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Hetero-Diels–Alder additions to pent-4-enofuranosides: concise synthesis of hydroxylated pyrrolizidines

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Abstract—A new facile method for the synthesis of hydroxylated pyrrolizidines of the alexine family has been developed, which involves hetero-Diels–Alder addition of ethyl 2-nitrosoacrylate to pent-4-enofuranosides and a further two-step reductive ring opening-ring closure treatment of the cycloadduct.

1. Introduction

Alkaloids mimicking the structures of monosaccharides are widespread in plants and microorganisms; among them, those with a nitrogen in the ring can be classified into five structural classes:[1] pyrrolidines, piperidines, pyrrolizidines, indolizidines and nortropanes. Many of them exhibit specific glycosidase inhibition, being thus potential therapeutical agents.[2] Glycosidases and glycosyltranferases are involved in a variety of important biological processes, such as intestinal digestion, post-translational processing of glycoproteins and the lysosomal catabolism of glycoconjugates. It has been shown that their inhibition is related to many diseases, such as viral and microbial infection, metastasis, diabetes and other metabolic disorders.

Natural pyrrolizidine alkaloids constitute a structurally diverse group of compounds.[3] Further to necines (with a hydroxymethyl group at the C-1 position), there are two more recently discovered families: that of alexine, australine, casuarine and related compounds, possessing a hydroxymethyl group at the C-3 carbon of the pyrrolizidine skeleton and the hyacinthacine family with a carbon branch both at C-3 and C-5 positions (Fig. 1). Because of their current interest as potential drugs, pyrrolizidine alkaloids have become popular synthetic targets[4] and a number of new synthetic analogs have been prepared. We now report an efficient synthesis of enantiomerically pure hydroxylated pyrrolizidines structurally related to the alexine, which represents a novel route to this family of alkaloids.[5]

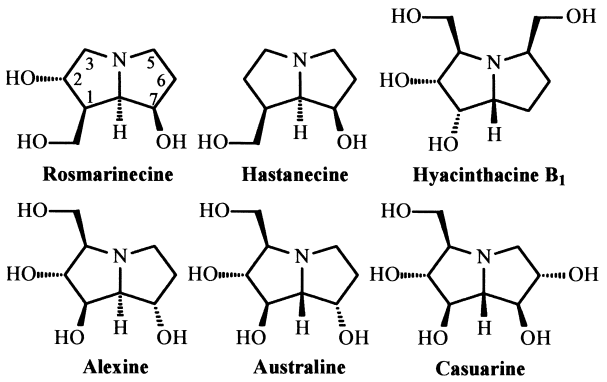

Figure 1.

2. Results and discussion

Retrosynthetic analysis in Scheme 1 shows that pyrrolizidines of the general structure **1** could be prepared by reductive condensation of an intermediate amino-keto-aldehyde **2**, generated in situ by reduction of species **3**, which in turn is the hetero-Diels–Alder adduct of ethyl 2-nitrosoacrylate **5** with the pent-4-enofuranoside **4**. Heterodiene **5**, easily prepared in situ from the oxime of ethyl bromopyruvate,[6,7] reacts with electron-rich alkenes (enol ethers, enamines, allylsilanes, etc) to give highly versatile oxazines.[7,8]

The requisite pent-4-enofuranoside **6** (Scheme 2) was easily prepared from D-ribose in three steps.[9] Treatment of **6** with two equivalents of the oxime of ethyl bromopyruvate at room temperature in the presence of aqueous sodium carbonate afforded in fairly good yield cycloadduct **7** as a single diastereoisomer. Although the absolute configuration

Keywords: pyrrolizidines; carbohydrates; carbohydrate mimetics; Diels–Alder reactions; hydrogenation.

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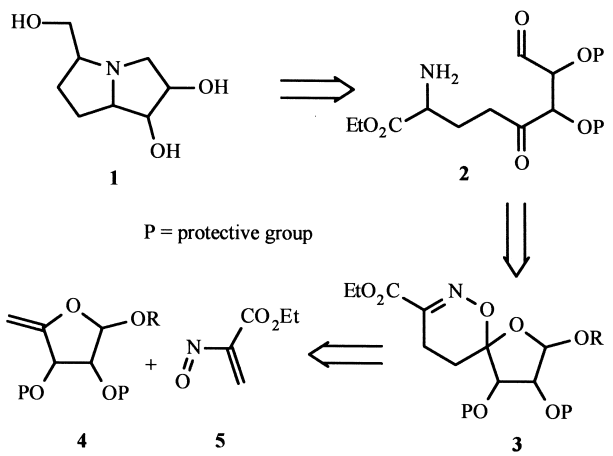
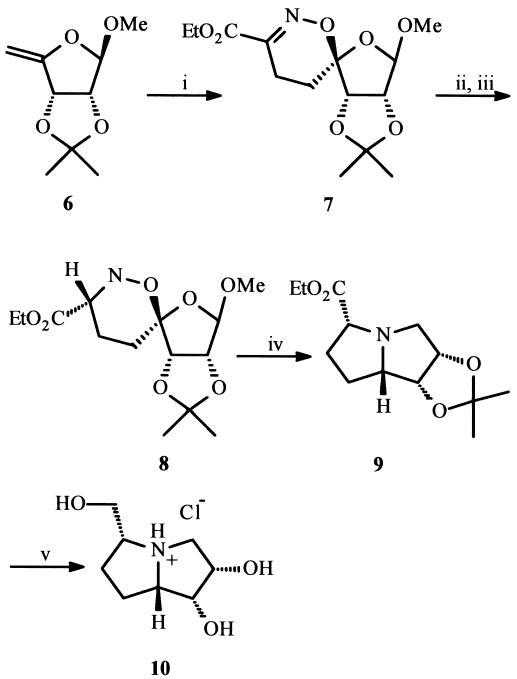


Scheme 1. Retrosynthetic analysis of pyrrolizidines **1**.



Scheme 2. *Reagents and conditions*: (i) $BrCH_2C(NOH)CO_2Et$ (2 equiv.), Na_2CO_3 (5 equiv.), CH_2Cl_2, 20°C, 24 h, 64%. (ii) $NaCNBH_3$ (4 equiv.), AcOH glacial, 20°C, 24 h. (iii) $CHCl_3$, Et_3N (cat.), reflux, 30 min, 80%. (iv) Raney Ni, H_2, 1 atm., H_3BO_3 (100 equiv.), MeOH, $MgSO_4$, 20°C, 24 h, 64%. (v) $LiBH_4$ (5 equiv.), THF, 20°C, 24 h, then MeOH, HCl, 69%.

of the spiro-carbon in **7** could not be unequivocally assigned by the existing spectroscopic data, the structure proposed is the most probable, resulting from the addition of the diene from the less hindered face of the double bond. Analogous structures have been assigned for the nitrile oxide cycloadducts to **6**.[10]

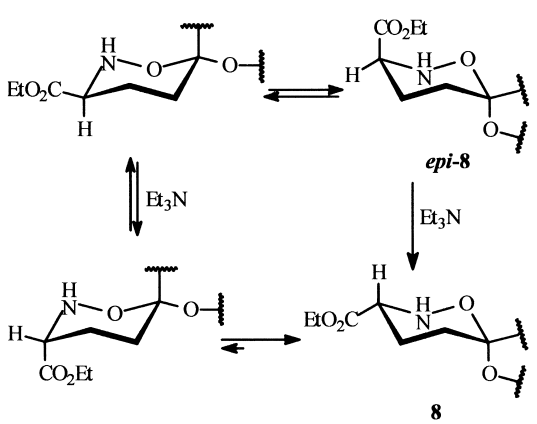
To access the target molecule, two further steps were needed: diastereocontrolled hydrogenation of the C=N double bond followed by reductive N–O bond cleavage. The later was expected to triger a sequence of reactions with intermediate formation of an amino-keto-aldehyde of the general structure **2** (Scheme 1), which under suitable reduction conditions could generate the pyrrolizidine ring. Although the transformation of **8** to a pyrrolizidine could be attempted in one step,[7] it was expected that the overall process would be of low diastereoselectivity.

Thus, the C=N double bond of **7** was easily reduced by $NaCNBH_3$[7a] to give a mixture of **8** and its epimer in very good yield, but the diastereoselectivity was poor. In fact, repeated experiments gave varying mixtures of the two epimers depending upon the reaction time. Chromatographic separation of the mixture gave only the fast-moving product (**8**) in pure form, the slow-moving one (*epi*-**8**) being always contaminated by the former, apparently because of partial isomerisation of the kinetic to the thermodynamic product either upon standing or in the column. Indeed, reflux of a solution of the mixture in $CHCl_3$ in the presence of Et_3N for 30 min caused quantitative conversion of the slow-moving to the fast-moving product.

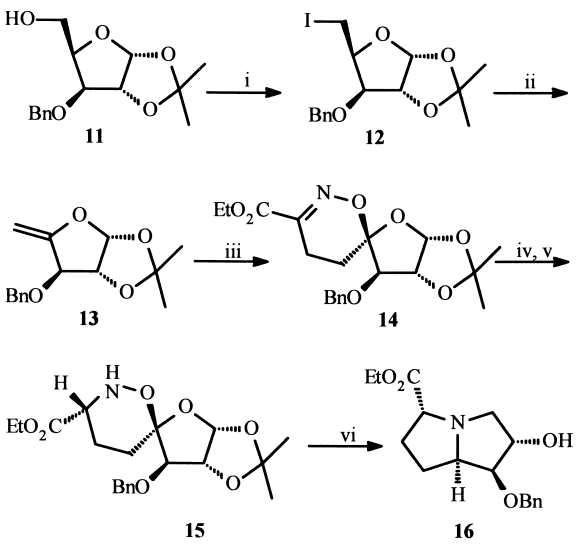
The absolute configuration of the newly formed stereocenter in product **8** was assigned in the next step. Having determined that the isolated product had the structure of **8**, this explained the easy conversion of *epi*-**8** to **8**, in which the oxazine ring adopts a chair-like conformation (Scheme 3) with two equatorial C-substituents and an axial O-substituent, the latter being favoured by the anomeric effect.

Among several attempts for conversion of **8** to **9** in the following step, the Raney Ni hydrogenation of **8** in MeOH in the presence of excess of H_3BO_3 was found to be the most suitable. Under these reaction conditions, compound **9** was the exclusive product in 64% yield (Scheme 2). It is apparent that the N–O bond cleavage by the hydrogenation led to the formation of the expected amino-keto-aldehyde, which was further transformed to **9** by a sequence of tandem condensation–hydrogenation reactions. Finally, reduction of the ester group in **9** with $LiBH_4$ in THF and further treatment with methanolic HCl yielded the unprotected pyrrolizidine as its hydrochloride **10**.

Comparing the structures of **6** and **10**, it becomes evident that the chirality of C-2 and C-3 (ribose numbering) in **6**, which have an *erythro* relative configuration, has been transferred to the C-6 and C-7 (pyrrolizidine numbering) of **10**. To obtain a pyrrolizidine with *threo*-stereochemistry, structurally more relative to casuarine, pent-4-enofuranoside **13** (Scheme 4) was used as a dienophile. This



Scheme 3.



Scheme 4. *Reagents and conditions*: (i) Ph_3P, I_2, imidazole, toluene, reflux, 2 h, 89%. (ii) DBU, DMSO, molecular sieves 3 Å, reflux, 3 h, 87%. (iii) $BrCH_2C(NOH)CO_2Et$ (7 equiv.), aqueous Na_2CO_3 (5 equiv.), CH_2Cl_2, 20°C, 72 h, 62%. (iv) $NaCNBH_3$ (4 equiv.), AcOH glacial, 20°C, 24 h. (v) $CHCl_3$, Et_3N (cat.), reflux, 2 h, 60%. (vi) $Pd(OH)_2/C$, H_2, 1 atm., MeOH, 20°C, 24 h, 66%.

compound was prepared from **11**, which in turn was accessible from 1,2:5,6-diacetone-D-glucose,[11] applying the literature methods.

Again, the addition of ethyl 2-nitrosoacrylate **5** to the pent-4-enofuranoside **13** proceeded highly diastereoselectively to give adduct **14** as the only product isolated. The mutual strong signal enhancements between the 3-H (δ 3.92, ribose numbering) and the close CH_2 group of the oxazine ring (δ 1.95) confirm the proximity of these protons, verifying thus the configuration of the spiro-carbon center. Apparently, the addition of the ethyl 2-nitrosoacrylate to **13** occurred again from the same face of the double bond, the diastereoselection being determined by the steric hindrance induced by the acetonide group of **13**. Compound **14** was treated in the same manner as **7** to give **15** in very good yield, with intermediate formation of both **15** and *epi*-**15**. However, the Raney Ni method failed to convert **15** to the desired pyrrolizidine **16**. After attempting a number of procedures we were able to achieve this transformation, by using $Pd(OH)_2/C$ as a hydrogenation catalyst.

The absolute configuration of the C-3 and C-7a stereocenters in compounds **9** and **16** (Fig. 2) was deduced from their ^1H NMR spectra and the observed NOE enhancements. The proton assignment in compound **9** was easily made by successive proton decouplings starting from the easily distinguishable signals of 3-H, 6-H and 7-H protons, which appeared at δ 3.22 (t, J=8.0 Hz), 4.86 (dt, J=5.1, 2.3 Hz) and 4.51 (t, J=5.1 Hz), respectively, whereas the 5-H_a, 5-H_b and 7a-H protons resonanced at δ 2.52 (dd, J=10.1, 5.1 Hz), 2.97 (dd, J=10.1, 2.3 Hz) and 2.83 (m), respectively. The strong NOE enhancements of both 7a-H (12%) and 6-H (13%) protons, when irradiating the 7-H signal disclose the *cis*-disposition of 7-H and 7a-H protons. In addition, the significant mutual NOE enhancements of 3-H, 5-H_a and 7a-H protons (6% of the 5-H_a and 9% of the 7a-H signals upon irradiation of the 3-H, 4% of each of 3-H and 7a-H signals when irradiating the 5-H_a and 4% of each of 3-H and 5-H_a signals when irradiating the 7a-H) are indicative of their proximity, and strongly support the proposed structure. The unequivocal assignment of the stereochemistry of **9** confirms therefore the structure of its precursors **7** and **8**.

For compound **16**, the signals of 3-H and 7-H overlap in a multiplet at δ 3.74. The signals of 5-H_a, 5-H_b, 6-H and 7a-H appeared at δ 2.75 (dd, J=10.7, 6.1 Hz), 3.29 (dd, J=10.7, 6.8 Hz), 4.37 (ddd, J=6.8, 6.1, 5.8 Hz) and 3.47 (ddd as q, J=7.0 Hz), respectively. As in the case of pyrrolizidine **9**, the proton assignements were made on the basis of their expected chemical shifts and successive decouplings. Despite the limitations of the overlapping signals of the two crucial protons, NOE measurements support the proposed structure **16**. Thus, upon saturation of the 5-H_a proton, a 5% enhancement of the multiplet at δ 3.74 (3-H and 7-H) is observed and mutually irradiation at δ 3.74 caused a 7% enhancement of the 5-H_a signal. This fact indicates that the 5-H_a proton is in proximity to 3-H one, taking into account the *trans*-disposition of 5-H_a and 7-H. Given the configuration of C-3, the strong signal enhancement of 7a-H (10%) when irradiating the 3-H and 7-H signal as well as the lack of any substantial mutual enhancement between 7a-H and 5-H_a or 6-H indicates a *cis*-arrangement of the 7-H and 7a-H protons.

In the sequence of reactions converting compounds **6** and **13** to pyrrolizidines **9** and **16**, respectively, two new chiral centers (C-3, C-7a) were created in each case. The chirality of the C-3 center was generated in **8** and **15**, as already discussed, by the $NaCNBH_3$ reduction of **7** and **14**, respectively, and the subsequent epimerisation with Et_3N, the later being determined by the diastereocontrolled addition of the diene to **6** and **13**. The C-7a chiral center, which was made in the catalytic hydrogenation step, has opposite absolute configuration in pyrrolizidines **9** and **16**, apparently its formation being determined by the exocyclic α-chiral center of the likely intermediate imines **17** and **18** (Fig. 3).

It was expected that starting from a hex-5-enopyranoside, the same reaction sequence could result in the formation of an indolizine derivative. So, addition of ethyl 2-nitrosoacrylate **5** to the hex-5-enopyranoside **19**, derived from

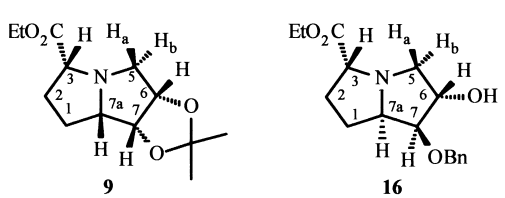


Figure 2.

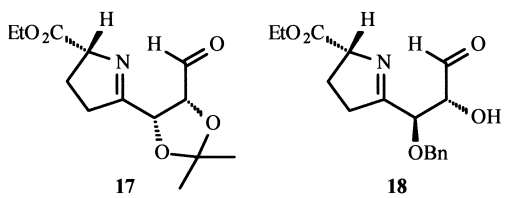
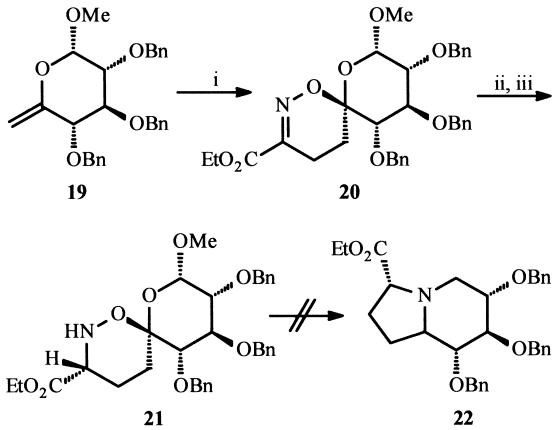


Figure 3.



Scheme 5. *Reagents and conditions*: (i) $BrCH_2C(NOH)CO_2Et$ (2.5 equiv.), aqueous Na_2CO_3 (5.5 equiv.), CH_2Cl_2, 20°C, 5 days, 72% on the consumed **17**. (ii) $NaCNBH_3$ (4 equiv.), AcOH glacial, 20°C, 4 h. (iii) $CHCl_3$, Et_3N (cat.), reflux, 90 min, 62%.

D-glucose,[10] led to the formation of the hetero-Diels–Alder adduct **20** as a single diastereoisomer, which was further converted to **21** by using the established procedures (Scheme 5). All methods, however, used to convert **21** into the indolizidine **22** (Raney Ni/H_2, Pd/C/H_2, Pd(OH)$_2$/H_2, Zn in CH_3CO_2H, etc) were unsuccessful. In all cases compound **21** was decomposed to a plethora of unidentified products.

Again, the absolute configuration of the spiro-carbon in **20** could not be unequivocally assigned by the existing spectroscopic data, the structure proposed being the most probable, resulting by the addition of the diene from the less hindered face of the double bond. Analogous structures have been assigned for the nitrile oxide cycloadducts to **19**.[10] Similarly, the absolute configuration of the newly formed stereocenter in **21** was not determined, its structure assigned by analogy to that of compounds **8** and **15**.

3. Conclusion

In conclusion, a new facile method for the synthesis of hydroxylated pyrrolizidines of the alexine family has been developed, which however failed to be applied to the synthesis of a hydroxylated indolizidine. Starting from easily available pent-4-enofuranosides, utilising cheap and commercial reagents, applying simple and convenient procedures, hydroxylated pyrrolizidines were prepared in three steps: (i) hetero-Diels–Alder addition of the in situ generated ethyl 2-nitrosoacrylate, (ii) C=N bond reduction by $NaCNBH_3$ followed by epimerisation of the product mixture to the thermodynamically more stable isomer, and (iii) reductive cyclisation reaction trigered by the N–O bond cleavage by catalytic hydrogenation. It is worth noting that all steps were highly diastereoselective and only one product was isolated in each step.

4. Experimental

4.1. General

Optical rotations were determined at room temperature on an A. Krüss P3000 Automatic Digital Polarimeter. The ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker 300 AM spectrometer, with tetramethylsilane (TMS) as internal standard. Microanalyses were performed on a Perkin–Elmer 2400-II Element analyser and high-resolution mass spectra (HRMS) were obtained on a VG ZAB-ZSE mass spectrometer under fast-atom bombardment (FAB) conditions with nitrobenzyl alcohol (NBA) as the matrix or on an IONSPEC FTMS spectrometer (matrix-assisted laser-desorption ionisation, MALDI) with 2,5-dihydroxybenzoic acid (DHB) as matrix.

4.1.1. Ethyl (2*R*,3*R*,4*S*,5*R*)-3,4-isopropylidenedioxy-2-methoxy-1,6-dioxa-7-azaspiro[4.5]dec-7-ene-8-carboxylate (7). To a solution of the oxime of ethyl bromopyruvate (1.56 g, 7.43 mmol) in CH_2Cl_2 (100 mL) were added **6** (1.38 g, 7.43 mmol) and Na_2CO_3 (3.9 g, 37 mmol) and the mixture was stirred at room temperature for 12 h. The same amount of the oxime of ethyl bromopyruvate (1.56 g, 7.43 mmol) was added again and the mixture was stirred at room temperature for another 12 h. H_2O (100 mL) was then added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic layer was dried over Na_2SO_4, the solvent was evaporated off and the resulting mixture was chromatographed on a column of silica gel with hexane/ethyl acetate 5:1 as the eluent to give adduct **7** (1.49 g, 64%) as a colorless oil. $[\alpha]_D$=+10.5 (*c* 1.7, $CHCl_3$); IR (neat) 1720, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.36 (t, 3H, *J*=6.7 Hz), 1.49 (s, 3H), 1.86 (ddd, 1H, *J*=13.3, 11.6, 7.4 Hz), 2.17 (ddd, 1H, *J*=13.3, 7.3, 3.2 Hz), 2.57 (ddd, 1H, *J*=14.7, 11.6, 3.2 Hz), 2.70 (ddd, 1H, *J*=14.7, 7.4, 7.3 Hz), 3.30 (s, 3H), 4.33 (two dq as m, 2H), 4.73 (d, 1H, *J*=5.9 Hz), 4.93 (d, 1H, *J*=5.9 Hz), 5.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 18.4, 21.8, 24.7, 26.0, 55.1, 61.9, 83.3, 84.7, 108.1, 109.0, 112.9, 150.7, 163.2; HRMS (MALDI-FTMS) calcd ($C_{14}H_{21}NO_7Na$) 338.1210 (M+Na), found 338.1220, σ 3.0 ppm.

4.1.2. Ethyl (2*R*,3*R*,4*S*,5*R*,8*R*)-3,4-isopropylidenedioxy-2-methoxy-1,6-dioxa-7-azaspiro[4.5]decane-8-carboxylate (8). To a solution of **7** (630 mg, 2 mmol) in glacial acetic acid (14 mL) was added $NaCNBH_3$ (503 mg, 8 mmol) and the mixture was stirred at room temperature for 24 h. The acetic acid was then neutralized by saturated aqueous Na_2CO_3, the mixture was extracted with CH_2Cl_2 (3×100 mL) and the organic layer was dried over Na_2SO_4. The solvent was then removed on a rotary evaporator and the residue was disolved in $CHCl_3$ (20 mL). After adding a drop of Et_3N, this solution was refluxed for 30 min, the volatiles were then evaporated off and the residue was chromatographed on a column of silica gel with hexane/ethyl acetate 5:1 as the eluent to give **8** (509 mg, 80%) as a colorless oil. $[\alpha]_D$=+46.3 (*c* 1.7, $CHCl_3$); IR (neat) 3350, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J*=7.2 Hz), 1.31 (s, 3H), 1.46 (s, 3H), 1.95 (m, 4H), 3.50 (s, 3H), 3.84 (br, 1H), 4.19 (q, 2H, *J*=7.2 Hz), 4.51 (d, 1H, *J*=6.0 Hz), 4.69 (d, 1H, *J*=6.0 Hz), 5.04 (s, 1H), 5.79 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 23.5, 24.8, 26.2, 27.2, 56.4, 58.5, 61.1, 83.6, 84.6, 108.5, 110.5, 112.7, 171.0; Anal. calcd for $C_{14}H_{23}NO_7$ C, 52.99, H, 7.31, N, 4.41. Found: C, 53.06, H, 7.46, N, 4.27.

4.1.3. Ethyl (3*S*,6*R*,7*S*,7a*R*)-6,7-isopropylidenedioxypyrrolizidine-3-carboxylate (9). To a solution of **8** (120 mg, 0.38 mmol) in MeOH (10 mL) were added H_3BO_3 (2.4 g, 38.7 mmol), catalytic amount of Raney Ni and $MgSO_4$ (200 mg) and the mixture was stirred under H_2 atmosphere at room temperature for 24 h. The H_3BO_3 was then neutralized by saturated aqueous Na_2CO_3, the mixture was extracted with CH_2Cl_2 (3×50 mL) and the organic layer was dried over Na_2SO_4. The solvent was then removed on a rotary evaporator and the residue was chromatographed on a column of silica gel with hexane/ethyl acetate 2:1 as the eluent to give **9** (62 mg, 64%) as a colorless oil. $[\alpha]_D$=+26.3 (*c* 0.34, $CHCl_3$); IR (neat) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J*=7.1 Hz), 1.34 (s, 3H), 1.55 (s, 3H), 1.63 (m, 1H), 1.94 (m, 1H), 2.26 (m, 2H), 2.52 (dd, 1H, *J*=10.1, 5.1 Hz), 2.83 (m, 1H), 2.97 (dd, 1H, *J*=10.1, 2.3 Hz), 3.22 (t, 1H, *J*=8.0 Hz), 4.19 (q, 2H, *J*=7.1 Hz), 4.51 (t, 1H, *J*=5.1 Hz), 4.86 (dt, 1H, *J*=5.1, 2.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.2, 25.7, 26.5, 30.1, 53.6, 60.6, 61.4, 70.5, 77.6, 84.3, 112.7, 172.2; HRMS (MALDI-FTMS) calcd ($C_{13}H_{22}NO_4$) 256.1543 (M^++H), found 256.1550, σ 2.7 ppm.

4.1.4. (1*R*,2*S*,5*R*,7a*S*)-1,2-Dihydroxy-5-(hydroxymethyl)-pyrrolizidinium chloride (10). To a solution of **9** (100 mg, 0.392 mmol) in THF (3.5 mL) was added $LiBH_4$ (44 mg, 2.04 mmol) and the mixture was stirred at room temperature for 24 h. CH_2Cl_2 (20 mL) and 10% H_3PO_4 (1.6 mL) were added dropwise, followed by addition of H_2O (50 mL). The mixture was then extracted with CH_2Cl_2 (3×40 mL) and the organic layer washed with brine (50 mL), dried and concentrated on a rotary evaporator. The residue was subsequently dissolved in MeOH (4 mL), concentrated HCl (0.15 mL) was added and after standing at room temperature for 1 h, the volatiles were evaporated off to give **10** as a colorless oil (57 mg, 69%). $[\alpha]_D$=−27.6 (*c* 0.4, MeOH); IR (neat) 3400 (br) cm^{-1}; ^1H NMR (D_2O) δ 1.53 (m, 1H), 1.83 (m, 2H), 2.05 (m, 1H), 2.97 (t, 1H, *J*=11.0 Hz), 3.27 (dd, 1H, *J*=9.9, 6.1, Hz), 3.54 (m, 2H), 3.73 (d, 1H, *J*=11.0 Hz), 4.04 (m, 1H), 4.13 (m, 2H); ^1H NMR ($CDCl_3$/DMSO-d_6) δ 1.67 (m, 1H), 1.86 (m, 2H), 2.16 (m, 1H), 3.07 (m, 1H), 3.20 (m, 1H), 3.60 (m, 3H), 4.05 (m, 3H), 5.40 (br, 1H), 5.53 (br, 2H), 10.80 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 23.1, 26.6, 47.3, 57.9, 65.0, 68.5, 69.4, 70.7; HRMS (MALDI-FTMS) calcd ($C_8H_{16}NO_3$) 174.1125 (M^+), found 174.1127, σ 1.1 ppm.

4.1.5. (3a*R*,5*S*,6*S*,6a*R*)-6-(Benzyloxy)-5-(iodomethyl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (12). A mixture of **11** (1.0 g, 3.57 mmol), Ph_3P (2.36 g, 9 mmol), I_2 (1.016 g, 4 mmol) and imidazole (517 mg, 7.6 mmol) in toluene (20 mL) was refluxed for 2 h and then decanted into saturated aqueous $NaHCO_3$ (200 mL) and diluted with CH_2Cl_2 (50 mL). The unreacted Ph_3P was oxidised by I_2 and its excess was removed by adding $Na_2S_2O_3$. The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated off and the residue was chromatographed on a column of silica gel with hexane/ethyl acetate 7:1 as the eluent to give **12** (1.245 g, 89%) as a colorless oil. $[\alpha]_D$=−74.1 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.33 (s, 3H), 1.52 (s, 3H), 3.33 (m, 2H), 4.09 (d, 1H, *J*=2.9 Hz), 4.47 (ddd, 1H, *J*=8.8, 5.9, 2.9 Hz), 4.58 (d, 1H, *J*=11.2 Hz), 4.62 (d, 1H, *J*=3.6 Hz), 4.69 (d, 1H, *J*=11.2 Hz), 5.95 (d, 1H, *J*=3.6 Hz), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ −1.1, 26.2, 26.8, 72.6, 81.1, 81.6, 82.0, 105.7, 111.9, 127.9, 128.0, 128.4, 137.2; Anal. calcd for $C_{15}H_{19}IO_4$ C, 46.17, H, 4.91. Found: C, 46.02, H, 4.88.

4.1.6. (3a*R*,6*R*,6a*R*)-6-(Benzyloxy)-2,2-dimethyl-5-methylenetetrahydrofuro[2,3-*d*][1,3]dioxole (13). A solution of **12** (500 mg, 1.28 mmol) in dry DMSO (7 mL) and DBU (0.4 mL) was refluxed for 3 h in the presence of 3 Å molecular sieves. H_2O (10 mL) was then added and the mixture was extracted with ethyl ether (30 mL). The organic layer was dried over Na_2SO_4, the solvent was evaporated off and the residue was chromatographed on a column of silica gel with hexane/ethyl acetate 20:1 as the eluent to give **13** (292 mg, 87%) as a colorless oil. $[\alpha]_D$=≈0.0 (*c* 0.5, $CHCl_3$); IR (neat) 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (s, 3H), 1.43 (s, 3H), 4.24 (d, 1H, *J*=2.0 Hz), 4.26 (s, 1H), 4.49 (d, 1H, *J*=11.7 Hz), 4.58 (d, 1H, *J*=3.4 Hz), 4.66 (d, 1H, *J*=2.0 Hz), 4.69 (d, 1H, *J*=11.7 Hz), 6.01 (d, 1H, *J*=3.4 Hz), 7.33 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 27.1, 27.9, 70.3, 80.5, 83.3, 88.7, 106.8, 113.7, 127.9, 128.3, 128.5, 137.2, 158.6; Anal. calcd for $C_{15}H_{18}O_4$ C, 68.69, H, 6.92. Found: C, 68.77, H, 6.83.

4.1.7. Ethyl (2*S*,3*R*,4*R*,5*R*)-4-(benzyloxy)-2,3-isopropylidenedioxy-1,6-dioxa-7-azaspiro[4.5]dec-7-ene-8-carboxylate (14). To a solution of the oxime of ethyl bromopyruvate (1.13 g, 5.76 mmol) in CH_2Cl_2 (50 mL) were added **13** (500 mg, 1.92 mmol) and Na_2CO_3 (1.0 g, 8.5 mmol) and the mixture was stirred at room temperature for 24 h. Additional amounts of the oxime of ethyl bromopyruvate (753 g, 3.84 mmol) were then added twice again after two 24 h periods. H_2O (50 mL) was then added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was dried over Na_2SO_4, the solvent was evaporated off and the resulting mixture was chromatographed on a column of silica gel with hexane/ethyl acetate 10:1 as the eluent to give adduct **14** (463 mg, 62%) as a colorless oil. $[\alpha]_D$=−10.6 (*c* 1.2, $CHCl_3$); IR (neat) 1720, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (t, 3H, *J*=6.8 Hz), 1.44 (s, 3H), 1.48 (s, 3H), 1.95 (m, 2H), 2.60 (m, 2H), 3.92 (d, 1H, *J*=3.4 Hz), 4.31 (two dq as m, 2H), 4.61 (d, 1H, *J*=12.7 Hz), 4.84 (d, 1H, *J*=12.7 Hz), 4.93 (dd, 1H, *J*=4.4, 3.4 Hz), 5.95 (d, 1H, *J*=4.4 Hz), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.0, 18.2, 23.9, 27.7, 28.0, 62.0, 72.3, 85.4, 86.8, 103.0, 104.4, 115.2, 128.0, 128.4, 128.6, 136.8, 150.4, 163.0; HRMS (MALDI-FTMS) calcd ($C_{20}H_{25}NO_7Na$) 414.1523 (M+Na), found 414.1527, σ 1.0 ppm.

4.1.8. Ethyl (2*S*,3*R*,4*R*,5*R*,8*R*)-4-(benzyloxy)-2,3-isopropylidenedioxy-1,6-dioxa-7-azaspiro[4.5]decane-8-carboxylate (15). To a solution of **14** (319 mg, 0.82 mmol) in glacial acetic acid (7 mL) was added $NaCNBH_3$ (206 mg, 3.28 mmol) and the mixture was stirred at room temperature for 24 h. The acetic acid was then neutralized by saturated aqueous Na_2CO_3, the mixture was extracted with CH_2Cl_2 (3×50 mL) and the organic layer was dried over Na_2SO_4. The solvent was then removed on a rotary evaporator and the residue was dissolved in $CHCl_3$ (10 mL). After adding a drop of Et_3N, this solution was refluxed for 2 h, the volatiles

were then evaporated off and the residue was chromatographed on a column of silica gel with hexane/ethyl acetate 5:1 as the eluent to give **15** (195 mg, 60%) as a colorless oil. $[\alpha]_D$=+61.5 (*c* 0.7, $CHCl_3$); IR (neat) 3350, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, 3H, *J*=6.8 Hz), 1.43 (s, 3H), 1.46 (s, 3H), 1.60 (m, 1H), 1.95 (m, 3H), 3.76 (d, 1H, *J*=3.4 Hz), 3.86 (dd as t, 1H, *J*=7.0 Hz), 4.18 (q, 2H, *J*=6.8 Hz), 4.63 (d, 1H, *J*=11.7 Hz), 4.80 (dd, 1H, *J*=4.4, 3.4 Hz), 4.85 (d, 1H, *J*=11.7 Hz), 5.80 (br, 1H), 5.89 (d, 1H, *J*=4.4 Hz), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1, 23.7, 27.7, 28.0, 29.2, 58.5, 61.1, 72.3, 85.4, 87.0, 103.6, 103.9, 115.1, 128.0, 128.1, 128.4, 136.8, 171.1; HRMS (MALDI-FTMS) calcd ($C_{20}H_{27}NO_7Na$) 416.1680 (M+Na), found 416.1681, σ 0.2 ppm.

4.1.9. Ethyl (3*R*,6*S*,7*S*,7a*S*)-7-(benzyloxy)-6-hydroxypyrrolizidine-3-carboxylate (16). To a solution of **15** (100 mg, 0.254 mmol) in MeOH (2 mL) was added catalytic amount of $Pd(OH)_2/C$ and the mixture was stirred under H_2 atmosphere at room temperature for 24 h. The solids were then filtered off, the organic layer was concentrated on a rotary evaporator and the residue was chromatographed on a column of silica gel with hexane/ethyl acetate 1:1 as the eluent to give **16** (52 mg, 66%) as a colorless oil. $[\alpha]_D$=+22.2 (*c* 0.5, $CHCl_3$); IR (neat) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, *J*=6.8 Hz), 1.87 (m, 1H), 2.07 (m, 3H), 2.75 (dd, 1H, *J*=10.7, 6.1 Hz), 2.90 (br, 1H) 3.29 (dd, 1H, *J*=10.7, 6.8 Hz), 3.47 (ddd as t, 1H, *J*=7.0 Hz), 3.74 (two dd overlaping as m, 2H), 4.17 (q, 2H, *J*=6.8 Hz), 4.37 (ddd, 1H, *J*=6.8, 6.1, 5.8 Hz), 4.62 (s, 2H), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 14.1, 28.9, 31.7, 53.5, 60.9, 63.4, 68.9, 72.0, 79.0, 89.9, 127.6, 128.4 (two overlaping peaks), 138.3, 174.4; HRMS (MALDI-FTMS) calcd ($C_{17}H_{24}NO_4$) 306.1700 (M^++H), found 306.1694, σ 2.0 ppm.

4.1.10. Ethyl (6*R*,8*S*,9*R*,10*R*,11*S*)-9,10,11-tris(benzyloxy)-8-methoxy-1,7-dioxa-2-azaspiro[5.5]undec-2-ene-3-carboxylate (20). To a solution of the oxime of ethyl bromopyruvate (233 mg, 1.1 mmol) in CH_2Cl_2 (25 mL) were added **19** (446 mg, 1.0 mmol) and Na_2CO_3 (583 mg, 5.5 mmol) and the mixture was stirred at room temperature for 24 h. Additional amount of the oxime of ethyl bromopyruvate (233 mg, 1.1 mmol) was then added four times again every 24 h. H_2O (25 mL) was then added, the organic layer was separeted and the aqueous layer was extracted with CH_2Cl_2 (3×25 mL). The combined organic layer was dried over Na_2SO_4, the solvent was evaporated off and the resulting mixture was chromatographed on a column of silica gel with hexane/ethyl acetate 10:1 as the eluent to give unchanged **19** firstly (213 mg, 48%), followed by adduct **20** (217 mg, 38%, 72% on the consumed **19**) as a colorless oil. $[\alpha]_D$=−25.0 (*c* 1.0, $CHCl_3$); IR (neat) 1720, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3H, *J*=7.2 Hz), 2.1–2.7 (m, 4H), 3.48 (s, 3H), 3.70 (dd, 1H, *J*=8.5, 3.5 Hz), 3.79 (d, 1H, *J*=8.9 Hz), 3.92 (dd, 1H, *J*=8.9, 8.5 Hz), 4.32 (q, 2H, *J*=7.2 Hz), 4.65–4.82 (m, 7H), 7.30 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 14.0, 17.0, 22.1, 58.1, 61.9, 73.9, 74.7, 75.2, 77.7, 78.8, 81.8, 99.5, 100.5, 127.5, 127.6, 127.8, 127.9, 128.0 (two overlaping peaks), 128.2 (two overlaping peaks), 128.4, 137.7, 137.9, 138.4, 151.0, 163.0; HRMS (MALDI-FTMS) calcd ($C_{33}H_{37}NO_8Na$) 598.2411 (M+Na), found 598.2431, σ 3.3 ppm.

4.1.11. Ethyl (3*R*,6*R*,8*S*,9*R*,10*R*,11*S*)-9,10,11-tris(benzyloxy)-8-methoxy-1,7-dioxa-2-azaspiro[5.5]undecane-3-carboxylate (21). To a solution of **20** (45 mg, 0.078 mmol) in glacial acetic acid (2 mL) was added $NaCNBH_3$ (20 mg, 0.32 mmol) and the mixture was stirred at room temperature for 4 h. The acetic acid was then neutralized by saturated aqueous Na_2CO_3, the mixture was extracted with CH_2Cl_2 (3×10 mL) and the organic layer was dried over Na_2SO_4. The solvent was then removed on a rotary evaporator and the residue was dissolved in $CHCl_3$ (5 mL). After adding a drop of Et_3N, this solution was refluxed for 1.5 h, the volatiles were then evaporated off and the residue was chromatographed on a column of silica gel with hexane/ethyl acetate 5:1 as the eluent to give **21** (28 mg, 62%) as a colorless oil. $[\alpha]_D$=+36.5 (*c* 0.85, $CHCl_3$); IR (neat) 3350, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.27 (t, 3H, *J*=7.1 Hz), 1.98 (m, 2H), 2.20 (m, 2H), 3.42 (d, 1H, *J*=9.1 Hz), 3.52 (s, 3H), 3.63 (dd, 1H, *J*=9.1, 3.8 Hz), 3.82 (br, 1H), 3.85 (dd as t, 1H, *J*=9.1 Hz), 4.18 (q, 2H, *J*=7.1 Hz), 4.63 (d, 1H, *J*=11.2 Hz), 4.67 (d, 1H, *J*=12.0 Hz), 4.69 (d, 1H, *J*=3.8 Hz), 4.77 (d, 1H, *J*=11.2 Hz), 4.79 (s, 2H), 4.82 (d, 1H, *J*=12.0 Hz), 6.05 (br, 1H), 7.32 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.8, 27.1, 57.5, 58.8, 61.0, 73.8, 74.8, 75.4, 77.5, 78.9, 83.1, 99.0, 100.9, 127.5, 127.6, 127.8, 127.9 (two overlapping peaks), 128.1, 128.2 (two overlaping peaks), 128.4, 138.1, 138.2, 138.5, 170.7; HRMS (MALDI-FTMS) calcd ($C_{33}H_{39}NO_8Na$) 600.2568 (M+Na), found 600.2557, σ 1.8 ppm.

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References

1. Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680.
2. (a) In *Iminosugars as Glycosidase Inhibitors, Nojirimycin and Beyond*; Stütz, A. E., Ed.; Wiley-VCH: Weinheim, 1999. (b) In *Carbohydrate Mimics, Concepts and Methods*. Chapleur, Y., Ed.; Wiley-VCH: Weinheim, 1998. (c) In *Carbohydrates in Drug Design*; Witczak, Z. J., Nieforth, K. A., Eds.; Marcel Dekker: New York, 1997. (d) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182–190. (e) Bols, M. *Acc. Chem. Res.* **1998**, *31*, 1–8. (f) Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 750–770. (g) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515–553.
3. (a) Rizk, A.-F. M. *Naturally Occurring Pyrrolizidine Alkaloids*; CRC: Boca Raton, 1991. (b) Mattocks, A. R. *Chemistry and Toxicology of Pyrrolizldine Alkaloids*; Academic: London, 1986. (c) Robins, D. J. *Nat. Prod. Rep.* **1990**, *7*, 377–386. (d) Robins, D. J. *Nat. Prod. Rep.* **1991**, *8*, 213–220. (e) Robins, D. J. *Nat. Prod. Rep.* **1992**, *9*, 313–322. (f) Robins, D. J. *Nat. Prod. Rep.* **1993**, *10*, 487–496. (g) Robins, D. J. *Nat. Prod. Rep.* **1994**, *11*, 613–620. (h) Liddell, J. R. *Nat. Prod. Rep.* **1995**, *12*, 413–418. (i) Liddell, J. R. *Nat. Prod. Rep.* **1996**, *13*, 187–194.

(j) Liddell, J. R. *Nat. Prod. Rep.* **1998**, *15*, 363–370. (k) Liddell, J. R. *Nat. Prod. Rep.* **2000**, *16*, 499–507. (l) Liddell, J. R. *Nat. Prod. Rep.* **2000**, *17*, 455–462. (m) Liddell, J. R. *Nat. Prod. Rep.* **2001**, *18*, 441–447. (n) Hudlicky, T.; Seoane, G.; Price, J. D.; Gadamasetti, K. *Synlett* **1990**, 433. (o) Dai, W.-M.; Nagao, Y.; Fugita, E. *Heterocycles* **1990**, *30*, 1231. (p) Broggini, G.; Zecchi, G. *Synthesis* **1999**, 905. (q) Casiraghi, G.; Zanardi, F.; Rassu, G.; Pinna, L. *Org. Prep. Proced. Int.* **1996**, *28*, 641. (r) 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*, 95–103. (s) 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*, 1–8.

4. Selected recent publications: (a) Hall, A.; Meldrum, K. P.; Therond, P. R.; Wightman, R. H. *Synlett* **1997**, 123–125. (b) Denmark, S. E.; Herbert, B. *J. Am. Chem. Soc.* **1998**, *120*, 7357–7358. (c) White, J. D.; Hmciar, P.; Yokochi, A. F. T. *J. Am. Chem. Soc.* **1998**, *120*, 7359–7360. (d) Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046–3056. (e) Denmark, S. E.; Hurd, A. R. *Org. Lett.* **1999**, *1*, 1311–1314. (f) de Vicente, J.; Arrayás, R. G.; Carretero, J. C. *Tetrahedron Lett.* **1999**, *40*, 6083. (g) Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **2000**, *65*, 2875–2886. (h) Denmark, S. E.; Herbert, B. *J. Org. Chem.* **2000**, *65*, 2887–2896. (i) Romero, A.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 8264–8268. (j) Wee, A. G. H. *Tetrahedron Lett.* **2000**, *41*, 9025–9029. (k) Denmark, S. E.; Cottell, J. J. *J. Org. Chem.* **2001**, *66*, 4276–4284. (l) Wee, A. G. H. *J. Org. Chem.* **2001**, *66*, 8513–8517. (m) Keun, D. K.; Duncan, D.; Livinghouse, T.; Reid, P. *Org. Lett.* **2001**, *3*, 2961–2963. (n) Rambaud, L.; Compain, P.; Martin, O. R. *Tetrahedron: Asymmetry* **2001**, *12*, 1807–1809. (o) Izquierdo, I.; Plaza, M. T.; Robles, R.; Franco, F. *Tetrahedron: Asymmetry* **2001**, *12*, 2481–2487. (p) Subramanian, T.; Lin, C.-C.; Lin, C.-C. *Tetrahedron Lett.* **2001**, *42*, 4079–4082. (q) Behr, J.-B.; Erard, A.; Guillerm, G. *Eur. J. Org. Chem.* **2002**, 1256–1262. (r) de Faria, A. R.; Salvador, E. L.; Correia, C. R. D. *J. Org. Chem.* **2002**, *67*, 3651–3661. (s) Lindsay, K. B.; Tang, M.; Pyne, S. G. *Synlett* **2002**, 731–734. (t) Pisaneschi, F.; Monica, C. D.; Cordero, F. M.; Brandi, A. *Tetrahedron Lett.* **2002**, *43*, 5711–5714.

5. For a preliminary account of this work see, Gallos, J. K.; Sarli, V. C.; Koftis, T. V.; Coutouli-Argyropoulou, E. *Tetrahedron Lett.* **2000**, *41*, 4819–4822.

6. (a) Gilchrist, T. L.; Roberts, T. G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1283–1292. (b) Gilchrist, T. L. *Chem. Soc. Rev.* **1983**, *12*, 53–73.

7. (a) Zimmer, R.; Arnold, T.; Homann, K.; Reissing, H.-U. *Synthesis* **1994**, 1050–1056. (b) Arnold, T.; Orschel, B.; Reissing, H.-U. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1033–1035. (c) Zimmer, R.; Reissing, H.-U. *Angew. Chem., Int. Ed. Engl.* **1988**, *31*, 1518–1519. (d) Hippeli, C.; Reissing, H.-U. *Liebigs Ann. Chem.* **1990**, 217–226. (e) Zimmer, R.; Homann, K.; Angermann, J.; Reissing, H.-U. *Synthesis* **1999**, 1223–1235. (f) Angermann, J.; Homann, K.; Reissing, H.-U.; Zimmer, R. *Synlett* **1995**, 1014–1016. (g) Paulini, K.; Gerold, A.; Reissing, H.-U. *Liebigs Ann. Chem.* **1995**, 667–671. (h) Zimmer, R.; Collas, M.; Roth, M.; Reissing, H.-U. *Liebigs Ann. Chem.* **1992**, 709–714. (i) Paulini, K.; Reissing, H.-U. *Chem. Ber.* **1994**, *127*, 685–689.

8. (a) Tsoungas, P. G. *Heterocycles* **2002**, *57*, 1149–1178. (b) Gilchrist, T. L.; Wood, J. E. *Comprehensive Heterocyclic Chemistry II*; Boulton, A. J., Ed.; Pergamon: Oxford, 1996; Vol. 6, pp 279–299.

9. Hill, J. M.; Hutchinson, E. J.; Le Grand, D. M.; Roberts, S. M.; Thorpe, A. J.; Turner, N. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1483–1487.

10. (a) Gallos, J. K.; Koftis, T. V.; Koumbis, A. E.; Moutsos, V. I. *Synlett* **1999**, 1289–1292. (b) Gallos, J. K.; Koftis, T. V. *J. Chem. Soc., Perkin Trans. 1* **2001**, 415–423.

11. (a) Patil, N. T.; John, S.; Sabharwal, S. G.; Dhavale, D. D. *Biorg. Med. Chem.* **2002**, *10*, 2155–2160. (b) Hori, M.; Nakatsubo, F. *Carbohydr. Res.* **1998**, *309*, 281–286. (c) Xie, M.; Berges, D. A.; Robins, M. J. *J. Org. Chem.* **1996**, *61*, 5178–5179.