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PAPER

Asymmetric aza-Michael addition under ultra-high pressure: short bias to polyhydroxylated piperidines†

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Two polyhydroxylated piperidines have been prepared in short sequences from diacetone *gluco*- and allofuranose. The key step is a piezo-aza-Michael addition of diphenylmethanamine to enoates bearing a sugar moiety in the γ-position. The combination of ultra-high pressure associated to the presence of readily available sugars chiral pool led to the expected chiral amines in good yields and excellent stereoselectivities.

Introduction

Chiral amines are present in numerous and important molecules with therapeutic applications.[1] Thus, significant efforts have been devoted to the development of transformations of inexpensive prochiral precursors into optically active amines. While the creation of a C–N bond is well-documented in the literature,[2] controlling the diastereoselectivity of the newly formed stereocentre still remains a challenge.

One of the supplier team described years ago the total synthesis of the polyhydroxylated piperidines **1**, **2** and **3** from commercial sugars (Fig. 1).[3] In this previous work, the stereocenter bearing the nitrogen atom was generated by an asymmetric catalytic hydrogenation of a β-ketoester, leading to the two possible β-hydroxyesters with a diastereomeric ratio (d.r.) up to 90% depending on the catalyst used. Then substitution of the activated hydroxyl group by an azide afforded the precursor of the desired amine. The azacycles **1**, **2** and **3** were obtained from diacetone D-allofuranose (**9**) or D-glucofuranose (**10**) in 14 steps in overall yields of 10, 13 and 6% respectively.

In the present investigation (Scheme 1), the azacycles **3** and **4** could be obtained from the same sugars through the amines **5** and **6** respectively. The *N*-bearing stereocenter could be directly introduced to the corresponding sugar-based enoate **7** and **8** *via* an aza-Michael reaction under ultra-high pressure (UHP)[4] which could shorten considerably the synthesis. However, the level of stereocontrol remains to be established in this case.

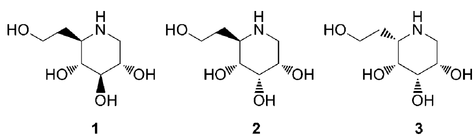
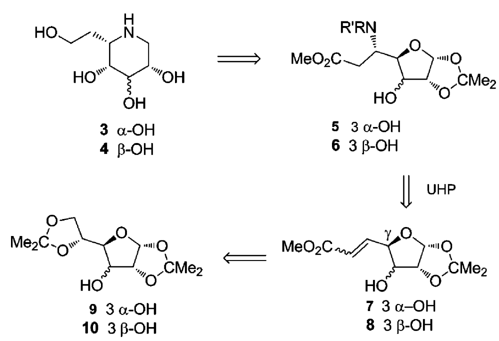


Fig. 1 Piperidines **1–3** prepared from commercial sugars.[3]



Scheme 1 Retrosynthetic analysis of piperidines **3** and **4**.

A very highly stereocontrolled conjugate addition of primary amines to crotonate bearing a chiral auxiliary at the ester group has been previously reported, producing the corresponding β-aminoesters in good chemical yield and excellent diastereomeric excess (d.e.) up to 99% thanks to the UHP activation.[5] In this context, we thought to study the UHP-induced stereocontrol of conjugate addition of amine from sugar based-enoate **7** and **8**, in which now the chiral element is set at the γ-position of the electron withdrawing group.

From a general point of view, the asymmetric aza-Michael addition is well-used in organic synthesis, as proven by the recent review of Krishna *et al.*[6] Stereoselectivity can be introduced *via* a chiral amine or lithium amide, a chiral catalyst, a chiral

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auxiliary or a chiral substrate. In the last case, it was reported that the chirality in the γ position of the enoate induced generally good *syn*-selectivities.[7] Enoates bearing sugars have been used as aza-Michael acceptors,[8,9] leading to the corresponding amines with good reported d.e. Notably, Dhavale *et al.*[8] studied well the reaction conditions of unsaturated ethyl enoate esters bearing a 3-benzylated glucose-derived sugar: when the reaction was run in the presence of lithium benzylamide in THF at −40 °C, the conjugate addition occurred in a 85% yield and a complete stereocontrol (d.e. 100%). Later, Sharma[9] applied the same conditions to the analogous 3-methoxy sugar and obtained as a major product the transamidated one. He proposed the efficient action of tetra-*n*-butylammonium fluoride (TBAF) which avoid the 1,2-addition in favor of the 1,4-one. The authors described an efficient method (around 75% of yield) with d.e. up to 90%. However, when we tested these conditions with a similar substrate (methyl ester instead of ethyl ester, and 3-OBn instead of 3-OMe), we obtained only 5% of selectivity for a yield of 35%. Unfortunately, changing the reaction time or solvent didn't enhance the results. We thus turned to a method based on the use of ultra-high pressure, which could circumvent these problems of substrate-dependency for the asymmetric aza-Michael addition.

Recently, alternative energies like microwave[10] and ultrasound[11] associated with the use of catalysts and/or solvent-free conditions have been developed, in agreement with the tendency and necessity of environmental friendly approach in organic chemistry. In this context, high-pressure techniques (0.1–2 GPa) have also been used in green organic synthesis with good results.[12] A great number of reactions that do not happen in standard conditions can be induced under these conditions.[13] It is a valuable and efficient tool, generally used for stimulating reluctant organic reactions like those that take place too slowly, require substantially elevated temperatures or are hindered by steric or electronic factors. As a result the application of high pressure favours, for example, reactions in which the molecularity decreases in the products (*e.g.* cycloadditions and condensations) and, in general, reactions characterized by a negative activation volume. Moreover, as a thermodynamical parameter, pressure modifies the physical and physicochemical properties of liquids considered as media for organic synthesis and most importantly affects solute-medium interactions associated with volume changes through two main pressure-sensitive interactions: electrostatic and solvophobic ones.

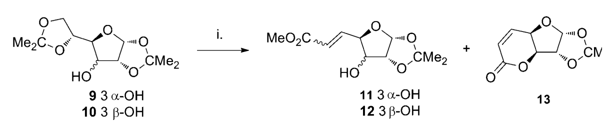
In our case, we assumed that the sugar substituent in γ-position of the α,β-unsaturated ester could induce an important diastereoselectivity in the piezo-aza-Michael reaction. Advantages are numerous: no need for the introduction of a chiral auxiliary meaning a gain of steps, energy and materials; waste reduction; use of encumbered amines to avoid transamidation side-reaction; no tedious purification needed as one only product is formed.

We described in this paper the preparation of several unsaturated methyl esters derived from sugars, then their introduction in asymmetric piezo-aza-Michael additions. Two of the resulting chiral amines have been shortly transformed into their corresponding polyhydroxylated piperidines, proving by the way the absolute configuration of the newly created stereocenter.

Results and discussion

The aza-Michael addition under high-pressure conditions has been tested recently. It has been demonstrated that weakly reactive amides, ureas and Michael acceptors could react by combination between Brønsted acid in pressures of 0.6 GPa with good results.[14] The combined effects of high pressures and alcohols in Aza-Michael addition reactions allow the synthesis of dense adducts bearing a nitrogen-tetrasubstituted centre adjacent to a quaternary carbon centre (QCC).[15] On the contrary, to our knowledge, no reports on the high-pressure promoted asymmetric aza-Michael addition appeared recently.

Optimized reaction conditions were established for the synthesis of α,β-systems based in sugars with configuration *cis* or *trans*. With the aim to study the influence of the enoate stereochemistry in the Michael addition under high pressure, we decided to prepare the *cis* and *trans*-isomers of each acceptor. One of the easier ways of α,β-unsaturated esters preparation is the well-known Wittig olefination. Concerning carbohydrate-derived aldehydes with stabilized ylides, the reaction has been studied and it is possible to reach preferentially the *E* or the *Z* isomer by changing the reaction conditions.[16] In particular, the shortest way giving the acceptor bearing a xylofuranose moiety from the commercial diacetone glucose has been described by a sequential hydrolysis-oxydation-Wittig olefination (SHOWO):[16d,f] the two products of the reaction were the expected *trans* ester and the lactone proceeding from the *cis* derivative. We introduced diacetone allose (**9**) or diacetone glucose (**10**) in a similar sequence, consisting in the hydrolysis in aqueous acetic acid, the periodic oxidation followed by the olefination in acetonitrile at reflux during 2 h. In the case of the *gluco*-derivative (OH-2 and OH-3 in *anti*), we obtained the two expected derivatives *trans* **12** and the lactone **13** (30% and 12% respectively in 3 steps). It is possible to obtain the *cis* isomer by making the Wittig olefination in acetonitrile under reflux during 30 min: we obtained in this case a *cis*/*trans* mixture of 29/71. In the case of the epimer in C-3 **9**, the two *cis*/*trans* isomers **11** (60/40) were formed with the good yield of 73% for the overall sequence (Scheme 2).



i. a) AcOH 75%, 24h; b) $NaIO_4$, 0 °C, 2h; c) $(Ph)_3PCHCOOCH_3$, CH_3CN, reflux, 2h.

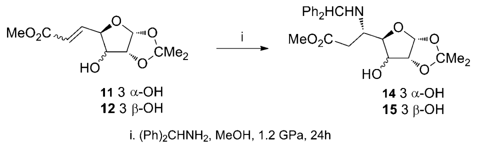
Scheme 2 Synthesis of 3-OH sugar-based α,β-systems.

We introduced first the *cis*/*trans* mixture of the derivatives **11** or **12** in the piezo aza-Michael reaction in the presence of 1.2 equivalents of diphenylmethanamine, 3.0 equivalents of methanol in tetrahydrofuran, during 24 h at room temperature and over 1.2 GPa (Table 1; Scheme 3). In both cases, the reaction occurred and a major product was formed, whose NMR spectral data were in accordance with the ones of the aminated **14** (63%) or **15** (73%) respectively, and their epimers in C-5 as minor product, with the d.r. of 80/20 for **14** and 78/22 for **15**. We assumed that the major diastereoisomer was in the configuration 5*S*,[17] based in the works of Sharma[9] and Dhavale[8] with the same substrate. We later proved this configuration. Satisfyingly, applying the same conditions to the *cis* isomer **11** led to the single

Table 1

		RT	40 °C
Substrate	Product	d.r. (yield %)	d.r. (yield %)
11*cis*/*trans*	**14**/(5-*epi*)-**14**	80/20 (63)	—
11*cis*	**14**/(5-*epi*)-**14**	95/5 (nd)	95/5 (82)
12*cis*/*trans*	**15**/(5-*epi*)-**15**	78/22 (73)	
12*cis*	**15**/(5-*epi*)-**15**	—	95/5 (92)

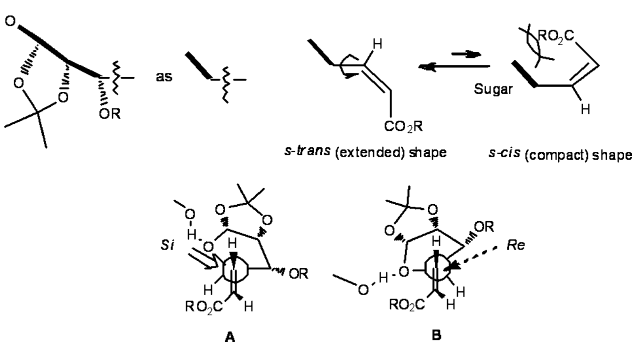
nd: yield not determined



Scheme 3 Piezo-Aza-Michael with derivatives **11** and **12**.

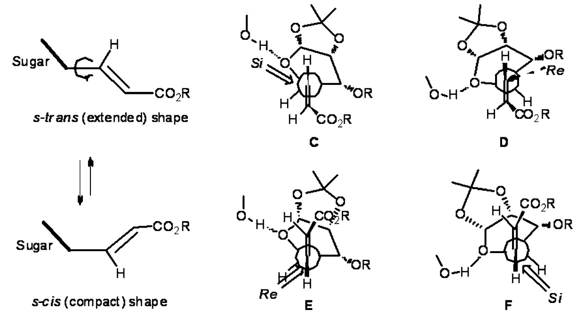
isomer **14** (from NMR spectral data; d.r. > 95/5). By heating at 40 °C, the reactions were complete after 24 h for **11***cis* and **12***cis*, with the excellent d.r. of 95/5 and excellent yields after purification.

The high stereocontrol observed with the *cis* isomer could be explained with a Felkin–Ahn model of the transition state as described by Dhavale.[8] It has been demonstrated that, under UHP, the ester oxygen atoms of the chiral crotonate are H-bonded to the methanol molecules and that the amine addition occurs in an *anti*-fashion relative to the electron withdrawing group, through an extended *s-trans* conformation.[5c] It seems likely that the sugar-based enoates also are H-bonded with methanol under pressure, at the both carbomethoxyl group and sugar part. The *cis* enoate isomers should exist mostly in the form of their *s-trans* (extended) conformations due to steric hindrance (Scheme 4). Thus, in the Felkin-Ahn models exemplified for compound **11***cis* in its *s-trans* conformations (**A** and **B**), it appears that the more favourable transition structure will resemble **A**: a *Si* approach of the amine, in which steric interactions would be minimized, would lead almost exclusively (d.r. 95/5) to the diastereomer having the 5*S* configuration (*talo* configuration **14**).



Scheme 4 Conformations for the Piezo-Aza-Michael exemplified with ***cis*** enoates derivatives **11**.

In comparison, the *trans* sugar-based enoates could present both *s-trans* (extended, **C** and **D**) and *s-cis* (compact, **E** and **F**) conformations (Scheme 5). The amine attack appears more favourable on conformations **C**, as precedently, and also on

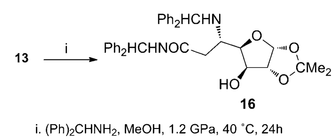


Scheme 5 Conformations for the Piezo-Aza-Michael exemplified with ***trans*** enoates derivatives **11**.

conformations **E** and **F**, by its approach near the less hindered side, leading thus to the corresponding Michael adducts with lower d.r.

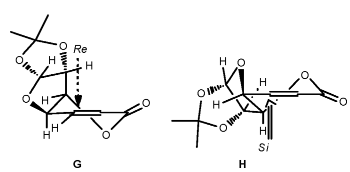
In these models, little or no influence of the 3-OR group can be expected, in contrast to related Michael addition conducted at atmospheric pressure,[8,9] and in concordance with our experimental results.

The introduction of the lactone **13** under the same conditions led to a unique product (d.r. > 95/5) and some initial material remaining (<10%). NMR studies of the product clearly showed the presence of two benzhydrylamino groups, and no more signal of the methyl ester. These facts were in concordance with the structure of derivative **16**, belonging from the opening of the lactone into the amide, and the expected aza-Michael addition (Scheme 6). The yield after purification by flash chromatography was 58%, which was the maximum possible with the introduction of the 1.2 equiv. of amine. Using 2 equiv. of amine allowed to obtain the amine **16** in a yield of 90% and a similar d.r.



Scheme 6 Piezo-aza-Michael with lactone **13**.

Whatever the order of events in this tandem "aza-Michael addition/lactone opening" or *vice versa*, examination of the amine *pseudo*-axial attack onto the two α,β-unsaturated lactone **13** twisted conformations **G** and **H** provide a convergent explanation of the preferred *Si* attack leading preferentially to the 5*S* isomers (Scheme 7).



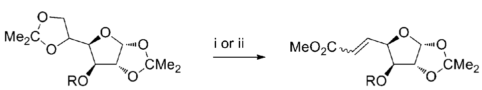
Scheme 7 Preferred axial attacks for the Piezo-Aza-Michael on the two conformations of lactone **13**.

The diacetone allofuranose (**9**) and glucofuranose (**10**) are also the precursors for the ethylenic esters protected in C-3 with a benzyloxy or a *tert*-butyldimethylsilyloxy group **19–22**. It is known that the nature of solvent in the Wittig reaction influenced the *cis*/*trans* ratio of the final product: protic polar solvent

Table 2

Solvent	T/°C	Time (h)	**19** *cis/trans*	Yield % (from **17**)
MeOH	−10	24	5.0/1	47
MeOH	0	1	9.0/1	55
MeOH	25	24	6.5/1	52
MeOH	80	24	2.7/1	59
CH_3CN	50	3	1.5/1	46
CH_3CN	80	2	2.2/1	53
Toluene	25	2	0.6/1	73
Toluene	50	3	0.8/1	69
Toluene	110	3	1.2/1	48

gives preferentially the *cis* derivative. Anyway, the reaction stereospecificity was sometimes to be very substrate dependant. We tested first the reaction starting from the diacetone glucose protected at position 3 by a benzyl group **17** (Scheme 8). A SHOWO using the method of Sartillo–Piscil[16d,f] or the previously described one (AcOH–H_2O 75/25 then $NaIO_4$ then ylide) led to the xylose derivative **19** *cis* or *trans* (Table 2).



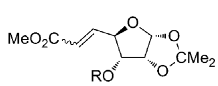
17 R = Bn
18 R = TBS

19 R = Bn
20 R = TBS

i. HIO_4, EtOAc, 3h then $(Ph)_3PCHCO_2Me$, MeOH, 0 °C, 1h;
ii. a) AcOH 75% in water, 24h; b) $NaIO_4$, 2h; c) $(Ph)_3PCHCO_2Me$, cf table 2.

Scheme 8 Synthesis of 3-*O*-protected xylose based α,β-systems.

As expected, the use of methanol was in favour of the *cis* isomer. Nevertheless, the best ratio was obtained at 0 °C (*cis/trans* : 9/1), and a decrease of the temperature at −10 °C following the protocol of Valverde[16b] didn't ameliorate the ratio. In acetonitrile or toluene, the ratio of *cis* product increased with the temperature, but the best one remained very modest (in refluxing acetonitrile: *cis/trans* 2.2/1). The use of toluene at room temperature was preferred for obtain the *trans* isomer (*cis/trans* 0.6/1). The *cis/trans* isomers were easily separated by flash chromatography. Then, we prepared the acceptors **20–22** (Fig. 2) with similar methods, respectively from **18**, (3-*epi*)-**17** and (3-*epi*)-**18** (Table 3). According to the solvent and reaction temperature, we reached preferentially one isomer or the other.



21 R = Bn
22 R = TBS

Fig. 2 3-α-OH enoates **21** and **22**.

In order to obtain a complete aza-Michael addition at 1.2 GPa, we analyzed the optimized time and temperature required. In our first experiments the reactions were kept for

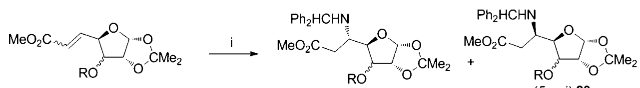
Table 3

		MeOH, 0 °C, 1 h	Toluene, 25 °C, 2 h
Substrate	Product	*cis/trans*	*cis/trans*
18	**20**	4.9/1	0.6/1
(3-*epi*)-**17**	**21**	3.0/1	0.7/1
(3-*epi*)-**18**	**22**	4.9/1	0.6/1

Table 4

Substrate (%)	MeOH	T °C	Products	d.r.	Yield
19*trans*	3.0 equiv.	25	**23**/(5-*epi*)-**23**	65/35	90
19*cis*	3.0 equiv.	25	**23**/(5-*epi*)-**23**	87/13	80
19*cis*	—	40	**23**/(5-*epi*)-**23**	70/30	65
19*cis*	3.0 equiv.	40	**23**/(5-*epi*)-**23**	80/20	>99
20*cis/trans*	3.0 equiv.	40	**24**/(5-*epi*)-**24**	71/29	95
20*cis*	3.0 equiv.	25	**24**/(5-*epi*)-**24**	93/7	92
21*cis*	3.0 equiv.	40	**25**/(5-*epi*)-**25**	55/45	>99
22*cis*	3.0 equiv.	25	**26**/(5-*epi*)-**26**	79/21	58

60 h under 1.2 GPa at room temperature in the presence of diphenylmethanamine (1.2 equiv.) and methanol (3.0 equiv.) in THF. We observed a complete conversion with loss of the *tert*-butyldimethylsilyl moiety when this one was used as the *O*-protecting group (substrates **20** or **22**). After 18 h at room temperature the reaction was not complete as around 15% of starting material remained. The best results were generally obtained at 40 °C for 24 h. In this case, we observed the complete addition reaction and no undesired transformations.[17] Best results are described in the Table 4 (Scheme 9).



19 3 β-OH; R = Bn
20 3 β-OH; R = TBS
21 3 α-OH; R = Bn
22 3 α-OH; R = TBS

23 3 β-OH; R = Bn
24 3 β-OH; R = TBS
25 3 α-OH; R = Bn
26 3 α-OH; R = TBS

(5-epi)-**23**
(5-epi)-**24**
(5-epi)-**25**
(5-epi)-**26**

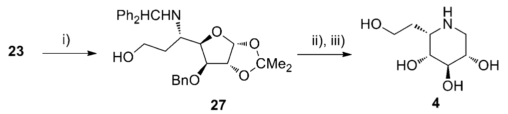
i. $(Ph)_2CHNH_2$, 1.2 GPa, 24h

Scheme 9 Piezo-aza-Michael with substrates **19–22**.

The benzylated derivatives **19***trans* and **19***cis* have been submitted separately to the piezo aza-Michael addition. At room temperature, reactions were not complete but the same product was obtained as the major stereoisomer (**23**/(5-*epi*)-**23**: 65/35 and 87/13, respectively).[18] The best excess was observed from the *cis* derivative, as previously (Tables 1 and 4). To establish the importance of the 3.0 equivalents of methanol,[5b] we ran the reaction in absence of this solvent: the reaction was then complete after 24 h at 40 °C under 1.2 GPa, but only 65% of the product was isolated with a **23**/(5-*epi*)-**23** ratio lower than the one obtained in the presence of methanol (70/30). The other product isolated (35%) was the **19***trans* isomer, whose formation could be explained by a reaction of aza-Michael followed by a retro aza-Michael, giving the more stable isomer. The methanol is then proved to be very important for the reaction: the reaction was complete at 40 °C with 3.0 equivalents of methanol, with a d.r. of 80/20.

The 3-epimer **21***cis* and the silylated derivatives **20***cis* and **22***cis* have been introduced in reaction: the corresponding amines were obtained in a range of d.e. from 10 to 86%.

Finally, two of these amines, namely **23** and **14**, have been transformed into the corresponding piperidines. The reduction of **23** by lithium aluminium tetrahydride led to the primary alcohol **27** in a yield of 64% (Scheme 10). A selective hydrolysis of the cyclic ketal followed by the amine deprotection led to the benzylated azacycle intermediate, which has been directely hydrogenolysed in acidic media. A purification through amberlyst (OH^-) afforded the expected polyhydroxylated piperidine **4** (70%

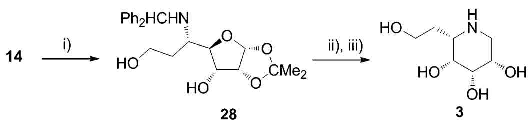


i) $LiAlH_4$, 0°C, 2h, 64%: ii) TFA, H_2O, 1h30, 40°C, 99%; iii) a) H_2, 10% PtO_2, 6 bars, MeOH; b) H_2, 10% Pd/C, HCl, 6 bars; c) Amberlyst; 70%.

Scheme 10 Synthesis of the piperidine **4**.

in three steps). The physical data of the final product were in accordance with the literature ones.[19]

We obtained the piperidine **3** in a very short way from **14** (Scheme 11): the reduction of the ester function gave **28** with a satisfying yield (57%). A two-step sequence, namely the acidic hydrolysis of the cyclic ketal followed by cyclising hydrogenolysis by treatment with PtO_2 under hydrogen atmosphere at 6 bars, ending with a purification over amberlyst (OH^-) gave **3** (65% in 2 steps).



i) $LiAlH_4$, 0°C, 2h, 57%; ii) TFA, H_2O, 1h30, 40°C, 99%; iii) a) H_2, 10% PtO_2, 6 bars, MeOH; b) Amberlyst; 65%.

Scheme 11 Synthesis of the piperidine **3**.

We have prepared the piperidines **3** and **4** from the commercial sugars with short sequences, with very good d.e. and global yields of 18% and 22% respectively. We showed that the aza-Michael addition under high pressure could induce very good diastereoselectivities for their formation. At last, a comparison of the physical data of the obtained piperidines with the ones of the literature allowed us to confirm the configuration of the major amine as 5*S* as proposed on examination of Michael adducts NMR data.

Conclusion

The use of ultra high pressure applied to aza-Michael additions is an efficient method for the asymmetric formation of a new C–N bond. With enoates bearing chiral encumbered γ-substituents such as sugars, d.r. are up to 95/5 whatever the 3-OR substituent in the pyranose derivative. This step is a very good alternative way to larger syntheses, as has been shown with the application of the synthesis of two polyhydroxylated piperidines in very short ways from commercial cheap sugars.

Experimental

Solvents were distilled according to *Purification of Laboratory Chemicals*, 4th Ed., W. L. F. Aramarego and D. D. Perrin, Butterwoth Heinemann, 1996. Flash chromatography was performed on silica gel chromagel 60 ACC 35–70 μm. Analytical TLC was performed using aluminium-backed silica gel Merck 60 F_{254} and visualised by UV radiation (254 nm) and/or a solution of phosphomolybdic acid in MeOH and heating and/or an ethanolic solution of H_2SO_4 and heating. Optical rotations were measured at 25 °C on a Perkin–Elmer 241 polarimeter (1 dm cell) using a sodium lamp as the light source (589 nm). NMR spectra were recorded on a Bruker AC 200, Avance 300 or ARX 400 apparatus with chemical shift values (δ) in ppm downfield from tetramethylsilane. Mass spectra were recorded on a XEVO Q-TOF Waters apparatus. All products gave consistent physicochemical data.

Typical procedure for the piezo aza-Michael: To a solution of enoate (0.25 mmol) in THF (0.5 mL) was added diphenylmethanamine (0.25 mmol, 46 mg, 1.0 equiv.) and methanol (23 μL; 3.0 equiv.). The solution was introduced with a syringe in a teflon or a pyrex glass cell. The cell was immersed into hexane which was contained in the high pressure apparatus. Then the mobile piston was inserted and the whole assembly was placed between the pistons of a hydraulic press. The reaction was performed at 1.2 GPa and 40 °C for 24 h. After decompression the solvent was removed and the crude was analyzed by NMR spectroscopy. The crude was analyzed by NMR spectroscopy to check the diastereomeric ratio and was then quickly purified by silica gel chromatography using mixtures of cyclohexane/AcOEt and 5% of triethylamine to afford the expected product. The amines were not stable enough to obtain satisfactory elemental analysis.

Methyl 5-(*N*-diphenylmethylamino)-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*talo*-heptofuranoronate (14)

NMR ^{1}H: δ_H (200 MHz, $CDCl_3$) 7.41–7.24 (10 H, m, Ar), 5.75 (1 H, d, *J* 3.8, 1-H), 5.07 (1 H, s, C*H*Ph_2), 4.57 (1 H, t, *J* 3.9, 2-H), 4.23 (1 H, dd, *J* 5.0, *J* 8.6, 4-H), 3.91 (1 H, dd, *J* 3.9, *J* 8.6, 3-H), 3.64 (3 H, s, OMe), 3.24 (1 H, m, 5-H), 2.67 (2 H, m, 6-H and 6′-H), 2.34 (2H, bs, OH+NH), 1.56 (3 H, s, Me), 1.38 (3 H, s, Me). ^{13}C: δ_C (100 MHz, $CDCl_3$) 172.6 (C=O), 144.7 and 144.4 (Ar), 128.9–127.1 (Ar), 112.8 (*C*Me_2), 103.9 (1-C), 82.1 (4-C), 79.2 (2-C), 72.0 (3-C), 64.3 (*C*HPh_2), 51.9 and 51.7 (5-C and O*C*H_3), 36.0 (6-C), 26.8 (Me), 26.7 (Me); HRMS: *m/z* $[M+H]^+$ calctd for $C_{24}H_{30}NO_6^+$: 428.199; found: 428.2070.

Methyl 5-(*N*-diphenylmethylamino)-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*ido*-heptofuranoronate (15)

NMR ^{1}H: δ_H (300 MHz, $CDCl_3$) 7.39–7.19 (10 H, m, Ar), 5.92 (1H, d, *J* 3.6, 1-H), 5.05 (1 H, s, C*H*Ph_2), 4.48 (1H, t, *J* 3.6, 2-H), 4.22 (1H, d, *J* 2.6, 3-H), 4.12 (1H, t, *J* 2.6, 4-H), 3.65 (3H, s, OMe), 3.54 (1H, m, 5-H), 2.66 (2 H, m, 6-H and 6′-H)), 2.12 (2H, bs, OH+NH), 1.33 (3 H, s, Me), 1.30 (3 H, s, Me). ^{13}C: δ_C (100 MHz, $CDCl_3$) 172.2 (C=O), 142.8 and 142.7 (Ar), 128.9–127.3 (Ar), 111.6 (*C*Me_2), 104.9 (1-C), 85.3 (2-C), 81.4 (4-C), 75.9 (3-C), 64.0 (*C*HPh_2), 52.4 and 51.8 (5-C and OMe), 36.8 (6-C), 26.9 (Me), 26.3 (Me); HRMS: *m/z* $[M+H]^+$ calctd for $C_{24}H_{30}NO_6^+$: 428.199; found: 428.2096.

Methyl 3-*O*-benzyl-5-(*N*-diphenylmethylamino)-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*ido*-heptofuranoronate (23)

NMR ^{1}H: δ_H (200 MHz, $CDCl_3$) 7.35–7.20 (15 H, m, Ar), 5.96 (1 H, d, *J* 3.9, 1-H), 5.14 (1 H, s, C*H*Ph_2), 4.65 (2 H, m, 2-H, OC*H*Ph), 4.39 (1 H, d, *J* 12.0, OC*H*Ph), 4.28 (1 H, dd, *J* 3.2, *J* 8.4, 4-H), 3.95 (1 H, d, *J* 3.2, 3-H), 3.58 (3 H, s, OMe), 3.47 (1 H, m, 5-H), 2.50 (1 H, dd, *J* 4.8, *J* 15.0, 6-H), 2.28 (1 H, dd, *J* 6.2, *J* 15.0, 6′-H), 1.49 (3 H, s, Me), 1.33 (3 H, s, Me); NMR ^{13}C: δ_C (75 MHz, $CDCl_3$) 172.5 (C=O), 144.4 and 144.0 (Ar), 128.5–126.6

(Ar), 111.5 (*C*Me$_2$), 104.9 (1-C), 82.6, 81.9 and 81.7 (2-C, 3-C and 4-C), 71.3 (*C*H$_2$Ph), 64.6 (5-C), 51.8 and 51.5 (OMe and *C*HPh$_2$), 36.8 (6-C), 26.8 (Me), 26.3 (Me); HRMS: *m*/*z* [M+H]$^+$ calctd for $C_{31}H_{36}NO_6^+$: 518.246; found: 518.2552.

Methyl 3-*O*-*tert*butyldimethylsilyl-5-(*N*-diphenylmethylamino)-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*ido*-heptofuranoronate (24)

NMR ^{1}H: δ_H (300 MHz, $CDCl_3$) 7.11-7.36 (10 H, m, Ar), 5.86 (1 H, d, *J* 3.6, 1-H), 5.17 (1 H, s, C*H*Ph$_2$), 4.29 (1 H, dd, *J* 3.6, 2-H), 4.21 (1 H, dd, *J* 2.7, *J* 9.0, 4-H), 4.13 (1 H, dd, *J* 2.7, 3-H), 3.58 (3 H, s, OMe), 3.30 (1 H, m, 5-H), 2.50 (1 H, dd, *J* 4.5, *J* 14.7, 6-H), 2.22 (1 H, dd, *J* 12.5, *J* 20.7, 6′-H), 1.44 (3 H, s, Me), 1.28 (3 H, s, Me), 0.69 (9 H, s, *t*BuSi), −0.06 (3 H, s, SiMe), – 0.07 (3 H, s, SiMe); NMR ^{13}C: δ_C (75 MHz, $CDCl_3$) 172.1 (C=O), 144.2 and 143.8 (Ar), 128.3–126.3 (Ar), 111.5 (*C*Me$_2$), 104.7 (1-C), 85.2 and 83.4 (2-C and 4-C), 75.8 (3-C), 64.5 (5-C), 51.4 and 50.9 (OMe and *C*HPh$_2$), 36.6 (6-C), 26.8 (Me), 26.3 (Me), 25.5 (C*Me$_3$*), −4.2 (SiMe), −5.3 (SiMe).

Methyl 3-*O*-benzyl-5-(*N*-diphenylmethylamino)-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*talo*-heptofuranoronate (25)

NMR ^{1}H: δ_H (300 MHz, $CDCl_3$) 7.27–7.05 (15H, m, Ar), 5.89 (1H, d, *J* 3.9, 1-H), 5.05 (1H, s, C*H*Ph$_2$), 4;51 (2H, C*H$_2$*Ph), 4.28 (1H, t, *J* 4.2, 3-H), 4.20 (1H, dd, *J* 3.0, *J* 8.1, 2-H), 3;84 (1H, dd, *J* 3.3, *J* 8.7, 4-H), 3.47 (3H, s, CO$_2$C*H$_3$*); 3.40 (1H, m, 5-H), 2.40 (1H, dd, *J* 4.8, *J* 15.0, 6-H), 2.23 (1H, dd, *J* 6.0, *J* 15.0, 6-H) 1.39 (3H, s), 1.21 (3H, s). NMR ^{13}C: δ_C (75 MHz, $CDCl_3$) 172.3 (C=O), 144.2 (C Ar), 143.0 (2C Ar), 128.7 to 127.0 (15CAr), 111.4 (*C*Me$_2$), 104.9 (1-C), 81.6 (2-C), 82.4 (4-C), 71.2 (3-C), 64.5 (*C*HPh$_2$), 51.7 (OMe), 51.2 (5-C), 36.7 (6-C), 26.8 (Me), 26.7 (Me); HRMS: *m*/*z* [M+H]$^+$ calctd for $C_{31}H_{36}NO_6^+$: 518.246; found: 518.2562.

Methyl 3-*O*-*tert*butyldimethylsilyl-5-(*N*-diphenylmethylamino)-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*talo*-heptofuranoronate (26)

NMR ^{1}H: δ_H (300 MHz, $CDCl_3$) 7.12–7.32 (10H, m, Ar), 5.81 (1H, d, *J* 3.9, 1-H), 5.11 (1H, s, C*H*Ph$_2$), 4.23 (1H, dd, *J* 3.6, 2-H), 4.13 (1H, dd, *J* 2.4, *J* 4.8, 4-H), 4.07 (1H, dd, *J* 2.7, 3-H), 3.56 (3H, s, CO$_2$C*H$_3$*); 3.27 (1H, m, 5-H), 2.44 (1H, dd, *J* 3.6, *J* 14.7, 6-H), 2.17 (1H, dd, *J* 6.6, *J* 14.7, 6-H) 1.45 (3H, s), 1.25 (3H, s), 0.85 (s, 9H, C(C*H$_3$*)$_3$), 0.21 (3H, s, SiC*H$_3$*), 0.10 (s, 3H SiC*H$_3$*). NMR ^{13}C: δ_C (75 MHz, $CDCl_3$) 173.0 (C=O), 144.1 and 142.7 (Ar), 129.2–126.3 (Ar), 121.9 (*C*Me$_2$), 109.3 (1-C), 90.0 (2-C), 87.5 (4-C), 76.3 (3-C), 62.3 (*C*HPh$_2$), 51.9 (OMe), 47.4 (5-C), 35.6 (6-C), 26.8 (Me), 26.5 (Me), 25.7 (C*Me$_3$*), −4.9 (SiMe), −5.1 (SiMe).

3-*O*-Benzyl-5-(*N*-diphenylmethylamino)-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*ido*-hepto-1,4-furanose (27)

To a solution of **23** (200 mg, 0.4 mmol) in dry THF (2 mL) at 0 °C under argon, was added $LiAlH_4$ (16 mg, 0.4 mmol, 1.1 equiv.). After stirring 2 h, water was added (5 mL) and the reaction mixture was extracted with AcOEt (4 × 3 mL). The organic layer was washed with brine (3 mL), dried, filtered and concentrated under *vacuum* for give 176 mg of yellow oil. A purification by flash chromatography (AcOEt/cyclohexane: 1/5 then 1/1) gave pure **27** (124 mg); yield 64%; $[\alpha]_D^{25}$ −80 (*c* 0.02, CH_2Cl_2); NMR ^{1}H: δ_H (200 MHz, $CDCl_3$) 7.31–7.22 (15 H, m, Ar), 7.07 (1 H, s, NH), 5.99 (1 H, d, *J* 3.9, 1-H), 5.38 (1 H, s, C*H*Ph$_2$), 4.67 (1 H, m, OCH), 4.61 (1 H, m, 2-H), 4.31 (1 H, d, *J* 11.9, OCH'), 4.19 (1 H, dd, *J* 2.8, *J* 9.1, 4-H), 3.81 (1 H, d, *J* 2.9, 3-H), 3.76 (1 H, m, 7-H), 3.63 (1 H, m, 7′-H), 3.33 (1 H, m, 5-H), 3.25 (1 H, s, OH), 1.56 (1 H, m, 6-H), 1.51 (3 H, s, Me), 1.44 (1 H, m, 6′-H), 1.34 (3 H, s, Me); NMR ^{13}C: δ_C(100 MHz, $CDCl_3$) 136.2–135.4 (Ar), 129.4–126.7 (Ar), 112.9 (*C*Me$_2$), 105.3 (1-C), 80.7 and 80.3 (2-C and 4-C), 71.3 (*C*H$_2$Ph), 68.0 (5-C), 65.1 (5-C), 57.3 (7-C), 57.3 (*C*HPh$_2$), 28.5 (6-C), 26.4 (Me), 26.2 (Me); HRMS: *m*/*z* [M+H]$^+$ calctd for $C_{30}H_{36}NO_5^+$: 490.252; found: 490.2587.

1,5,6-Trideoxy-1,5-imino-L-*ido*-heptitol (4)

The derivative **27** (100 mg) was stirred in a mixture TFA/H_2O : 3/2 (1.5 mL) at 40 °C during 1.5 h. After concentration under reduced pressure, the overall was dissolved in MeOH (4.5 mL) and PtO_2 (10%) was added. A vigorous stirring under hydrogen atmosphere at 600 kPa during 12 h, followed by a filtration over celite and an evaporation of the solvent under reduced pressure gave the intermediate benzylated piperidine. The later was retaken in EtOH (3 mL) and 6 drops of aqueous HCl (37%) and catalytic Pd/C were added. The overall was stirred under hydrogen atmosphere at 600 kPa during 48 h. After filtration over celite and concentration, a purification over amberlyst (OH^-) gave the pure **4** (24 mg); yield 70%; $[\alpha]_D^{25}$ −10.1 (*c* 1.8, MeOH), lit.[19] $[\alpha]_D$ −13.8 (*c* 0.8, H_2O).

5-(*N*-diphenylmethylamino)-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-*talo*-hepto-1,4-furanose (28)

The same procedure for obtaining **27** has been applied to **14**. After purification by flash chromatography (AcOEt/cyclohexane: 1/2 then AcOEt) the product **28** (111 mg) was obtained; yield 57%; $[\alpha]_D^{25}$ −5.3 (*c* 1.3, DCM); NMR ^{1}H: δ_H (200 MHz, $CDCl_3$) 7.42–7.22 (10 H, m, Ar), 5.76 (1 H, s, 1-H), 5.16 (1 H, s, C*H*Ph$_2$), 4.54 (1 H, s, 2-H), 3.98 (2 H, m, 3-H and 4-H), 3.73 (2 H, m, 7-H and 7′-H), 3.18 (1 H, s, OH), 2.98 (1 H, m, 5-H), 1.89 (1 H, m, 6-H), 1.78 (1 H, m, 6′-H), 1.58 (3 H, s, Me), 1.37 (3 H, s, Me); NMR ^{13}C: δ_C(75 MHz, $CDCl_3$) 143.5 and 143.0 (Ar), 128.8–127.2 (Ar), 112.7 (*C*Me$_2$), 103.5 (1-C), 81.3 and 78.8 (2-C and 4-C), 72.5 (3-C), 63.8 (5-C), 60.7 (7-C), 54.5 (*C*HPh$_2$), 31.1 (6-C), 26.6 (Me), 26.5 (Me); HRMS: *m*/*z* [M+H]$^+$ calctd for $C_{23}H_{30}NO_5^+$: 400.205; found: 400.2128.

1,5,6-Trideoxy-1,5-imino-L-*talo*-heptitol (3)

The derivative **28** (100 mg) was stirred in a mixture TFA/H_2O: 3/2 (1.5 mL) at 40 °C during 1.5 h. After concentration under reduced pressure, the overall was retaken with MeOH (4.5 mL) and PtO_2 (10%) was added. A vigorous stirring under hydrogen atmosphere at 600 kPa during 12 h, followed by a filtration over celite and an evaporation of the solvent under reduced pressure gave a crude (150 mg) whose purification over amberlyst (OH^-) gave the pure **3** (29 mg); yield 67%; $[\alpha]_D^{25}$ +23 (*c* 0.8, MeOH), lit.[3b] $[\alpha]_D$ +24 (*c* 0.6, MeOH).

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