JOC Note
pubs.acs.org/joc

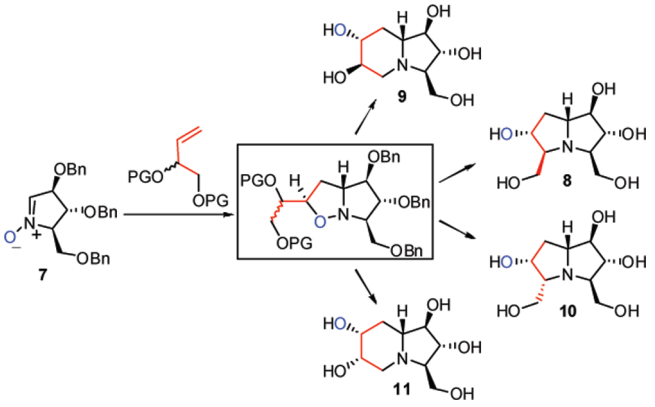
Synthesis of Pentahydroxylated Pyrrolizidines and Indolizidines†

Juan A. Tamayo,* Francisco Franco, Daniele Lo Re, and Fernando Sánchez-Cantalejo

Department of Medicinal and Organic Chemistry, Faculty of Pharmacy, University of Granada, Campus de Cartuja, s/n 18071 Granada, Spain

jtamayo@ugr.es

Received April 17, 2009



1,3-Dipolar cycloaddition reaction of nitrone **7** and chemo-enzymatically obtained alkenediols **12** and **13** has been used in the synthesis of pentahydroxylated pyrrolizidines (**8** and **10**) and indolizidines (**9** and **11**). The pyrrolizidinic and indolizidinic skeletons were built after internal *n*-alkylation of the suitably functionalized pyrroloisoxazolidine intermediates obtained by the necessary protecting group manipulations. This method expands the scope of cycloaddition reactions in the synthesis of new and highly polyhydroxylated sugar-like alkaloids.

Polyhydroxylated alkaloids are a well-known group of natural compounds. They are normally isolated from water-soluble fractions of medicinal plants,[1] and microbial cultures.[2] Also known as iminosugars or azasugars this family of compounds is classified into five different classes according to their structure: pyrrolidines, piperidines, pyrrolizidines, indolizidines, and *nor*-tropanes, all of them presenting several polyhydroxylation patterns within each group. Because of the resemblance to carbohydrates, they have been employed as tools in glycobiology to study recognition processes, particularly those concerning the reactions catalyzed by glycosidases and glycosyltranferases.[3] The ubiquity of these enzymes in living organisms, the tasks they play in vital processes like cell function and recognition,[4] and their role in the etiology of diseases like cancer, HIV, and diabetes[5] have raised the need for new and active compounds against them.

Iminosugars are recognized by glycoside-processing enzymes because of their similarity to saccharides. In their catalytic site, these carbohydrate mimics can be protonated by a carboxylic moiety thus rendering the enzyme inhibition.[6] In this respect, polyhydroxylated alkaloids contain in their structure several stereogenic centers susceptible of being modified, and hence making possible the synthesis of a variety of stereoisomers with potential value as therapeutic agents.[5] (+)-Casuarine (**1**) and (+)-castanospermine (**2**) are two examples of natural polyhydroxylated pirrolizidine and indolizidine, respectively, both among the most active discovered so far.[7] In addition, and like Hyacinthacines C_1 (**3**), C_2 (**4**), C_3 (**5**), and C_5 (**6**) (Figure 1), compounds **1** and **2** represent some of the most highly oxygenated natural amino-sugars analogues identified.[8] Several syntheses of these

† Dedicated to Professor M[a] Teresa Plaza López-Espinosa on the occasion of her retirement.

*To whom correspondence should be addressed. Fax: 0034-958-243845.

(1) (a) Yagi, M.; Kouno, T.; Aoyagi, Y.; Murai, H. *Nippon Nogeikagaku Kaishi* **1976**, *50*, 571. (b) Murao, S.; Miyata, S. *Agric. Biol. Chem.* **1980**, *44*, 219. (c) Watanabe, S.; Kato, H.; Nagayama, K.; Abe, H. *Biosci. Biotechnol. Biochem.* **1995**, *59*, 936.

(2) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, 256.

(3) (a) Sinnot, M. L. *Chem. Rev.* **1990**, *90*, 1171. (b) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319. (c) Fleet, G. W. J.; Winchester, B. *Glycobiology* **1992**, *2*, 199. (d) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645.

(4) (a) Asano, N. *Glycobiology* **2003**, *13*, 93R. (b) Davies, G. J.; Gloster, T. M.; Henrissat, B. *Curr. Opin. Struct. Biol.* **2005**, *15*, 637. (c) Rempel, B. P.; Withers, S. G. *Glycobiology* **2008**, *18*, 570. (d) Nash, R. J. *Bioactive Natural Products*; Colegate, S. M., Molyneux, R. J., Ed.; Summit Wales Limited: Aberystwyth, UK, 2008; p 407. (e) Asano, N. *Modern Alkaloids* **2008**, 111.

(5) (a) *Iminosugars as Glycosidases Inhibitors: Norjirmycin and Beyond*; Stütz, A., Ed.; Wiley-VCH: Weinheim, Germany, 1999. (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. Tetrahedron: Asymmetry 2000, 11, 1645. (c) Asano, N. Curr. Top. Med. Chem. 2003, 3, 471. (d) Cipolla, L.; La Ferla, B.; Nicotra, F. Curr. Top. Med. Chem. 2003, 3, 485. (e) Butters, T. D.; Dwek, R. A.; Platt, F. M. Curr. Top. Med. Chem. 2003, 3, 561. (f) Martin, O. R.; Compain, P. Curr. Top. Med. Chem. 2003, 3, 541. (g) de Melo, E. B.; Gomes, A. D.; Carvalho, I. Tetrahedron 2006, 62, 10277.

(6) (a) Asano, N.; Kato, A.; Oseki, K.; Kizu, H.; Matsui, K. *Eur. J. Biochem.* **1995**, *229*, 369. (b) Legler, G. Glycosidase Inhibition by Basic Sugar Analogs and the Transition State of Enzymatic Glycoside Hydrolysis. In *Iminosugars as Glycosidase Inhibitors*; Stütz, A., Ed.; Wiley-VCH: Weinheim, Germany, 1999, p 31. (c) Rye, C. S.; Withers, S. G. Curr. Opin. Chem. Biol. 2000, 4, 573. (d) Jensen, H. H.; Lyngbye, L.; Bols, M. Angew. Chem., Int. Ed. 2001, 40, 3447. (e) Varrot, D.; Tarling, C. A.; Macdonald, J. M.; Stick, R. V.; Zechel, D. L.; Withers, S. G.; Davies, G. J. J. Am. Chem. Soc. 2003, 125, 7496.

(7) For Castanospermine see: (a) Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res.* **1986**, *46*, 5215. (b) Walker, B. D.; Kowalski, M.; Goh, W. C.; Kozarsky, K.; Krieger, M.; Rosen, C.; Rohrschneider, L.; Haseltine, W. A.; Sodroski, J. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 8120. (c) Sunkara, P. S.; Taylor, D. L.; Kang, M. S.; Bowling, T. L.; Liu, P. S.; Tyms, A. S. *Lancet* **1989**, 1206. For Casuarine see: (d) Bell, A. A.; Pickering, L.; Watson, A. A.; Nash, R. J.; Pan, Y. T.; Elbein, A. D.; Fleet, G. W. J. *Tetrahedron Lett.* **1997**, *38*, 5869. (e) Cardona, F.; Parmeggiani, C.; Faggi, E.; Bonaccini, C.; Gratteri, P.; Sim, L.; Gloster, T. M.; Roberts, S.; Davies, G. J.; Rose, D. R.; Goti, A. *Chem.—Eur. J.* **2009**, *15*, 1627.

(8) (a) Kato, A.; Adachi, I.; Miyauchi, M.; Ikeda, K.; Komae, T.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Wormald, M. R.; Fleet, G. W. J.; Asano, N. *Carbohydr. Res.* **1999**, *316*, 95. (b) Asano, N.; Kuroi, H.; Ikeda, K.; Kizu, H.; Kameda, Y.; Kato, A.; Adachi, I.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1. (c) Kato, A.; Kato, N.; Adachi, I.; Hollinshead, J.; Fleet, G. W. J.; Kuriyama, C.; Ikeda, K.; Asano, N.; Nash, R. J. *J. Nat. Prod.* **2007**, *70*, 993.

DOI: 10.1021/jo900801c Published on Web 07/02/2009

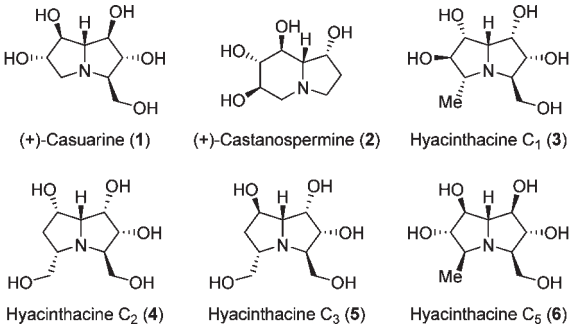


FIGURE 1. Examples of natural polyhydroxylated azasugar alkaloids.

and related compounds can be found in the literature.[9] One popular and successful approach, because of its simplicity and high overall yield, are 1,3-dipolar cycloaddition reactions on cyclic nitrones.[10] This method allows the introduction of the nitrogen functionality into the cyclic system and the formation of two crucial bonds, C−C and C−O, in a single step, with the advantage of a high diastereoselectivity.[10f]

A retrosynthetic analysis for indolizidine and pyrrolizidine structures (Scheme 1) shows that their bicyclic rings can both be achieved in several steps by means of intermediate **A**. This substrate may result from a 1,3-dipolar cycloaddition reaction of protected nitrone **7** and alkenediol derivative **B**. Subsequent protecting group modifications with the introduction of the necessary leaving group would afford pyrroloisoxazolidine intermediates (**C** and **D**). Final N−O cleavage of these intermediates would yield, after intramolecular *N*-alkylation, both the indolizidine and pyrrolizidine skeletons.

We report in this note on the synthesis of new pentahydroxy pyrrolizidines and indolizidines (**8**, **10** and **9**, **11**, respectively, Figure 2) by means of a 1,3-dipolar cycloaddition of suitably protected cyclic nitrone **7**, derived from D-arabinose, with chemoenzymatically prepared 3-buten-1,2-diol derivatives **12** and **13**. The use of Chirazyme L-2, c.-f., C2, lyo from *Candida antarctica* lipase-B in the regioselective transesterification of racemic mixtures of diols has

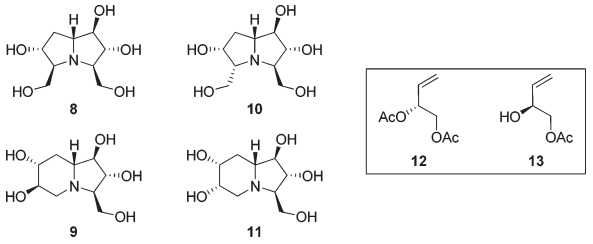
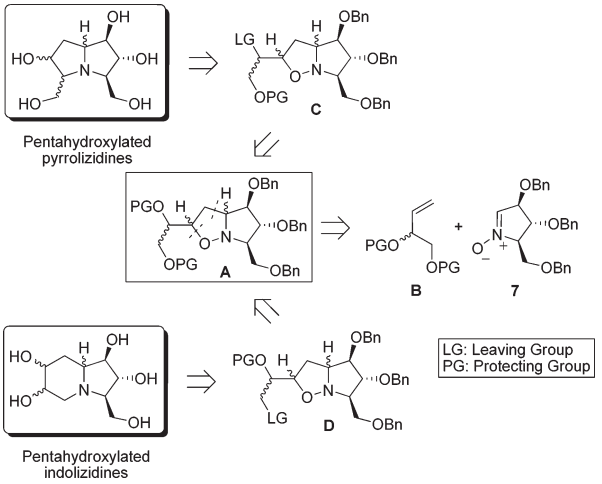


FIGURE 2. Novel non-natural pentahydroxylated pyrrolizidines (**8**, **10**), indolizidines alkaloids (**9**, **11**), and dipolarophiles **12** and **13**.

SCHEME 1. Retrosynthetic Analysis for Pentahydroxylated Pyrrolizidines and Indolizidines



been described.[11] Thus, when (*R*,*S*)-3-buten-1,2-diol was reacted with vinyl acetate in the presence of Chirazyme L-2, c.-f. at room temperature, the chemoenzymatic reaction caused selective acetylation of the mixture yielding first (*R*)-di-*O*-acetyl-3-buten-1,2-diol (**12**, 44%, 64% ee) and second (*S*)-1-*O*-acetyl-3-buten-1,2-diol (**13**, 46%, 61% ee)[12] (Scheme 2), which were easily separated by flash chromatography. With chirons **12** and **13** in our hands we attempted the cycloaddition reaction (Scheme 2). In this regard, nitrone **7**[10d,10e,13] was initially reacted with derivative **13**. Pyrroloisoxazolidine **14** (70%) was isolated as the major adduct and its absolute configuration was confirmed by NOE experiments. As predicted, the cycloaddition reaction proceeded through an *exo*-mode to achieve predominantly the *exo-anti* cycloadduct **14**, *anti* referring to the relative position of the nitrone C-2 substituent and the direction of the incoming alkene.[10b,10e,10f,10h−10j]

Cycloadduct **14** was next transformed into mesylate **15**. To our delight, N−O cleavage of **15** using Zn/AcOH afforded

(9) For selected syntheses of Castanospermine and analogues see: (a) Zhao, H.; Mootoo, D. R. *J. Org. Chem.* **1996**, *61*, 6762. (b) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 625. (c) Karanjule, N. S.; Markad, S. D.; Shinde, V. S.; Dhavale, D. D. *J. Org. Chem.* **2006**, *71*, 4667. (d) Izquierdo, I.; Tamayo, J. A.; Rodriguez, M.; Franco, F.; Lo Re, D. *Tetrahedron* **2008**, *64*, 7910. (e) Machan, T.; Davis, A. S.; Liawruangrath, B.; Pyne, S. G. *Tetrahedron* **2008**, *64*, 2725. For selected syntheses of Casuarine and analogues see: (f) Bell, A. A.; Pickering, L.; Watson, A. A.; Nash, R. J.; Pan, Y. T.; Elbein, A. D.; Fleet, G. W. J. *Tetrahedron Lett.* **1997**, *38*, 5869. (g) Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **2000**, *65*, 2875. (h) Izquierdo, I.; Plaza, M. T.; Tamayo, J. A. *Tetrahedron* **2005**, *61*, 6527. (i) Izquierdo, I.; Plaza, M. T.; Tamayo, J. A. *J. Carbohydr. Chem.* **2006**, *25*, 281. (j) Van Ameijde, J.; Horne, G.; Wormald, M. R.; Dwek, R. A.; Nash, R. J.; Jones, P. W.; Evinson, E. L.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2006**, *17*, 2702.

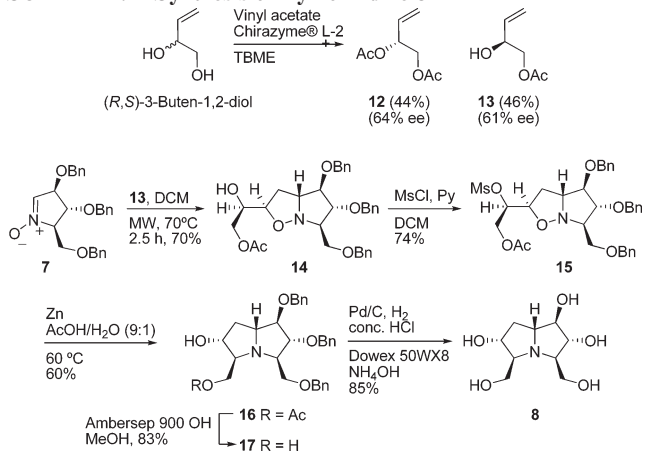
(10) For selected synthesis see : (a) McCaig, A. E.; Wightman, R. H. *Tetrahedron Lett.* **1993**, *34*, 3939. (b) Goti, A.; Cicchi, S.; Cacciarini, M.; Cardona, F.; Fedi, V.; Brandi, A. *Eur. J. Org. Chem.* **2000**, 3633. (c) Goti, A.; Cicchi, S.; Cacciarini, M.; Cardona, F.; Fedi, V.; Brandi, A. *Org. Lett.* **2001**, *3*, 1367. (d) Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 2315. (e) Carmona, A. T.; Wightman, R. H.; Robina, I.; Vogel, P. *Helv. Chim. Acta* **2003**, *86*, 3066. (f) Cordero, F. M.; Pisaneschi, F.; Batista, K. M.; Valenza, S.; Machetti, F.; Brandi, A. *J. Org. Chem.* **2005**, *70*, 856. (g) Akai, S.; Tanimoto, K.; Kanao, Y.; Omura, S.; Kita, Y. *Chem. Commun.* **2005**, *18*, 2369. (h) Argyropoulos, N. G.; Panagiotidis, T.; Coutouli-Argyropoulou, E.; Raptopoulou, C. *Tetrahedron* **2007**, *63*, 321. (i) Revuelta, J.; Cicchi, S.; Goti, A.; Brandi, A. *Syntheis* **2007**, *4*, 485–504. (j) Stecko, S.; Jurczak, M.; Urbanczyk-Lipkowska, Z.; Solecka, J.; Chmielewski, M. *Carbohydr. Res.* **2008**, *343*, 2215.

(11) (a) Izquierdo, I.; Plaza, M. T.; Rodriguez, M.; Tamayo, J. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1749. (b) Naoshima, Y.; Kamezawa, M.; Kimura, T.; Okimoto, F.; Watanabe, M.; Tachibana, H.; Ohtani, T. *Recent Res. Dev. Org. Bioorg. Chem.* **2001**, *4*, 1. (c) Izquierdo, I.; Plaza, M. T.; Rodriguez, M.; Tamayo, J. A. *Eur. J. Org. Chem.* **2002**, *2*, 309. (d) Izquierdo, I.; Plaza, M. T.; Rodriguez, M.; Tamayo, J. A. *Synthesis* **2003**, *9*, 1357. (e) Adachi, S. *Handbook of Industrial Biocatalysis*; Taylor & Francis/CRC: Boca Raton, FL, 2005; pp 10/1−10/15.(f) Izquierdo, I.; Plaza, M. T.; Tamayo, J. A.; Franco, F.; Sanchez-Cantalejo, F. *Tetrahedron* **2008**, *64*, 4993.

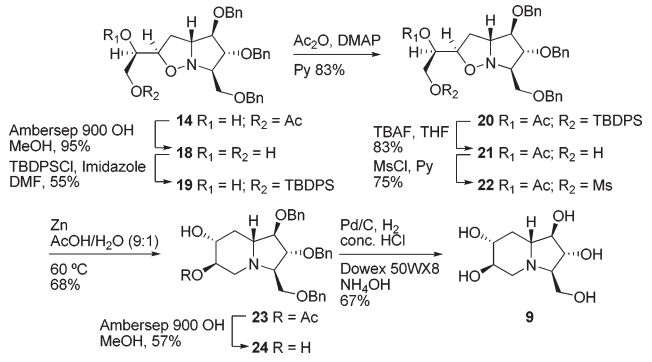
(12) The ee of (*R*)-di-*O*-acetyl-3-buten-1,2-diol (64% ee) and (*S*)-1-*O*-acetyl-3-buten-1,2-diol (61% ee) were determined by chiral GLC (see Supporting Information).

(13) (a) Desvergnes, S.; Py, S.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 1459. (b) Cicchi, S.; Marradi, M.; Vogel, P.; Goti, A. *J. Org. Chem.* **2006**, *71*, 1614.

SCHEME 2. Synthesis of Pyrrolizidine 8



SCHEME 3. Synthesis of Indolizidine 9

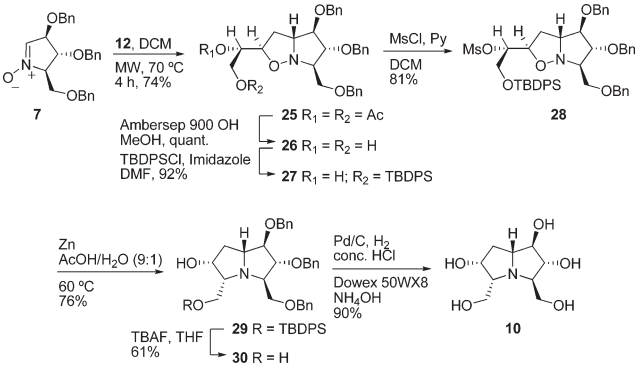


pyrrolizidine **16** (60%) in a single step through intramolecular *N*-alkylation that took place spontaneously after basic workup (TLC evidence). The stereochemistry of **16** was confirmed by analytical and spectroscopic analysis and matched with the one predicted. Deacetylation of **16** with Ambersep 900 (OH^- form) resin to diol **17** (83%) and subsequent catalytic hydrogenation in acidic media afforded pyrrolizidine **8** (22% overall yield).

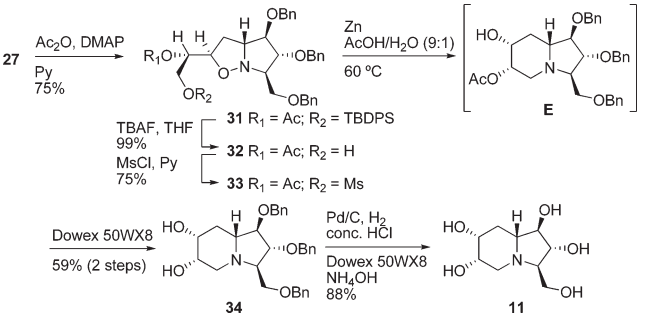
On a similar approach, introduction of a leaving group at the primary OH group at C-2′ in pyrroloisoxazolidine **14** could give rise to the indolizidine skeleton (see intermediate **D**, Scheme 1). Hence, attempts to orthogonally protect the OH group at C-1′ in **14** with MEMCl, TBDMSCl, or TESCl proved unsuccessful, probably because of the steric hindrance posed by the benzyl groups at the C-4 and C-6 positions. Only acetylation was effective at the cost of an increased number of steps. Thus (see Scheme 3), intermediate **21**, obtained from alcohol **14** in four steps (36% yield), was transformed into methanesulfonyl derivative **22** and, as described for derivative **15**, converted into indolizidine **23** (68%). Its absolute configuration was confirmed by NOE experiments. Protecting groups removal of **23** afforded indolizidine **9** in 6% overall yield.

Once we probed the convenience of this methodology in the synthesis of pyrrolizidine **8** and indolizidine **9** alkaloids, chiron **12** was used in the synthesis of compounds **10** and **11**, epimers at C-5 and C-6 of **8** and **9**, respectively. Hence, compound **25** was obtained as the major product (74% yield) in the cycloaddition reaction of nitrone **7** with alkene **12** (Scheme 4). **25** was

SCHEME 4. Synthesis of Pyrrolizidine 10



SCHEME 5. Synthesis of Indolizidine 11



then chemically modified in two steps to afford silyl derivative **27**. As described before, leaving group introduction in **27** followed by N−O cleavage and intramolecular *N*-alkylation afforded pyrrolizidine **29** through intermediate **28**. Protecting group removal yielded **10** (31% overall yield, from **25**).

Likewise, cycloadduct **25** was employed in the synthesis of indolizidine **11**. Alcohol **27**, previously obtained from **25**, was conveniently transformed into methanesulfonate **33**. As described in Scheme 5, **33** was transformed into indolizidine **34** by means of intermediate **E** (not isolated). Final benzyl groups removal in **34** yielded indolizidine **11** (28% overall yield from **27**).

In conclusion, a convenient and efficient method to synthesize chemical libraries of pyrrolizidines and indolizidines alkaloids is described. By way of 1,3-dipolar cycloaddition reaction and intramolecular *N*-alkylation as key reactions, four new highly polyhydroxylated azasugar alkaloids (**8**, **9**, **10**, and **11**) have been characterized. This is an example of diversity-oriented organic synthesis[14] based on the versatility of two chemoenzymatically prepared alkenediols **12** and **13**. To the best of our knowledge these are the first examples of pyrrolizidine and indolizidine alkaloids presenting such hydroxylation patterns. Further investigations on the biological activity of these compounds will be published in due course.

Experimental Section

Enzymatic Acetylation of Racemic 3-Buten-1,2-diol. To a gently stirred solution of (*R*,*S*)-3-buten-1,2-diol (8.8 g, 100 mmol) and

(14) For selected reviews see: (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Spring, D. R. *Org. Biomol. Chem.* **2003**, *1*, 3867. (c) Spandl, R. J.; Bender, A.; Spring, D. R. *Org. Biomol. Chem.* **2008**, *6*, 1149.

vinyl acetate (18.5 mL, 200 mmol) in TBME−ether (1:1, 150 mL) was added Chirazyme L-2, c.-f. C2 (200 mg), and the mixture was maintained at rt with stirring. The reaction was monitored by GLC analysis (see the Supporting Information) and after 7 h revealed the absence of starting material and the presence of two higher retention time compounds. The enzyme was removed by filtration and thoroughly washed with ether. The filtrate and washings were concentrated to a residue that was subjected to column chromatography (Et_2O−hexane, 1:1) to afford first (*R*)-di-*O*-acetyl-3-buten-1,2-diol (**12**, 7.7 g, 44%),[15] t_R = 4.25 min (conditions A: see the Supporting Information); t_R = 10.73 min (conditions B); ee 64%, $[\alpha]^{25}_D$ −3.4, $[\alpha]^{24}_{577}$ −4.2, $[\alpha]^{25}_{546}$ −5.8, $[\alpha]^{25}_{405}$ −8.5 (*c* 1 in $CHCl_3$) [lit.[15] $[\alpha]^{25}_D$ +4.9, $[\alpha]^{24}_{577}$ +6.9, $[\alpha]^{25}_{546}$ +9.8 (*c* 2.1 in $CHCl_3$) for (*S*)-**12**]. Second was obtained (*S*)-1-*O*-acetyl-3-buten-1,2-diol (**13**, 6.12 g, 46.4%), $[\alpha]^{24}_D$ −3.7 (*c* 2 in $CHCl_3$), t_R = 3.03 min (conditions A). Conventional acetylation of (*S*)-**13** (260 mg, 1.97 mmol) in anhydrous pyridine (1 mL) and Ac_2O (0.5 mL) gave, after column chromatography (Et_2O−hexane, 1:1), (*S*)-(+)-**12** (289 mg, 84%), t_R = 4.25 min (conditions A), t_R = 10.24 min (conditions B), ee 61%, $[\alpha]^{27}_D$ +3.8 (*c* 2.6 in $CHCl_3$). The spectroscopic data of **13** were identical with those previously reported.[16]

(1′*S*,2*R*,3a*R*,4*R*,5*R*,6*R*)-4,5-Dibenzyloxy-6-benzyloxymethyl-2-(1,2-diacetyloxyethyl)hexahydropyrrolo[1,2-*b*]isoxazole (25). A solution of **7** (54 mg, 0.13 mmol) and **12** (60 mg, 0.46 mmol) in anhydrous DCM (0.2 mL) was heated at 70 °C under microwave irradiation in a sealed tube with an Ar atmosphere. After 4 h, TLC (AcOEt−hexane, 3:1) revealed the presence of a new compound of higher R_f. The solvent was removed and the residue was purified by FC (AcOEt−hexane, 1:3) yielding **25** (56 mg, 74%) as a colorless syrup: $[\alpha]^{30}_D$ −51 (*c* 1 in $CHCl_3$); IR ν_{max}/cm^{-1} 1748 (CO); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44−7.22 (m, 15H, 3Ph), 5.16 (dt, 1H, $J_{8,9'}$ = 6.2, $J_{2,8}$ = 5.8, $J_{8,9}$ = 3.2 Hz, H-8), 4.64−4.48 (m, 6H, 3 CH_2Ph), 4.39 (dd, 1H, $J_{9,9'}$ = 12.2 Hz, H-9), 4.31 (br q, 1H, H-2), 4.11 (dd, 1H, H-9′), 4.07 (dd, 1H, $J_{5,6}$ = 5.6, $J_{4,5}$ = 4.1 Hz, H-5), 3.98 (t, 1H, $J_{3a,4}$ = 3.7 Hz, H-4), 3.83−3.74 (m, 1H, H-3a), 3.71 (dd, 1H, $J_{7,7'}$ = 9.9 Hz, $J_{6,7}$ = 4.6 Hz, H-7), 3.61 (dd, 1H, $J_{6,7'}$ = 6.4 Hz, H-7′), 3.34 (br q, 1H, H-6), 2.33 (ddd, 1H, $J_{3,3'}$ = 12.6 Hz, $J_{3,3a}$ = 8.8 Hz, $J_{2,3}$ = 7.0 Hz, H-3), 2.24 (dt, 1H, $J_{3',3a}$ = 7.23 Hz, $J_{2,3'}$ = 8.8 Hz, H-3′), 2.1 and 2.08 (2s, 6H, 2 Ac); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 and 170.3 (2 Ac), 138.5, 138.2, 138.0, 128.8, 128.7, 128.6, 128.13, 128.09, 128.06, 128.04, 128.00, 127.8 (Ph), 87.4 (C-4), 84.2 (C-5), 75.4 (C-2), 73.6, 72.5, 72.1 (3 *C*H_2Ph), 71.5 (C-8), 70.3 (C-6), 70.1 (C-7), 68.4 (C-3a), 63.1 (C-9), 36.4 (C-3), 21.3 and 21.0 (2 *C*H_3CO); HRMS (NALDI-TOF) cacld for $C_{34}H_{40}NO_8$ $[M+H]^+$ 612.2573, found 612.2524.

(1*R*,2*R*,3*R*,5*R*,6*R*,7a*R*)-1,2-Benzyloxy-3-benzyloxymethyl-5-*tert*-butyldiphenylsilyloxymethyl-6-hydroxypyrrolizidine (29). A mixture of **28** (133 mg, 0.16 mmol) and Zn dust (80 mg) in AcOH/H_2O 9:1 (2 mL) was heated to 60 °C for 6 h. TLC (AcOEt−hexane, 3:1) showed the absence of **28** and the presence of a compound with a lower R_f. The reaction mixture was filtered through cotton and washed with AcOEt. The solvent was washed with a saturated solution of Na_2CO_3 and evaporated to a residue that was purified by FC (AcOEt−hexane, 3:1) to afford **29** (90 mg, 76%) as a colorless syrup. $[\alpha]^{25}_D$ −2.3, $[\alpha]^{25}_{405}$ −38 (*c* 0.5 in $CHCl_3$); IR ν_{max}/cm^{-1} 3417 (OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74−7.21 (m, 25H, 5 Ph), 4.51−4.35 (m, 6H, CH_2Ph), 4.27 (br d, 1H, H-6), 4.11 (m, 2H, H-2,9), 4.05 (dd, 1H, $J_{9,9'}$ = 10.6 Hz, $J_{5,9'}$ = 6.0 Hz, H-9′), 4.00 (br s, 1H, H-1), 3.72 (br t, 1H, H-3), 3.63 (m, 1H, H-7a), 3.42 (m, 2H, H-8,8′), 3.31 (br dd, 1H, H-5), 2.29 (ddd, 1 H, $J_{7,7'}$ = 14.0 Hz, J = 6.0 Hz, J = 9.5 Hz, H-7), 1.84 (ddd, 1H, J = 5.2 Hz, J = 7.9 Hz), 1.07 (s, 9H, CMe_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 138.1, 137.3, 135.7, 133.3, 133.2, 129.7, 128.4, 128.2, 128.0, 127.9, 127.8, 127.73, 127.70, 127.61, 127.57, 127.4, (Ph), 88.6 (C-1), 86.2 (C-2), 74.2 (C-6), 73.0 (Bn), 72.6 (C-8), 71.8 (Bn), 71.5 (Bn), 68.2 (C-7a), 67.5 (C-5), 62.9 (C-3), 61.3 (C-9), 39.4 (C-7), 26.9 (C*Me*$_3$), 19.2 (*C*Me$_3$); HRMS (NALDI-TOF) cacld for $C_{46}H_{54}NO_5Si$ $[M+H]^+$ 728.3777, found 728.3771.

Acknowledgment. Major support was provided by Ministerio de Educación y Ciencia of Spain (Project ref. CTQ2006-14043). Additional support was provided by Junta de Andalucía (Group BIO-250). We also acknowledge the University of Granada (Spain) for a grant (D.L.R.) and Fundación Ramón Areces for a grant (F.S.-C.).

Supporting Information Available: Characterization data, full experimental procedures and copies of NMR spectra and chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) (a) Kowalczyk, A.; Harris, C. M.; Harris, T. M. *Chem. Res. Toxicol.* **2001**, *14*, 746. (b) Ono, H.; Retboll, M. Japanese Patent 2002-105028, April 10, 2002.

(16) Kirsch, S. F.; Overman, L. E. *J. Am. Chem. Soc.* **2005**, *127*, 2866.