Regio- and Enantioselective Synthesis of Novel Functionalized Pyranopyrrolidines by 1,3-Dipolar Cycloaddition of Carbohydrates

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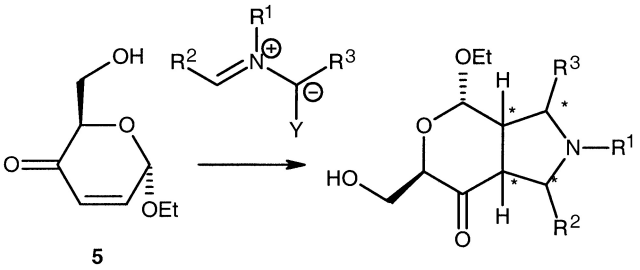
Abstract: A new methodology is described for the rapid enantiomeric synthesis of a novel series of pyranopyrrolidines from readily available and inexpensive carbohydrate compounds. The major feature of the method is a highly selective [3+2] cycloaddition reaction of different azomethine ylides with a chiral carbohydrate-derived enone. The reaction proved to be extremely regio- and stereoselective, giving rise to single enantiomeric compounds in all cases. Moreover, the method is totally atom-efficient and amenable to diversity, since structural diversity of the new compounds is dictated by the choice of the starting materials employed.

Key words: cycloaddition, carbohydrates, azomethine ylides, pyranopyrrolidines, asymmetric synthesis

Pyrrolidinic bicyclic systems are constituents of many biologically active compounds, such as, for example, antagonists of neuroexcitatory amino acids,[1] which intervene in disorders like epilepsies or Huntington's chorea. They are also useful as intermediates for total synthesis of more complex therapeutic molecules.[2] As such, it is of interest to develop the synthesis of such target molecules, using methods allowing control of stereochemistry and permitting diversity.

One of the most versatile methods for the synthesis of pyrrolidines is the [3+2] cycloaddition reaction involving azomethine ylides derived from α-aminoesters, an aldehyde and a suitable dipolarophile.[3] The generation of azomethine ylides from imines by formal 1,2-prototropy, metal salt–tertiary amine combinations provides a simple, regio-and stereospecific process for the synthesis of polysubstitued pyrrolidines.[4] We describe herein a novel and potentially widely adaptable methodology for the synthesis of pyranopyrrolidines from carbohydrate derivatives using azomethine ylides (Scheme 1). The method is atom-economical, with no loss of chiral inducing fragments. Indeed, the carbohydrate moiety maintains its specific stereochemistry and induces regio- and stereoselectivity to the cycloaddition reaction, providing the new pyranopyrrolidines in a controlled manner.

By this approach, we considered that an easily accessible common key intermediate would provide diversely substituted fused pyrrolidines when treated with a variety of 1,3-dipolar azomethine ylides. As such, our strategy uses commonly available carbohydrates and a short and flexible sequence of reactions, leading to the final key step.



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Scheme 1

Thus, the synthesis of the chiral enone **5**[5] was undertaken as indicated in Scheme 2, in which the required compound was prepared in few steps using commonplace reactions, the judicious choice of which led to a relatively high overall yield. This key intermediate then underwent cycloaddition reaction in a stereo- and regiocontrolled manner to afford the required compounds. In each case, a single isomer was obtained, indicating the excellent induction conferred during the cyclization.

As an example starting material, we used the commercially available and inexpensive 1-bromo-tetra-*O*-acetyl glucose (**1**), which was firstly submitted to reductive elimination[6] using zinc/aqueous acetic acid to afford glycal **2** in 78% yield. Treatment with catalytic boron trifluoride diethyl etherate in ethanol[7,8] and toluene led to effective 1,4-substitution of one acetoxy group, with migration of the double bond to provide the 1-ethoxy-2,3-alkene **3** as a mixture of two anomeric isomers (α:β 10:90) in 94% yield. The acetyl protecting groups of the two hydroxyl functions were removed using 0.1 N sodium methoxide in methanol[9] to provide the diol **4** in 91% yield as a single α-anomer. The basic conditions are most probably responsible for this total isomerization to the single α-anomer. Alternatively, the deprotection was attempted using triethylamine in methanol–water,[10] but the yield was much lower at only 72%. The next step, involving the oxidation of the reactive allylic 4-hydroxyl function was achieved by either of two methods, namely using manganese dioxide (MnO_2) in dichloromethane (24 h at r.t., 65% yield), or the Dess–Martin periodinane method[11] (CH_2Cl_2, 4 h, r.t.). The latter proved more efficient, providing the expected chiral enone **5** in a higher, yet non-optimized yield of 76%.

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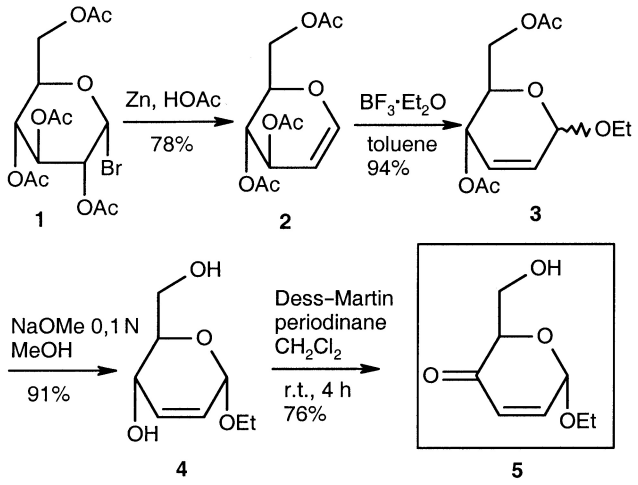
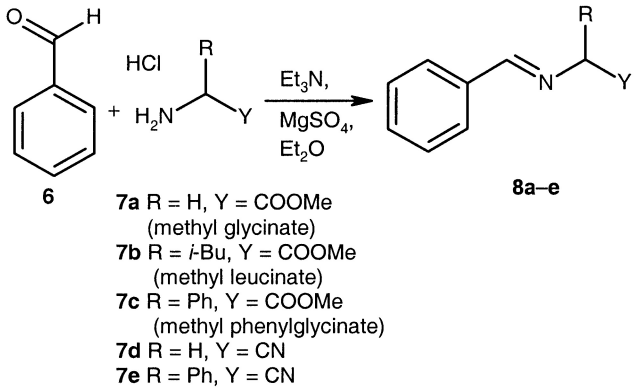


Scheme 2

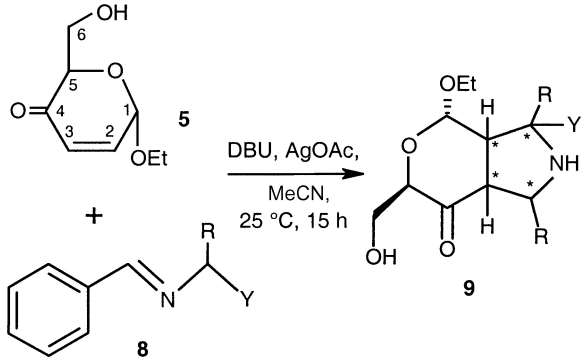
With this versatile intermediate in hand, the following step was the key to our strategy, in which a [3+2] cycloaddition reaction would provide the novel pyranopyrrolidines in a single step. For this, a series of *N*-benzylimine derivatives of five different α-amino esters or α-aminonitriles were prepared. Thus, as examples, three α-aminoesters (glycinate, leucinate and phenylglycinate), and two α-aminonitriles in their hydrochloride form, were treated with benzaldehyde in presence of triethylamine and magnesium sulfate (Scheme 3). The expected benzylimines **8a**–**e** were obtained efficiently in this manner and were employed as such in the cycloaddition step.



Scheme 3

Compounds **8a**–**e** were then used to generate the corresponding metallo-azomethine ylide in situ in presence of the enone **5** (Scheme 4). This was achieved by treating a solution of enone **5** and benzylimine **7** in acetonitrile with silver acetate (AgOAc) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature.

Indeed, under these conditions, cycloaddition did occur successfully and the expected pyranopyrrolidines **9a**–**c** were obtained[12] in relatively good yields when the *N*-benzylimines of α-aminoesters **7a**–**c** were employed. However, the α-aminonitrile benzylimines **7d**,**e** led to inseparable mixtures of numerous products. The results are summarized in Table 1.

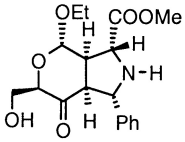
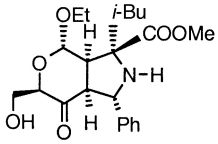
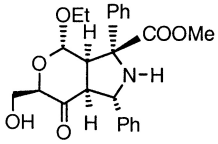


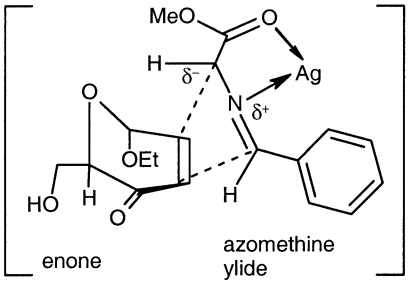
Scheme 4

Compounds **9a**–**c** (Table 1) were obtained as single enantiomeric compounds in spite of the potentially numerous regio- or stereoisomers that could have been formed. We suggest that the newly formed pyrrolidine unit was created by the exclusive addition of the dipole from the face opposing that of the anomeric aglycone ethoxide group. In the case of the unsubstituted (glycinate) derivative, the conformation of the approaching ylide is such that the carboxyl group is opposed to the carbohydrate moiety (Figure 1). Thus in compound **9a** the resulting *syn* ring junction is of *endo*-configuration, and the carboxyl group is *anti* with respect to the α-ethoxy group.

In a similar manner, the phenyl substituent would occupy the less hindered face when the ylide approaches the dipolarophile. By analogous reasoning, substituted aminoester derivatives (leucine and phenylalanine), the bulkier alkyl groups should be oriented furthest from the carbohydrate moiety (Figure 2), thus giving rise to compounds **9b** and **9c.**

Table 1 Pyranopyrrolidines by Cycloaddition

Entry	R	Y	Product	Yield (%)
1	H	COOMe		59
2	*i*-Bu	COOMe		65
3	Ph	COOMe		66
4	H	CN	Mixtures	–
5	Ph	CN	Mixtures	–



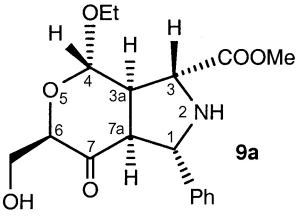
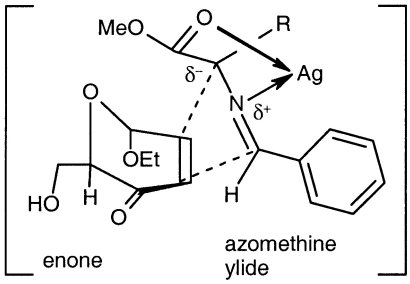
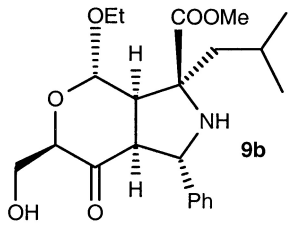


Figure 1 Controlled cycloaddition by the glycinate-derived ylide





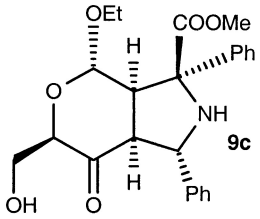


Figure 2 Controlled cycloaddition to the chiral enone

The stereochemistry of all the chiral centers was determined by NMR spectroscopic analysis. The 300 MHz ^{1}H NMR spectrum of **9a** indicated a singlet at δ = 5.12 ppm for H-4, with no coupling constant. This is indeed the observation that would be expected of a *trans* relationship between adjacent protons H-4 and H-3a since the dihedral angle between them is normally between 90° and 100°. A *cis* relationship would have given rise to a coupling constant $J_{4,3a}$ value of at least 3 Hz (dihedral angle of 60° or less). We thus concluded that the configuration of the junction in compound **9a** was 3a*R*. Next, studies by two dimensional ^{1}H-^{1}H NMR clearly showed correlations between H-3a and H-3 ($J_{3a,3}$ = 9.4 Hz) and between H-7a and H-1 ($J_{7a,1}$ = 7.2 Hz).

Finally, to determine the configuration at C-1, α to the pyrrolidine nitrogen, that is, the relative orientations of the phenyl and ester groups, we performed a NOE analysis. We observed a spatial proximity for H-4, H-3 and H-1. Since the absolute configuration of the 'anomeric' carbon C-4 was known, we concluded that the synthesized compound **9a** was methyl-(1*S*,3*R*,3a*R*,7a*S*)-4-ethoxy-6-hydroxymethyl-7-oxo-1-phenyl-octahydro-pyrano[3,4-*c*]pyrrole-3-carboxylate.

Similar observations were made for compound **9b**. The signal for H-4 appeared as a doublet with $J_{4,3a}$ = 1,9 Hz, corresponding once again to a *trans*-configuration between H-4 and H-3a. In a similar manner, examination of the NOE analysis results, indicated spatial proximity for H-1 and the methylene protons of the 6-hydroxymethyl group. Hence we concluded that C-1 was of (*S*) configuration. Further studies, by the ^{1}H NOESY technique, showed correlations between the aromatic protons of the 1-phenyl substituent and protons of the isobutyl (leucine-derived) side-chain. We therefore concluded that the [3+2] cycloaddition reaction proceeded once again with high regio- and stereoselectivity, to give methyl-(1*S*,3*S*,3a*R*,7a*S*)-4-ethoxy-6-hydroxymethyl-2-methyl-propyl-7-oxo-1-phenyl-octahydro-pyrano[3,4-*c*]pyrrole-3-carboxylate (**9b**) as the only isolated product. Reaction between enone **7** and benzylimine **8c** was also regio- and stereospecific, and provided exclusively pyranopyrrolidine **9c**.

In view of the results, we conclude that the reactions described herein provide a versatile methodology for the highly stereoselective synthesis of novel pyranopyrrolidines possessing variable substituents. The major features of this method include the use of a chiral enone derived from carbohydrates and the selective, chirally induced addition of differently substituted azomethine ylides in a [3+2] cycloaddition. The process is efficient, employing readily accessible and inexpensive starting materials. Indeed, the choice of functionality on the starting materials determines the substitution pattern present in the final molecules, thus allowing for diversity in this class of compounds.

References

(1) Goldberg, O.; Luini, A.; Teichberg, V. I. *J. Med. Chem.* **1983**, *26*, 39; and references cited therein.
(2) (a) Orlek, B. S.; Wadsworth, H.; Wyman, P.; Hadley, M. S. *Tetrahedron Lett.* **1991**, 1241. (b) Kende, A. S.; Luzzio, M. J.; Mendoza, J. S. *J. Org. Chem.* **1990**, 918.
(3) (a) Bashiardes, G.; Safir, I.; Mohamed, A. S.; Barbot, F.; Laduranty, J. *Org. Lett.* **2003**, *5*, 4915. (b) Grigg, R.; McMeekin, P.; Sridharan, V. *Tetrahedron* **1995**, *51*, 13347. (c) Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2475.

(4) Vogel, A. I. *Practical Organic Chemistry*, 3rd ed.; Longmans: London, **1956**, 452.
(5) De Freitas, J. R.; Srivastava, R. M.; Da Silva, W. J. P.; Cottier, L.; Sinou, D. *Carbohydr. Res.* **2003**, *338*, 673; and references cited therein.
(6) Kozikowski, A. P.; Lee, L. *J. Org. Chem.* **1990**, *55*, 863.
(7) Ferrier, R. J. In *Carbohydrates*; Pigman, W.; Horton, D., Eds.; Academic Press: New York, **1980**, 843–880.
(8) Toshima, K.; Ishizuka, T.; Matsuo, G.; Nakata, M. *Synlett* **1995**, 306.
(9) Thompson, A.; Wolfrom, M. L.; Pacsu, E. In *Methods in Carbohydrate Chemistry*, Vol. 2; Whistler, R. L.; Wolfrom, M. L., Eds.; Academic Press: New York, **1963**, 215–220.
(10) Fraser-Reid, B.; Walker, D. L. *Can. J. Chem.* **1980**, *58*, 2694.
(11) Clark, D. *Tetrahedron* **2000**, *56*, 6181.
(12) All compounds were purified by the appropriate techniques and fully characterized by spectroscopic means.
Typical Experimental Procedure – Synthesis of Methyl-(1*S*,3*R*,3a*R*,7a*S*)-4-ethoxy-6-hydroxymethyl-7-oxo-1-phenyl-octahydro-pyrano[3,4-*c*]pyrrole-3-carboxylate (9a).
To a solution of methyl-*N*-benzylideneglycinate (**7a**, 0.23 g, 1.3 mmol, 1.5 equiv) in 20 mL of dry MeCN in a two-necked, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser were added enone **5** (0.15 g, 0.9 mmol), AgOAc (0.18 g, 1.05 mmol, 1.2 equiv), and 0.16 mL of DBU (1.05 mmol, 1.2 equiv). The mixture was stirred at r.t. during 4 h in absence of light (flask covered in aluminium foil). After filtration on celite and evaporation of the solvent under reduced pressure, the resulting brown oil was dissolved in 15 mL of CH_2Cl_2 and washed with 20 mL of NH_4Cl solution. The organic layer was then dried over $MgSO_4$, and the solvent was removed under reduced pressure. The resulting oil was purified by flash chromatography on silica gel (EtOAc–pentane 70:30, R_f = 0.30) to provide **9a** in 60% yield as a viscous colorless oil. ^{1}H NMR and ^{13}C NMR spectroscopy revealed two conformers.
Major conformer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, J = 7.1 Hz, 3 H, ethyl-CH_3), 2.86 (dd, $J_{3a,7a}$ = 9.4 Hz, $J_{3a,3}$ = 9.0 Hz, 1 H, H-3a), 3.07 (dd, $J_{7a,3a}$ = 9.4 Hz, $J_{7a,1}$ = 5.7 Hz, 1 H, H-7a), 3.51–3.98 (m, 5 H, H-5, CH_2-O and ethyl-CH_2), 3.77 (s, 3 H, ester-CH_3), 4.04 (d, $J_{3,3a}$ = 9.0 Hz, 1 H, H-3), 4.69 (d, $J_{1,7a}$ = 5.7 Hz, 1 H, H-1), 5.12 (br s, 1 H, H-4α), 7.25–7.46 (m, 5 H, H-arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.7 (ethyl-CH_3), 48.3 (C-3a), 52.5 (ester-CH_3), 55.7 (C-7a), 62.1 (ethyl-CH_2), 62.7 (C-3), 63.0 (C-1), 63.8 (CH_2-O), 76.8 (C-6), 97.0 (C-4), 124.9–139.3 (C-Ar), 172.8 (ester C=O), 207.4 (C-7) ppm. IR = 3362 (OH), 3059 (arom. C-H), 2972, 2929, 2905 (CH_n), 1736 (C=O ester), 1715 (C=O ketone), 1606 (arom. C=C), 1180, 1132, 1063 (C-O), 736 (arom. C-H), 702 (arom. C-H) cm^{-1}.
Minor conformer: ^{1}H NMR (300MHz, $CDCl_3$): δ = 1.17 (t, J = 7.1 Hz, 3 H, ethyl-CH_3), 3.12–3.15 (m, 1 H, H-3a, 3.25 (dd, $J_{7a,3a}$ = 7.7 Hz, $J_{7a,1}$ = 7.2 Hz, 1 H, H-7a), 3.51–3.98 (m, 5 H, H-5, CH_2-O and ethyl-CH_2), 3.86 (s, 3 H, ester-CH_3), 4.19 (d, $J_{3,3a}$ = 9.4 Hz, 1 H, H-3), 4.41 (d, $J_{1,7a}$ = 7.2 Hz, 1 H, H-1), 5.12 (br s, 1 H, H-4α), 7.25–7.46 (m, 5 H, H-arom.) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.2 (ethyl-CH_3), 45.9 (C-3a), 52.3 (ester-CH_3), 52.4 (C-7a), 60.9 (C-1), 62.0 (ethyl-CH_2), 63.7 (CH_2-O), 65.9 (C-3), 75.5 (C-6), 96.1 (C-4), 124.9–139.3 (C-Ar), 172.2 (ester C=O), 207.4 (C-7).