Tetrahedron 67 (2011) 2617–2622

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Highly diastereoselective indium-mediated synthesis of β-lactam carbohydrates from imines

Raquel G. Soengas *, Yuri Segade, Carlos Jiménez, Jaime Rodríguez

Departamento de Química Fundamental, Facultad de Ciencias, Universidad de A Coruña, 15071 A Coruña, Spain

ARTICLE INFO

Article history:
Received 11 December 2010
Received in revised form 28 January 2011
Accepted 1 February 2011
Available online 1 March 2011

In memoriam of Professor Jose M. Concellón

Keywords:
β-Lactams
Indium
Reformatsky reaction
Azetidines

ABSTRACT

A simple and very effective approach to versatile carbohydrate β-lactam synthons of predictable absolute configuration has been developed. The procedure, which is based on the indium-mediated reaction of imines and bromoesters, was applied to the enantioselective synthesis of 3-monosubstituted and 3-disubstituted β-lactams from readily available carbohydrates. The opening of the β-lactamic ring gave rise to the corresponding sugar-derived β-amino acids. Transformation of the β-lactams into the corresponding azetidines was also achieved.

1. Introduction

β-Lactams are a very important class of compounds because of their well-known biological activity.[1] Since the advent of penicillin, the β-lactam antibiotics have been the subject of much discussion and investigation within both the scientific and public sectors. β-Lactam antibiotics have occupied a central role in the fight against pathogenic bacteria and the subsequent rise in the quality of life for the world population as a whole.[2] Additionally, these compounds have been very useful as key intermediates in organic synthesis[3] and also provide ideal building blocks[4] for the construction of many nitrogen-containing organic molecules with fundamental biological activities.[5] Since β-lactams may be regarded as cyclized forms of β-amino acids, the most obvious application is the synthesis of these interesting derivatives.[6] The interest in these compounds lies in the high propensity of their oligomers to fold into a range of secondary structures, such as α-helices, β-turns and β-sheets, which have proved to be resistant to peptidase degradation.[7] Moreover, the conformational stability of these systems facilitates interactions with receptors and enzymes.

Among the plethora of amino acids, those linked to a carbohydrate moiety are of particular interest. The structural diversity found in sugars—together with their biological role in molecular recognition processes—justifies the continued chemical and biological interest of carbohydrates.[8] In the search for carbohydrate mimetics, particular attention has been paid to the design and development of hybrid molecules, including sugar amino acids (SAA). These compounds represent a class of carbohydrate derivatives bearing an amino and a carboxylic acid functionality and they can be classified according to the position of the amino acid moiety on the cyclic polyol.[9] These compounds are present in the post-translational modification of proteins where the attachment of carbohydrates to the amino acids constitutes one of the most important ways to modify the structure and activity of the protein.[10] In addition, the presence of several stereogenic centres on these rings can be exploited to create chemical diversity and the protection or deprotection of hydroxyl substituents opens up opportunities to access hydrophobic or hydrophilic peptidomimetics.

Although numerous synthetic methods have been developed for the formation of the β-lactam ring, including [2+2]-cycloadditions, cyclization reactions, carbene insertion reactions and rearrangement of heterocyclic compounds,[11] the application of these procedures to the preparation of β-lactams linked to a carbohydrate, which are precursors of sugar amino acids and aminosugars, is very limited in the literature.[12]

As part of our continued interest in the synthetic usefulness of indium in carbohydrate chemistry,[13] we decided to investigate the scope and limitations of the indium-mediated lactamization of sugar-derived imines and the application of this approach to the preparation of sugar β-amino acids.

* Corresponding author. E-mail address: rsoengas@udc.es (R.G. Soengas).

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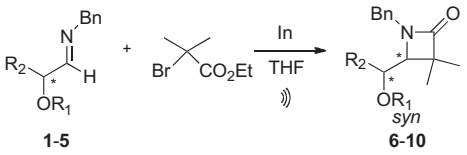
doi:10.1016/j.tet.2011.02.006

Some previous studies on metal-mediated lactamization of imines have been reported. For example, the Reformatsky reactions of an imine, 2-bromoesters and zinc dust in the synthesis of β-lactams has been widely studied.[14] However, the indium-mediated lactamization of imines using haloesters is far less common.[15] Thus, the reported synthesis of 3-unsubstituted β-lactams using ethyl bromoacetate, indium and imines in THF under reflux was only effective for imines derived from aryl aldehydes. Furthermore, the yields were only moderate to low and stereospecific approaches were not investigated. The enantiomeric synthesis of α-substituted β-lactams from imines derived from appropriately protected sugars using acid chlorides by the Staudinger reaction has been reported.[12] However, the indium-mediated reaction of 2-bromoesters with carbohydrate imine derivatives has not been explored to date.

We wish to report here a simple and versatile method for the stereoselective synthesis of carbohydrate-derived β-lactams based on an indium-mediated reaction of bromoesters and imines.

2. Results and discussion

We started our investigation by focusing on the reaction of ethyl α-bromoisobutyrate with several sugar-derived imines. Iminosugars **1**–**5** were reacted with ethyl α-bromoisobutyrate and indium powder in THF under sonication (Scheme 1) and this reaction afforded the corresponding diastereoisomerically pure β-lactams **6**–**10** in good yields in all cases (Table 1).



Scheme 1. Reaction of ethyl α-bromoisobutyrate with sugar-derived imines **1**–**5**.

Regarding the mechanism, as stated in previously reported indium-mediated additions to imines,[16] attack of the indium enolate on a chelated intermediate in which a five-membered ring is created by chelation between indium and the nitrogen and the oxygen atoms in *E*-imine **1** would give the transition state model **TS** depicted in Fig. 1. This situation could explain the highly stereoselective generation of *syn* isomers **6**–**10**.

Taking into account these satisfactory results, and once the reaction had proven to be of broad scope regarding the sugar imine structure, we decided to investigate the influence of the α-substituent on the bromoester.

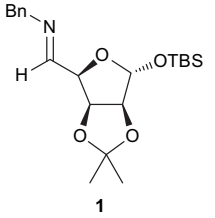
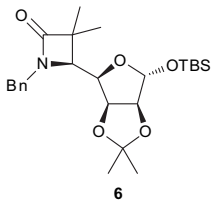
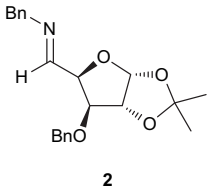
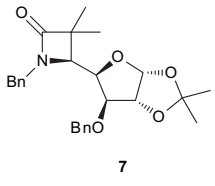
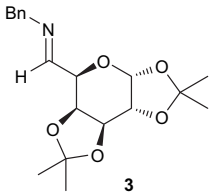
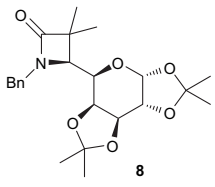
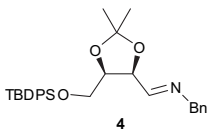
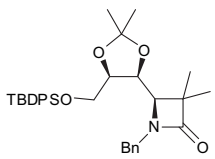
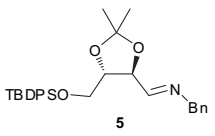
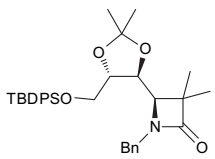
Reaction of the sugar imine **1** with α-bromoesters **11**–**13** (Scheme 2) under the same conditions as above afforded an epimeric mixture of sugar-β-lactams **14**–**16** in all cases (Table 2).

The absolute configuration of isomer **14b** was unequivocally determined by X-ray diffraction (Fig. 2).

Once again the chelation of the indium to the nitrogen atom and the oxygen atom in the proposed transition states $\mathbf{TS_1}$ and $\mathbf{TS_2}$ depicted in Fig. 3 might explain the diastereoselectivity observed in the case of 2-monosubstituted-2-bromoesters **11**–**13**. Thus, the steric interaction between the α-substituent of the bromoester and the sugar ring of the imine in the transition state $\mathbf{TS_1}$ (which is absent in $\mathbf{TS_2}$) could explain the preference for the formation of the 6*S* isomer.

The α-bromoisobutyrate addition product was chosen to initiate these studies because the resulting α,α-disubstituted β-lactam derivatives are precursors of the corresponding α,α-disubstituted β-amino acids, which are of great interest in the preparation of conformationally restricted peptidomimetics.[17] β-Lactam **7** was heated with sodium methoxyde in methanol (Scheme 3) to give, after aqueous work-up, the pure β-amino acids **17**.

Table 1
Sugar-β-lactams **6**–**10** from iminosugars **1**–**5**

Imine	β-Lactam	Yield (%)
 **1**	 **6**	69
 **2**	 **7**	70
 **3**	 **8**	68
 **4**	 **9**	72
 **5**	 **10**	75

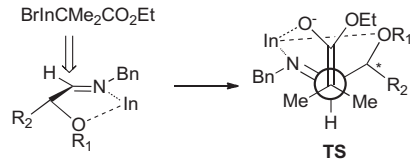
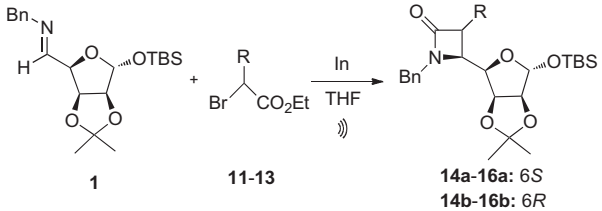


Fig. 1. Proposed transition state leading exclusively to *syn* isomers.



Scheme 2. Reaction of sugar imine **1** with ethyl 2-bromoesters **11**–**13**.

Another very useful application of these sugar-derived lactams is the preparation of azetidines. Azetidines constitute an important class of azaheterocycles, exhibiting a wide range of biological activities, such as antihypertensive, anti-inflammatory, antiarrhythmic, antidepressant, and monoamine oxidase inhibitory activities.[18]

Table 2
Influence of the α-substituent of the bromoester on the diastereoisomeric ratio and the yield of the β-lactams

α-Bromoester	R	β-Lactams	Ratio *R*/*S*	Yield (%)
11	−Ph	**14a**+**14b**	1:3	61
12	−Me	**15a**+**15b**	2:3	39[a]
13	−Pr	**16a**+**16b**	1:3	47[a]

[a] Some of the open-chain ester was obtained as a side product.

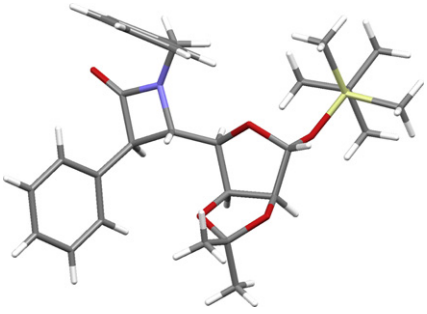


Fig. 2. ORTEP diagram for **14b**.

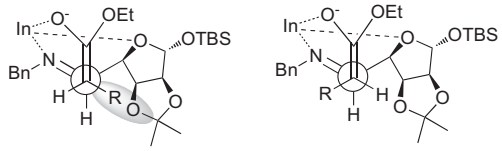
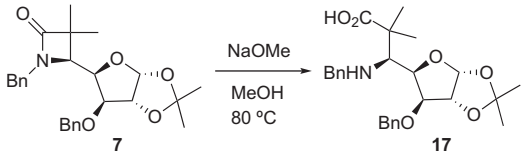


Fig. 3. Proposed transition states leading to the epimeric mixture of β-lactams.



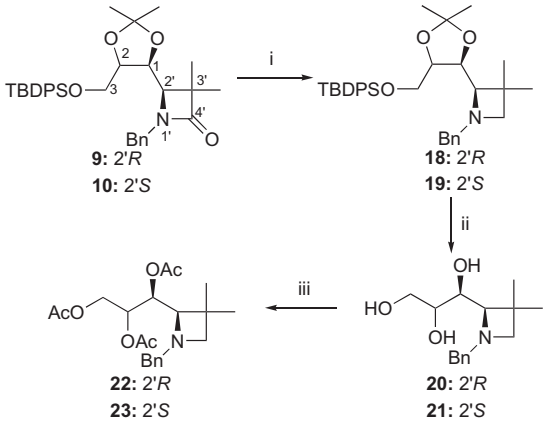
Scheme 3. Preparation of β-amino acid **17** from β-lactam **7**.

However, the azetidine skeleton has been one of the most difficult amines to synthesize because of the ring strain.

A powerful method is reduction of β-lactams by nucleophilic hydrides to afford the corresponding azetidines.

However, this transformation cannot be generalized because many reactions of β-lactams with reducing agents, e.g., diborane, do not lead to azetidines but instead give rise to γ-amino alcohols.[19]

Interestingly, treatment of lactams **9** and **10** with LAH in refluxing THF afforded the corresponding azetidine derivatives (Scheme 4). In these conditions, the silyl protecting group was also cleaved. Azetidines **18** and **19** were then submitted to acidic hydrolysis of the isopropylidene group to afford the corresponding triols **20** and **21**, which were then polyacetylated with acetic anhydride and pyridine in the presence of DMAP, to yield the protected azetidines **22** and **23**.



Scheme 4. Reagents and conditions: (i) LAH, THF, reflux, 24 h, 47% for **18** and 45% for **19**; (ii) TFA/H_2O, 12 h; (iii) Ac_2O, DMAP, Py, 12 h, 65% for **22** and 65% for **23**.

3. Conclusions

A very simple and highly effective approach to versatile carbohydrate β-lactam derivatives has been developed. The procedure is applicable to the preparation 3-monosubstituted and 3-disubstituted β-lactams. The β-lactam formation is stereoselective at the new nitrogenated stereocentre. Furthermore, the configuration at this centre can be predicted based solely on the absolute configuration of the chiral centre next to the imino group. On using 2-monosubstituted-2-bromoesters, an additional stereocentre is formed at C-3. A mixture of epimeric β-lactams at C-3, in which presumably the kinetically controlled product is the major isomer, is obtained in all cases.

Moreover, the novel carbohydrate-derived 3,3-disubstituted β-lactams reported here were used in the straightforward synthesis of α,α-disubstituted-β-amino acids and azetidines.

Work is in progress in our laboratory aimed at the preparation of peptidomimetics based on these novel highly substituted β-amino acids as well as for the biological evaluation of the novel azetidine derivatives obtained.

4. Experimental section

4.1. General experimental procedure for the reaction of ethyl 2-bromoisobutyrate and imines 1–5

To a suspension of indium powder (0.5 mmol) and ethyl 2-bromoisobutyrate (0.75 mmol) in THF (1 mL) was added the corresponding imine (0.5 mmol) and the mixture was sonicated for 6 h. The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate (10 mL) and extracted with ether (3×25 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The residue was purified by flash column chromatography in mixtures of ethyl acetate/hexane to give the compounds shown in Table 1.

*4.1.1. 4-(1-Benzyl-3,3-dimethyl-4-oxoazetidin-2-yl)-1-O-tert-butyldimethylsilyl-2,3-O-isopropyliden-β-L-erytrofuranose (**6**).* Purification by flash column chromatography (ethyl acetate/hexane 1:8) to obtain lactam **6** (0.16 g, 69%) as a yellow oil. $[\alpha]_D^{25}$ +52.5 (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): 0.11, 0.14 (2× s, 6H, −Si(CH_3)$_2$); 0.98 (s, 9H, −SiC(CH_3)$_3$); 1.22, 1.26, 1.29, 1.31 (4× s, 12H, 4× −CH_3); 3.36 (d, 1H, $J_{2'4}$=9.1 Hz, H-2′); 4.05 (d, 1H, *J*=14.8 Hz, −CHPh); 4.11 (dd, 1H, $J_{42'}$=9.1 Hz, J_{43}=4.1 Hz, H-4); 4.52 (d, 1H, J_{23}=5.6 Hz, H-2); 4.76–4.81 (m, 2H, −CHPh, H-3); 5.38 (s, 1H, H-1); 7.26–7.31 (m, 5H, 5×HAr). ^{13}C NMR (125 MHz,

$CDCl_3$): −5.3, −4.4 (−Si(CH_3)$_2$); 17.3, 21.9, 24.8, 25.8 (4× −CH_3); 18.0 (−SiC(CH_3)$_3$); 25.6 (−SiC(CH_3)$_3$); 44.9 (−CH_2Ph); 53.3 (C-3′); 62.1 (C-2′); 80.0, 81.6, 86.7 (C-2, C-3, C-4); 101.1 (C-1); 112.5 (−C−); 127.3, 128.4, 128.5 (5× CHAr); 136.6 (CAr), 173.7 (C=O). LRMS (ESI, *m*/*z*, %): 923.53 (100, $[2M+H]^+$); 462.27 (89, $[M+H]^+$). HRMS for $C_{25}H_{40}NO_5Si$ ($[M+H]^+$) calculated 462.2670. Found: 462.2663.

*4.1.2. 4-(1-Benzyl-3,3-dimethyl-4-oxoazetidin-2-yl)-3-O-benzyl-1,2-O-isopropyliden-β-L-threofuranose (**7**).* Purification by flash column chromatography (ethyl acetate/hexane 2:3) to obtain lactam 7 (0.15 g, 70%) as a yellow oil. $[\alpha]_D^{25}$ +2.8 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 1.06, 1.11, 1.33, 1.46 (4× s, 12H, 4× −CH_3); 3.47−3.49 (m, 1H, H-2′); 3.99 (d, 1H, J_{12}=6.1 Hz, H-2); 4.12 (d, 1H, *J*=11.4 Hz, −CHPh); 4.18−4.24 (m, 1H, H-3); 4.39 (d, 1H, *J*=16.0 Hz, −CHPh); 4.59−4.70 (m, 3H, 2× −CHPh, H-4); 5.94 (d, 1H, J_{12}=5.9 Hz, H-1); 7.24−7.31 (m, 10H, 10× HAr). ^{13}C NMR (125 MHz, $CDCl_3$): 17.2, 22.2, 26.3, 26.8 (4× −CH_3); 44.9 (−CH_2Ph); 51.9 (C-3′); 61.3 (C-2′); 71.5 (−CH_2Ph); 81.6, 81.8, 82.3 (C-2, C-3, C-4); 104.8 (C-1); 111.6 (−C−); 127.2, 128.3, 128.4, 128.5 (5× CHAr); 136.5, 130.7 (2× CAr), 173.2 (C=O). LRMS (ESI, *m*/*z*, %): 875.45 (80, $[2M+H]^+$); 438.23 (100, $[M+H]^+$). HRMS for $C_{26}H_{32}NO_5$ ($[M+H]^+$) calculated 438.2274. Found: 438.2284.

*4.1.3. 5-(1-Benzyl-3,3-dimethyl-4-oxoazetidin-2-yl)-1,2:3,4-di-O-isopropyliden-β-L-arabinopyranose (**8**).* Purification by flash column chromatography (ethyl acetate/hexane 2:5) to obtain lactam 8 (0.14 g, 68%) as a yellow oil. $[\alpha]_D^{25}$ −20.9 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 1.20, 1.25, 1.28, 1.31, 1.33, 1.49 (6×s, 18H, 6×−CH_3); 3.40 (d, 1H, $J_{2'4}$=9.0 Hz, H-2′); 3.90 (dd, 1H, $J_{52'}$=9.0 Hz, J_{53}=3.1 Hz, H-5); 3.88−3.92 (m, 2H, H-3, −CHPh); 4.33 (dd, 1H, J_{21}=6.2 Hz, J_{23}=3.1 Hz, H-2); 4.33 (dd, 1H, *J*=8.9, 2.9 Hz, H-4); 4.76 (d, 1H, *J*=14.3 Hz, −CHPh); 5.57 (d, 1H, J_{12}=6.2 Hz, H-1); 7.22−7.29 (m, 5H, 5×HAr). ^{13}C NMR (125 MHz, $CDCl_3$): 17.9, 21.7, 24.7, 24.8, 25.8, 25.9 (6× −CH_3); 45.0 (−CH_2Ph); 51.6 (C-3′); 60.7 (C-2′); 69.2, 69.9, 70.6, 71.2 (C-2, C-3, C-4, C-5); 96.0 (C-1); 108.7, 109.7 (2× −C−); 127.0, 128.2, 128.5 (5× CHAr); 136.8 (CAr), 173.6 (C=O). LRMS (ESI, *m*/*z*, %): 418.22 (100, $[M+H]^+$). HRMS for $C_{23}H_{32}NO_6$ ($[M+H]^+$) calculated 418.2224. Found: 418.2231.

*4.1.4. 1-(1-Benzyl-3,3-dimethyl-4-oxoazetidin-2-yl)-3-O-terc-butyldiphenylsilyl-1,2-O-isopropyliden-D-glycerol (**9**).* Purification by flash column chromatography (ethyl acetate/hexane 1:5) to obtain lactam 9 (0.20 g, 73%) as a yellow oil. $[\alpha]_D^{25}$ −27.8 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 0.94 (s, 3H); 0.98 (s, 9H); 1.51 (s, 3H); 3.38 (d, 1H); 3.45 (dd, 1H); 3.57 (dd, 1H); 4.18 (m, 3H); 4.65 (d, 1H); 7.37 (m, 10H); 7.64 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): 16.8 (−CH_3); 19.0 (−CH_3); 22.0 (−CH_3); 25.2 (−CH_3); 26.8 −(CH_3); 27.4 (−CH_3); 45.1 (−CH_2); 51.6 (−CH−); 61.5 (−CH−); 63.5 (−CH_2); 78.6; 108.6 (−C−); 127.4 (−CH−); 127.8 (−CH−); 128.6 (−CH−); 129.8; 135.0; 135.7 (−CH−). LRMS (ESI, *m*/*z*, %): 558.30 (61, $[M+H]^+$). HRMS for $C_{34}H_{44}NO_4Si$ ($[M+H]^+$) calculated 558.3034. Found: 558.3023.

*4.1.5. 1-(1-Benzyl-3,3-dimethyl-4-oxoazetidin-2-yl)-3-O-tert-butyldiphenylsilyl-1,2-O-isopropyliden-L-glycerol (**10**).* Purification by flash column chromatography (ethyl acetate/hexane 1:5) to obtain lactam 10 (0.21 g, 76%) as a yellow oil. $[\alpha]_D^{25}$ −30.2 (*c* 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 0.99 (s, 9H); 1.19 (s, 3H); 1.23 (s, 3H); 1.33 (d, 3H); 3.32 (d, 1H); 3.65 (m, 2H); 3.78 (ddd, 1H); 4.05 (d, 1H); 4.17 (dd, 1H); 4.94 (d, 1H); 7.34 (m, 10H); 7.59 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) ppm: 15.3 (−CH_3); 17.4 (−CH_3); 19.1 (−CH_3); 22.6 (−CH_3); 26.8 (−CH_3); 27.2 (−CH_3); 27.(−CH_3); 44.9 (−CH_2−); 52.9 (−CH)−; 62.5 (−CH−); 63.1 (−CH−); 64.2 (−CH_2−); 79.5 (−CH−); 109.9 (−C−); 127.5 (−CH−); 127.8 (−CH−); 128.5 (−CH−); 129.6 (−CH−); 174.1 (−C−). LRMS (ESI, *m*/*z*, %): 558.30 (52, $[M+H]^+$). HRMS for $C_{34}H_{44}NO_4Si$ ($[M+H]^+$) calculated 558.3034. Found: 558.3021.

4.2. General experimental procedure for the reaction of imine 1 and ethyl 2-bromo-alkanoates 11–13

To a suspension of indium powder (0.5 mmol) and the corresponding ethyl 2-bromo-alkanoate (0.75 mmol) in THF (1 mL) was added imine **1** (0.5 mmol) and the mixture was sonicated for 6 h. The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate (10 mL) and extracted with ether (3×25 mL). The combined organic layers were dried over magnesium sulfate, filtered and evaporated in vacuo. The residue was purified by flash column chromatography in mixtures of ethyl acetate/hexane to give the compounds shown in Table 2.

*4.2.1. 4-[(2R,3S)-1-Benzyl-3-phenyl-4-oxoazetidin-2-yl]-1-O-tert-butyldimethylsilyl-2,3-O-isopropyliden-β-L-erytrofuranose (**14a**) and 4-[(2R,3R)-1-benzyl-3-phenyl-4-oxoazetidin-2-yl]-1-O-tert-butyldimethylsilyl-2,3-O-isopropyliden-β-L-erytrofuranose (**14b**).* Purification by flash column chromatography (ethyl acetate/hexane 1:8) to obtain lactam **14a** (0.10 g, 42%) as a yellow oil and lactam **14b** (0.05 g, 19%) as a yellow oil which was crystallized from diethyl ether/hexane.

Data for **14a**: $[\alpha]_D^{25}$ −11.0 (*c* 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 0.15, 0.16 (2× s, 6H, −Si(CH_3)$_2$); 0.92 (s, 9H, −SiC(CH_3)$_3$); 1.25, 1.34 (2× s, 6H, 2× −CH_3); 3.85 (dd, 1H, $J_{2'3'}$=2.2 Hz, $J_{2'4}$=7.0 Hz, H-2′); 4.11 (dd, 1H, J_{43}=3.5 Hz, $J_{2'4}$=7.0 Hz, H-4); 4.32−4.40 (m, 3H, −CHPh, H-3, H-3′); 4.52 (d, 1H, J_{23}=5.9 Hz, H-2); 4.68 (d, 1H, *J*=15.3 Hz, −CHPh); 5.34 (s, 1H, H-1); 7.28−7.37 (m, 5H, 5× HAr). ^{13}C NMR (125 MHz, $CDCl_3$): −5.2, −4.2 (−Si(CH_3)$_2$); 24.5, 25.9 (2× −CH_3); 18.0 (−SiC(CH_3)$_3$); 25.7 (−SiC(CH_3)$_3$); 45.2 (−CH_2Ph); 58.6, 58.9 (C-2′, C-3′); 79.7, 80.5, 87.5 (C-2, C-3, C-4); 101.4 (C-1); 112.7 (−C−); 127.3, 127.7, 128.4, 128.6, 128.7 (10× CHAr); 135.4, 136.9 (2× CAr), 168.9 (C=O). LRMS (ESI, *m*/*z*, %): 510.27 (100, $[M+H]^+$). HRMS for $C_{29}H_{40}NO_5Si$ ($[M+H]^+$) calculated 510.2670. Found: 510.2675.

Data for **14b**: ^{1}H NMR (300 MHz, $CDCl_3$): 0.17, 0.18 (2× s, 6H, −Si(CH_3)$_2$); 0.94 (s, 9H, −SiC(CH_3)$_3$); 1.23 (s, 6H, 2× −CH_3); 3.86 (dd, 1H, $J_{2'3'}$=2.3 Hz, $J_{2'4}$=8.6 Hz, H-2′); 4.12−4.27 (m, 3H, −CHPh, H-4, H-3′); 4.57 (d, 1H, J_{23}=5.8 Hz, H-2); 4.87 (dd, 1H, J_{34}=3.8 Hz, J_{23}=5.8 Hz, H-3); 4.94 (d, 1H, *J*=14.8 Hz, −CHPh); 5.42 (s, 1H, H-1); 7.24−7.35 (m, 5H, 5× HAr). ^{13}C NMR (125 MHz, $CDCl_3$): −5.1, −4.2 (−Si(CH_3)$_2$); 25.0, 25.9 (2× −CH_3); 18.2 (−SiC(CH_3)$_3$); 25.8 (−SiC(CH_3)$_3$); 45.6 (−CH_2Ph); 57.5, 57.9 (C-2′, C-3′); 80.3, 83.6, 87.0 (C-2, C-3, C-4); 102.2 (C-1); 112.9 (−C−); 127.3, 127.7, 127.8, 128.6, 128.7, 128.8 (10× CHAr); 134.9, 136.6 (2× CAr), 167.7 (C=O). LRMS (ESI, *m*/*z*, %): 1019.53 (100, $[2M+H]^+$); 510.27 (88, $[M+H]^+$). HRMS for $C_{29}H_{40}NO_5Si$ $[M+H]^+$ calculated 510.2670. Found: 510.2686.

*4.2.2. 4-[(2R,3S)-1-Benzyl-3-methyl-4-oxoazetidin-2-yl]-1-O-tert-butyldimethylsilyl-2,3-O-isopropyliden-β-L-erytrofuranose (**15a**+**15b**).* Purification by flash column chromatography (ethyl acetate/hexane 1:8) to obtain a mixture of lactams **15a**+**15b** (0.11 g, 47%) as a yellow oil. Further purification afforded pure lactam **15a** (0.03 g). Data for **15a**: ^{1}H NMR (300 MHz, $CDCl_3$): 0.09, 0.10, 0.12, 0.14 (4× s, 12H, 2× −Si(CH_3)$_2$); 0.87, 0.92 (2× s, 18H, 2× −SiC(CH_3)$_3$); 1.19−1.39 (m, 15H, 5× −CH_3); 3.05−3.12 (m, 1H, H-3′); 3.50−3.55 (m, 1H, H-2′); 3.92−3.95 (m, 1H); 4.28−4.39 (m, 3H); 4.75−4.82 (m, 2H); 5.35 (s, 1H, H-1); 7.28−7.32 (m, 5H, 5× HAr). ^{13}C NMR (125 MHz, $CDCl_3$): −5.2, −4.3 (−Si(CH_3)$_2$); 13.9 (−CH_3); 14.8 (C-3′); 18.0 (−SiC(CH_3)$_3$); 24.6, 25.7, 25.9, 26.2 (4× −CH_3); 45.2 (−CH_2Ph); 51.9, 54.5 (C-2′, C-3′); 79.9, 81.3, 87.2 (C-2, C-3, C-4); 101.4 (C-1); 112.7 (−C−); 127.5, 128.4, 128.7 (5× CHAr); 136.8 (2× CAr), 171.2 (C=O). LRMS (ESI, *m*/*z*, %): 448.25 (100, $[M+H]^+$).

4.2.3. 4-[(2R,3R,S)-1-Benzyl-3-propyl-4-oxoazetidin-2-yl]-1-O-tert-butyldimethylsilyl-2,3-O-isopropyliden-β-l-erytrofuranose

(***16a***+***16b***). Purification by flash column chromatography (ethyl acetate/hexane 1:8) to obtain a mixture of lactams **16a**+**16b** (0.11 g, 47%) as a yellow oil. $[\alpha]_D^{25}$ +35.3 (*c* 2.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): 0.09, 0.10, 0.12, 0.15 (4× s, 12H, 2× $-Si(CH_3)_2$); 0.88, 0.92 (2× s, 18H, 2× $-SiC(CH_3)_3$); 1.26, 1.28, 1.33, 1.38 (4× s, 12H, 4× $-CH_3$); 1.41–1.81 (m, 14H); 3.08–3.13 (m, 1H, H-3′); 3.17–3.24 (m, 1H, H-3′); 3.44 (dd, 1H, *J*=2.8, 6.1 Hz, H-2′); 3.77 (dd, 1H, *J*=9.0, 6.2 Hz, H-2′); 3.92–3.95 (m, 1H); 4.08–4.19 (m, 3H); 4.36–4.38 (m, 1H); 4.47–4.63 (m, 3H); 4.77–4.82 (m, 2H); 5.27 (s, 1H, H-1); 5.38 (s, 1H, H-1); 7.29–7.32 (m, 10H, 10× HAr). ^{13}C NMR (125 MHz, $CDCl_3$): −5.3, −5.2, −4.3 (2× $-Si(CH_3)_2$); 14.1, 14.3 (C-3′); 18.0, 18.1 (2× $-SiC(CH_3)_3$); 20.3, 21.3 (2× $-CH_2-$); 24.6, 24.9, 25.7, 25.8, 25.9, 26.0 (10× $-CH_3$); 28.2, 29.8 (2× $-CH_2-$); 45.0, 45.3 (2× $-CH_2Ph$); 51.3, 53.6, 54.4, 56.4 (2× C-2′, 2× C-3′); 79.8, 80.0, 80.4, 81.4, 87.1, 87.5 (2× C-2, 2× C-3, 2× C-4); 101.3, 101.4 (C-1); 112.5, 112.8 (−C−); 127.4, 127.5, 128.3, 128.5, 128.6, 128.7 (10× CHAr); 136.7, 137.2 (2× CAr), 170.5, 171.4 (C═O). LRMS (ESI, *m*/*z*, %): 476.28 (100, $[M+H]^+$). HRMS for $C_{26}H_{42}NO_5Si$ $[M+H]^+$ calculated 476.2826. Found: 476.2845.

*4.2.4. 5-Benzylamino-3-O-benzyl-5-deoxy-6,6-dimethyl-1,2-O-isopropyliden-α-L-idofuranuronic acid (**17**).* A solution of sodium methoxide (35% in MeOH, 5 mL) was added to lactam **7** (0.20 g, 0.46 mmol) and the resulting mixture was refluxed for 16 h. After cooling at rt, water was added (10 mL) and the mixture was stirred for 30 min and then extracted with ethyl acetate (3×15 mL), which was then washed with water until neutral, dried, filtered and evaporated under reduced pressure to obtain amino acid 17 (0.21 g, quant.) as clear oil. $[\alpha]_D^{25}$ −31.6 (*c* 0.7, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): 1.23, 1.27, 1.42, 1.56 (4× s, 12H, 4× $-CH_3$); 3.21 (d, 1H, J_{54}=6.1 Hz, H-5); 3.85 (d, 1H, *J*=14.9 Hz, −CHPh); 3.97–4.10 (m, 2H, −CHPh, H-3); 4.36–4.39 (m, 1H, H-4); 4.59 (d, 1H, *J*=15.0 Hz, −CHPh); 4.79–4.85 (m, 2H, −CHPh, H-2); 6.00 (d, 1H, J_{12}=6.1 Hz, H-1); 7.26–7.31 (m, 10H, 10× HAr). ^{13}C NMR (125 MHz, $CDCl_3$): 21.2, 24.5, 26.6, 27.2 (4× $-CH_3$); 43.9 (C-6); 54.2 ($-CH_2Ph$); 60.2 (C-5); 72.5 ($-CH_2Ph$); 77.8, 82.3, 83.4 (C-2, C-3, C-4); 104.5 (C-1); 112.5 (-C-); 128.3, 128.6, 128.9, 129.0, 129.1 (10× CHAr); 136.7, 137.2 (2× CAr), 178.8 (C═O). LRMS (ESI, *m*/*z*, %): 456.24 (100, $[M+H]^+$). HRMS for $C_{26}H_{34}NO_6$ $[M+H]^+$ calculated 456.2380. Found: 456.2401.

*4.2.5. 1-(1-Benzyl-3,3-dimethyl-oxoazetidin-2-yl)-3-O-tert-butyldiphenylsilyl-1,2-O-isopropyliden-D-glycerol (**18**).* To a solution of lactam **9** (0.53 g, 1.1 mmol) in THF (17 mL) LAH was added (0.08 g, 2.2 mmol) and the suspension was refluxed for 24 h. The reaction mixture was cooled to rt, quenched with water and filtered through Celite. The filtrate was extracted with EtOAc and the combined organic extracts were washed with aqueous NaOH (5%, 15 mL) and H_2O (20 mL), dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified by flash column chromatography (ethyl acetate/hexane 2:1) to obtain azetidine **18** (0.16 g, 45%) as a clear oil. $[\alpha]_D^{25}$ −41.8 (*c* 0.8, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): 0.99 (s, 3H); 1.02 (s, 3H); 1.41 (s, 3H); 3.04 (s, 3H); 3.51 (d, 2H); 3.71 (d, 2H); 3.90 (dd, 2H); 4.15 (m, 1H); 4.33 (dd, 1H); 7.30 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): 20.8 ($-CH_3$); 24.4 ($-CH_3$); 25.1 ($-CH_3$); 27.2 ($-CH_3$); 38.9 (−CH)−; 54.9 ($-CH_2-$); 62.2 (−CH−); 62.7 ($-CH_2-$); 72.5 ($-CH_2-$); 107.9 (−C−); 127.4 (−CH−); 128.5 (−CH−); 128.6 (−CH−); 139.5 (−C−). LRMS (ESI, *m*/*z*, %): 543.32 (100, $[M+H]^+$).

*4.2.6. 1-(1-Benzyl-3,3-dimethyl-4-oxoazetidin-2-yl)-1,2,3-O-acetyl-D-glycerol (**22**).* A solution of the protected azetidine **18** (0.07 g, 0.2 mmol) in TFA/H_2O 1:1 (3 mL) was stirred at rt for 6 h. Solvents were evaporated in vacuo and coevaporated with toluene, and the residue was dissolved in acetic anhydride (3 mL) and pyridine (1.3 mL). DMPA (4 mg) was added and the resulting mixture was stirred at rt 14 h. After evaporation of the solvents under reduced pressure, the residue was purified by flash column chromatography (dichloromethane/methanol 95:5) to yield protected azetidine **22** (0.10 g, 65%) as a yellow oil. $[\alpha]_D^{25}$ −28.3 (c 1.1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): 1.15 (s, 3H); 1.37 (s, 3H); 1.98 (s, 3H); 2.09 (s, 6H); 2.5 (d, 1H); 2.97 (m, 2H); 3.32 (d, 1H); 3.92 (d, 1H); 4.16 (dd, 1H); 4.42 (dd, 1H); 5.04 (ddd, 1H); 5.54 (dd, 1H); 7.25 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): 20.6 ($-CH_3$); 20.8 ($-CH_3$); 20.9 ($-CH_3$); 22.7 ($-CH_3$); 27.8($-CH_3$); 34.2 ($-CH_3$); 61.9 ($-CH_2-$); 63.3 ($-CH_2-$); 64.7 ($-CH_2-$); 70.3 (−CH−); 71.5 (−CH−); 73.6 (−CH−); 128.3 (−CH−); 138.2 (−C−); 169.8 (−C−); 170.2 (−C−); 170.6 (-C−). LRMS (ESI, *m*/*z*, %): 392.21 (100, $[M+H]^+$). HRMS for $C_{21}H_{30}NO_6$ $[M+H]^+$ calculated 392.2073. Found: 392.2063.

*4.2.7. 1-(1-Benzyl-3,3-dimethyl-azetidin-2-yl)-3-O-tert-butyldiphenylsilyl-1,2-O-isopropyliden-L-glycerol (**19**).* Lactam **10** (0.10 g, 0.2 mmol) was reduced following the same procedure described for **7** to obtain azetidine **19** (0.025 g, 45%) as a clear oil. ^1H NMR (300 MHz, $CDCl_3$): 1.09 (s, 3H); 1.27 (s, 3H); 1.39 (s, 3H); 1.48 (s, 3H); 2.56 (d, 1H); 3.01 (m, 2H); 3.39 (d, 1H); 3.66 (d, 2H); 4.01 (m, 2H); 4.12 (d, 1H); 7.27(m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): 23.5 (CH_3); 27.3 (CH_3); 27.7 (CH_3); 28.7 (CH_3); 34.8 ($-CH_3$); 62.4 ($-CH_2-$); 62.8 ($-CH_2-$); 64.8($-CH_2-$); 79.6 (−CH−); 108.7 (−C−); 126.9 −(CH−); 128.2 (−CH−); 128.9 (−CH−); 137.8 (−C−). LRMS (ESI, *m*/*z*, %): 543.32 (100, $[M+H]^+$).

*4.2.8. 1-(1-Benzyl-3,3-dimethyl-azetidin-2-yl)-1,2,3-O-acetyl-L-glycerol (**23**).* Azetidine **19** (0.025 g, 0.08 mmol) was acetylated following the same procedure described for **18** to obtain protected amino alditol **23** (0.04 g, 65%) as a yellow oil. $[\alpha]_D^{25}$ +9.2 (*c*, 0.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): 0.95 (s, 3H); 1.23 (s, 3H); 1.96 (s, 3H); 1.97 (s, 3H); 2.41 (d, 1H); 3.07 (m, 2H); 3.26 (d, 1H); 3.96 (m, 2H); 4.3 (dd, 1H); 5.15 (ddd, 1H); 5.49 (dd, 1H); 7.26 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): 20.7 ($-CH_3$); 20.8 ($-CH_3$); 20.8 ($-CH_3$); 22.7 ($-CH_3$); 27.7 ($-CH_3$); 33.7 ($-CH_3$); 62.5 ($-CH_2-$); 63.4 ($-CH_2-$); 64.6 ($-CH_2-$); 69.3 (−CH−); 70.4 (−CH−); 128.2 (−CH−); 170.1 (−C−); 170.5 (−C−); 170.8 (−C−). LRMS (ESI, *m*/*z*, %): 392.21 (100, $[M+H]^+$). HRMS for $C_{21}H_{30}NO_6$ $[M+H]^+$ calculated 392.2073. Found: 392.2065.

Acknowledgements

This work was supported by the Spanish Ministry of Science and Innovation (CTQ2008-06493). R.G.S. thanks the Xunta de Galicia for financial support (Isidro Parga Pondal program).

Supplementary data

^{13}C NMR of compounds **6**–**10**, **14**–**17**, **22** and **23** and cif archive for **14b**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.02.006. These data include MOL files and InChiKeys of the most important compounds described in this article.

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