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A divergent, versatile synthesis of d-aminoalkenes and related compounds from carbohydrates; selective formation of polyalkoxypiperidines and polyalkoxypyrans.

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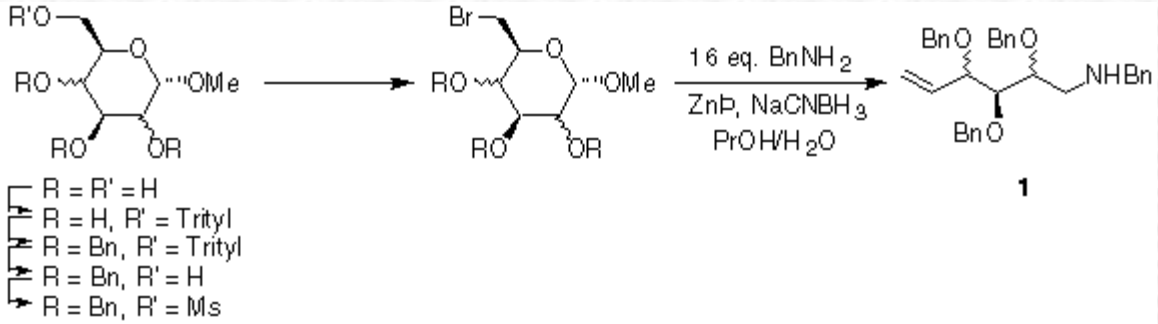
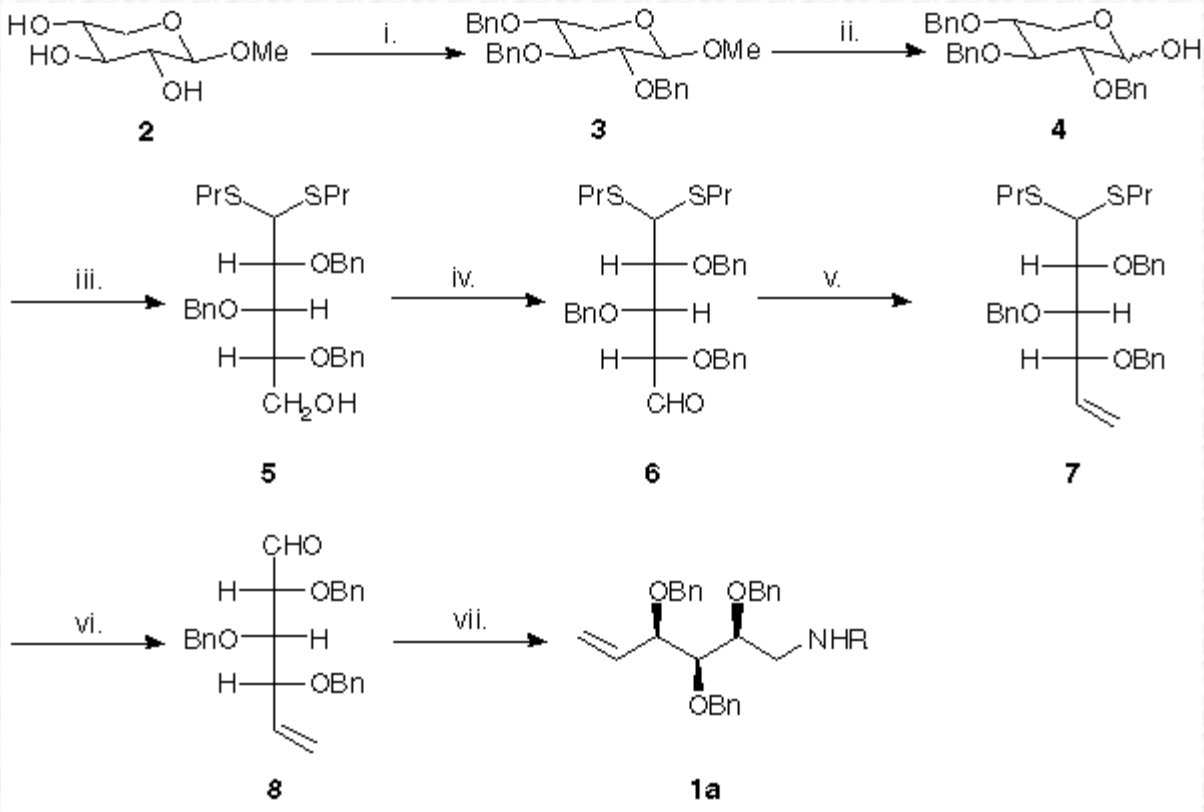
A versatile synthesis of xylose derived d-aminoalkenes is presented. We have previously reported on the stereoselective synthesis of polyhydroxypiperidines.[1] An extension to the methodology to incorporate more exotic *N*-substituted compounds was sought. This communication reports, in particular, the result of the completion of a synthetic sequence for the preparation of carbohydrate derived d-aminoalkenes.



Scheme 1 Preparation of δ-Aminoalkenes

Scheme 1 summarises the general d-aminoalkene preparation employed previously.[1,2] In Scheme 1 the final reductive cleavage/reductive amination employs 16 equivalents of the amine.[3] This excess limits the amines that might be installed in the resultant d-aminoalkenes to those that are cheap and readily available. A second feature of this reductive amination is the use of zinc dust to effect the reductive cleavage. This tends to limit the double bond formed to a terminal alkene, which may prevent some lines of synthetic elaboration.

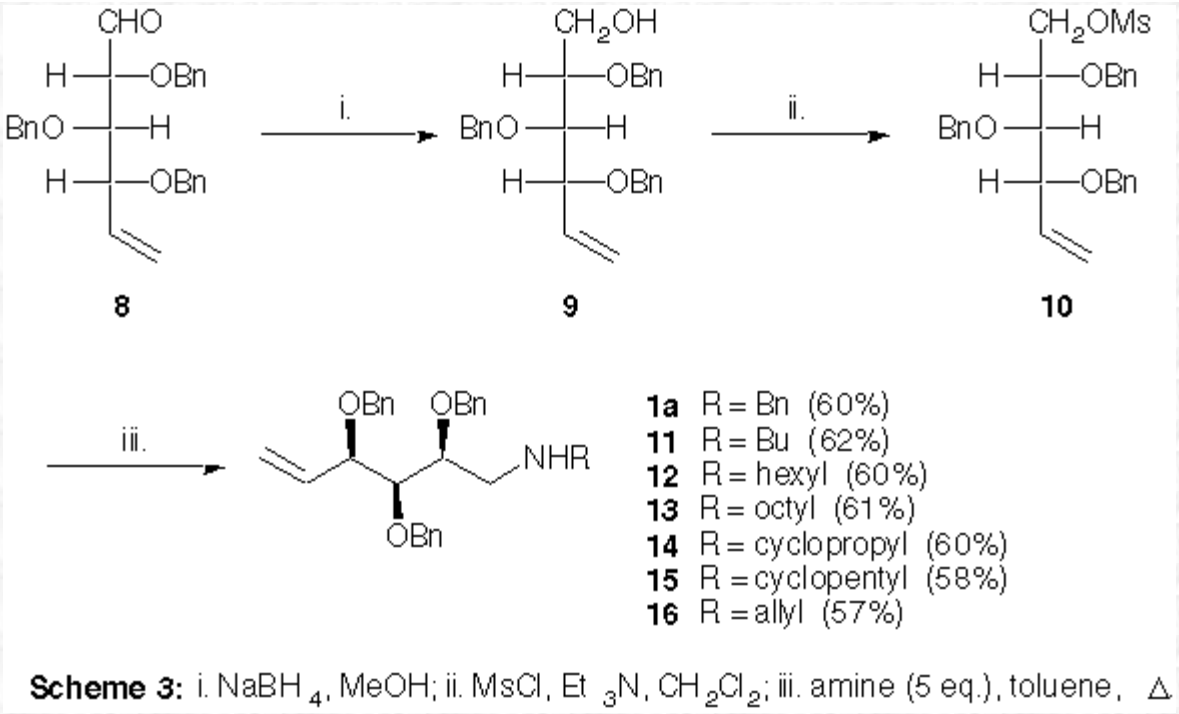
The Scheme 1 approach starts with hexose sugars and so all the carbons of the final aminoalkene skeleton are present. In our approach, reported herein, the alkene was formed separately using Wittig chemistry and so the starting material required was a pentose sugar. In the initial scheme (Scheme 2) the aim was to prepare the d-aminoalkene **1**[1] prepared previously for the purpose of comparison with Scheme 1.



Scheme 2: i. NaH, BnBr, DMF; ii. aq. CH_3COOH, H_2SO_4; iii. PrSH, cHCl; iv. PCC, CH_2Cl_2; v. nBuLi, $CH_3P^+PPh_3\ I^-$, THF; vi. $HgCl_2$, CH_3CN, H_2O; vii. reductive amination.

D-Xylose has the requisite configurations of the secondary alcohols for construction of the aminoalkene **1a**. Thus commercial methyl b-D-xylopyranoside **2** was perbenzylated (74%) under standard conditions and then the glycoside **3**[4] was hydrolysed with a mixture of sulfuric acid and aqueous acetic acid to give the hemiacetal **4** (84%). The aldehyde was hen trapped as the dithiopropyl acetal **5** (86%). Elaboration to the double bond could then proceed. The 1˚ alcohol **5** was oxidised with pyridinium chlorochromate (PCC) in dichloromethane to give the aldehyde **6** (79%). This reaction was also attempted using standard Swern conditions but the yield was very low. The methylene ylid derived from treatment of methyl triphenylphosphonium iodide with n-butyl lithium in THF underwent a Wittig reaction with the aldehyde **6** to give the expected alkene **7** (80%). The dithioacetal was removed using mercuric chloride/mercuric oxide in water/acetonitrile to give the aldehyde **8** (92%).

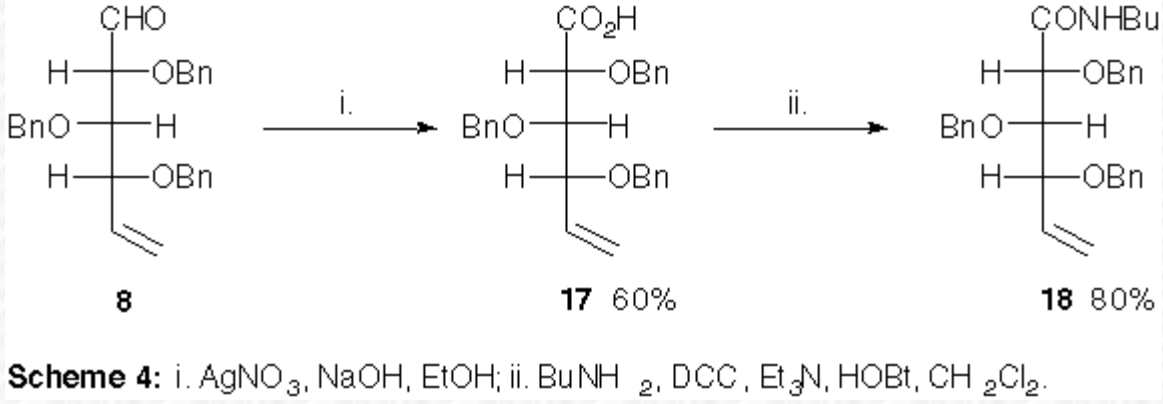
At this point it was attractive to complete the sequence by reductive amination to afford the d-aminoalkene **1a**. There are exemplary reductive aminations in the literature.[5] However, despite our best efforts, reductive amination of the aldehyde **8**, particularly with simple 1˚-alkyl amines, gave poor yields of aminated material. There is evidence that reductive amination reactions do not proceed well in the case of the simple alkyl amines[6] though our continuing researches in this area will be reported in due course.



Scheme 3: i. $NaBH_4$, MeOH; ii. MsCl, Et_3N, CH_2Cl_2; iii. amine (5 eq.), toluene, Δ

The aldehyde **8** was, however, reduced efficiently with sodium borohydride to give the alcohol **9** (95%) (Scheme 3). This alcohol was activated toward displacement by formation of the corresponding methanesulfonate **10** (75%). Heating the sulfonate ester in toluene with 5 equivalents of various amines caused displacement reactions to give the required d-aminoalkenes **1a** and **11**-**16**.

Spectroscopic data for the aminoalkene **1a** were in complete agreement with the literature.[1] The data for aminoalkenes **11**-**16** were in accord with expectations. The reason for making these compounds is to study their mercuriocyclisation reactions. Another possibility for their cyclisation is an intramolecular palladium mediated amination. However, amino groups bind tightly to palladium and can act as catalyst poisons requiring the reactions to be conducted stoichiometrically. This propensity needs to be reduced for the development of an efficient reaction catalytic in palladium. *N*-Acylated or sulfonylated amines or amides are one solution to this problem.[7]



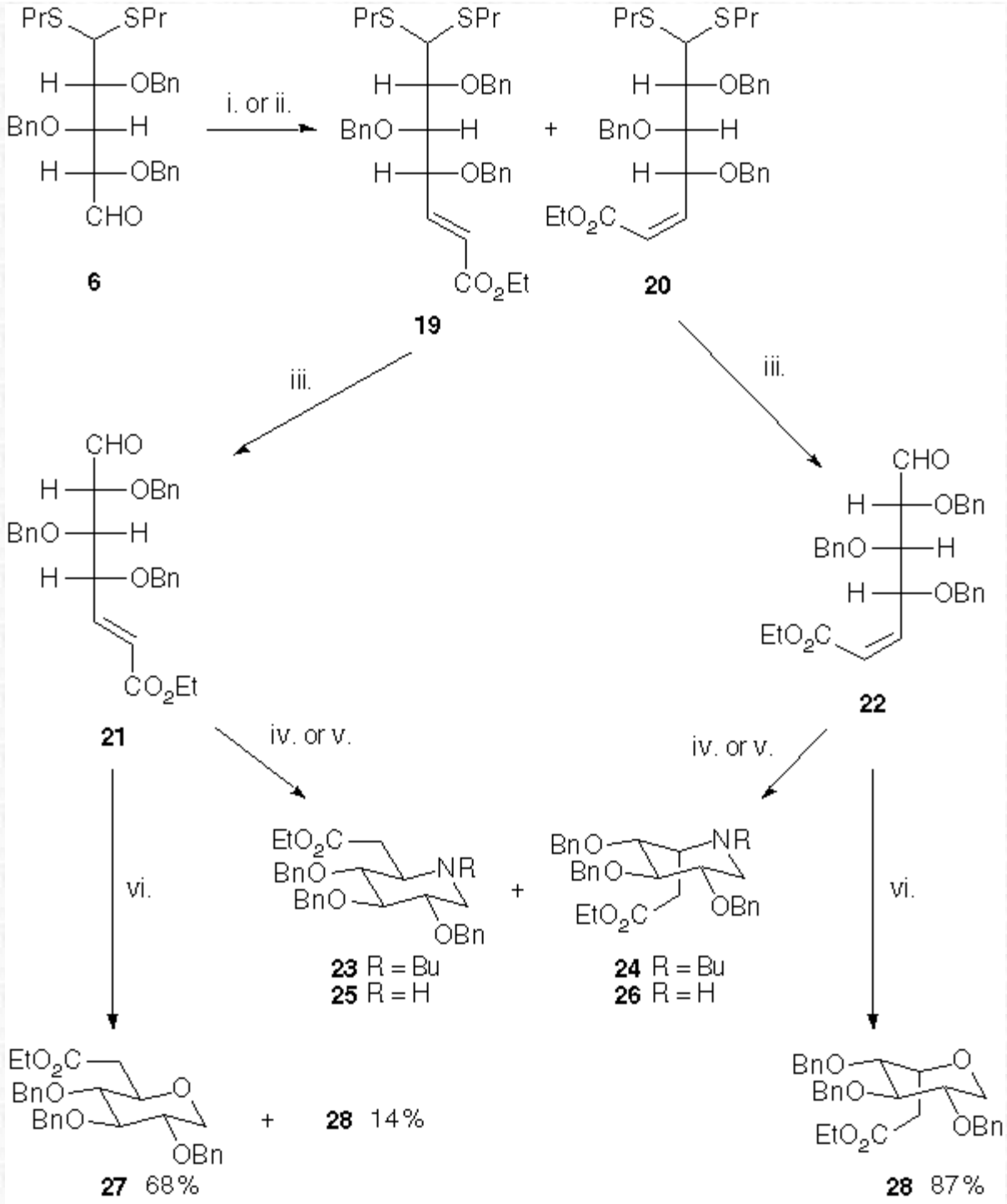
Scheme 4: i. $AgNO_3$, NaOH, EtOH; ii. $BuNH_2$, DCC, Et_3N, HOBt, CH_2Cl_2.

Thus the aldehyde **8** was oxidised with silver nitrate to give the acid **17** (60%) (Scheme 4). A dicyclohexyl carbodiimide (DCC) mediated coupling of butyl amine then gave the amide **18** (80%) which was the first intermediate desired for proposed palladiocyclisations.

Finally, Banwell *et al*. recently reported stereoselective intramolecular Michael cyclisations of d-hydroxy and d-amino *E*- and *Z*-a, b-unsaturated esters.[8] This report inspired us to consider similar transformations, which applied to sugar derived intermediates would give access to polyhydroxypyrans and polyhydroxypiperidines. Accordingly, the aldehyde **6** undergoes a Horner-Wadsworth-Emmons (HWE) reaction with triethylamine in the presence of lithium bromide to

give a 78:22 mixture (75% combined yield) of the enoates **19** and **20** (**19** d 7.06, 1H, dd, $J_{5,6}$ 16.0 and $J_{5,4}$ 5.5 Hz, H5, 6.09, 1H, d, $J_{6,5}$ 16.0 Hz, H6; **20** d 6.36, 1H, dd, $J_{5,6}$ 11.8 and $J_{5,4}$ 8.6 Hz, H5, 5.86, 1H, d, $J_{6,5}$ 11.8 Hz, H6) (Scheme 5). The enoates **19** and **20** were separated by flash column chromatography. In complementary fashion the HWE reaction employing fresh n-butyl lithium as base gave reversed selectivity for the mixture of enoates **19** and **20** (33:67) (80% combined yield).

The dithioacetal **19** was treated with mercuric chloride and mercuric oxide in water/acetonitrile to give the aldehyde **21** (90%) (Scheme 5). Reductive amination of the aldehyde **21** with butyl amine produces a secondary amine, which undergoes a Michael reaction *in situ* with the a,b-unsaturated ester to give a mixture of the piperidines **23** and **24** (75% combined yield). Similarly, the dithioacetal **20** was converted to the aldehyde **22** (92%) and then subjected to reductive amination with butyl amine to give the same piperidines **23** and **24** (58% combined yield).



Scheme 5: i. Et_3N, LiBr, $(MeO)_2POCH_2CO_2Et$, THF; ii. nBuLi, $(MeO)_2POCH_2CO_2Et$, THF; iii. $HgCl_2$, HgO, H_2O, CH_3CN; iv. $BuNH_2$, $NaCNBH_3$, MeOH; v. NH_4OAc, $NaCNBH_3$, MeOH; vi. $NaBH_4$, EtOH.

Reductive amination/cyclisation with ammonium acetate was also trialed. The aldehyde **21** gave a mixture of the piperidines **25** and **26** (58% combined yield). While the aldehyde **22** gave a mixture of the piperidines **25** and **26** (52% combined yield). The data (NMR in particular) on the compounds **23**-**26** are complex. The results of analysis of the NMR spectra to determine the configuration of the new asymmetric centre in each compound will be reported in due course. The production of the piperidines **25** and **26** and their *N*-butyl derivatives **23** and **24** represents a successful approach to the synthesis of homo-azasugars [9] akin to such biologically active polyhydroxypiperidines as deoxynojirimycin.[10] Thus they are of interest for their potential SAR as well as their elaboration to other natural products.

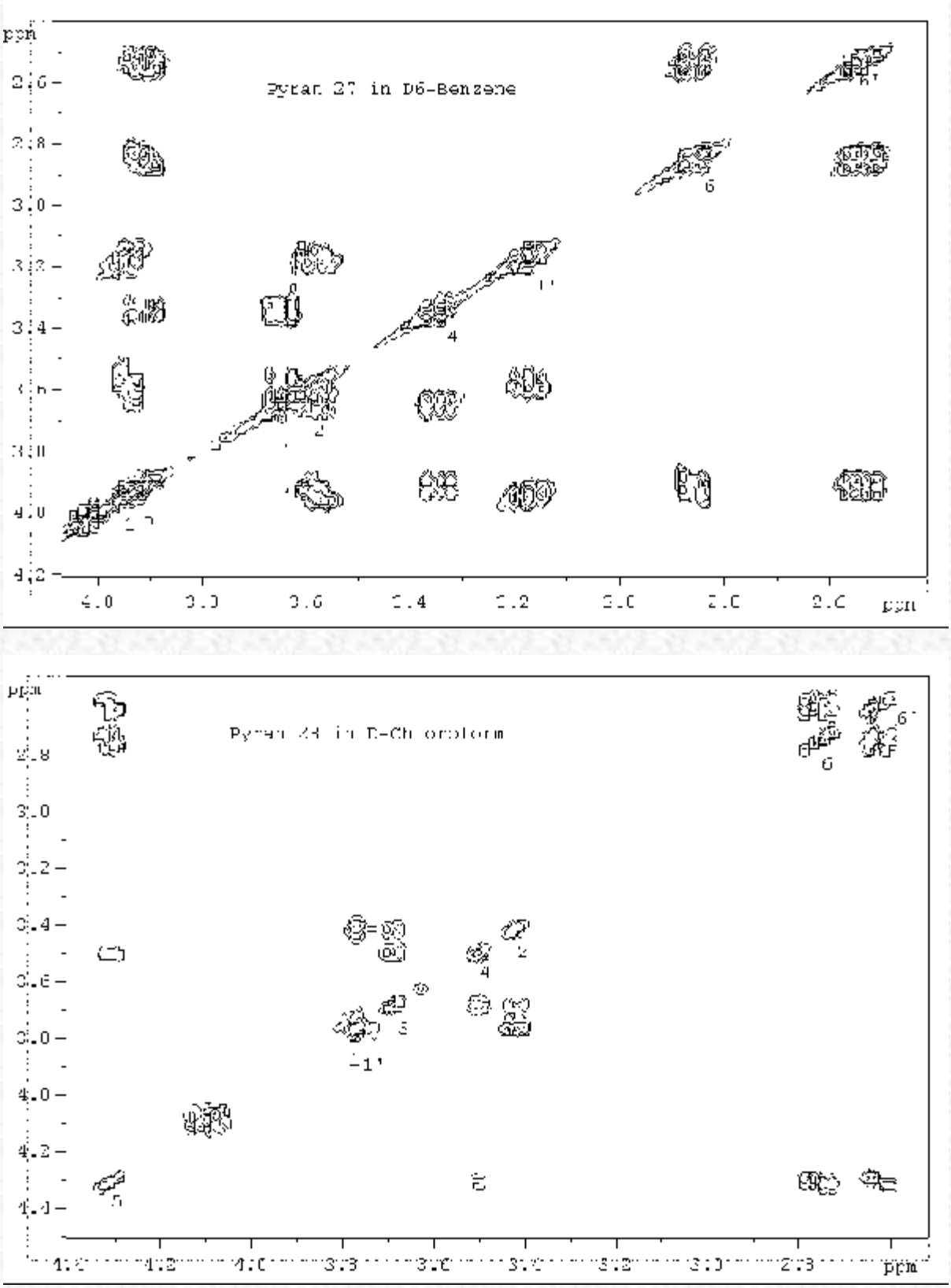


Figure 1: COSY spectra of compounds **27** and **28** acquired at 400 MHz.

Omission of the amine from the reduction of compounds **21** and **22** facilitates the Michael cyclisation to form the pyrans **27** and **28**. In the case of compound **21** a 5:1 mixture of pyrans **27** and **28** was formed in 82% yield. Compound **22** gave exclusively pyran **28** (88%) under the same reaction conditions.

The assignments of the ^{1}H NMR spectra and determination of the configuration of the C-5 of compounds **27**[11] and **28**

[12] were achieved through the analysis of COSY spectra (Figure 1). It is clear that the chemical shifts of the ring protons are considerably different in the two isomers. The assignment of structures **27** and **28** was based on the expected coupling patterns of the H5 protons. For compound **27**, H5 is expected to have a di-axial coupling to H4 (9.0 Hz), whereas in pyran **28** axial-equatorial coupling (3.6 Hz) is present.

Our results in the formation of the pyrans **27** and **28** from the enoates **21** and **22** appear to be consistent with an extended chair-like conformation of the substrate during cyclisation possibly under chelation control. Thus we have successfully met the aim of designing a divergent synthesis of a range of *N*-alkylated d-aminoalkenes. And demonstrated the versatility of the sequence with the preparation of a d-amidoalkene for proposed palladiocyclisations. Finally, the formation of the a,b-unsaturated esters **21** and **22** allowed the generation of piperidines **23**-**26** and the novel pyrans **27** and **28**. Further variations of this chemistry that will give access to stereoisomers such as the corresponding ribose derived species and compounds such as isomeric d-amidoalkenes and more substituted alkenes are being elaborated and will be reported at a later date.

Acknowledgement

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11. Compound **27** ^{1}H NMR (400 MHz, $CDCl_3$) d 7.34-7.11, 15H, m, ArH; 4.98, 1H, d, J_{AB} 10.9 Hz, OC**H**HPh; 4.92, 1H, d, J_{AB} 11.1 Hz, OC**H**HPh; 4.83, 1H, d, J_{AB} 10.9 Hz, OCH**H**Ph; 4.70, 1H, d, J_{AB} 11.6 Hz, OC**H**HPh; 4.61, 1H, d, J_{AB} 11.6 Hz, OCH**H**Ph; 4.60, 1H, d, J_{AB} 11.1 Hz, OCH**H**Ph; 4.10, 2H, q, J 7.1 Hz, OC$\mathbf{H}_2$CH$_3$; 3.95, 1H, dd, $J_{1,2}$ 5.1, $J_{1,1'}$ 11.5 Hz, H1; 3.68-3.56, 3H, m, H2, H4, H5; 3.27, 1H, apparent t, J 9.0 Hz, H3; 3.20, 1H, apparent t, J 10.6 Hz, H1'; 2.73, 1H, dd, $J_{6,5}$ 3.4, $J_{6,6'}$ 15.2 Hz, H6; 2.35, 1H, dd, $J_{6',5}$ 8.7, $J_{6',6}$ 15.2 Hz, H6'; 1.21, 3H, t, J 7.1 Hz, CH$_2$C$\mathbf{H}_3$.

Compound **27** ^{1}H NMR (400 MHz, C_6D_6) d 7.40-7.04, 15H, m, ArH; 5.02, 1H, d, J_{AB} 11.3 Hz, OC**H**HPh; 4.97, 1H, d, J_{AB} 11.4 Hz, OC**H**HPh; 4.83, 1H, d, J_{AB} 11.3 Hz, OCH**H**Ph; 4.57, 1H, d, J_{AB} 11.4 Hz, OCH**H**Ph; 4.44, 1H, J_{AB} 11.9 Hz, OC**H**HPh; 4.36, 1H, d, J_{AB} 11.9 Hz, OCH**H**Ph; 4.01, 2H, q, *J* 7.0 Hz, C**H**$_2$CH$_3$; 3.96-3.88, 2H, m, H1, H5; 3.65, apparent t, *J* 8.7 Hz, H3; 3.61-3.54, 1H, m, H2; 3.34, 1H, apparent t, *J* 9.0 Hz, H4; 3.17, 1H, apparent t, *J* 10.7 Hz, H1'; 2.86, 1H, dd, $J_{6,5}$ 2.9, $J_{6,6'}$ 15.2 Hz, H6; 2.53, 1H, dd, $J_{6',5}$ 8.4, $J_{6',6}$ 15.1 Hz, H6'; 0.99, 3H, t, *J* 6.9 Hz, CH$_2$C**H**$_3$.

12. Compound **28** ^{1}H NMR (400 MHz, $CDCl_3$) d 7.24, 15H, m, ArH; 4.60-4.43, 6H, m, OCH$_2$Ph ´ 3; 4.25, 1H, ddd, $J_{5,6}$ 8.5, $J_{5,6'}$ 5.5, $J_{5,4}$ 3.6 Hz, H5; 4.08-4.00, 2H, m, OC**H**$_2$CH$_3$; 3.73-3.70, 2H, m, H1, 1'; 3.63, 1H, apparent t, *J* 5.3 Hz, H3; 3.44, 1H, dd, $J_{4,5}$ 3.6, $J_{4,3}$ 5.4 Hz, H4; 3.37, 1H, dd, $J_{2,3}$ 4.4, $J_{2,1}$ 9.1 Hz, H2; 2.70, 1H, dd, $J_{6,5}$ 8.4, $J_{6,6'}$ 15.9 Hz, H6; 2.56, 1H, dd, $J_{6',5}$ 5.5, $J_{6',6}$ 15.9 Hz, H6'; 1.66, 3H, t, *J* 7.2 Hz, CH$_2$C**H**$_3$.

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