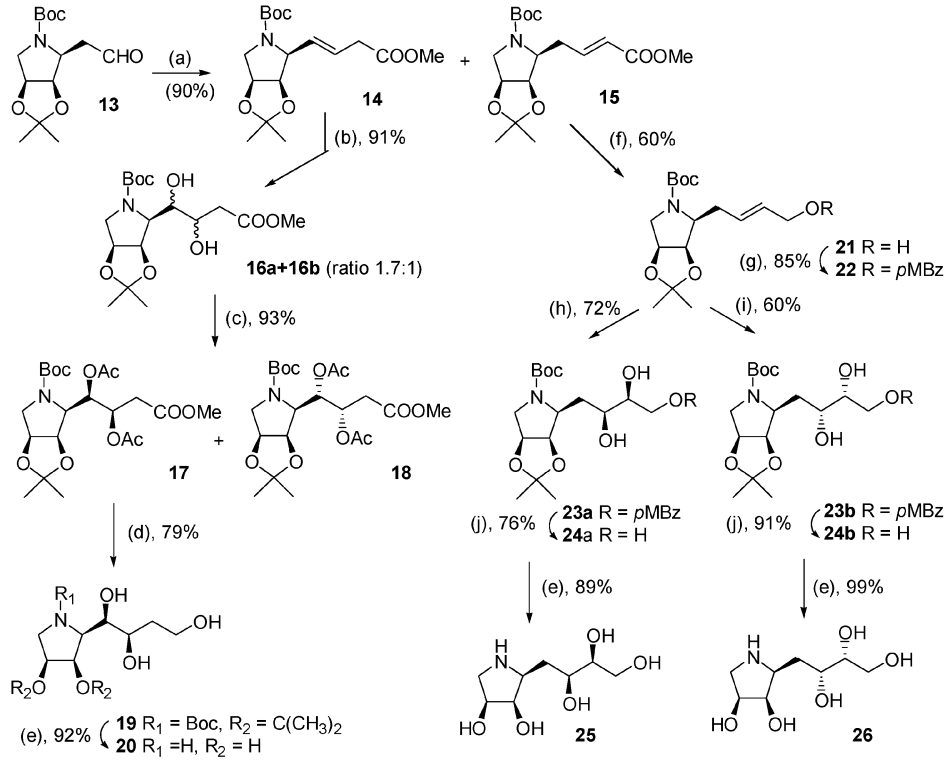
(21) From unsaturated sulfones: (a) Carretero, J. C.; Arrayás, R. G. *J. Org. Chem.* **1998**, *63*, 2993−3005 and references therein. (b) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543−4552.

(22) Preparation of D-(−)-swansonine. From D-mannose: (a) Suami, T.; Tadano, K.; Iimura, Y. *Chem. Lett.* **1984**, 513−516. (b) Suami, T.; Tadano, K.; Iimura, Y. *Carbohydr. Res.* **1985**, *136*, 67−75. (c) Yasuda, N.; Tsutsumi, H.; Takaya, T. *Chem. Lett.* **1984**, 1201−1204. From D-erythronolactone: Pearson, W. H.; Hembre, E. J. *J. Org. Chem.* **1996**, *61*, 7217−7221. From D-glucose: (a) Tadano, K.; Iimura, Y.; Hotta, Y.; Fukabori, C.; Suami, T. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3885−3892. (b) Iimura, Y.; Hotta, Y.; Fukabori, C.; Tadano, K.; Suami, T. *J. Carbohydr. Chem.* **1986**, *5*, 147−152.

(23) Preparation of D-(−)-swainsonine: Setoi, H.; Takeno, H.; Hashimoto, M. *J. Org. Chem.* **1985**, *50*, 3948−3950.

(24) Lennartz, M.; Steckhan, E. *Tetrahedron* **2001**, *57*, 675−680.

SCHEME 1[a]



[a] Reaction conditions: (a) $HOOCCH_2COOMe$, Py, piperidine, 100 °C; (b) OsO_4, NMO, acetone/H_2O; (c) Ac_2O, Py, DMAP; (d) $LiAlH_4$, THF, 0 °C; (e) (1) TFA aq, (2) Dowex50WX8; (f) DIBALH,CH_2Cl_2, −20 °C; (g) *p*-methoxybenzoyl chloride, CH_2Cl_2, TEA; (h) AD-mixα, tBuOH/H_2O, $MeSO_2NH_2$, 0 °C, 24 h, de 97%; (i) AD-mix*β*, tBuOH/H_2O, $MeSO_2NH_2$, 0 °C, 48 h, de 91%; (j) NaOMe, MeOH.

olefin metathesis starting from 5-allyl-4-hydroxy-2-pyrrolidone. Finally, several syntheses of enantiopure stereoisomeric 1,2,7,8-tetrahydroxyindolizidines have been reported.[25] For instance, Fleet and co-workers[26] have reported the synthesis of *cis*- and *trans*-7-hydroxy-L-swainsonine **11a** and **11b** starting from glucoheptonolactone.

Small modifications on the structure of indolizidines induce significant changes in their biological activity, their potency, or their specificity as inhibitors of glycosidases or as ligands or receptors.[27] It is therefore justified to develop better methodologies to generate more polyhydroxyindolizidines. In a preliminary report,[28] we have described a convenient route to novel polyhydroxylated indolizidines. We now report on the synthesis of new imino-*C*-polyols and their cyclization into different types of polyhydroxy-indolizidines, including derivatives of (−)- and (+)-swainsonine. The synthesis relies on the olefination of 1,4-dideoxy-1,4-iminohexoses followed by stereoselective dihydroxylations of the resulting alkenes. Evaluation of the new compounds as glycosidase inhibitors is also reported.

Results and Discussion

Starting from 3,6-(*tert*-butoxycarbonyl)imino-2,3,6-trideoxy-4,5-*O*-isopropylidene-L-*arabino*-hexose (**13**),[7m] the Knoevenagel−Doebner reaction[29] with hydrogen methyl malonate gave a mixture of the two possible *trans*-regioisomeric alkenes **14** and **15** in 50% and 40% yield, respectively (Scheme 1). Direct dihydroxylation of **14** with *N*-methylmorpholine-*N*-oxide[30] and a catalytic amount of osmium tetraoxide gave a mixture of the corresponding *syn*-diols **16a** and **16b** in 91% yield and in a ratio of 1.7:1. This indicates that the sugar moiety exerts a weak control on the stereoselectivity of the dihydroxylation. Sharpless asymmetric dihydroxylation[31] with the reagents AD-mix-α and AD-mix-*β* gave no reaction, probably due to the high steric hindrance between the catalyst and the bulky protecting groups of the substrates. Compounds **16a** + **16b** could not be separated as such, but their acetates **17** and **18** were separated by column chromatography. Reduction of acetate **17** with $LiAlH_4$ at 0 °C (→**19**) followed by acidic cleavage of the protecting groups gave 1,4,7-trideoxy-1,4-imino-octitol, **20**. The same

(25) For preparation of (1*S*,2*R*,7*R*,8*S*)-, (1*S*,2*S*,7*S*,8*R*)-, and (1*S*,2*S*,-7*R*,8*S*)-1,2,6,7-tetrahydroxyindolizidines, see: Paolucci, C.; Mattioli, L. *J. Org. Chem.* **2001**, *66*, 4787−4794. For the preparation of (1*S*,2*S*,7*R*,8*R*)-1,2,7,8-tetrahydroxyindolizidine, see: Lombardo, M.; Trombini, C. *Tetrahedron* **2000**, *56*, 323−326.

(26) Davis, B.; Bell, A. A.; Nash, R. J.; Watson, A. A.; Griffiths, R. C.; Jones, M. G.; Smith, C.; Fleet, G. W. J. *Tetrahedron Lett.* **1996**, *37*, 8565−8568.

(27) (a) Saul, R.; Ghidoni, J. J.; Molyneux, R. J.; Elbein, A. D. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 93. (b) Winchester, B. G.; Al Daher, S.; Carpenter, N. C.; Cenci di Bello, I.; Choi, S. S.; Fairbanks, A. J.; Fleet, G. W. J. *Biochem. J.* **1993**, *290*, 743−749. (c) Cenci di Bello, I.; Fleet, G. W. J.; Namgoong, S. K.; Tadano, K. I.; Winchester, B. G. *Biochem. J.* **1989**, *259*, 855−861.

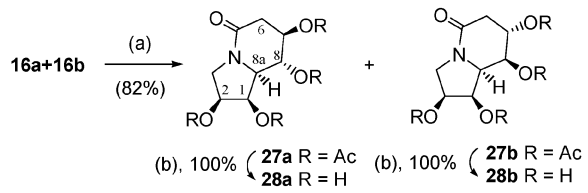
(28) Carmona, A. T.; Fuentes, J.; Robina, I. *Tetrahedron Lett.* **2002**, *43*, 8543−8546.

(29) López-Herrera, F. J.; Pino González, M. S. *Carbohydr. Res.* **1986**, *152*, 283−291 and references therein.

(30) Donohoe, T. J.; Moore, P. R.; Beddoes, R. L. *J. Chem. Soc., Perkin Trans 1* **1997**, 43−51.

(31) Kolb, K. C.; van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

SCHEME 2[a]



[a] Reaction conditions: (a) (1) TFA aq, 2 h, (2) NaOMe,MeOH reflux 16 h, (3) Ac_2O, Py, DMAP; (b) NaOMe, MeOH.

treatment applied to compound **18** was not successful, perhaps because of partial reduction of the Boc-group. The configurations of the glycol moiety have been established by the product of cyclization. (Scheme 2).

Deprotection of **16a** + **16b** with trifluoroacetic acid followed by heating with NaOMe in MeOH at reflux afforded a mixture of indolizidinones that, after acetylation under standard conditions, gave **27a** and **27b** that could be separated in 47% and 35% yield, respectively. Zemplén methanolysis furnished the corresponding indolizidinones **28a** and **28b** in quantitative yield. The spectroscopic ^{1}H NMR data of **27a** and **27b** established the proposed structure. In the case of **27a**, a NOE between pair of protons H8a(δ = 3.80)/H7(δ = 5.21) confirmed the *R* configuration for C(7) and C(8). In the case of **27b**, NOE between pair of protons H1(δ = 5.61)/H8(δ = 5.32) confirmed the *S* configuration for C-7 and C-8. In addition, an antiperiplanar relationship between H7/H8 and H8/H8a ($J_{7,8} = J_{8,8a}$ = 9.4 Hz) for **27a** and a *gauche* relationship between the same protons ($J_{7,8}$ = 5.2 Hz; $J_{8,8a}$ = 3.1 Hz) for **27b** are consistent with the relative configurations proposed and with a chair conformation for the six-membered ring compounds. In the previously mentioned cyclization reaction, compound **27a** is the major one, indicating that the OsO_4-catalyzed dihydroxylation has taken place with preference for the top face.

The direct dihydroxylation of **15** with *N*-methylmorpholine-*N*-oxide/OsO_4 (cat.) gave a 1.3:1 mixture of the expected diastereoisomeric diols in quantitative yield. With the hope of increasing the diastereoselectivity, asymmetric dihydroxylation was performed on the *p*-methoxy benzoyl ester **22** obtained from **15** by reduction with DIBALH (60%) first to give **21**, and subsequent reaction with *p*-methoxy benzoyl chloride in the presence of triethylamine and (dimethylamino)pyridine (85%). Allylic ester **22** is expected to be a good substrate for asymmetric dihydroxylation due to its aromatic−aromatic interactions with the pseudoenantiomeric Cinchona alkaloid ligands of Sharpless reagents.[32] Thus, reaction of **22** with AD-mixα gave diol **23a** as major compound (72% yield, de = 97%). Alternatively, reaction of **22** with AD-mixβ gave **23b** as major compound (60% yield, de = 91%). Deprotection of these compounds gave the imino-*C*-polyols **25** and **26**, respectively. The regioselective (Scheme 3) tosylation of **24a** provided tosylate **29** in 42% yield. It was cyclized into indolizidine **30** in 94% yield upon treatment with CF_3COOH/H_2O first and then with aqueous ammonia. Similarly, **24b** was converted into **31** (38% yield), and then into a mixture of indolizidine **32** and pyrrolizidine **33** (Scheme 3), that were separated by column chromatography on silica gel and isolated in 69% and 28% yield, respectively.

The structures of **30**, **32**, and **33** were deduced from their mode of formation and from their spectral data. The ^{1}H NMR spectrum of **30** showed NOEs between pairs of protons H6(δ = 3.50)/H8′(β)(δ = 1.68), H7(δ = 3.40)//H8-(α)(δ = 1.97), and H7(δ = 3.40)/H8a(δ = 2.28). Similarly, in the case of **32**, NOEs were found for the proton pair H7(δ = 3.94)/H8′(β) (δ = 1.79) that were consistent with the *trans*-relationship between the 6-OH and 7-OH groups in both indolizidines **30** and **32**. Further proof for our assignments was given by the ^{1}H NMR spectra of the corresponding peracetates that showed typical deshielding effects compared with the corresponding polyols for the four signals assigned to H1, H2, H6, and H7 in their ^{1}H NMR spectra. An average chair conformation was indicated for **30** by the coupling constant measured between protons H6, H7, H8(β), and H8a ($J_{6,7}$ = 8.9 Hz, $J_{7,8\beta}$ = 11.0 Hz, $J_{8a,8\beta}$ = 11.7 Hz) in its ^{1}H NMR spectrum. This confirmed a *trans*-diaxial relationship for these pairs of protons. A similar chair conformation can be proposed for **32**. An antiperiplanar relationship between H8a/H8α ($J_{8a,8\alpha}$ = 12.5 Hz) and a *gauche* relationship between proton pairs H6/H7, H7/H8(α), and H7/H8(β) ($J_{6,7} = J_{7,8\alpha} = J_{7,8\beta}$ = 3.0) were indicated by the ^{1}H NMR spectrum of **32**. The pyrrolizidine structure of **33** is supported by a loss of a hydroxymethylene group in the CIMS spectrum and by the observation of NOEs between proton pairs H3(δ = 3.46)/H8(δ = 3.92), H5(δ = 3.52)/H7(α)(δ = 2.48), H6(δ = 4.26)/H7′(β)(δ=1.92), and H7a(δ = 4.43)/H7(α)(δ = 2.48). Furthermore, the coupling constants $J_{6,7}$ = 8.0 Hz and $J_{7a,7'}$ = 9.9 Hz indicate *trans*-relationships between proton pairs H6/H7(α) and H7a/H7′(β), as well as *gauche* arrangements for proton pairs H7(α)/7a, H6/H7′(β), H7a/H1 ($J_{7,7a} = J_{7a,1}$ = 4.1 Hz, $J_{6,7}$ = 6.2 Hz).

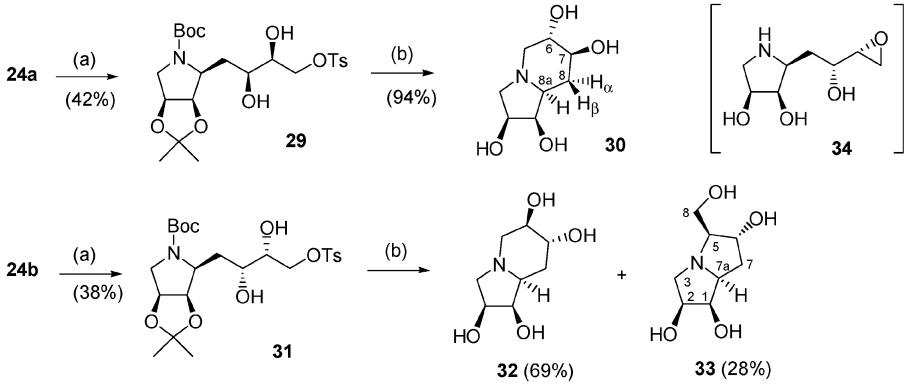
The formation of pyrrolizidine **33** can be interpreted in terms of the formation of an intermediate epoxide **34** on treatment of tosylate **31** with CF_3COOH/H_2O and then with ammonia. *Endo-Tet* cyclization by reaction between the pyrrolidine nitrogen nucleophile and the epoxide moiety of **34** generates indolizidine **32**, whereas the *Exo-Tet* ring opening furnishes **33** (Scheme 3).

Applying a similar synthetic route to ester **35**, we have prepared new derivatives of D-(−)-swainsonine (Scheme 4). Ester **35** was readily obtained from D-arabinose.[33] Its Boc-protection into **36** (92% yield) and then reduction with DIBALH gave aldehyde **37** in 72% yield. Knoevenagel−Doebner homologation[29] of **37** gave the *trans*-regioisomers **38** and **39** in 78% yield that were separated by column chromatography on silica gel. Dihydroxylation of **38** afforded a mixture of *syn* diastereoisomers **40a** + **40b** in 84% yield and 1.7:1 ratio. Treatment of this mixture with CF_3COOH, followed by refluxing with NaOMe/MeOH and conventional acetylation, furnished, after column chromatography, indolizidinones **41** and **42** in 55% and 31% yield, respectively. Reduction of **41** with $BH_3{\cdot}SMe_2$ and subsequent Zemplén methanolysis gave tetrahydroxyindolizidine **44** in 53% yield. Similarly, **42** was converted into **46** in 58% overall yield. Indolizidine **44** is a 7-hydroxy derivative of D-(−)-swain-

(32) Guzmán Pérez, A.; Corey, E. J. *Tetrahedron Lett.* **1997**, *38*, 5941−5944.

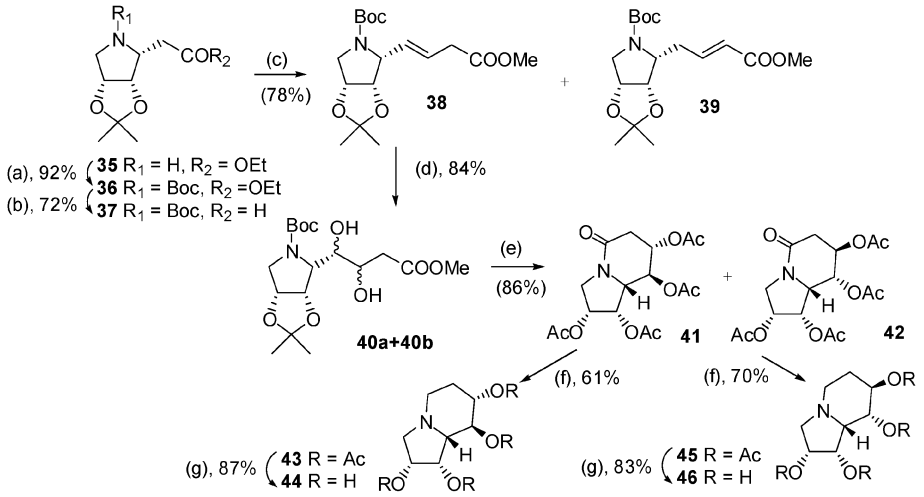
(33) Robina, I.; Gearing, R. P.; Buchanan, J. G.; Wightman, R. H. *J. Chem. Soc., Perkin Trans 1* **1990**, 2622−2624.

SCHEME 3[a]



[a] Reaction conditions: (a) TsCl, Py, −15 °C; (b) (1) TFA aq, (2) NH_4OH.

SCHEME 4[a]



[a] Reaction conditions: (a) $(Boc)_2O$, Py; (b) DIBALH, DCM, −78 °C; (c) $HOOC(CH_2)COOMe$, Py-piperidine, 100 °C, 2 h; (d) OsO_4 (cat.), NMO, acetone/H_2O 4:1, 48 h; (e) (i) TFA aq, 2 h; (ii) NaOMe, MeOH reflux, 16 h; (iii) Ac_2O, Py, DMAP, 16 h; (f) $BH_3{\cdot}SMe_2$, THF, rt, 4 h; (g) NaOMe, MeOH, 2 h.

sonine. Its spectral data were identical to those reported by Fleet and co-workers[26] for its enantiomer: *trans*-7-hydroxy-L-(+)-swainsonine.

The inhibitory activities toward 26 commercially available enzymes were evaluated applying well-established assay techniques.[14a,16a,34] The results are summarized in Table 1. Compounds **20**, **25**, **26**, **28a**, **28b**, **30**, **32**, **44**, and **46** did not show any inhibitory activity at 1 mM concentration toward the following enzymes: α-L-fucosidase from bovine epididymis, α-galactosidases from coffee beans, *Aspergillus niger* and from *Escherichia coli*, *β*-galactosidases from *Escherichia coli*, *Aspergillus niger*, *Aspergillus orizae* and from "jack bean", α-glucosidase (maltase) from yeast and from rice, isomaltase from baker yeast, amyloglucosidase from *Aspergillus niger* and from *Rhizopus mold*, *β*-glucosidase from almond, *β*-mannosidase from *Helix pomatia*, *β*-xylosidase from *Aspergillus niger*, α-*N*-acetylgalactosaminidase from chicken liver, and *β*-*N*-acetylglucosaminidase from "jack bean" and bovine epididymis A and B. Simple *meso*-3,4-dihydroxypyrrolidine **47** is a weak and nonspecific inhibitor of several glycosidases[35] (Figure 2). For instance, it inhibits *β*-galactosidases and α-mannosidases, and by adding a hydroxymethyl group as in **48**, the inhibitory activity toward α-mannosidase is slightly reduced, but the inhibitory activity toward *β*-glucosidase becomes significant, thus demonstrating that a relatively minor modification in structure changes the inhibitory spectrum of the dihydroxypyrrolidine significantly (Table 1). The introduction of an additional hydroxymethylene group at C(5) of **48** (as in **49**) reduces the inhibitory activity toward *β*-galactosidase and *β*-glucosidase and completely suppresses that toward α-mannosidases.

Indolizidines **30** and **32** are structurally related to (+)-castanospermine (**51**) which is a potent inhibitor of α- and *β*-glucosidases.[5] We can deduce that the presence of a hydroxy group at C-2 and/or the absence of a hydroxy group at C-8 generates a compound with lower enzymatic activity than castanospermine itself. Also, the absolute configuration of C-6 and C-7 has an influence on its activity; compound **30** which has the same configuration

(34) Tropea, J. E.; Molyneaux, R. J.; Kaushal, G. P.; Pan, Y. T.; Mitchell, M.; Elbein, A. D. *Biochemistry* **1989**, *28*, 2027−2034.

(35) Popowycz, F.; Gerber-Lemaire, S.; Demange, R.; Rodríguez-García, E.; Carmona Asenjo, A. T.; Robina, I.; Vogel, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2489−2492.

TABLE 1. Inhibitory Activity of Imino-Octitols and Indolizidine Derivatives: Percentage of Inhibition at 1 mM (IC_{50} and K_i in μM)[a]

enzyme/compd	ref	β-Gal-ase (bovine liver)	β-Glc-ase (*Caldocellum saccharol.*)	α-Man-ase (jack bean)	α-Man-ase (almonds)	naringinase (*Penicillium decumbens*)
20		26%	NI	30%	NI	IC_{50} = 11000
25		42%	NI	NI	NI	ND
26		52% IC_{50} = 11 000	NI	NI	NI	
47	35	25%	NI	70% IC_{50} = 400	40%	ND
48	35	51%	90% IC_{50} = 85 K_i = 19 (C)	54% IC_{50} = 800	37%	ND
49	35	32%	40%	NI	NI	ND
11b	26					IC_{50} = 50
12	26					IC_{50} = 0.3 K_i = 0.4
28a		38%	NI	NI	NI	IC_{50} = 14000
28b		52%	NI	NI	NI	NI
30		66% IC_{50} = 540	69% IC_{50} = 145 K_i = 139 (NC)	NI	NI	NI
32		74% IC_{50} = 275	22%	NI	NI	NI
44		71% IC_{50} = 415	32%	92% IC_{50} = 65 K_i = 23 (C)	94% IC_{50} = 48 K_i = 19 (C)	NI
46		62%	NI	43%	55%	NI
50	5	NI	NI	100% IC_{50} = 0.2	100% IC_{50} = 0.4	NI

[a] Inhibitions: (C) competitive, (NC) noncompetitive; NI, no inhibition at 1 mM concentration; ND, not determined.

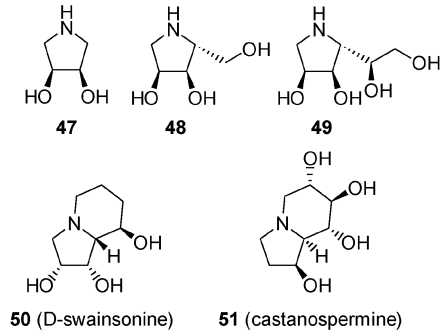


FIGURE 2.

as (+)-castanospermine has a higher inhibitory effect. Indolizidines **30** and **32** can also be viewed as analogues of L-swainsonine (**12**), a compound reported to be a potent inhibitor of naringinase (α-L-rhamnosidase) from *Penicillium decumbens*.[26] However, indolizidines **30** and **32** showed no inhibitory activity toward this enzyme (Table 1).

Bicyclic lactams **28a** and **28b** are moderate inhibitors of β-galactosidases from bovine liver and almost inactive toward the other glycosidases. This is not surprising due to their neutrality (amides instead of amines). Compound **28a**, which is a precursor of *trans*-hydroxy-L-swainsonine (**11b**),[26] has proven to be a much weaker inhibitor of naringinase than **11b** (see Table 1).

Interestingly, **44** which is (7*S*)-hydroxy-D-swainsonine is a moderate inhibitor of α-mannosidases although about 100 times less active than D-swainsonine **50** itself. The decrease in enzymatic inhibition due to the introduction of an additional OH at C(7) has also been observed in the L-swainsonine derivatives toward naringinase (see Table 1, **11b** and **12**). Compound **46** has shown a weaker inhibitory activity than **44** toward mannosidases, demonstrating the importance of the configuration of C(8) of the indolizidine ring.

The inhibitory activity of *trans*-7-hydroxy-L-swainsonine (**11b**) toward naringinase (IC_{50} = 50 μM) and of *trans*-7-hydroxy-D-swainsonine (**44**) toward mannosidases (IC_{50} = 65 μM, jack bean; IC_{50} = 48 μM, almonds) is additional evidence of the "enantiomeric affinities" of both enzymes reported previously.[26]

Conclusion

Short and efficient syntheses of 1,4-dideoxy-1,4-imino-octitols and of 1,2,6,7- and 1,2,7,8-tetrahydroxyindolizidines have been carried out starting from the readily available 3,6-(*tert*-butoxycarbonyl)imino-2,3,6-trideoxy-4,5-*O*-isopropylidene-L-*arabino*- and D-*arabino*-hexose (**13** and **37**). The synthesis is based on Knoevenagel homologation followed by asymmetric dihydroxylation and cyclization. Three new imino-octitols, two new indolizidinones, and four new indolizidines have been obtained and tested for their inhibitory activities toward 26 glycosidases. The enzymatic inhibition of *trans*-7-hydroxy-D-(−)-swainsonine (**44**) toward α-mannosidases is similar to that described for *trans*-7-hydroxy-L-(+)-swainsonine (**11b**) toward naringinase (α-L-rhamnosidase from *Penicilium decumbens*), reinforcing the described[26] "enantiomeric affinity" of both enzymes. A (7*S*)-hydroxy substituent reduces by a factor of ca. 100 the inhibitory activity of D-swainsonine toward α-mannosidases.

Experimental Section

General Procedures. Optical rotations were measured in a 1.0 cm tube with a spectropolarimeter. ^{1}H NMR and ^{13}C NMR spectra were obtained for solutions in $CDCl_3$,

DMSO-d_6, CD_3OD, and D_2O; J values are given in Hz and δ in ppm. All the assignments were confirmed by two-dimensional NMR experiments. The FAB mass spectra were obtained with glycerol or 3-nitrobenzyl alcohol as matrix. TLC was performed on silica gel HF_{254} (Merck), with detection by UV light Pancaldi reagent [$(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O]. Silica gel 60 (Merck, 230 mesh) was used for preparative chromatography. Anhydrous solvents and reagents were freshly distilled under N_2 prior to use. The inhibition constants (K_i) and the type of inhibition (competitive, noncompetitive, mixed) were determined from Lineweaver−Burk plots.[14a,16a,36] For each plot, a blank and two concentrations of inhibitor were used corresponding to IC_{50} and $IC_{50}/2$.

Methyl (*E*)-*N*-(*tert*-Butoxycarbonyl)-2,3,4,5,8-pentadeoxy-5,8-imino-6,7-*O*-isopropylidene-L-*arabino*-oct-3-enonate (14) and Methyl (*E*)-*N*-(*tert*-Butoxycarbonyl)-2,3,4,5,8-pentadeoxy-5,8-imino-6,7-*O*-isopropylidene-L-*arabino*-oct-2-enonate (15). To a solution of **13**[7m] (1.38 g, 4.83 mmol) and methyl monomalonate[29] (684 mg, 5.80 mmol) in dry pyridine (5 mL) was added a catalytic amount of piperidine (15 μL). The mixture was heated at 100 °C for 2 h and then concentrated. The residue was dissolved in CH_2Cl_2 (100 mL), washed with a saturated aqueous solution of $NaHCO_3$ (50 mL) and brine, dried (Na_2SO_4), and evaporated. Column chromatography (ether/light petroleum ether 1:5 → 1:2) afforded **14** (836 mg, 51%) and **15** (654 mg, 40%), both as colorless oils. Data for **14**: $[\alpha]_D^{22}$ +45 (*c* 1, CH_2Cl_2); IR (film) 1740, 1697, 1165, 988 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6 90 °C, *J* Hz) δ 5.66−5.51 (m, H-3, H-4), 4.73 (ddd, $J_{7,6} = J_{7,8} = 6.3$, $J_{7,8'} = 2.8$, H-7), 4.69 (t, $J_{6,5} = 6.2$, H-6), 4.24 (t, $J_{5,4} = 6.0$, H-5), 3.65 (dd, $^2J_{8,8'} = 12.7$, H-8), 3.61 (s, COOCH_3), 3.26 (dd, H-8′), 3.09 (d, $J_{2,3} = 5.3$, H-2), 1.40 and 1.26 (2s, C(CH_3)$_2$), 1.37 (s, C(CH_3)$_3$); ^{13}C NMR (75.4 MHz) δ 170.6 (*C*OOMe), 153.2 (C=O), 130.0, 122.3 (C-3, C-4), 111.3 (*C*(CH$_3$)$_2$), 80.3, 76.8 (C-6, C-7), 78.3 (*C*(CH$_3$)$_3$), 60.8 (C-5), 50.6 (COO*C*H$_3$), 50.0 (C-8), 36.4 (C-2), 27.5 (C(*C*H$_3$)$_3$), 25.7 and 24.7 (C(*C*H$_3$)$_2$); FABMS *m*/*z* 364 [100%, (M + Na)$^+$], 242 [80%, (M − Boc + 2H)$^+$]. Anal. Calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97; N, 4.10. Found: C, 59.85; H, 7.89; N, 4.28. Data for **15**: $[\alpha]_D^{22}$ +41 (*c* 0.85, CH_2Cl_2); IR (film) 1721, 1697, 1167, 984 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6 90 °C, *J* Hz) δ 6.94 (dt, $J_{3,2} = 15.7$, $J_{3,4} = J_{3,4'} = 7.2$, H-3), 5.85 (dt, $^4J_{2,4} = {}^4J_{2,4'} = 1.5$, H-2), 4.77−4.70 (m, H-6, H-7), 3.93 (m, H-5), 3.70 (dd, $^2J_{8,8'} = 12.2$, $J_{8,7} = 7.0$, H-8), 3.65 (s, COOCH_3), 3.18 (dd, $J_{8',7} = 2.7$, H-8′), 2.64 (dddd, $J_{4,5} = 5.6$, $^2J_{4,4'} = 13.1$, H-4), 2.55 (dddd, $J_{4',5} = 7.1$, H-4′), 1.40 (s, C(CH_3)$_3$), 1.45 and 1.30 (2s, C(CH_3)$_2$); ^{13}C NMR (75.4 MHz) δ 165.4 (*C*OOMe), 153.1 (C=O), 145.9 (C-3), 121.5 (C-2), 111.5 (*C*(CH$_3$)$_2$), 79.1, 76.8 (C-7, C-6), 78.6 (*C*(CH$_3$)$_3$), 58.0 (C-5), 50.3 (COO*C*H$_3$), 49.9 (C-8), 31.4 (C-4), 27.5 (C(*C*H$_3$)$_3$), 25.6 and 24.4 (C(*C*H$_3$)$_2$); FABMS *m*/*z* 364 [45%, (M + Na)$^+$], 242 [100%, (M − Boc + 2H)$^+$]. Anal. Calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97; N, 4.10. Found: C, 59.62; H, 7.95; N, 3.98.

Methyl 3,4-Di-*O*-acetyl-*N*-(*tert*-butoxycarbonyl)-2,5,8-trideoxy-5,8-imino-6,7-*O*-isopropylidene-L-*glycero*-L-*galacto*-octanoate (17) and Methyl 3,4-Di-*O*-acetyl-*N*-(*tert*-butoxycarbonyl)-2,5,8-trideoxy-5,8-imino-6,7-*O*-isopropylidene-L-*glycero*-L-*ido*-octanoate (18). To a solution of **14** (1.79 g, 5.25 mmol) in acetone were added, in succession, H_2O 4:1 (165 mL), *N*-methyl-morpholine-*N*-oxide (2.84 g, 21 mmol), and OsO_4 (2.5% in ^{t}BuOH, 4.9 mL, 0.39 mmol). The solution was stirred for 48 h at rt. After addition of Na_2SO_3 (14 g), the mixture was poured into a saturated aqueous solution of NaCl and extracted with AcOEt (4 × 100 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. Column chromatography (CH_2Cl_2/acetone 25:1 → 10:1) gave a mixture of methyl *N*-(*tert*-butoxycarbonyl)-2,5,8-trideoxy-5,8-imino-6,7-*O*-isopropylidene-L-*glycero*-L-*galacto* (and L-*glycero*-L-*ido*) octanoates **16a** + **16b** (1.79 g, 91%, ratio 1.7:1). Conventional acetylation (Ac_2O, Py, DMAP) followed by column chromatography (ether/light petroleum ether 1:3 → 1:1) afforded **17** (463 mg, 56%) as a white solid and **18** (307 mg, 37%) as an oil. Data for **17**: $[\alpha]_D^{22}$ +60 (*c* 0.9, CH_2Cl_2); IR (film) 1748, 1699 (C=O), 1101 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6 90 °C, *J* Hz) δ 5.57 (dt, $J_{3,4} = J_{3,2} = 5.7$, $J_{3,2'} = 7.6$, H-3), 5.40 (t, $J_{4,5} = 5.7$, H-4), 4.84 (t, $J_{6,7} = J_{6,5} = 7.1$, H-6), 4.73 (td, $J_{7,8} = 7.1$, $J_{7,8'} = 5.0$, H-7), 4.22 (dd, H-5), 3.86 (dd, $^2J_{8,8'} = 12.0$, H-8), 2.99 (dd, H-8′), 2.98 (s, COOCH_3), 2.68 (dd, $^2J_{2,2'} = 15.8$, H-2), 2.55 (dd, H-2′), 1.98 and 1.93 (2s, CH_3CO), 1.41 (s, C(CH_3)$_3$), 1.47 and 1.28 (2s, C(CH_3)$_2$); ^{13}C NMR (75.4 MHz) δ 169.2, 168.9, 168.5 (3 *C*OOMe), 152.6 (C=O), 112.8 (*C*(CH$_3$)$_2$), 79.2 (*C*(CH$_3$)$_3$), 78.6 (C-6), 77.2 (C-7), 71.1 (C-4), 68.0 (C-3), 57.8 (C-5), 50.9 (COO*C*H$_3$), 50.0 (C-8), 35.3 (C-2), 27.5 (C(*C*H$_3$)$_3$), 25.4 and 24.3 (C(*C*H$_3$)$_2$), 20.0 (CO*C*H$_3$). FABMS *m*/*z* 482 [5%, (M + Na)$^+$], 360 [100%, (M − Boc + 2H)$^+$]. Anal. Calcd for $C_{21}H_{33}NO_{10}$: C, 54.89; H, 7.24; N, 3.05. Found: C, 54.74; H, 7.21; N, 3.02. Data for **18**: $[\alpha]_D^{25}$ −11 (*c* 0.95, CH_2Cl_2); FABMS *m*/*z* 482 [100%, (M + Na)$^+$]. Anal. Calcd for $C_{21}H_{33}NO_{10}$: C, 54.89; H, 7.24; N, 3.05. Found: C, 55.01; H, 7.29; N, 3.06. For IR and NMR data, see Supporting Information.

***N*-(*tert*-Butoxycarbonyl)-1,4,7-trideoxy-1,4-imino-2,3-*O*-isopropylidene-D-*glycero*-L-*manno*-octitol (19).** To a suspension of $LiAlH_4$ (100 mg, 2.66 mmol) in dry THF (2 mL) at 0 °C was added a solution of **17** (204 mg, 0.44 mmol) in THF (4 mL) dropwise. After stirring at 0 °C for 15 min, the mixture was diluted with ether and quenched with a saturated aqueous solution of Na_2SO_4. The salts were filtered through Celite and rinsed with ether and CH_2Cl_2. The solvents were evaporated, and the residue was purified by column chromatography (CH_2Cl_2/MeOH 55:1) to yield **19** (121.5 mg, 79%) as a white solid: $[\alpha]_D^{21}$ +22 (*c* 1.5, CH_2Cl_2); FABMS *m*/*z* 370 [100%, (M + Na)$^+$]. CIMSHR calcd for $C_{16}H_{30}NO_7$ (M + H$^+$) 348.2022, found 348.2025. For IR and NMR data, see Supporting Information.

1,4,7-Trideoxy-1,4-imino-D-*glycero*-L-*manno*-octitol (20). A solution of **19** (34.7 mg, 0.1 mmol) in 80% aqueous TFA (3.4 mL) was stirred for 2 h at rt. The mixture was poured into a Dowex 50WX8 ion-exchange column and was sequentially eluted with MeOH (30 mL), H_2O (30 mL), and NH_4OH 10% (50 mL) to give **20** (19.1 mg, 92%). $[\alpha]_D^{22}$ +12 (*c* 0.64, H_2O); ^{1}H NMR (300 MHz, D_2O, *J* Hz) δ 4.31 (td, $J_{2,3} = 4.1$, $J_{2,1} = J_{2,1'} = 8.4$, H-2), 4.18 (dd, $J_{3,4} = 3.7$, H-3), 3.77 (ddd, $J = 8.9$, $J = 4.3$, $J = 1.3$, H-6), 3.71−3.63 (m, H-5, H-8, H-8′), 3.31 (dd, $J_{4,5} = 9.4$, H-4), 3.19 (dd, $^2J_{1,1'} = 11.1$, H-1), 2.75 (dd, H-1′), 1.73 (m, H-7), 1.71 (ddd, $J = 7.2$, $J = 2.7$, $^2J_{7,7'} = 14.3$, H-7′); ^{13}C NMR (75.4 MHz) δ 72.1 (C-2), 71.6 (C-3, C-5), 67.7 (C-6), 60.6 (C-4), 58.7 (C-8), 48.3 (C-1), 35.4 (C-7). CIMS *m*/*z* 208 [55%, (M + H)$^+$]. CIMSHR calcd for $C_8H_{18}NO_5$ 208.1185, found 208.1179.

(1*R*,2*S*,7*R*,8*R*,8a*S*)-1,2,7,8-Tetraacetoxyindolizidin-5-one (27a) and (1*R*,2*S*,7*S*,8*S*,8a*S*)-1,2,7,8-Tetraacetoxyindolizidin-5-one (27b). The mixture of diols **16a** + **16b** (165 mg, 0.44 mmol) was treated with 80% aqueous TFA (15 mL) for 1.5 h at rt and then evaporated. The residue was dissolved in H_2O (5 mL), and NH_4OH was added until basic pH. The solvent was removed, the crude product was dissolved in dry MeOH (20 mL), and NaOMe (22 mg, 0.88 mmol) was added. The mixture was heated at reflux for 16 h, the solvent was removed, and the obtained residue was conventionally acetylated. Column chromatography (ether/acetone 5:1) afforded **27a** (76.6 mg, 47%) as a solid and **27b** (56.5 mg, 35%) as a syrup. Data for **27a**: $[\alpha]_D^{28}$ 0 (*c* 0.93, CH_2Cl_2); IR (film) 1760 (C=O), 1655 (HNC=O), 1069 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$, *J* Hz) δ 5.52 (dd, $J_{1,2} = 3.9$, $J_{1,8a} = 3.0$, H-1), 5.32 (ddd, $J_{2,3} = 8.6$, $J_{2,3'} = 9.2$, H-2), 5.27 (t, $J_{8,8a} = J_{8,7} = 9.4$, H-8), 5.21 (ddd, $J_{7,6} = 6.9$, $J_{7,6'} = 8.8$, H-7), 3.87 (dd, $^2J_{3,3'} = 11.9$, H-3), 3.80 (dd, H-8a), 3.52 (dd, H-3′), 3.04 (dd, $^2J_{6,6'} = 17.8$, H-6), 2.49 (dd, H-6′), 2.13, 2.04 (2s, CH_3CO), 2.03 (s, 2 CH_3CO); ^{13}C NMR (75.4 MHz) δ 169.8, 169.7, 169.6, 169.3 (4 CH_3CO), 165.3 (C=O), 69.3 (C-1), 69.1 (C-2), 68.7 (C-7), 66.9 (C-8), 59.3 (C-8a), 46.3 (C-3), 36.0 (C-6), 20.6 and 20.3 (2 *C*H$_3$CO), 20.4

(36) (a) Martin, O. R.; Saavedra, O. M.; Xie, F.; Liu, L.; Picasso, S.; Vogel, P.; Kizu, H.; Asano, N. *Bioorg. Med. Chem. Lett.* **2001**, *9*, 1269−1278. (b) Robina, I.; Moreno-Vargas, A. J.; Fernández-Bolaños, J. G.; Fuentes, J.; Demange, R.; Vogel, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2555−2559.

(2 CH_3CO); CIMS *m/z* 372 [100%, $(M + H)^{+\bullet}$]. Anal. Calcd for $C_{16}H_{21}NO_9$: C, 51.75; H, 5.70; N, 3.77. Found: C, 51.41; H, 5.63; N, 4.05. Data for **27b**: $[\alpha]_D^{28}$ +61 (*c* 0.85, CH_2Cl_2); IR (film) 1748 (C=O), 1653 (HNC=O), 1105 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, *J* Hz) δ 5.61 (t, $J_{1,8a} = J_{1,2} = 4.6$, H-1), 5.35 (ddd, $J_{2,3} = 6.9$, $J_{2,3'} = 7.4$, H-2), 5.32 (dd, $J_{8,8a} = 3.1$, H-8), 5.17 (td, $J_{7,6} = J_{7,8} = 5.2$, $J_{7,6'} = 2.8$, H-7), 4.21 (dd, H-8a), 3.77 (d, H-3), 2.82 (dd, $^2J_{6,6'} = 18.5$, H-6), 2.53 (dd, H-6′), 2.09 (s, 2 CH_3CO), 2.06, 2.04 (2s, CH_3CO); ^{13}C NMR (75.4 MHz) δ 169.7, 169.5, 169.1, 169.0 (4 CH_3CO), 165.6 (C=O), 71.6 (C-1), 68.9 (C-2), 66.8 (C-7), 64.9 (C-8), 56.1 (C-8a), 46.6 (C-3), 33.8 (C-6), 20.8 (2 CH_3CO), 20.5 (2 CH_3CO); CIMS *m/z* 372 [100%, $(M + H)^+$]. CIMSHR calcd for $C_{16}H_{22}NO_9$ $(M + H^+)$ 372.1294, found 372.1293.

(1*R*,2*S*,7*R*,8*R*,8a*S*)-1,2,7,8-Tetrahydroxyindolizidin-5-one (28a). To a solution of **27a** (10 mg, 0.027 mmol) in dry MeOH (0.5 mL) was added 1 M NaOMe/MeOH until basic pH. After stirring for 1 h at rt, the mixture was neutralized with IRA-120 (H^+) resin, filtered, and concentrated to afford **28a** (5.5 mg, 100%). $[\alpha]_D^{21}$ +18 (*c* 0.65, MeOH); CIMS *m/z* 204 [95%, $(M + H)^+$]. CIMSHR Calcd for $C_8H_{14}NO_5$ 204.0872, found 204.0871. For IR and NMR data, see Supporting Information.

(1*R*,2*S*,7*S*,8*S*,8a*S*)-1,2,7,8-Tetrahydroxyindolizidin-5-one (28b). Conventional deacylation of **27b** (10 mg, 0.027 mmol) with NaOMe in MeOH as already indicated afforded **28b** (5.5 mg, 100%). $[\alpha]_D^{21}$ +17 (*c* 0.48, MeOH); CIMS *m/z* 204 [5%, $(M + H)^+$]. CIMSHR Calcd for $C_8H_{14}NO_5$ 204.0872, found 204.0874. For IR and NMR data, see Supporting Information.

(*E*)-*N*-(*tert*-Butoxycarbonyl)-2,3,4,5,8-pentadeoxy-5,8-imino-6,7-*O*-isopropylidene-L-*arabino*-oct-2-enitol (21). To a solution of **15** (1.03 g, 3.02 mmol) cooled at −20 °C in dry CH_2Cl_2 (25 mL) was added DIBALH (1 M in CH_2Cl_2, 6.7 mL) dropwise under argon. After 20 min, the reaction was quenched with MeOH (5.5 mL) and allowed to warm to rt. The mixture was diluted with ether (15 mL), solid $MgSO_4$ (5.5 g) and saturated aqueous solutions of NaCl (5.5 mL) were added and stirred for 1 h at rt. After filtration and evaporation, the residue was chromatographed on silica gel (CH_2Cl_2/acetone 30:1 → 10:1) to give **21** (570 mg, 60%) as an oil. $[\alpha]_D^{30}$ +51 (*c* 1.47, CH_2Cl_2); IR (film) 3439 (OH), 1684 (C=O), 1597, 1167, 982 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6 90 °C, *J* Hz) δ 5.66 (ddt, $J_{3,2} = 15.5$, $J_{3,4} = 5.6$, $^4J_{3,1} = {}^4J_{3,1'} = 0.9$, H-3), 5.60 (m, H-2), 4.72−4.68 (m, H-6, H-7), 4.17 (bt, OH), 3.90 (bt, H-1, H-1′), 3.75 (m, H-5), 3.66 (dd, $J_{8,7} = 7.1$, $^2J_{8,8'} = 12.1$, H-8), 3.15 (dd, $J_{8',7} = 3.1$, H-8′), 2.52 (m, H-4), 2.36 (m, H-4′), 1.41 (s, $C(CH_3)_3$), 1.45 and 1.29 (2s, $C(CH_3)_2$); ^{13}C NMR (75.4 MHz) δ 153.3 (C=O), 132.9 (C-3), 126.3 (C-2), 111.2 ($C(CH_3)_2$), 79.2 (C-6), 78.3 ($C(CH_3)_3$), 76.6 (C-7), 61.0 (C-1), 59.2 (C-5), 50.2 (C-8), 31.3 (C-4), 27.6 ($C(CH_3)_3$), 25.9 and 24.6 ($C(CH_3)_2$); CIMS *m/z* 314 [35%, $(M + H)^{+\cdot}$]. CIMSHR calcd for $C_{16}H_{28}NO_5$ 314.1967, found 314.1961.

***(E)*-*N*-(*tert*-Butoxycarbonyl)-2,3,4,5,8-pentadeoxy-5,8-imino-6,7-*O*-isopropylidene-1-*O*-(*p*-methoxybenzoyl)-L-*arabino*-oct-2-enitol (22).** A solution of allylic alcohol **21** (545 mg, 1.74 mmol) in dry CH_2Cl_2 (8 mL) was treated with TEA (485 μL), *p*-methoxybenzoyl chloride (355 mg, 2.08 mmol), and DMAP (cat.). After stirring at rt for 4 h, the mixture was diluted with CH_2Cl_2 (40 mL), poured into water (30 mL), and extracted with CH_2Cl_2. The organic phase was washed with HCl 1 M (30 mL) and saturated aqueous solutions of $NaHCO_3$ (2 × 50 mL) and brine (40 mL), dried, filtered, and concentrated. Chromatography purification (ether/light petroleum ether 1:3 → 1:1) of the residue afforded **22** (659 mg, 85%) as an oil. $[\alpha]_D^{30}$ +35 (*c* 1.08, CH_2Cl_2); FABMS *m/z* 470 [40%, $(M + Na)^+$], 348 [80%, $(M - Boc + 2H)^+$]. Anal. Calcd for $C_{24}H_{33}NO_7$: C, 64.41; H, 7.43; N, 3.13. Found: C, 64.39; H, 7.50; N, 3.10. For IR and NMR data, see Supporting Information.

***N*-(*tert*-Butoxycarbonyl)-1,4,5-trideoxy-1,4-imino-2,3-*O*-isopropylidene-8-*O*-(*p*-methoxybenzoyl)-L-*threo*-L-*lyxo*-octitol (23a).** To a 0 °C solution of **22** (225 mg, 0.503 mmol) in *t*-BuOH/H_2O 1:1 (6 mL) were added AD-mix α (0.704 g) and $MeSO_2NH_2$ (44 mg, 0.503 mmol). The mixture was vigorously stirred at 0 °C for 24 h and quenched by addition of Na_2SO_3 (0.75 g). After warming to rt, the mixture was stirred for 1 h, diluted with AcOEt, and extracted. The organic phase was dried with Na_2SO_4, filtered, and concentrated. Column chromatography (CH_2Cl_2/acetone 20:1) afforded **23a** (175 mg, 72%) and unreacted **22** (22 mg, 10%). $[\alpha]_D^{21}$ +25 (*c* 1, CH_2Cl_2); IR (film) 3428 (OH), 1704 and 1672 (C=O), 1607 (C=C), 1105, 770, 698 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6 90 °C, *J* Hz) δ 7.97−7.90 (m, Ph), 7.03−6.98 (m, Ph), 4.71−4.69 (m, H-2, H-3), 4.52 (bd, $J_{OH,H} = 5.9$, OH), 4.30 (dd, $J_{8,7} = 5.0$, $^2J_{8,8'} = 11.0$, H-8), 4.23 (dd, $J_{8',7} = 6.4$, H-8′), 4.02−3.96 (m, H-4, OH), 3.84 (s, CH_3O), 3.78−3.66 (m, H-6, H-7, H-1), 3.14 (dd, $J_{1',2} = 3.3$, $^2J_{1',1} = 11.9$, H-1′), 1.90 (t, $J_{5,4} = J_{5,6} = 6.6$, H-5), 1.39 (s, $C(CH_3)_3$), 1.40 and 1.28 (2s, $C(CH_3)_2$); ^{13}C NMR (75.4 MHz) δ 165.0 (C=O), 162.8 (C-4 of Ph), 153.7 (C=O), 130.8 (Ph), 122.1 (C-1 of Ph), 113.5 (Ph), 111.3 ($C(CH_3)_2$), 79.6, 76.8 (C-2, C-3), 78.6 ($C(CH_3)_3$), 70.8, 68.2 (C-6, C-7), 65.4 (C-8), 56.6 (C-4), 55.1 (CH_3O), 49.7 (C-1), 32.4 (C-5), 27.6 ($C(CH_3)_3$), 25.9 and 24.7 ($C(CH_3)_2$). FABMS *m/z* 504 [30%, $(M + Na)^+$], 382 [100%, $(M - Boc + 2H)^+$]. Anal. Calcd. for $C_{24}H_{35}NO_9$: C, 59.86; H, 7.33, N, 2.91. Found: C, 59.61; H, 7.50, N, 2.96.

***N*-(*tert*-Butoxycarbonyl)-1,4,5-trideoxy-1,4-imino-2,3-*O*-isopropylidene-8-*O*-(*p*-methoxybenzoyl)-D-*threo*-L-*lyxo*-octitol (23b).** Asymmetric dihydroxylation of **22** (385 mg, 0.861 mmol) with AD-mixβ for 48 h as already indicated afforded, after column chromatography (CH_2Cl_2/acetone 20:1), **23b** (259 mg, 60%), **23a** (30 mg, 7%), and unreacted **22** (18.4 mg, 5%). $[\alpha]_D^{25}$ +58 (*c* 1, CH_2Cl_2); IR (film) 3444 (OH), 1699 and 1686 (C=O), 1105, 855, 772, 698 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6 90°C, *J* Hz) δ 7.98−7.91 (m, Ph), 7.04−6.99 (m, Ph), 4.74 (t, $J_{3,4} = J_{3,2} = 6.3$, H-3), 4.69 (ddd, $J_{2,1} = 6.4$, $J_{2,1'} = 3.8$, H-2), 4.47 (bd, $J_{OH,H} = 5.8$, OH), 4.27 (dd, $J_{8,7} = 5.2$, $^2J_{8,8'} = 11.2$, H-8), 4.22 (dd, $J_{8',7} = 6.0$, H-8′), 4.06−3.99 (m, H-4, OH), 3.84 (s, CH_3O), 3.83−3.68 (m, H-6, H-7), 3.63 (dd, H-1), 3.19 (dd, $^2J_{1',1} = 12.0$, H-1′), 2.10 (ddd, $J_{5,4} = 9.6$, $J_{5,6} = 4.7$, H-5), 1.82 (ddd, $J_{5',4} = 9.9$, $J_{5',6} = 3.2$, $^2J_{5',5} = 13.1$, H-5′), 1.40 (s, $C(CH_3)_3$), 1.39 and 1.37 (2s, $C(CH_3)_2$); ^{13}C NMR (75.4 MHz) δ 165.0 (C=O), 162.8 (C-4 of Ph), 153.5 (C=O), 130.7 (Ph), 122.1 (C-1 of Ph), 113.5 (Ph), 111.0 ($C(CH_3)_2$), 79.4 (C-3), 78.3 ($C(CH_3)_3$), 76.7 (C-2), 71.3, 67.8 (C-6, C-7), 65.4 (C-8), 56.5 (C-4), 55.1 (CH_3O), 50.4 (C-1), 32.5 (C-5), 27.7 ($C(CH_3)_3$), 26.0 and 24.6 ($C(CH_3)_2$); CIMS *m/z* 482 [7%, $(M + H)^+$], 382 [100%, $(M - Boc + 2H)^+$]. CIMSHR calcd for $C_{24}H_{36}NO_9$ 482.2390, found 482.2391; calcd for $C_{19}H_{27}NO_7$ 382.1866, found 382.1866.

***N*-(*tert*-Butoxycarbonyl)-1,4,5-trideoxy-1,4-imino-2,3-*O*-isopropylidene-L-*threo*-L-*lyxo*-octitol (24a).** Conventional deacylation of **23a** (121 mg, 0.252 mmol) with NaOMe in MeOH as indicated for the preparation of **28a** afforded, after column chromatography (CH_2Cl_2/MeOH 25:1 → 20:1), **24a** (66.4 mg, 76%): $[\alpha]_D^{28}$ +31 (*c* 1, CH_2Cl_2); CIMS *m/z* 348 [5%, $(M + H)^{+\cdot}$], *m/z* 248 [100%, $(M - Boc + 2H)^{+\bullet}$]. CIMSHR calcd for $C_{16}H_{30}NO_7$ 348.2022, found 348.2010; calcd for $C_{11}H_{22}NO_5$ 248.1498, found 248.1493. For IR and NMR data, see Supporting Information.

1,4,5-Trideoxy-1,4-imino-L-*threo*-L-*lyxo*-octitol (25). Compound **24a** (37.5 mg, 0.108 mmol) was stirred in 80% aqueous TFA 80% (3.5 mL) for 2 h at rt. The mixture was poured into a Dowex 50WX8 column and sequentially washed with MeOH, H_2O, and NH_4OH 10% to afford **25** (20 mg, 89%): $[\alpha]_D^{21}$ −2 (*c* 1.8, MeOH); ^1H NMR (300 MHz, MeOD, *J* Hz) δ 4.27 (td, $J_{2,3} = 4.5$, $J_{2,1} = J_{2,1'} = 7.0$, H-2), 3.97 (dd, $J_{3,4} = 4.0$, H-3), 3.73 (dt, $J_{6,7} = J_{6,5'} = 3.3$, $J_{6,5} = 9.6$, H-6), 3.65 (dd, $J_{8,7} = 5.1$, $^2J_{8,8'} = 11.1$, H-8), 3.57 (dd, $J_{8',7} = 6.1$, H-8′), 3.48 (m, H-7), 3.30 (m, H-4), 3.10 (dd, $^2J_{1,1'} = 11.3$, H-1), 2.88 (dd, H-1′), 1.92 (ddd, $J_{5,4} = 5.2$, $^2J_{5,5'} = 14.4$, H-5), 1.78 (ddd, $J_{5',4} = 8.6$, H-5′); ^{13}C NMR (125.7 MHz) δ 75.9 (C-7), 73.9 (C-3), 73.6 (C-2), 70.1 (C-6), 64.4 (C-8), 60.1 (C-4), 50.8 (C-1), 33.7 (C-5); CIMS *m/z* 208 [100%, $(M + H)^{+\cdot}$]. CIMSHR calcd for $C_8H_{18}NO_5$ 208.1185, found 208.1179.

***N*-(*tert*-Butoxycarbonyl)-1,4,5-trideoxy-1,4-imino-2,3-*O*-isopropylidene-D-*threo*-L-*lyxo*-octitol (24b).** Conventional deacylation of **23b** (206.5 mg, 0.429 mmol) with NaOMe

in MeOH as indicated for the preparation of **24a** afforded, after column chromatography (CH_2Cl_2/MeOH 25:1 → 20:1), **24b** (135.5 mg, 91%): $[\alpha]_D^{25}$ +57.8 (*c* 0.4, CH_2Cl_2); FABMS *m*/*z* 370 [100%, $(M + Na)^+$]. Anal. Calcd for $C_{16}H_{29}NO_7$: C, 55.32; H, 8.41; N, 4.03. Found: C, 54.88; H, 8.25; N, 4.03. For IR and NMR data, see Supporting Information.

1,4,5-Trideoxy-1,4-imino-D-*threo*-L-*lyxo*-octitol (26). Deprotection of compound **24b** (37 mg, 0.107 mmol) in 80% aqueous TFA as indicated for the preparation of **25** afforded **26** (22 mg, 99%): $[\alpha]_D^{22}$ +23 (*c* 0.6, D_2O); ^{1}H NMR (300 MHz, D_2O, *J* Hz) δ 4.35 (td, $J_{2,3} = 4.4$, $J_{2,1} = J_{2,1'} = 7.7$, H-2), 4.08 (dd, H-3), 3.73 (dt, $J_{6,7} = J_{6,5} = 3.5$, $J_{6,5'} = 9.5$, H-6), 3.63 (dd, $J_{8,7} = 6.7$, $^2J_{8,8'} = 18.4$, H-8), 3.61 (dd, $J_{8',7} = 7.2$, H-8′), 3.57 (td, H-7), 3.30 (td, $J_{4,3} = 3.5$, $J_{4,5} = J_{4,5'} = 7.3$, H-4), 3.16 (dd, $^2J_{1,1'} = 11.7$, H-1), 2.83 (dd, H-1′), 1.87 (ddd, $J_{5,6} = 4.0$, $^2J_{5,5'} = 14.2$, H-5), 1.72 (ddd, $J_{5',6} = 9.7$, H-5′); ^{13}C NMR (75.4 MHz) δ 74.2 (C-7), 72.0, 71.6 (C-2, C-3), 69.4 (C-6), 62.9 (C-8), 58.3 (C-4), 48.4, (C-1), 31.7 (C-5); CIMS *m*/*z* 208 [100%, $(M + H)^{+\cdot}$]. CIMSHR calcd for $C_8H_{18}NO_5$ 208.1185, found 208.1184.

(1*R*,2*S*,6*S*,7*S*,8a*S*)-1,2,6,7-Tetrahydroxyindolizidine (30). To a −20 °C solution of **24a** (60.5 mg, 0.174 mmol) in dry pyridine (1.5 mL) was added TsCl (83 mg, 0.435 mmol). After 3.5 h at −20 °C, water was added (0.5 mL), and the mixture was allowed to warm to rt. Solvent was removed, and the residue was diluted with AcOEt, washed with HCl 1 M and saturated, aqueous solutions of $NaHCO_3$ and brine, dried, and concentrated. Purification by column chromatography (CH_2Cl_2/MeOH 100:1 → 30:1) afforded **29** (36 mg, 42%) which was treated with 80% aqueous TFA at rt for 2 h and then evaporated. The residue was dissolved in water and treated with NH_4OH until basic pH. Solvent evaporation and purification by column chromatography (CH_2Cl_2/MeOH/NH_4OH 10% 4:2:0.5) afforded **30** (10 mg, 94%): $[\alpha]_D^{25}$ +47 (*c* 1, MeOH); ^{1}H NMR (300 MHz, MeOD, *J* Hz) δ 4.31 (ddd, $J_{2,3'} = 7.5$, $J_{2,1} = 6.1$, $J_{2,3} = 2.4$, H-2), 3.99 (dd, $J_{1,8a} = 3.9$, H-1), 3.50 (ddd, $J_{6,5'} = 10.0$, $J_{6,7} = 8.9$, $J_{6,5} = 4.8$, H-6), 3.40 (ddd, $J_{7,8} = 4.9$, $J_{7,8'} = 11.0$, H-7), 3.17 (dd, $^2J_{5,5'} = 10.8$, H-5), 2.93 (dd, $^2J_{3,3'} = 10.8$, H-3), 2.57 (dd, H-3′), 2.28 (dt, $J_{8a,8'} = 11.7$, H-8a), 2.04 (t, $J_{5',6} = 10.5$, H-5′), 1.97 (ddd, $J_{8,8a} = 2.6$, $^2J_{8,8'} = 13.1$, H-8), 1.68 (ddd, H-8′); ^{13}C NMR (75.4 MHz) δ 74.6 (C-7), 72.7 (C-6), 72.1 (C-1), 71.1 (C-2), 68.0 (C-8a), 61.7 (C-3), 57.2 (C-5), 31.9 (C-8); CIMS *m*/*z* 190 [100%, $(M + H)^+$]. CIMSHR calcd for $C_8H_{16}NO_4$ 190.1079, found 190.1081.

(1*R*,2*S*,6*R*,7*R*,8a*S*)-1,2,6,7-Tetrahydroxyindolizidine (32) and (1*R*,2*S*,5*S*,6*R*,7a*S*)-1,2,6,7-Tetrahydroxypyrrolizidine (33). Tosylation of **24b** (100 mg, 0.287 mmol) as already indicated afforded **31** (54 mg, 38%) as an oil. Acidic deprotection with TFA and subsequent treatment with NH_4OH as indicated for the preparation of **30** gave indolizidine **32** (10 mg, 69%) and pyrrolizidine **33** (4 mg, 28%). Data for **32**: $[\alpha]_D^{22}$ 0 (*c* 0.6, MeOH); ^{1}H NMR (300 MHz, MeOD, *J* Hz) δ 4.42 (ddd, $J_{2,3} = 3.6$, $J_{2,1} = 5.4$, $J_{2,3'} = 8.2$, H-2), 4.06 (dd, $J_{1,8a} = 3.2$, H-1), 3.94 (q, $J_{7,6} = J_{7,8} = J_{7,8'} = 3.0$, H-7), 3.76 (m, H-6), 3.23−3.06 (m, H-3, H-3′, H-5, H-5′, H-8a), 2.30 (ddd, $J_{8,8a} = 12.5$, $^2J_{8,8'} = 14.5$, H-8), 1.79 (dt, $J_{8',8a} = 2.7$, H-8′); ^{13}C NMR (75.4 MHz) δ 72.2 (C-1), 68.9 (C-2), 68.4 (C-7), 67.2 (C-6), 64.2 (C-8a), 60.8, 54.4 (C-3, C-5), 27.6 (C-8); CIMS *m*/*z* 190 [100%, $(M + H)^+$]. CIMSHR calcd for $C_8H_{16}NO_4$ 190.1079, found 190.1081. Data for **33**: $[\alpha]_D^{25}$ −48.5 (*c* 0.4, MeOH); ^{1}H NMR (500 MHz, MeOD, *J* Hz) δ 4.43 (dt, $J_{7a,7'} = 9.9$, $J_{7a,7} = J_{7a,1} = 4.1$, H-7a), 4.33 (ddd, $J_{2,1} = 4.0$, $J_{2,3} = 6.3$, $J_{2,3'} = 10.4$, H-2), 4.26 (ddd, H-6), 4.07 (t, H-1), 3.92 (dd, $J_{8,5} = 3.6$, $^2J_{8,8'} = 13.0$, H-8), 3.81 (dd, $J_{8',5} = 9.1$, H-8′), 3.52 (td, $J_{5,6} = 8.6$, H-5), 3.46 (dd, $^2J_{3,3'} = 10.8$, H-3), 3.27 (t, H-3′), 2.48 (ddd, $J_{7,6} = 8.0$, $^2J_{7,7'} = 12.6$, H-7), 1.92 (dd, $J_{7',6} = 6.2$, H-7′); ^{13}C NMR (75.4 MHz) δ 72.5, 72.0 (C-2, C-7a), 70.8, 70.5 (C-1, C-5), 68.9 (C-6), 58.6 (C-8), 49.8 (C-3), 32.5 (C-7); CIMS *m*/*z* 190 [100%, $(M + H)^+$], 158 [50%, $(M - CH_2OH)^+$]. CIMSHR calcd for $C_8H_{16}NO_4$ 190.1079, found 190.1069.

Ethyl *N*-(*tert*-Butoxycarbonyl)-2,3,6-trideoxy-3,6-imino-4,5-*O*-isopropylidene-D-*arabino*-2-hexonate (36). To a solution of **35** (2.87 g, 12.5 mmol) in dry pyridine (35 mL) was added di-*tert*-butyl dicarbonate (3.06 g, 13.8 mmol) in pyridine (20 mL). After stirring for 2 h at rt, solvent was evaporated, and the residue diluted with AcOEt and washed with brine. The organic phase was dried, filtered, and concentrated. Purification by column chromatography (ether/light petroleum ether 1:5 → 1:2) afforded **36** (3.78 g, 92%) as an oil: $[\alpha]_D^{26}$ −68 (*c* 1.2, CH_2Cl_2); IR (film) 1720, 1699 (C=O), 1092 (C−O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6 90 °C, *J* Hz) δ 4.76 (m, H-4), 4.73 (m, H-5), 4.13 (m, H-3), 4.08 (q, $J_{H,H} = 7.1$, CH_2CH_3), 3.60 (dd, $J_{6,5} = 6.5$, $^2J_{6,6'} = 12.7$, H-6), 3.26 (dd, $J_{6',5} = 2.4$, H-6′), 2.85 (dd, $J_{2,3} = 4.7$, $^2J_{2,2'} = 16.0$, H-2), 2.50 (dd, $J_{2',3} = 9.6$, H-2′), 1.40 (s, $C(CH_3)_3$), 1.41 and 1.27 (2s, $C(CH_3)_2$), 1.19 (t, CH_2CH_3); ^{13}C NMR (75.4 MHz) δ 170.0 (C=O), 153.3 (C=O), 111.1 ($C(CH_3)_2$), 78.9 (C-4), 78.7 ($C(CH_3)_3$), 76.9 (C-5), 59.0 (CH_2CH_3), 56.0 (C-3), 50.0 (C-6), 33.8 (C-2), 27.6 ($C(CH_3)_3$), 25.4 and 24.5 ($C(CH_3)_2$), 13.4 (CH_2CH_3); CIMS *m*/*z* 330 [60%, $(M + H)^{+\cdot}$]. Anal. Calcd for $C_{16}H_{27}NO_6$: C, 58.34; H, 8.26; N, 4.25. Found: C, 58.49; H, 8.16; N, 4.32.

***N*-(*tert*-Butoxycarbonyl)-2,3,6-trideoxy-3,6-imino-4,5-*O*-isopropylidene-D-*arabino*-2-hexose (37).** DIBALH (1 M) in CH_2Cl_2 (4.6 mL, 4.6 mmol) was added dropwise under argon atmosphere to a −78 °C solution of **36** (0.76 g, 2.32 mmol) in dry CH_2Cl_2 (10 mL). After stirring at −78 °C for 2 h, MeOH (4 mL) was added and the mixture slowly warmed to rt. Then, HCl 1 M (10 mL) was added at 0 °C and the mixture extracted with CH_2Cl_2. The organic phase was washed with brine, dried, filtered, and concentrated. Column chromatography (ether/light petroleum ether 1:4 → 1:2) gave **37** (0.48 g, 72%) as a thick oil. $[\alpha]_D^{22}$ −80 (*c* 0.68, CH_2Cl_2); IR (film) 2936, 1723 (C=O), 1090 (C−O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6 90 °C, *J* Hz) δ 9.69 (t, $J_{1,2} = 1.7$, CHO), 4.79−4.71 (m, H-4, H-5), 4.21 (q, $J_{3,2} = J_{3,2'} = J_{3,4} = 6.6$, H-3), 3.60 (dd, $J_{6,5} = 6.4$, $^2J_{6,6'} = 12.3$, H-6), 3.29 (dd, $J_{6',5} = 2.3$, H-6′), 2.74 (dd, H-2, H-2′), 1.40 (s, $C(CH_3)_3$), 1.41 and 1.27 (2s, $C(CH_3)_2$); ^{13}C NMR (75.4 MHz) δ 200.0 (CHO), 153.4 (C=O), 111.1 ($C(CH_3)_2$), 79.0, 76.8 (C-4, C-5), 78.9 ($C(CH_3)_3$), 55.2 (C-3), 50.3 (C-6), 42.9 (C-2), 27.6 ($C(CH_3)_3$), 25.6 and 24.5 ($C(CH_3)_2$); FABMS *m*/*z* 286 [20%, $(M + H)^+$]. Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.69; H, 8.39; N, 5.16.

Methyl (*E*)-*N*-(*tert*-Butoxycarbonyl)-2,3,4,5,8-pentadeoxy-5,8-imino-6,7-*O*-isopropylidene-D-*arabino*-oct-3-enonate (38) and Methyl (*E*)-*N*-(*tert*-Butoxycarbonyl)-2,3,4,5,8-pentadeoxy-5,8-imino-6,7-*O*-isopropylidene-D-*arabino*-oct-2-enonate (39). Aldehyde **37** (1.27 g, 4.46 mmol) in dry pyridine (5 mL) was treated with monomethylmalonate (632 mg, 5.36 mmol) and piperidine (15 μL) as indicated for **13** to give, after column chromatography (ether/light petroleum ether 1:5→1:1), the two alkenes **38** (746 mg, 49%) and **39** (445 mg, 29%), both as oils. Data for **38**: $[\alpha]_D^{25}$ −46.3 (*c* 1, CH_2Cl_2). Anal. Calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97; N, 4.10. Found: C, 59.70; H, 8.07; N, 4.23. This product showed IR and NMR spectra identical to those of its enantiomer **14**. Data for **39**: $[\alpha]_D^{22}$ −40 (*c* 0.96, CH_2Cl_2). Anal. Calcd for $C_{17}H_{27}NO_6$: C, 59.81; H, 7.97; N, 4.10. Found: C, 60.07; H, 8.15; N, 4.00. This product showed IR and NMR spectra identical to those of its enantiomer **15**.

Methyl *N*-(*tert*-Butoxycarbonyl)-2,5,8-trideoxy-5,8-imino-6,7-*O*-isopropylidene-D-*glycero*-D-*galacto*-(and D-*glycero*-D-*ido*) Octanoates (40a + 40b). Treatment of alkene **38** (696 mg, 2.04 mmol) in acetone/H_2O 4:1 (65 mL) with *N*-methyl-morpholine-*N*-oxide (1.11 g, 8.2 mmol) and OsO_4 (2.5% in ^{t}BuOH, 2.6 mL, 0.02 mmol) as indicated for **14** afforded, after column chromatography (CH_2Cl_2/acetone 25:1→10:1), **40a** + **40b** (641.6 mg, 84%, ratio 1.7:1).

(1*S*,2*R*,7*S*,8*S*,8a*R*)-1,2,7,8-Tetraacetoxyindolizidin-5-one (41) and (1*S*,2*R*,7*R*,8*R*,8a*R*)-1,2,7,8-Tetraacetoxyindolizidin-5-one (42). The mixture of diols **40a** + **40b** (353 mg, 0.94 mmol) was treated with 80% aqueous TFA (30 mL) for 1.5 h at rt and then evaporated. The residue was dissolved in H_2O (10 mL), and NH_4OH was added until basic pH. The solvent was removed, the crude product was dissolved in dry MeOH (45 mL), and NaOMe (44 mg, 1.76 mmol) was added.

The mixture was heated at reflux for 16 h, the solvent removed and the residue conventionally acetylated. Column chromatography (ether/acetone 5:1) afforded **41** (192.5 mg, 55%) as a solid and **42** (107 mg, 31%) as a syrup. Data for **41**: $[\alpha]_D^{22}$ 0 (*c* 0.56, CH_2Cl_2); CIMS *m*/*z* 372 [100%, $(M + H)^+$]; CIMSHR calcd for $C_{16}H_{22}NO_9$ 372.1294, found 372.1292. This product showed IR and NMR spectra identical to those of its enantiomer **27a**. Data for **42**: $[\alpha]_D^{22}$ −65 (*c* 0.47, CH_2Cl_2); CIMS *m*/*z* 372 [100%, $(M + H)^+$]. CIMSHR calcd for $C_{16}H_{22}NO_9$ 372.1294, found 372.1291. This product showed IR and NMR spectra identical to those of its enantiomer **27b**.

(1*S*,2*R*,7*S*,8*S*,8a*R*)-1,2,7,8-Tetraacetoxyindolizidine (43). To a 0 °C solution of lactam **41** (50 mg, 0.135 mmol) in dry THF (3 mL) was added $BH_3{\cdot}SMe_2$ (65 μL, 0.687 mmol) dropwise under argon, and the reaction mixture was kept at rt for 4 h. The excess of reducing agent was quenched by slow addition of EtOH (4 mL). After evaporation of the solvent, the residue was dissolved in EtOH (6 mL) and heated at reflux for 2 h. The cooled mixture was then evaporated and purified by column chromatography (CH_2Cl_2/acetone 30:1) to afford **43** (30 mg, 61%): $[\alpha]_D^{25}$ −6.5 (*c* 0.8, CH_2Cl_2); CIMS *m*/*z* 358 [98%, $(M + H)^+$]. Anal. Calcd for $C_{16}H_{23}NO_8$: C, 53.78; H, 6.49; N, 4.07. Found: C, 53.78; H, 6.64; N, 3.89. For IR and NMR data, see Supporting Information.

(1*S*, 2*R*, 7*S*, 8*S*, 8a*R*)-1,2,7,8-Tetrahydroxyindolizidine (*trans*-7-hydroxy-D-(−)-swainsonine) (44). To a solution of **43** (25 mg, 0.070 mmol) in dry MeOH (1 mL) was added NaOMe/MeOH 1 M until basic pH. After stirring for 2 h at rt, the mixture was neutralized with IRA-120 (H^+) resin. Filtration of the resin and washing with MeOH, H_2O, and NH_4OH gave a filtrate that, after evaporation, afforded **44** (11.6 mg, 87%): $[\alpha]_D^{22}$ −6.5 (*c* 0.8, H_2O); ^{1}H NMR (300 MHz, D_2O, *J* Hz) δ 4.36 (ddd, $J_{2,3} = 2.6$, $J_{2,1} = 6.0$, $J_{2,3'} = 8.2$, H-2), 4.20 (dd, $J_{1,8a} = 3.6$, H-1), 3.56 (t, $J_{8,7} = J_{8,8a} = 9.2$, H-8), 3.46 (ddd, $J_{7,6} = 5.0$, $J_{7,6'} = 11.0$, H-7), 2.92 (ddd, $J_{5,6} = 2.3$, $J_{5,6'} = 4.4$, $^2J_{5,5'} = 11.6$, H-5), 2.85 (dd, $^2J_{3,3'} = 11.2$, H-3), 2.57 (dd, H-3′), 2.12 (td, $J_{5',6'} = 12.5$, H-5′), 2.06 (dd, H-8a), 1.93 (dddd, H-6), 1.51 (dddd, $^2J_{6',6} = 12.9$, H-6′); ^{13}C NMR (75.4 MHz) δ 75.9 (C-7), 73.3 (C-8), 73.0 (C-8a), 72.1 (C-2), 71.8 (C-1), 62.2 (C-3), 51.5 (C-5), 33.6 (C-6); CIMS *m*/*z* 189 [30%, $(M)^+$]. CIMSHR calcd for $C_8H_{15}NO_4$ 189.1001, found 189.1001.

(1*S*,2*R*,7*R*,8*R*,8a*R*)-1,2,7,8-Tetraacetoxyindolizidine (45). Reduction of lactam **42** (65.4 mg, 0.176 mmol) with $BH_3{\cdot}SMe_2$ (84 μL, 0.88 mmol) as indicated for **41** gave, after chromatographic purification (ether/acetone 12:1), **45** (43.7 mg, 70%): $[\alpha]_D^{20}$ −43 (*c* 1, CH_2Cl_2); IR (film) 1748 (C═O), 1254 (C—O), 1103 cm^{-1}; CIMS *m*/*z* 358 [100%, $(M + H)^+$]. CIMSHR calcd for $C_{16}H_{24}NO_8$ 358.1502, found 358.1504.

(1*S*,2*R*,7*R*, 8*R*, 8a*R*)-1,2,7,8-Tetrahydroxyindolizidine (46). Deacylation of **45** (19 mg, 0.054 mmol) with NaOMe/MeOH as indicated for **43** afforded **46** (8.5 mg, 83%): $[\alpha]_D^{22}$ −10 (*c* 0.8, H_2O); ^{1}H NMR (300 MHz, D_2O, *J* Hz) δ 4.37 (dd, $J_{1,8a} = 4.3$, $J_{1,2} = 6.0$, H-1), 4.29 (ddd, $J_{2,3'} = 7.5$, $J_{2,3} = 2.2$, H-2), 4.09 (m, H-8), 3.84 (ddd, H-7), 2.90 (dd, $^2J_{3,3'} = 11.2$, H-3), 2.84 (m, H-5), 2.52 (dd, H-3′), 2.48 (dd, H-8a), 2.34 (td, $J_{5',6} = 2.5$, $^2J_{5',5} = 13.3$, H-5′), 2.05 (m, $^2J_{6,6'} = 14.8$, H-6), 1.62 (m, H-6′); ^{13}C NMR (75.4 MHz) δ 72.7 (C-1), 69.5 (C-8), 68.7 (C-2), 66.8 (C-7), 62.4 (C-8a), 60.0 (C-3), 47.1 (C-5), 26.3 (C-6); CIMS *m*/*z* 190 [100%, $(M + H)^+$]. CIMSHR calcd for $C_8H_{16}NO_4$ 190.1079, found 190.1081.

Acknowledgment. We thank the Dirección General de Investigación Científica y Técnica of Spain for financial support (Grants BQU 2001-3740 and BQU 2001-3779) and for the award of a grant to A.T.C., the Junta de Andalucía, the Swiss National Science Foundation, and the "Office Féderal de l'Education et de la Science" (Bern). This work is part of the European COST Program, working groups COST-D13-0001/98 and D25-0001/02.

Supporting Information Available: IR, ^{1}H NMR, and ^{13}C NMR data of compounds **18**, **19**, **22**, **24a**, **24b**, **28a**, **28b**, and **43**. ^{1}H and ^{13}C NMR of **19**, **20**, **23b**, **25**, **26**, **28a**, **30**, **32**, **33**, **44**, and **46**. ^{13}C NMR of **21**, **27b**, and **28b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026688A