PAPER

Pushing the limits of catalytic C−H amination in polyoxygenated cyclobutanes†

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A synthetic route to a new class of conformationally constrained iminosugars based on a 5-azaspiro[3.4] octane skeleton has been developed by way of Rh(ɪɪ)-catalyzed C(sp^3)−H amination. The pivotal stereo-controlled formation of the quaternary C−N bond by insertion into the C−H bonds of the cyclobutane ring was explored with a series of polyoxygenated substrates. In addition to anticipated regioselective issues induced by the high density of activated α-ethereal C−H bonds, this systematic study showed that cyclobutane C−H bonds were, in general, poorly reactive towards catalytic C−H amination. This was demonstrated *inter alia* by the unexpected formation of a oxathiazonane derivative, which constitutes a very rare example of the formation of a 9-membered ring by way of catalyzed C(sp^3)−H amination. A complete stereocontrol could be however achieved by activating the key insertion position as an allylic C−H bond in combination with reducing the electron density at the undesired C−H insertion sites by using electron-withdrawing protecting groups. Preliminary biological evaluations of the synthesized spiro-iminosugars were performed, which led to the identification of a new class of correctors of the defective F508del-CFTR gating involved in cystic fibrosis.

Introduction

Over the past decade, catalytic C–H amination of C(sp^3)–H bonds has established itself as a powerful tool for the synthesis of relevant nitrogen-containing compounds.[1] The direct and selective functionalization of unactivated C–H bonds is indeed a strategy of choice to achieve a major simplification of synthetic sequences since no prior incorporation of functional groups is needed.[2] Based on pioneering studies by Breslow and Gellman,[3] the group of Du Bois developed in the early 2000s a powerful process for the intramolecular amination of C(sp^3)–H bonds through Rhodium nitrene intermediates using carbamate or sulfamic ester substrates (Fig. 1).[1,4] In the following years, various catalytic systems and new nitrene precursors were identified, and relevant mechanistic insights were dis-
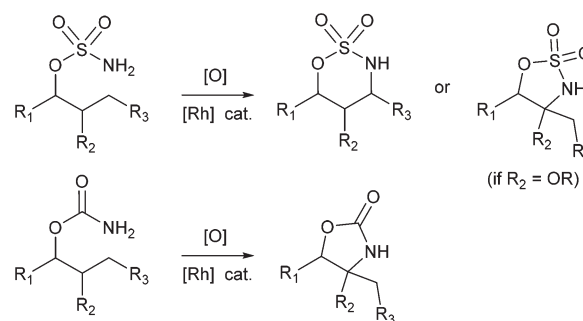
Fig. 1 Intramolecular catalysed C−H amination of sulfamic esters and carbamates.

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closed.[1] The process developed by Du Bois is still the best method in terms of practicality, mild experimental conditions and functional group tolerance. The broad synthetic utility of Rh(ɪɪ)-catalyzed C–H amination has been indeed superbly demonstrated by the total synthesis of complex natural molecules such as (−)-tetrodotoxin.[5] In addition, this highly regioselective, stereospecific process is valuable in the retro-synthetic analysis of enantiopure target molecules since it occurs with complete retention of configuration at the insertion site. Another strategic advantage of synthetic design is that the regioselectivity of the amination reaction may be
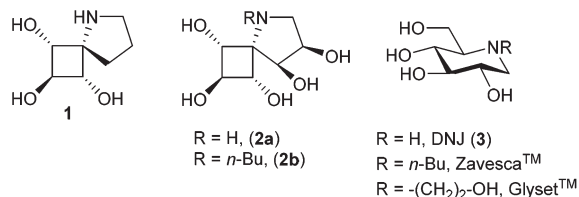
Fig. 2 Some examples of iminosugars and of constrained analogues thereof.

predicted. Amination reactions performed with carbamates led almost exclusively to five-membered rings whereas sulfamic esters afforded, in general, six-membered rings.[1] In addition to structural parameters related to elongated S–N/S–O bonds and unfavourable compression of the N–S–O angle in 5-membered cyclic sulfamates,[1,4] electronic factors are also at play. Sites adjacent to electron-donating groups as well as benzylic, allylic and tertiary C–H bonds are generally favoured. Recent examples concerning the formation of 5- to 10-membered products from sulfamate substrates[6] have nevertheless complicated the matter further. In some cases, conformational control, in combination or not with stereoelectronic effects, may dominate purely electronic factors.[6] The major challenge associated with C(sp[3])–H amination thus remain the control of regioselectivity in C–N bond formation, especially for complex substrates displaying "non-classical" conformation or a high density of reactive C–H bonds.

In connection with our interest in biologically relevant glycomimetics,[7] we recently described the synthesis of the first examples of conformationally constrained iminosugars **1–2** based on four-membered ring-containing spirocycles (Fig. 2).[8]

These compounds were designed as analogues of 1-deoxynojirimycin (DNJ, **3**), a common motif found in many bioactive iminosugars, such as the antidiabetic Glyset™ or Zavesca™ (Gaucher disease, cystic fibrosis).[9,10] In addition to exploring unfrequented regions of chemical and intellectual property spaces, we were interested in performing the first catalytic C–H amination of cyclobutanes[11] to generate the pivotal C–N spiranic bond. An additional challenge was to design efficient strategies to secure high regioselectivity in polyoxygenated substrates with up to four contiguous reactive C–H bonds. Herein we wish to describe the full details of this synthetic study that led to unexpected regioselectivity and to a new class of bioactive iminosugars.

Results and discussion

The consecutive retrosynthetic analyses presented hereafter were mainly focused on achieving a high level of regiocontrol in the C–H amination critical step. Our synthetic strategies were based on guidelines established in the literature and competition experiments employing bifunctional substrates. From these precedents, the order of reactivity for C–H bond insertion may be roughly formulated as follows: allylic

> α-ethereal ~ 3° ~ benzylic > 2° ≫ 1°.[1l,12–14] Sites adjacent to electron-withdrawing groups are strongly disfavoured.[4b]

First strategy: C–H amination of non-allylic C–H bonds using sulfamate esters

Our first synthetic strategy takes advantage of cyclobutanol **4**, an advanced intermediate synthesized recently in our group from vitamin C (Fig. 3).[7a] The sulfamate function was easily introduced on the carbon side chain at C4 by the two-step conversion of the ester group in **4**.

Sulfamic ester **7** was expected to be a promising reaction substrate in terms of regioselectivity since C–H insertion into a tertiary C–H bond to form a 6-membered cyclic sulfamide is supposed to be highly favoured. Insertion into the α-ethereal C–H bonds at C1 or C3 to form a less favourable 7-membered ring could nevertheless not be ruled out. We first envisioned original iminosugars of type **I** since sulfamidates **II** could be direct precursors to 1-azaspiro[3.3]heptanes following a two-step protocol involving a ring-opening/ring-closing cascade.[15] After the activation of the oxathiazinane ring by N-acylation, the desired azetidine ring was indeed expected to be obtained by a one-pot reaction with NaI followed by NaH. Compound **7** was obtained in 3 steps from **4** (Scheme 1). First attempts to protect the secondary alcohol in **4** with a benzyl group under classical basic conditions (NaH, BnBr) led to sluggish conversion. Better results were obtained for protection as a silyl ether and **5** could be eventually obtained in 80% yield. After the reduction of ester **5** with LAH, the corresponding alcohol **6** was reacted with sulfamoyl chloride and DMAP to afford sulfamic ester **7**. Quite surprisingly, exposure of **7** to the standard C–H amination protocol using PhI(OAc)$_2$, MgO and a catalytic amount of Rh$_2$(OAc)$_4$ did not lead to any expected C–H insertion products but instead afforded alcohol **8** in 32% yield. The structure of **8** was unambiguously determined by using a heteronuclear multiple-bond correlation (HMBC) between benzylic protons and C-2 (see the ESI† for the HMBC spectrum of **8**). The highly regioselective deprotection of the benzyloxy group at C1 could be explained by the formation of a 9-membered cyclic sulfamidate (Scheme 1). C–H insertion into the activated methylene of the benzylic ether would generate a labile hemiaminal that could be readily hydrolysed during the
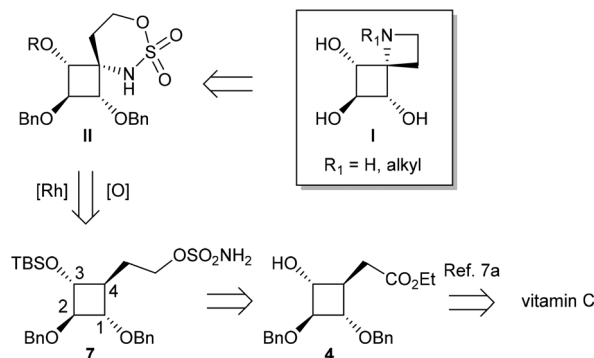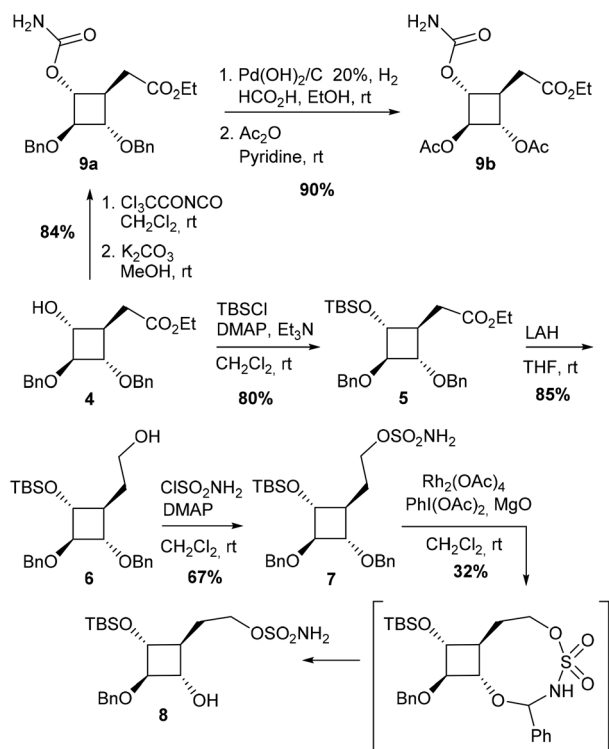

Fig. 3 Retrosynthetic analysis.

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Org. Biomol. Chem., 2016, **14**, 2780–2796 | **2781**

Scheme 1 Synthesis of compounds **7** and **9**.

work-up procedure to give **8**. It is noteworthy that only one example of the formation of a 9-membered ring by way of intramolecular-catalyzed C–H amination has been reported so far in the literature.[6c] In the aforementioned study, the macrocyclic sulfamidate was nevertheless obtained in low yields (16%) from (Z)-hex-4-en-1-yl sulfamate, the major product being the corresponding expected oxathiazinane derivative.

The unexpected outcome of the C–H amination of **7** prompted us to adopt a different strategy since the regioselectivity observed showed quite clearly that C–H bonds in cyclobutane were poorly reactive. No C–H insertions were indeed observed either at C4 or at C1 or C3 despite the fact that tertiary C–H bonds and tertiary α-ethereal C–H bonds are known to be favoured towards Rh(II)-catalyzed C–H amination. These results are consistent with the significantly lower s-character of the exocyclic bonds on four-membered hydrocarbon rings.[11b]

Second strategy: C–H amination of non-allylic C–H bonds using carbamates

To synthesize more rapidly substrates for C–H amination and to reduce the number of possible regioisomers, we turned our attention to the synthesis of carbamate **9a** (Scheme 1). This compound was obtained in 84% yield from **4** by treatment with $Cl_3CC(O)NCO$ followed by K_2CO_3. Reaction of carbamate **9a** with different Rh(II) catalysts and stoichiometric amounts of $PhI(OAc)_2$ and MgO afforded hemiaminal **11a** in 46–61% yields as the only regioisomer (Table 1, entries 1–3). The presence of the ester in the β-position is likely to have strongly deactivated the position at C4. These results were nonetheless encouraging since they demonstrated that catalytic amination of cyclobutane C–H bonds was feasible. To favour the formation of the desired regioisomer **10a**, the benzyloxy group was replaced by a much more electron-withdrawing protecting group to reduce the electronic density at C2. Hydrogenolysis of **9a** afforded the corresponding diol which was protected as acetates to yield compound **9b** (Scheme 1). Unfortunately, the presence of four electron-withdrawing groups around the cyclobutane ring completely abolished the reactivity of the cyclobutane C–H bonds and no C–H amination product could be obtained (Table 1, entries 4 and 5).
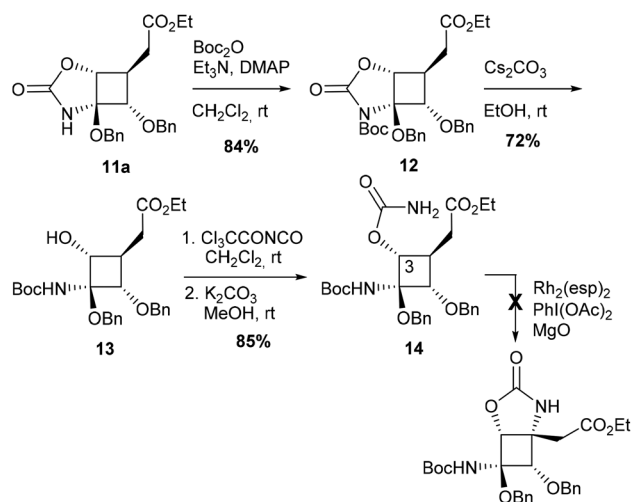
A different tactic was designed to generate the desired C–N bond at C4, taking advantage of the C–H amination product **11a**. The objective was to cleave the oxazolidinone ring to afford a hemiaminal function, as a masked ketone, and a secondary alcohol at C3 (compound **13**) that may be converted
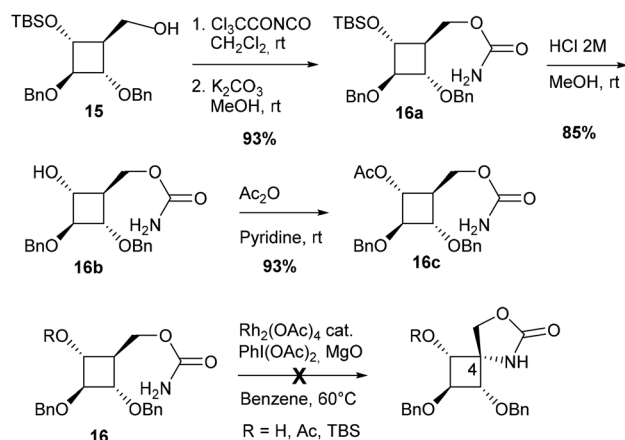
Table 1 C–H amination of carbamates **9**[a]

Entry	Cat. (mol%)	Solvent	Reaction time (h)	R	10	11[b]	9[c]
1	$Rh_2(OAc)_4$ (5)	CH_2Cl_2	7	Bn	—	54%	12%
2	$Rh_2(esp)_2$ (2)	CH_2Cl_2	7	Bn	—	61%	18%
3	$Rh_2(tpa)_4$ (5)	CH_2Cl_2	15	Bn	—	46%	31%
4	$Rh_2(esp)_2$ (2)	CH_2Cl_2	8	Ac	—	—	72%
5	$Rh_2(tpa)_4$ (10)	C_6H_6[d]	8	Ac	—	—	~10%

[a] See the Experimental section for the experimental conditions. [b] Isolated yields. [c] Recovered after purification on a silica gel. [d] The reaction was performed at 60 °C.

2782 | Org. Biomol. Chem., 2016, **14**, 2780–2796

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Scheme 2 Synthesis and evaluation of carbamate **14** as the substrate for C–H amination.

Scheme 3 Synthesis and evaluation of carbamates **16** as the substrate for C–H amination.

into the corresponding carbamate to perform a second C–H amination reaction (Scheme 2).

After N-Boc protection, oxazolidinone **12** was reacted with cesium carbonate[16] to provide alcohol **13** which was converted into the corresponding carbamate **14** in 51% yield for the three steps. Unfortunately, despite several attempts using typical rhodium-catalyzed conditions, no C–H amination product could be obtained from **14** and only the starting material was recovered in up to 52% yield.

Another strategy to avoid regioselectivity issues was to introduce the carbamate function on the carbon side chain at C4 (Scheme 3). Due to the strong bias of carbamates for 5-membered ring formation, C–H insertion was expected to occur exclusively at C4 from substrates **16**. Three carbamates protected (Ac, TBS) or not at C3 were synthesized from alcohol **15**.[7a] None of these compounds led to the desired azaspiranic products under typical Rh(II)-catalyzed C–H amination con-
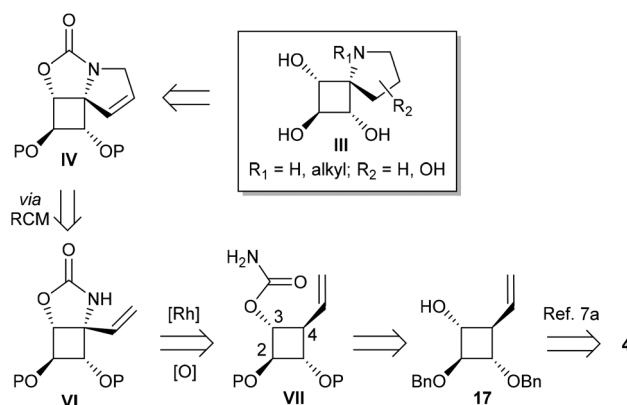
ditions. In each case, the starting material was the only compound that could be isolated by chromatography on a silica gel.

These results indicated that even in the absence of a strong electron-withdrawing group in the β-position, as in carbamate **9**, the cyclobutane tertiary C–H bond was not reactive enough to undergo the C–H insertion process.

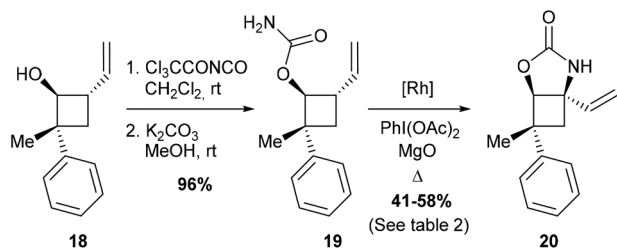## Third strategy: C–H amination of allylic C–H bonds using carbamates

Considering the apparent low reactivity of the tertiary C–H bond at C4 discussed above and the regioselectivity issues due to the high density of α-oxygenated C–H bonds, we decided to introduce a vinylic group onto the cyclobutane skeleton (Fig. 4). Allylic C–H bonds were indeed shown in several studies to be favoured over α-oxygenated C–H bonds.[12] To further discriminate between cyclobutane C–H bonds, the carbamate function was directly introduced on the 4-membered ring to deactivate the α-oxygenated C–H bond at C3. With these substrates **VII** thus designed, we shifted our focus towards iminosugars of type **III** based on a 5-azaspiro[3.4] octane skeleton (Fig. 4). The next logical step to rapidly obtain spiranic iminosugars was indeed to perform olefin ring-closing metathesis (RCM) of the C–H amination products **VI** after N-allylation.

Combining C–H amination and RCM has two main advantages in terms of synthetic efficiency. First of all, the vinylic group introduced to direct the C–H insertion at C4 is directly involved in the construction of the second ring of our azaspiranic targets. Secondly, no additional steps are required to avoid the poisoning of the metathesis catalyst since the nitrogen atom is deactivated by an electron-withdrawing group.[17] The feasibility of our strategy was first evaluated on a simplified cyclobutane derivative, carbamate **19** (Scheme 4). This compound was synthesized by carbamoylation of the readily available racemic alcohol **18** obtained in 2 steps from vinyl epoxide.[18] Another advantage of using **19** as a model substrate is that it reproduces the same structural pattern found in
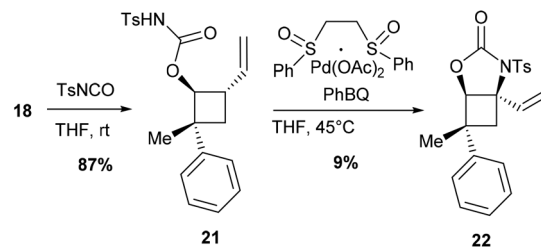

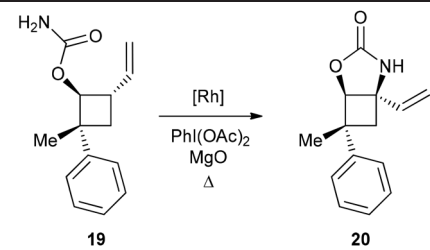Fig. 4 Retrosynthetic analysis towards azaspiro[3.4]octane derivatives.

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Org. Biomol. Chem., 2016, **14**, 2780–2796 | **2783**

Scheme 4 Model study on compound **19**.

Scheme 5 Model study on compound **21**.

Table 2 C–H amination of model carbamates **19** [a]

Entry	Cat. (mol%)	Solvent	Reaction time (h)	T	20 [b]	19 [c]
1	Rh$_2$(esp)$_2$ (10)	CH$_2$Cl$_2$	17	Δ	41%	39%
2	Rh$_2$(oct)$_4$ (10)	CH$_2$Cl$_2$	32	Δ	41%	6%
3	Rh$_2$(esp)$_2$ (20)	CH$_2$Cl$_2$	55	Δ	52%	19%
4	Rh$_2$(esp)$_2$ (15)	DCE	43	Δ	58%	16%
5 [d]	Rh$_2$(esp)$_2$ (15)	CH$_2$Cl$_2$	32	Δ	47%	22%

[a] See the Experimental section for the experimental conditions.
[b] Isolated yields. [c] Recovered after purification on a silica gel.
[d] PhI(OPiv)$_2$ was used instead of PhI(OAc)$_2$.

VII – a *trans*-1-carbamoyl-2-vinylcyclobutane motif – but with minimal regioselectivity issues.

Encouragingly, treatment of **19** with 10 mol% of Rh(esp)$_2$ or Rh$_2$(oct)$_4$ and stoichiometric amounts of PhI(OAc)$_2$ and MgO in CH$_2$Cl$_2$ provided the expected C–H insertion product **20** in 41% yield (Table 2, entries 1 and 2). Increasing the amount of catalyst to 20 mol% or performing the reaction in refluxing dichloroethane (DCE) led to improved yields up to 58% (entries 3 and 4). Replacing PhI(OAc)$_2$ with PhI(OPiv)$_2$ did not increase the efficiency of the C–H insertion process (entry 5). The modest yields observed for the formation of cyclic carbamate **20** further confirmed the low reactivity of cyclobutane C–H bonds towards catalytic C–H amination.

The C–H allylic bonds also provide an opportunity for performing C–H amination *via* π-allyl species. To apply the methodology recently developed by the group of White based on electrophilic Pd(II)/sulfoxide catalysis,[19] alcohol **18** was converted into the corresponding *N*-tosylcarbamate **21** by treatment with TsNCO (Scheme 5). Under standard allylic C–H amination conditions using phenyl bis-sulfoxide/Pd(OAc)$_2$ and a stoichiometric amount of phenyl-benzoquinone (PhBQ), the desired *N*-tosylcarbamate **22** was obtained in only 9% yield (15% based on the recovered starting materials). In addition,
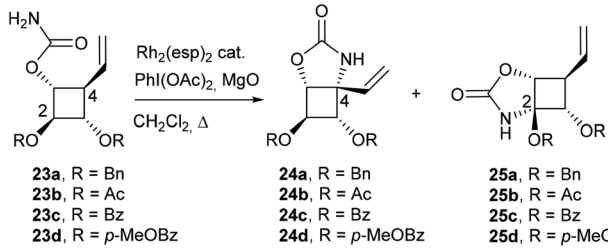
22 is obtained as a mixture with PhBQ since the two compounds are difficult to separate by flash chromatography. No improvement was obtained when the reaction was performed under an oxygen atmosphere or in the presence of additives including AcOH,[20] Na$_2$S$_2$O$_8$, PhI(OAc)$_2$ or Ag$_2$CO$_3$. To the best of our knowledge, this result is a very rare example of a C–H amination of a tertiary allylic C–H bond using White's methodology.[21]

Despite the modest yields observed in the model study, carbamate **23a** was synthesized by carbamoylation of alcohol **17**[7a,8] and subjected to a Rh(II)-catalyzed C–H amination (Table 3, entry 1). Disappointingly, in contrast to previous results obtained with pyran or acyclic substrates,[12] the regioselectivity of insertion was strongly in favor of the methine group adjacent to the oxygen atom over the allylic C–H bond at C4. After an extensive study, the best results in terms of yields and regioselectivity were obtained when carbamate **23a** was treated with 20 mol% of Rh$_2$(esp)$_2$ and stoichiometric amounts of PhI(OAc)$_2$ and MgO in refluxing CH$_2$Cl$_2$.[8] These reaction conditions led to a complete conversion of **23a** and to the desired allylic C–H insertion **24a** but in only 17% yield, carbamate **25a** being still the major product (56% yield). To overcome this unexpected obstacle, we designed a strategy to strongly disfavour the formation of the unwanted regioisomer **25**. Our objective was to reduce the electron density of the α-oxygenated C–H bond at C2 by using electron-withdrawing protecting groups instead of benzyloxy groups. However, such a tactic may be seen as a double-edged sword since the presence of three electron-withdrawing groups around the cyclobutane ring may also reduce the reactivity of the C–H bond at C4. Acetate and benzoate esters were firstly selected as hydroxyl-protecting groups.

To fine tune the electronic environment around the reactive cyclobutane C–H bond, *para*-methoxybenzoate ester **23d** was also prepared as a close analogue of substrate **23c**. The esters **23b**, **23c** and **23d** were synthesized in 2 steps from carbamate **23a** by deprotection of the benzyl group followed by treatment with Ac$_2$O, BzCl or *para*-methoxybenzoyl chloride (*p*-MeOBzCl) in the presence of pyridine (Scheme 6).

To our delight, the electron-withdrawing group strategy reached its goal, allowing complete regioselectivity towards the desired C–H insertion products **24** (Table 3, entries 2–6). As with substrate **23a**, the reaction time has to be relatively long (~24 h) to ensure total conversion of the starting material

2784 | *Org. Biomol. Chem.*, 2016, **14**, 2780–2796

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Table 3 C–H amination of carbamates **23** [a]

Entry	Rh$_2$(esp)$_2$ (mol%)	Reaction time (h)	R	δ(H2) ppm[b]	δ(H4) ppm[b]	**24**[c]	**25**[c]	**23**[d]
1	20	27	Bn	3.95	2.48	17%	56%	—
2	15	8	Ac	5.09	2.65	26%	—	10%
3	15	24	Ac	5.09	2.65	31%	—	—
4	20	23	p-MeOBz	5.49	2.85	40%	—	12%
5	20	23	Bz	5.53	2.90	40%	—	10%
6[e]	25	40	Bz	5.53	2.90	32%	—	23%

[a] See the Experimental section for the experimental conditions. [b] From the ^{1}H NMR spectrum of compounds **23** recorded in CDCl$_3$. [c] Isolated yields. [d] Recovered after purification on a silica gel. [e] DCE was used instead of CH$_2$Cl$_2$.
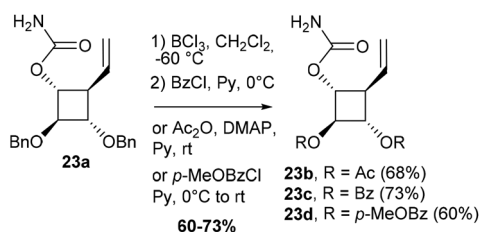
Scheme 6 Synthesis of compounds **23**.
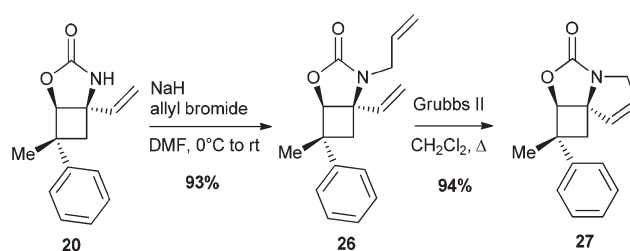
Scheme 7 Model study (RCM reaction).

(entries 2 and 3) and acetate-protected carbamate **24b** was obtained in up to 31% yield. The use of the more electron-withdrawing benzoate group was found to increase the yield by ~20% (entries 3 and 5). In contrast to the results obtained in the model study (Table 2), reactions performed in DCE do not increase the yield of the process (entry 6). The addition of an electron-donating group to the benzoate phenyl ring had no impact on the yield of the C–H amination reaction and carbamate **24d** was obtained in 40% yield (entry 4). As shown by the ^{1}H NMR of compounds **23** (Table 3), the signals of H2 shifted downfield upon increasing the electron-withdrawing ability of the hydroxyl protecting groups, an observation consistent with a decrease of electron density around H2. The H2 chemical shifts correlated nicely with the yields of carbamates **24** and the level of regiocontrol achieved. As suggested by the down-field shifts of H4 protons from 2.48 ppm (R = Bn) to 2.90 ppm (R = Bz), the addition of two electron-withdrawing groups impacted also the electron density at C4 and thus the efficiency of the desired C–H amination reaction. Despite the modest yields observed, the electron-withdrawing group strategy was nonetheless efficient if one considers the complete regiocontrol achieved and the yields obtained with the related carbamate **19**, a substrate with minimal regioselectivity issues. In addition, the yields of the C–H amination reaction provided

the azaspiranic intermediate **24c** in quantities sufficient to complete the synthesis of the targeted iminosugars **1–2**. To pursue our synthetic goal, we took advantage of the readily available model substrate **26** obtained by N-allylation of **20** to evaluate the key RCM step. Pleasingly, the highly constrained cyclobutane-containing tricycle **27** was obtained in 94% yield using 5 mol% Grubbs II catalyst in refluxing CH$_2$Cl$_2$ (Scheme 7). This result provides a further example of the power-fulness of the RCM process considering the large additional ring strain generated by the 5-membered ring closure.

The same process was applied to carbamate **24c** with a similar efficiency for the RCM step (89% yield) to provide the 5-azaspiro[3.4]octane skeleton of our targets. The spiranic iminosugars **1–2** were then obtained in 2 or 3 steps from the common intermediate **28** thus generated (Scheme 8).[8]

Biological evaluation

The potential of the three DNJ analogues **1–2** was first evaluated for the treatment of cystic fibrosis. This life-threatening inherited disease is caused by a mutation in the gene for the protein Cystic Fibrosis Transmembrane conductance Regulator (CFTR).[22] Zavesca™ (N-Bu DNJ), a clinical candidate for the treatment of cystic fibrosis,[22b] is able to act as a CFTR corrector
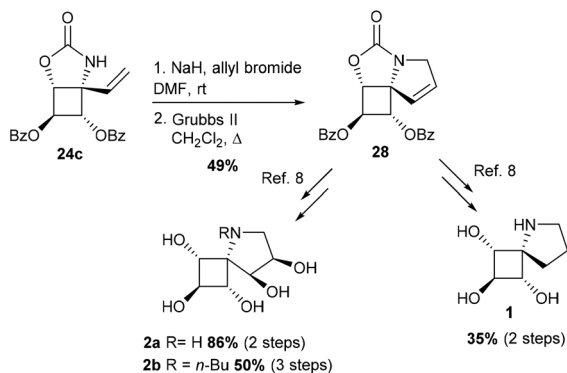
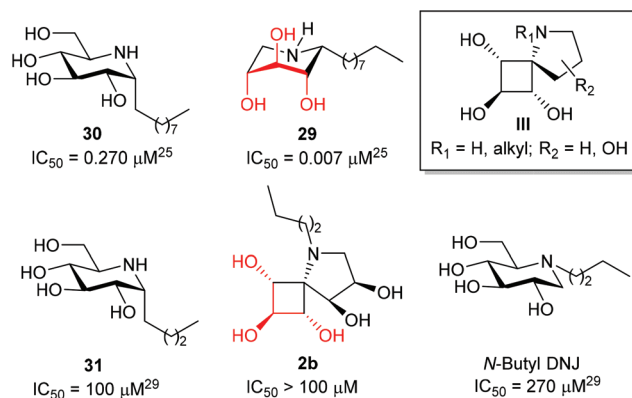**Scheme 8** Synthesis of spiranic iminosugars **1** and **2**.
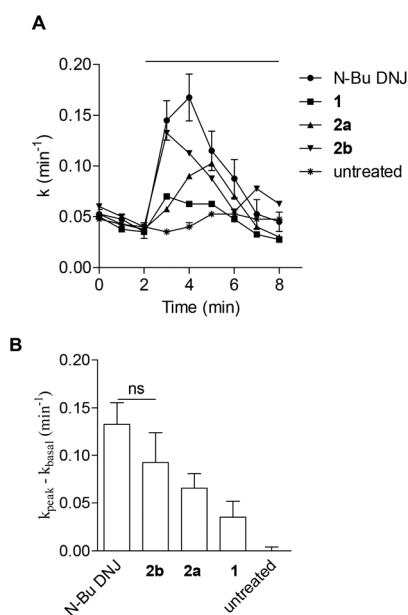

Fig. 6 Inhibition of GCase.

Fig. 5 (A) Rescue of functional F508del-CFTR activity: iodide efflux curves on untreated or iminosugar-treated F508del-CFTR stably transfected HeLa cells. Iodide effluxes were stimulated by forskolin/genistein as indicated by the horizontal bar above the traces. Each value represents the mean $\pm$ SEM (n = 4). (B) Summary of the functional evaluation of F508del-CFTR: histograms represent the mean ($\pm$SEM) of four experiments obtained by the iodide efflux technique in CF cells untreated or treated for 4 h with 100 μM of iminosugar as indicated. A mixture of forskolin (10 μM) + genistein (30 μM) was used to activate CFTR. ns, not significant.

by inhibiting endoplasmic reticulum-resident trimming α-glucosidases and thus overcoming the processing defect of the mutant protein.[23] To evaluate the impact of a constrained iminosugar conformation on F508del-CFTR defective trafficking, the rescue of the F508del-CFTR function was assessed using the iodide efflux technique on CF cells treated for 4 hours with 100 μM of iminosugars (Fig. 5).[24] In these experiments, N-Bu DNJ was used as a reference compound with regard to its therapeutic potential. Results presented in Fig. 5A show the

rescue of the F508del-CFTR function by N-Bu DNJ but also by N-butyl spiranic iminosugar **2b** and to a less extent by **2a**. The presence of a butyl chain and of more than three hydroxyl groups was found to play an important role since the best corrector of the spiranic series, iminosugar **2b**, displayed an F508del-CFTR activity rescue not significantly different from the N-Bu DNJ-induced one.

In our previous study on Gaucher disease, a rare genetic disorder caused by the deficiency of β-glucocerebrosidase (GCase), we identified α-1-C-nonyl-iminoxylitol (**29**) as a promising lead for a pharmacological chaperone therapy (Fig. 6).[25] This therapeutic strategy is based on the use of competitive inhibitors capable of enhancing GCase residual hydrolytic activity at sub-inhibitory concentrations.[26,27] Reversible competitive inhibitors are indeed believed to modify and/or stabilize the three-dimensional structure of the deficient but still catalytically active glycosidase, preventing its premature degradation by the endoplasmic reticulum quality-control system before trafficking to lysosomes.[27] α-1-C-Nonyl-iminoxylitol (**29**) was found to be a very specific nanomolar inhibitor of GCase.[25] It was hypothesized that the qualitative leap in inhibitory potency between **29** and **30**,[25] the corresponding analogue in the D-gluco series, was due to a piperidine ring inversion from a classical $^4C_1$(D) to a $^1C_4$(D) conformation in which all hydroxyl groups are axial and the alkyl chain is equatorial.[25,26,28]

In a preliminary study, we evaluate whether further improvement of the activity might be gained for structures of type **III** that may be considered constrained mimetics of iminosugar **29** with the hydroxyl groups in pseudo axial orientation. Considering that the presence of an alkyl chain is important for GCase inhibitory activity but cytotoxicity may be associated with long alkyl chain iminosugar derivatives, first preliminary inhibitory assays were performed with spiro-iminosugar **2b** (Fig. 6). This compound was found to display weak inhibitory activity (IC$_{50}$ > 100 μM) and showed no significant improvement in the inhibition of GCase relative to the corresponding analogues in the D-gluco series, α-1-C-butyl DNJ (**31**)[29] and N-butyl DNJ (Zavesca™).

2786 | Org. Biomol. Chem., 2016, **14**, 2780–2796

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Conclusions

In conclusion we have developed a synthetic route to conformationally constrained iminosugars based on four-membered ring-containing spirocycles. The key step of our strategy was the formation of the pivotal quaternary C–N bond of the 5-azaspiro[3.4]octane skeleton by way of Rh(ɪɪ)-catalyzed C(sp^3)–H amination. In addition to the goal of developing a new class of bioactive iminosugars, our aim was to explore the limits of this powerful stereospecific process with a series of substrates. The main anticipated challenge was to secure a high level of regioselectivity from polyoxygenated substrates with a high density of activated α-ethereal C–H bonds. An additional and rather unexpected issue was found to be the low reactivity of cyclobutane C–H bonds towards catalytic C–H amination, which led to modest yields and unusual regioselectivity. A complete stereocontrol could be nevertheless achieved by using a combination of electron-withdrawing and activating groups. The mere introduction of a vinylic group was indeed not sufficient to reach high regioselectivity even though insertion into allylic C–H bonds has been described to be favoured over α-ethereal C–H bonds. Consequently, electron-withdrawing protecting groups were required to reduce the electron density at the undesired C–H insertion site. First preliminary biological evaluations of the potential of the synthesized spiro-iminosugars for the treatment of Gaucher disease and cystic fibrosis were performed, which led to the identification of a new class of CFTR correctors.

Experimental section

Tetrahydrofuran (THF) was dried by passing through an activated alumina column under Ar or distilled over Na/benzophenone under Ar. Dichloromethane (CH$_2$Cl$_2$) and dichloroethane (DCE) were distilled over CaH$_2$ under Ar. Pyridine and triethylamine were distilled over KOH under Ar and stored over KOH. Dried DMF was purchased from Sigma-Aldrich. All the reactions were performed in standard glassware under Ar unless otherwise specified. Flash chromatographies were performed on silica gel 60 (230–400 mesh, 0.040–0.063 mm) purchased from E. Merck or using an automatic flash chromatography device. Thin Layer Chromatography (TLC) was performed on aluminum sheets coated with silica gel 60 F$_{254}$ purchased from E. Merck. IR spectra (cm^{-1}) were recorded on a Perkin-Elmer Spectrum One spectrophotometer. NMR spectra were recorded on 300 MHz or 400 MHz spectrometers with solvent peaks as the reference. Carbon multiplicities were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. The ^{1}H and ^{13}C signals were assigned by 2D experiments (COSY, HSQC, HMBC). For convenience, the assignment of ^{1}H and ^{13}C for all the molecules were based on the same numbering (see the ESI†). ESI-HRMS mass spectra were recorded on a TOF-spectrometer. Specific rotations were determined at room temperature (20 °C) on a Perkin-Elmer 241 polarimeter for sodium (λ =

589 nm). Rh$_2$(esp)$_2$ (CAS: 819050-89-0), Rh$_2$(OAc)$_4$ (CAS: 15956-28-2), Rh$_2$(oct)$_4$ (CAS: 73482-96-9) and Rh$_2$(tpa)$_4$ (CAS: 142214-04-8) were purchased from Sigma-Aldrich.

Ethyl 2-((1S,2S,3R,4R)-2,3-bis(benzyloxy)-4-((*tert*-butyldimethylsilyl)oxy)cyclobutyl)acetate (5)

To a solution of alcohol 4^{7a} (200 mg, 0.54 mmol, 1 equiv.) in CH$_2$Cl$_2$ (1 mL) were added TBSCl (122 mg, 0.81 mmol, 1.5 equiv.), DMAP (33 mg, 0.27 mmol, 0.5 equiv.) and Et$_3$N (0.15 mL, 1.08 mmol, 2 equiv.). The solution was stirred for 18.5 h. Water was added and the product was extracted with Et$_2$O (3×). The combined organic layer was dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1 : 19) to afford the desired cyclobutane 5 (209 mg, 80%) as a pale yellow oil.

R_f 0.26 (EtOAc/petroleum ether, 1 : 19), $[\alpha]_D^{20}$ +0.5 (c 1.0, CHCl$_3$), IR (film) 1733, 1097, 835 cm^{-1}, ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.41–7.28 (m, 10H, Ph), 4.66 (d, J = 11.7 Hz, 1H, CH$_2$Ph), 4.61 (d, J = 11.7 Hz, 1H, CH$_2$Ph), 4.56 (s, 2H, CH$_2$Ph), 4.16 (q, J = 7.1 Hz, 2H, CH$_2$CH$_3$), 3.83 (m, 1H, H-2), 3.65 (m, 1H, H-1 or H-3), 3.49 (m, 1H, H-1 or H-3), 2.57 (dd, J = 15.0, 5.9 Hz, 1H, H-1′a), 2.50 (dd, J = 14.9, 6.9 Hz, 1H, H-1′b), 2.17 (m, 1H, H-4), 1.28 (t, J = 7.2 Hz, 3H, CH$_2$CH$_3$), 0.95 (s, 9H, C(CH$_3$)$_3$), 0.14 (s, 3H, SiCH$_3$), 0.12 (s, 3H, SiCH$_3$), ^{13}C NMR (100 MHz, CDCl$_3$) δ 171.7 (CO), 138.4 (Cq-Ar), 138.2 (Cq-Ar), 128.42 (2 CH-Ar), 128.40 (2 CH-Ar), 127.8 (4 CH-Ar), 127.70 (CH-Ar), 127.67 (CH-Ar), 86.0 (C-2), 77.3 (C-1 or C-3), 71.6 (2 CH$_2$Ph), 71.1 (C-1 or C-3), 60.5 (CH$_2$CH$_3$), 41.2 (C-4), 36.3 (C-1′), 25.8 (C(CH$_3$)$_3$), 18.0 (C(CH$_3$)$_3$), 14.3 (CH$_2$CH$_3$), −4.5 (SiCH$_3$), −4.6 (SiCH$_3$), HRMS (ESI) m/z 507.250 ([M + Na]$^+$, calcd for C$_{28}$H$_{40}$O$_5$SiNa: 507.254).

2-((1S,2S,3R,4R)-2,3-Bis(benzyloxy)-4-((*tert*-butyldimethylsilyl)oxy)cyclobutyl)ethanol (6)

LiAlH$_4$ (23 mg, 0.61 mmol, 1.5 equiv.) was added to a solution of ester 5 (199 mg, 0.41 mmol, 1 equiv.) in THF (2.3 mL), cooled to 0 °C. The solution was stirred at rt for 2.5 h. After cooling to 0 °C, water (0.02 mL), 10% aqueous NaOH (0.03 mL) and water (0.05 mL) were successively added. The solution was stirred for 40 min at rt, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1 : 9 to 1 : 3) to afford the desired alcohol 6 (155 mg, 85%) as a colorless oil.

R_f 0.51 (EtOAc/petroleum ether, 1 : 3), $[\alpha]_D^{20}$ −5 (c 1.0, CHCl$_3$), IR (film) 3449, 1061, 836 cm^{-1}, ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.40–7.27 (m, 10H, Ph), 4.63 (d, J = 11.6 Hz, 1H, CH$_2$Ph), 4.61–4.54 (m, 2H, CH$_2$Ph), 4.52 (d, J = 11.6 Hz, 1H, CH$_2$Ph), 3.80 (t, J = 5.7 Hz, 1H, H-2), 3.67 (m, 2H, H-2′), 3.53 (m, 1H, H-1 or H-3), 3.36 (m, 1H, H-1 or H-3), 2.50 (t, J = 6.6 Hz, 1H, OH), 1.86–1.68 (m, 3H, H-4, H-1′), 0.90 (s, 9H, C(CH$_3$)$_3$), 0.11 (s, 3H, SiCH$_3$), 0.09 (s, 3H, SiCH$_3$), ^{13}C NMR (75 MHz, CDCl$_3$) δ 138.1 (Cq-Ar), 137.9 (Cq-Ar), 128.6 (2 CH-Ar), 128.5 (2 CH-Ar), 128.0 (3 CH-Ar), 127.9 (2 CH-Ar), 127.8 (CH-Ar), 86.0 (C-2), 77.8 (C-1 or C-3), 71.9 (C-1 or C-3), 71.8 (CH$_2$Ph), 71.7 (CH$_2$Ph), 61.9 (C-2′), 42.7 (C-4), 34.9 (C-1′),

25.8 (C(CH_3)_3), 17.9 (*C*(CH_3)_3), −4.4 (SiCH_3), −4.5 (SiCH_3), **HRMS** (ESI) *m/z* 465.241 ([M + Na]^+, calcd For C_26H_38O_4SiNa: 465.243).

2-((1R,2S,3S,4R)-2,3-Bis(benzyloxy)-4-((tert-butyldimethylsilyl) oxy)cyclobutyl)ethyl sulfamate (7)

Preparation of sulfamoyl chloride: formic acid (0.78 mL, 20.7 mmol, 0.9 equiv.) was added slowly to chlorosulfonyl iso-cyanate (2 mL, 23.0 mmol, 1 equiv.) cooled at 0 °C. The solution was stirred at rt for 4.5 h. The solution was cooled at 0 °C and benzene (30 mL) was added. The solution was filtered and concentrated under reduced pressure to give a white to brown solid of ClSO_2NH_2 (1.44 g, 40%) which was used without further purification.

IR (neat) 1374, 1174 cm^{−1}.

DMAP (91 mg, 0.75 mmol, 2 equiv.) followed by ClSO_2NH_2 (65 mg, 0.56 mmol, 1.5 equiv.) were added to a solution of **6** (165 mg, 0.37 mmol, 1 equiv.) in CH_2Cl_2 (5.8 mL). After 2 h of stirring, a second portion of DMAP (91 mg, 0.75 mmol, 2 equiv.) followed by ClSO_2NH_2 (65 mg, 0.56 mmol, 1.5 equiv.) were added. The solution was stirred for 15 h. Water (a few drops) was added and the solution was filtered. The organic layer was dried over MgSO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1 : 5 to 1 : 1) to afford **7** (130 mg, 67%) as a colorless oil.

*R*_f 0.42 (EtOAc/petroleum ether, 1 : 3), [*α*]_D^{20} +5 (*c* 0.9, MeOH), **IR** (film) 3355, 1359 cm^{−1}, **¹H NMR** (300 MHz, CDCl_3) δ 7.41–7.27 (m, 10H, Ph), 4.75 (s, 2H, NH_2), 4.65 (d, *J* = 11.7 Hz, 1H, C*H*_2Ph), 4.60–4.52 (m, 2H, C*H*_2Ph), 4.48 (d, *J* = 11.2 Hz, 1H, C*H*_2Ph), 4.22 (m, 2H, H-2′), 3.79 (t, *J* = 5.6 Hz, 1H, H-2), 3.53 (m, 1H, H-1 or H-3), 3.39 (m, 1H, H-1 or H-3), 2.07 (m, 1H, H-4), 1.84 (m, 2H, H-1′), 0.91 (s, 9H, C(CH_3)_3), 0.11 (s, 3H, SiCH_3), 0.09 (s, 3H, SiCH_3), **¹³C NMR** (75 MHz, CDCl_3) δ 137.9 (Cq-Ar), 137.5 (Cq-Ar), 128.8 (2 CH-Ar), 128.6 (2 CH-Ar), 128.4 (2 CH-Ar), 128.3 (CH-Ar), 128.0 (3 CH-Ar), 86.3 (C-2), 77.6 (C-1 or C-3), 72.3 (C-1 or C-3), 71.79 (*C*H_2Ph), 71.76 (*C*H_2Ph), 69.6 (C-2′), 41.1 (C-4), 31.6 (C-1′), 25.9 (C(*C*H_3)_3), 18.0 (*C*(CH_3)_3), −4.2 (SiCH_3), −4.5 (SiCH_3), **HRMS** (ESI) *m/z* 544.212 ([M + Na]^+, calcd for C_26H_39NO_6SSiNa: 544.216).

2-((1S,2R,3R,4S)-3-(Benzyloxy)-2-((tert-butyldimethylsilyl)oxy)-4-hydroxycyclobutyl)ethyl sulfamate (8)

MgO (10 mg, 0.25 mmol, 2.3 equiv.), PhI(OAc)_2 (39 mg, 0.12 mmol, 1.1 equiv.) and Rh_2(OAc)_2 (2.4 mg, 0.0055 mmol, 0.05 equiv.) were added to a solution of **7** (58 mg, 0.11 mmol, 1 equiv.) in degassed CH_2Cl_2 (0.69 mL). The solution was stirred at rt for 7 h. After filtration through Celite, the solution was concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1 : 7 to 4 : 1) to afford **8** (15 mg, 32%) as a white solid.

*R*_f 0.25 (EtOAc/petroleum ether, 2 : 1), [*α*]_D^{20} −8 (*c* 1.0, MeOH), **IR** (neat) 3386, 1385 cm^{−1}, **¹H NMR** (300 MHz, CD_3OD) δ 7.40–7.22 (m, 5H, Ph), 4.69 (d, *J* = 11.7 Hz, 1H, C*H*_2Ph), 4.57 (d, *J* = 11.7 Hz, 1H, C*H*_2Ph), 4.20 (t, *J* = 6.9 Hz, 2H, H-2′), 3.60 (t, *J* = 6.1 Hz, 1H, H-2), 3.48 (m, 1H, H-1 or H-3),

3.40 (m, 1H, H-1 or H-3), 2.12–1.87 (m, 2H, H-1′), 1.66 (m, 1H, H-4), 0.90 (s, 9H, C(CH_3)_3), 0.10 (s, 6H, 2 SiCH_3), **¹³C NMR** (75 MHz, CD_3OD) δ 139.6 (Cq-Ar), 129.5 (2 CH-Ar), 129.0 (2 CH-Ar), 128.8 (CH-Ar), 88.7 (C-2), 72.60 (C-1 or C-3), 72.57 (C-1 or C-3), 72.3 (*C*H_2Ph), 69.2 (C-2′), 44.0 (C-4), 32.5 (C-1′), 26.4 (C(*C*H_3)_3), 18.9 (*C*(CH_3)_3), −4.2 (SiCH_3), −4.3 (SiCH_3), **HRMS** (ESI) *m/z* 454.169 ([M + Na]^+, calcd for C_19H_33NO_6SSiNa: 454.169).

Ethyl 2-((1S,2S,3R,4R)-2,3-bis(benzyloxy)-4-(carbamoyloxy) cyclobutyl)acetate (9a)

Trichloroacetyl isocyanate (84 μL, 0.70 mmol, 1.2 equiv.) was added to a solution of **4**^{7a} (218 mg, 0.59 mmol, 1 equiv.) in CH_2Cl_2 (1.6 mL) cooled to 0 °C. The solution was stirred at rt for 7 h and concentrated under reduced pressure. The residue was dissolved in MeOH (1.3 mL) and K_2CO_3 (8 mg, 0.059 mmol, 0.1 equiv.) was added. The solution was stirred for 14 h. Saturated aqueous NH_4Cl (2 mL) was added and the product was extracted with CH_2Cl_2 (3×). The combined organic layer was washed with brine, dried over MgSO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1 : 5 to 1 : 1) to afford the desired carbamate **9a** (205 mg, 84%) as a white solid.

*R*_f 0.45 (EtOAc/petroleum ether, 1 : 2), [*α*]_D^{20} = −12 (*c* 1.0, MeOH), **IR** (neat) 3440, 1723, 1666, cm^{−1}, **¹H NMR** (300 MHz, CDCl_3) δ 7.40–7.23 (m, 10H, Ph), 4.64–4.46 (m, 7H, 2 CH_2Ph, NH_2, H-3), 4.12 (q, *J* = 7.2 Hz, 2H, C*H*_2CH_3), 3.94 (m, 1H, H-2), 3.55 (m, 1H, H-1), 2.65 (dd, *J* = 16.1, 7.4 Hz, 1H, H-1′a), 2.56 (dd, *J* = 16.1, 6.2 Hz, 1H, H-1′b), 2.27 (m, 1H, H-4), 1.24 (t, *J* = 7.1 Hz, 3H, CH_2C*H*_3), **¹³C NMR** (75 MHz, MeOD) δ 173.4 (CO), 158.8 (NCO), 139.4 (Cq-Ar), 139.2 (Cq-Ar), 129.38 (2 CH-Ar), 129.35 (2 CH-Ar), 129.1 (2 CH-Ar), 128.9 (2 CH-Ar), 128.8 (2 CH-Ar), 83.8 (C-2), 77.9 (C-1), 73.2 (C-3), 72.7 (*C*H_2Ph), 72.3 (*C*H_2Ph), 61.7 (*C*H_2CH_3), 40.4 (C-4), 36.8 (C-1′), 14.5 (CH_2*C*H_3), **HRMS** (ESI) *m/z* 436.172 ([M + Na]^+, calcd for C_23H_27NO_6Na: 436.173).

(1S,2R,3R,4S)-3-(Carbamoyloxy)-4-(2-ethoxy-2-oxoethyl) cyclobutane-1,2-diyl diacetate (9b)

Pd(OH)_2/C 20% (15 mg) and HCO_2H (2 drops) were added to a solution of **9a** (95 mg, 0.23 mmol, 1 equiv.) in EtOH (3 mL). The solution was placed under a H_2 atmosphere and stirred until disappearance of the starting material (25 h). The solution was filtered through Celite and concentrated under reduced pressure. The residue was dissolved in pyridine (6 mL) and Ac_2O (1.7 mL) was added. The solution was stirred at rt for 17 h. The solution was concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1 : 1 to 2 : 1) to afford the desired ester **9b** (66 mg, 90%) as a white solid.

*R*_f 0.31 (silica gel, EtOAc/petroleum ether, 2 : 1), [*α*]_D^{20} = +2 (*c* 1.0, CHCl_3), **IR** (film) 3474, 1725, 1225 cm^{−1}, **¹H NMR** (300 MHz, CDCl_3) δ 5.09 (t, *J* = 6.3 Hz, 1H, H-2), 5.02 (br s, 2H, NH_2), 4.68 (dd, *J* = 7.7, 6.3 Hz, 1H, H-1 or H-3), 4.61 (dd, *J* = 7.8, 6.3 Hz, 1H, H-1 or H-3), 4.08 (q, *J* = 7.2 Hz, 2H, C*H*_2CH_3),

2788 | *Org. Biomol. Chem.*, 2016, **14**, 2780–2796

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2.72 (m, 2H, H-1'), 2.38 (m, 1H, H-4), 2.04 (s, 3H, CH$_3$), 2.03 (s, 3H, CH$_3$), 1.21 (t, J = 7.2 Hz, 3H, CH$_2$CH$_3$), ^{13}C NMR (75 MHz, CDCl$_3$) δ 171.4 (CO), 170.4 (CO), 170.0 (CO), 155.8 (NCO), 74.4 (C-2), 70.7 (C-1 or C-3), 70.0 (C-1 or C-3), 60.7 (CH$_2$CH$_3$), 38.9 (C-4), 35.4 (C-1'), 20.8 (2 CH$_3$), 14.2 (CH$_2$CH$_3$), **HRMS** (ESI) m/z 340.099 ([M + Na]$^+$, calcd for C$_{13}$H$_{19}$NO$_8$Na: 340.100).

General procedure A for C–H amination of carbamates (Tables 1–3)

MgO (2.3 equiv.), PhI(OAc)$_2$ (1.4 equiv.) and catalyst (2 mol%–20 mol%) were added to a solution of carbamate (1 equiv., 0.2 mmol) in degassed CH$_2$Cl$_2$, DCE or benzene (1.8 ml). The solution was refluxed (CH$_2$Cl$_2$, DCE) or heated at 60 °C (benzene). After cooling, the solution was filtered through a pad of Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography.

Ethyl 2-((1R,5R,6S,7S)-5,6-bis(benzyloxy)-3-oxo-2-oxa-4-azabicyclo[3.2.0]heptan-7-yl)acetate (11a) (Table 1, entries 1–3)

According to general procedure A, **11a** was obtained as a white solid after flash chromatography (EtOAc/petroleum ether, 1:5 to 1:1).

R_f 0.22 (EtOAc/petroleum ether, 1:2), $[\alpha]_D^{20}$ −25 (c 1.0, CHCl$_3$), **IR** (film) 3286, 1757, 1730 cm^{-1}, ^{1}**H NMR** (300 MHz, CDCl$_3$) δ 7.40–7.24 (m, 10H, Ph), 5.61 (s, 1H, NH), 4.62–4.48 (m, 3H, CH$_2$Ph), 4.48–4.41 (m, 2H, CH$_2$Ph, H-3), 4.14 (q, J = 7.1 Hz, 2H, CH$_2$CH$_3$), 4.00 (dd, J = 6.9, 1.1 Hz, 1H, H-1), 2.56 (dd, J = 16.0, 5.9 Hz, 1H, H-1'a), 2.44 (dd, J = 16.0, 7.4 Hz, 1H, H-1'b), 2.33 (m, 1H, H-4), 1.24 (t, J = 7.1 Hz, 3H, CH$_2$CH$_3$), ^{13}C **NMR** (75 MHz, CDCl$_3$) δ 170.9 (CO), 158.7 (NCO), 137.4 (Cq-Ar), 136.9 (Cq-Ar), 128.69 (2 CH-Ar), 128.66 (2 CH-Ar), 128.4 (CH-Ar), 128.3 (2 CH-Ar), 128.2 (CH-Ar), 127.8 (2 CH-Ar), 91.7 (C-2), 80.8 (C-1 or C-3), 75.8 (C-1 or C-3), 72.8 (CH$_2$Ph), 65.8 (CH$_2$Ph), 61.0 (CH$_2$CH$_3$), 42.3 (C-4), 34.7 (C-1'), 14.3 (CH$_2$CH$_3$), **HRMS** (ESI) m/z 434.154 ([M + Na]$^+$, calcd for C$_{23}$H$_{25}$NO$_6$Na: 434.157).

Ethyl 2-(N-tertbutyloxycarbonyl-(1R,5R,6S,7S)-5,6-bis(benzyloxy)-3-oxo-2-oxa-4-azabicyclo[3.2.0]heptan-7-yl)acetate (12)

Boc$_2$O (83 mg, 0.38 mmol, 2 equiv.), Et$_3$N (53 μL, 0.38 mmol, 2 equiv.) and DMAP (7 mg, 0.057 mmol, 0.3 equiv.) were added to a solution of **11a** (78 mg, 0.19 mmol, 1 equiv.) in CH$_2$Cl$_2$ (5 mL). The solution was stirred for 3 h and concentrated under reduced pressure. The residue was dissolved in EtOAc (6 mL). The organic phase was washed with water and brine, dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:5 to 1:2) to afford the desired bicyclic compound **12** (82 mg, 84%) as a white solid.

R_f 0.56 (EtOAc/petroleum ether, 1:2), $[\alpha]_D^{20}$ −42 (c 1.0, CHCl$_3$), **IR** (film) 1816, 1736 cm^{-1}, ^{1}**H NMR** (300 MHz, CDCl$_3$) δ 7.40–7.24 (m, 10H, Ph), 4.78 (d, J = 12.1 Hz, 1H, CH$_2$Ph), 4.59 (d, J = 11.2 Hz, 1H, CH$_2$Ph), 4.53 (d, J = 11.9 Hz, 1H, CH$_2$Ph), 4.47 (d, J = 11.2 Hz, 1H, CH$_2$Ph), 4.36 (m, 1H, H-1 or H-3), 4.10 (q, J = 7.1 Hz, 2H, CH$_2$CH$_3$), 4.09–4.02 (m, 1H, H-1 or H-3),

2.50 (m, 1H, H-1'a), 2.41–2.27 (m, 2H, H-1'b, H-4), 1.47 (s, 9H, C(CH$_3$)$_3$), 1.22 (t, J = 7.2 Hz, 3H, CH$_2$CH$_3$), ^{13}C **NMR** (75 MHz, CDCl$_3$) δ 170.7 (CO), 152.8 (NCO), 149.1 (NCO), 137.7 (Cq-Ar), 136.4 (Cq-Ar), 128.7 (2 CH-Ar), 128.5 (2 CH-Ar), 128.3 (CH-Ar), 128.0 (3 CH-Ar), 127.8 (2 CH-Ar), 94.3 (C-2), 84.2 (C(CH$_3$)$_3$), 80.2 (C-1 or C-3), 73.1 (CH$_2$Ph), 72.8 (C-1 or C-3), 66.4 (CH$_2$Ph), 61.1 (CH$_2$CH$_3$), 42.3 (C-4), 34.5 (C-1'), 28.0 (C(CH$_3$)$_3$), 14.3 (CH$_2$CH$_3$), **HRMS** (ESI) m/z 534.204 ([M + Na]$^+$, calcd for C$_{28}$H$_{33}$NO$_8$Na: 534.204).

Ethyl 2-((1R,2S,3S,4R)-2,3-bis(benzyloxy)-3-((tert-butoxycarbonyl)amino)-4-hydroxycyclobutyl)acetate (13)

Cs$_2$CO$_3$ (10 mg, 0.029 mmol, 0.2 equiv.) was added to a solution of **12** (83 mg, 0.16 mmol, 1 equiv.) in EtOH (6 mL). The solution was stirred for 21 h and concentrated under reduced pressure. Water (2 mL) was added and pH was adjusted to 7 with 0.1 N HCl. The product was extracted with CH$_2$Cl$_2$ (5×). The combined organic layer was dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:5 to 1:1) to afford the desired cyclobutane **13** (57 mg, 72%) as a colorless oil.

R_f 0.49 (EtOAc/petroleum ether, 1:2), $[\alpha]_D^{20}$ −25 (c 1.0, CHCl$_3$), **IR** (film) 3417, 1732, 1483 cm^{-1}, ^{1}**H NMR** (300 MHz, CDCl$_3$) δ 7.40–7.23 (m, 10H, Ph), 5.98 (br s, 1H, NH), 4.61 (d, J = 11.7 Hz, 1H, CH$_2$Ph), 4.56 (d, J = 11.9 Hz, 1H, CH$_2$Ph), 4.55 (d, J = 11.4 Hz, 1H, CH$_2$Ph), 4.43 (d, J = 11.6 Hz, 1H, CH$_2$Ph), 4.13 (q, J = 7.2 Hz, 2H, CH$_2$CH$_3$), 3.91 (d, J = 7.8 Hz, 1H, H-1 or H-3), 3.56 (d, J = 7.8 Hz, 1H, H-1 or H-3), 2.51 (dd, J = 6.9, 2.3 Hz, 2H, H-1'), 2.24 (m, 1H, H-4), 1.45 (s, 9H, C(CH$_3$)$_3$), 1.24 (t, J = 7.1 Hz, 3H, CH$_2$CH$_3$), ^{13}C **NMR** (75 MHz, CDCl$_3$) δ 172.3 (CO), 156.3 (NCO), 138.1 (Cq-Ar), 137.6 (Cq-Ar), 128.6 (2 CH-Ar), 128.5 (2 CH-Ar), 128.21 (CH-Ar), 128.17 (2 CH-Ar), 127.9 (2 CH-Ar), 127.7 (CH-Ar), 89.3 (C(CH$_3$)$_3$ or C-2), 80.9 (C(CH$_3$)$_3$ or C-2), 77.7 (C-1 or C-3), 73.6 (C-1 or C-3), 72.6 (CH$_2$Ph), 65.7 (CH$_2$Ph), 60.8 (CH$_2$CH$_3$), 41.8 (C-4), 36.2 (C-1'), 28.3 (C(CH$_3$)$_3$), 14.3 (CH$_2$CH$_3$), **HRMS** (ESI) m/z 508.223 ([M + Na]$^+$, calcd for C$_{27}$H$_{35}$NO$_7$Na: 508.231).

Ethyl 2-((1S,2S,3R,4R)-2,3-bis(benzyloxy)-3-((tert-butoxycarbonyl)amino)-4-(carbamoyloxy)cyclobutyl)acetate (14)

Trichloroacetyl isocyanate (35 μL, 0.29 mmol, 1.3 equiv.) was added to a solution of **13** (109 mg, 0.22 mmol, 1 equiv.) in CH$_2$Cl$_2$ (1 mL) cooled to 0 °C. The solution was stirred at rt for 16 h and concentrated under reduced pressure. The residue was dissolved in MeOH (0.7 mL) and K$_2$CO$_3$ (3 mg, 0.022 mmol, 0.1 equiv.) was added. The solution was stirred for 7.5 h. Saturated aqueous NH$_4$Cl (2 mL) was added and the product was extracted with CH$_2$Cl$_2$ (3×). The combined organic layer was washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1:2 to 1:1) to afford the desired carbamate **14** (101 mg, 85%) as a white solid.

R_f 0.13 (silica gel, EtOAc/petroleum ether, 1 : 2), $[\alpha]_D^{20}$ −33 (*c* 1.0, CHCl$_3$), **IR** (film) 3423, 2931, 1724, 1158 cm^{-1}, **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.37–7.17 (m, 10H, Ph), 5.69 (br s, 1H, N*H*Boc), 4.87 (br s, 2H, NH$_2$), 4.78 (d, *J* = 7.6 Hz, 1H, H-1 or H-3), 4.65 (m, 1H, C*H*$_2$Ph), 4.56–4.37 (m, 3H, C*H*$_2$Ph), 4.05 (q, *J* = 7.1 Hz, 2H, C*H*$_2$CH$_3$), 3.58 (d, *J* = 7.5 Hz, 1H, H-1 or H-3), 2.59–2.44 (m, 2H, H-1′), 2.38 (m, 1H, H-4), 1.42 (s, 9H, C(CH$_3$)$_3$), 1.18 (t, *J* = 7.2 Hz, 3H, CH$_2$C*H*$_3$), **^{13}C NMR** (100 MHz, CDCl$_3$) δ 171.5 (CO), 155.3 (2 NCO), 138.2 (Cq-Ar), 137.7 (Cq-Ar), 128.6 (2 CH-Ar), 128.4 (3 CH-Ar), 128.1 (3 CH-Ar), 127.9 (CH-Ar), 127.6 (CH-Ar), 89.3 (C-2), 79.8 (*C*(CH$_3$)$_3$), 78.5 (C-1 or C-3), 73.4 (C-1 or C-3), 73.0 (*C*H$_2$Ph), 65.9 (*C*H$_2$Ph), 60.8 (*C*H$_2$CH$_3$), 40.6 (C-4), 36.0 (C-1′), 28.3 (C(*C*H$_3$)$_3$), 14.3 (CH$_2$*C*H$_3$), **HRMS** (ESI) *m/z* 551.230 ([M + Na]$^+$, calcd for C$_{28}$H$_{36}$N$_2$O$_8$Na: 551.236).

(1*S*,2*S*,3*R*,4*R*)-2,3-Bis(benzyloxy)-4-((*tert*-butyldimethylsilyl)oxy)cyclobutyl)methyl carbamate (16a)

Trichloroacetyl isocyanate (27 μL, 0.22 mmol, 1.3 equiv.) was added to a solution of **15**^{7a} (74 mg, 0.17 mmol, 1 equiv.) in CH$_2$Cl$_2$ (0.5 mL) cooled to 0 °C. The solution was stirred for 15 h and concentrated under reduced pressure. The residue was dissolved in MeOH (0.42 mL) and K$_2$CO$_3$ (2 mg, 0.017 mmol, 0.1 equiv.) was added. The solution was stirred for 23.5 h. Saturated aqueous NH$_4$Cl (1 mL) was added and the product was extracted with CH$_2$Cl$_2$ (3×). The combined organic layer was washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1 : 5 to 1 : 3) to afford the desired carbamate **16a** (76 mg, 93%) as a white solid.

R_f 0.41 (EtOAc/petroleum ether, 1 : 2), $[\alpha]_D^{20}$ −2 (*c* 1.0, CHCl$_3$), **IR** (film) 3353, 1720, 1331 cm^{-1}, **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.30–7.16 (m, 10H, Ph), 4.64 (br s, 2H, NH$_2$), 4.55 (d, *J* = 11.7 Hz, 1H, C*H*$_2$Ph), 4.49 (d, *J* = 11.7 Hz, 1H, C*H*$_2$Ph), 4.48 (d, *J* = 11.9 Hz, 1H, C*H*$_2$Ph), 4.43 (d, *J* = 11.7 Hz, 1H, C*H*$_2$Ph), 4.09 (m, 2H, H-1′), 3.76 (t, *J* = 5.6 Hz, 1H, H-2), 3.59 (m, 1H, H-1 or H-3), 3.41 (m, 1H, H-1 or H-3), 1.93 (m, 1H, H-4), 0.82 (s, 9H, C(CH$_3$)$_3$), 0.02 (s, 3H, CH$_3$), 0.00 (s, 3H, CH$_3$), **^{13}C NMR** (75 MHz, CDCl$_3$) δ 156.8 (NCO), 138.2 (Cq-Ar), 138.1 (Cq-Ar), 128.54 (2 CH-Ar), 128.52 (2 CH-Ar), 127.92 (2 CH-Ar), 127.86 (4 CH-Ar), 86.0 (C-2), 74.7 (C-1 or C-3), 71.74 (*C*H$_2$Ph), 71.73 (*C*H$_2$Ph), 68.4 (C-1 or C-3), 63.9 (C-1′), 44.3 (C-4), 25.8 (C(*C*H$_3$)$_3$), 18.0 (*C*(CH$_3$)$_3$), −4.5 (CH$_3$), −4.7 (CH$_3$), **HRMS** (ESI) *m/z* 494.237 ([M + Na]$^+$, calcd for C$_{26}$H$_{37}$NO$_5$SiNa: 494.233).

(1*R*,2*S*,3*S*,4*R*)-2,3-Bis(benzyloxy)-4-hydroxycyclobutyl)methyl carbamate (16b)

HCl (2 M, 0.5 mL, 1.0 mmol, 2 equiv.) was added to a solution of **16a** (240 mg, 0.51 mmol, 1 equiv.) in MeOH (2 mL). The solution was stirred at rt for 2.5 h. NaHCO$_3$ was added and the solution was stirred for 5 min. Water was added and the product was extracted with EtOAc (3×). The combined organic layer was dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash

chromatography (MeOH/CH$_2$Cl$_2$, 5 : 95) to afford the desired alcohol **16b** (155 mg, 85%) as a white solid.

R_f 0.16 (MeOH/CH$_2$Cl$_2$, 5 : 95), $[\alpha]_D^{20}$ −4 (*c* 1.0, CHCl$_3$), **IR** (film) 3351, 1705, 1331 cm^{-1}, **^{1}H NMR** (300 MHz, CD$_3$OD) δ 7.39–7.23 (m, 10H, Ph), 4.65 (d, *J* = 11.7 Hz, 1H, C*H*$_2$Ph), 4.57 (d, *J* = 11.7 Hz, 1H, C*H*$_2$Ph), 4.56 (d, *J* = 11.7 Hz, 1H, C*H*$_2$Ph), 4.51 (d, *J* = 11.9 Hz, 1H, C*H*$_2$Ph), 4.12 (d, *J* = 5.1 Hz, 2H, H-1′), 3.78 (t, *J* = 5.8 Hz, 1H, H-2), 3.57 (m, 1H, H-1 or H-3), 3.49 (m, 1H, H-1 or H-3), 1.92 (m, 1H, H-4), **^{13}C NMR** (75 MHz, CD$_3$OD) δ 159.8 (NCO), 139.6 (Cq-Ar), 139.4 (Cq-Ar), 129.36 (2 CH-Ar), 129.34 (2 CH-Ar), 129.0 (4 CH-Ar), 128.74 (CH-Ar), 128.70 (CH-Ar), 86.6 (C-2), 75.7 (C-1 or C-3), 72.6 (*C*H$_2$Ph), 72.2 (*C*H$_2$Ph), 68.9 (C-1 or C-3), 64.4 (C-1′), 45.5 (C-4), **HRMS** (ESI) *m/z* 380.145 ([M + Na]$^+$, calcd for C$_{20}$H$_{23}$NO$_5$Na: 380.147).

(1*R*,2*R*,3*S*,4*S*)-2,3-Bis(benzyloxy)-4-((carbamoyloxy)methyl)cyclobutyl acetate (16c)

Ac$_2$O (1 mL) was added to a solution of **16b** (68 mg, 0.19 mmol, 1 equiv.) in pyridine (5 mL). The solution was stirred at rt for 15 h. Water was added and the product was extracted with EtOAc (1×). The organic layer was washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1 : 1) to afford the desired ester **16c** (71 mg, 93%) as a white solid.

R_f 0.17 (EtOAc/petroleum ether, 1 : 1), $[\alpha]_D^{20}$ = −5 (*c* 1.0, CHCl$_3$), **IR** (film) 3363, 2923, 1738, 1238 cm^{-1}, **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.41–7.24 (m, 10H, Ph), 4.71 (br s, 2H, NH$_2$), 4.63–4.55 (m, 4H, H-1 or H-3, C*H*$_2$Ph), 4.52 (d, *J* = 11.7 Hz, 1H, C*H*$_2$Ph), 4.28 (dd, *J* = 11.4, 4.5 Hz, 1H, H-1′a), 4.18 (dd, *J* = 11.4, 5.5 Hz, 1H, H-1′b), 3.97 (t, *J* = 5.8 Hz, 1H, H-2), 3.66 (m, 1H, H-1 or H-3), 2.13 (m, 1H, H-4), 2.03 (s, 3H, CH$_3$), **^{13}C NMR** (75 MHz, CDCl$_3$) δ 170.3 (CO), 156.7 (NCO), 138.0 (Cq-Ar), 137.8 (Cq-Ar), 128.59 (2 CH-Ar), 128.57 (2 CH-Ar), 128.1 (2 CH-Ar), 128.01 (CH-Ar), 127.98 (CH-Ar), 127.9 (2 CH-Ar), 82.7 (C-2), 74.7 (C-1 or C-3), 72.0 (*C*H$_2$Ph), 71.8 (*C*H$_2$Ph), 69.2 (C-1 or C-3), 63.6 (C-1′), 42.6 (C-4), 21.0 (CH$_3$), **HRMS** (ESI) *m/z* 422.153 ([M + Na]$^+$, calcd for C$_{22}$H$_{25}$NO$_6$Na: 422.157).

(1*S**,2*R**,4*S**)-2-Methyl-2-phenyl-4-vinylcyclobutyl carbamate (19)

Trichloroacetyl isocyanate (0.11 mL, 0.94 mmol, 1.3 equiv.) was added to a solution of **18**^{18} (135 mg, 0.72 mmol, 1 equiv.) in CH$_2$Cl$_2$ (2 mL) cooled to 0 °C. The solution was stirred at rt for 15 h and concentrated under reduced pressure. The residue was dissolved in MeOH (1.8 mL) and K$_2$CO$_3$ (10 mg, 0.072 mmol, 0.1 equiv.) was added. The solution was stirred for 8 h. Saturated aqueous NH$_4$Cl (2 mL) was added and the product was extracted with CH$_2$Cl$_2$ (3×). The combined organic layer was washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1 : 5 to 1 : 3) to afford the desired carbamate **19** (169 mg, 96%) as a white solid.

R_f 0.44 (EtOAc/toluene, 2 : 8), **IR** (neat) 3354, 1715, cm^{-1}, **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.37–7.27 (m, 2H, Ph), 7.24–7.14

2790 | *Org. Biomol. Chem.*, 2016, **14**, 2780–2796

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(m, 3H, Ph), 5.99 (ddd, J = 17.2 Hz, 10.3, 6.6 Hz, 1H, H-1′), 5.15 (d, J = 8.0 Hz, 1H, H-3), 5.08 (dt, J = 17.5, 1.5 Hz, 1H, H-2′a), 5.02 (dt, J = 10.4, 1.4 Hz, 1H, H-2′b), 4.92 (br s, 2H, NH$_2$), 3.14–3.01 (m, 1H, H-4), 2.20 (t, J = 10.4 Hz, 1H, H-1a), 1.84 (t, J = 10.3 Hz, 1H, H-1b), 1.46 (s, 3H, CH$_3$), ^{13}C NMR (100 MHz, CDCl$_3$) δ 156.3 (NCO), 149.8 (Cq-Ar), 139.0 (C-1′), 128.5 (2 CH-Ar), 126.0 (CH-Ar), 125.1 (2 CH-Ar), 114.6 (C-2′), 78.0 (C-3), 45.7 (C-2), 42.7 (C-4), 32.8 (C-1), 24.5 (CH$_3$), **HRMS** (ESI) m/z 254.116 ([M + Na]$^+$, calcd for C$_{14}$H$_{17}$NO$_2$Na: 254.115).

(1R*,5R*,7R*)-7-Methyl-7-phenyl-5-vinyl-2-oxa-4-azabicyclo-[3.2.0]heptan-3-one (20) (Table 2)

According to general procedure A, **20** was obtained as a white solid after flash chromatography (EtOAc/petroleum ether, 1 : 9 to 1 : 3).

R_f 0.27 (EtOAc/ toluene, 2 : 8), **IR** (film) 3281, 1750 cm^{-1}, ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.44–7.30 (m, 2H, Ph), 7.29–7.15 (m, 3H, Ph), 6.49 (br s, 1H, NH), 5.90 (dd, J = 17.2 Hz, 10.6 Hz, 1H, H-1′), 5.26 (d, J = 17.5 Hz, 1H, H-2′a), 5.21 (d, J = 10.7 Hz, 1H, H-2′b), 4.97 (s, 1H, H-3), 2.81 (d, J = 12.9 Hz, 1H, H-1a), 2.48 (d, J = 12.9 Hz, 1H, H-1b), 1.55 (s, 3H, CH$_3$), ^{13}C NMR (75 MHz, CDCl$_3$) δ 160.8 (NCO), 148.3 (Cq-Ar), 137.8 (C-1′), 128.9 (2 CH-Ar), 126.5 (CH-Ar), 125.3 (2 CH-Ar), 116.3 (C-2′), 86.5 (C-3), 59.7 (C-4), 45.5 (C-2), 43.6 (C-1), 26.3 (CH$_3$), **HRMS** (ESI) m/z 252.100 ([M + Na]$^+$, calcd for C$_{14}$H$_{15}$NO$_2$Na: 252.099).

(1S*,2R*,4S*)-2-Methyl-2-phenyl-4-vinylcyclobutyl tosylcarbamate (21)

p-Toluenesulfonyl isocyanate (184 µL, 1.2 mmol, 1 equiv.) was added dropwise to a solution of **18**[18] (227 mg, 1.2 mmol, 1 equiv.) in THF (3.2 mL) cooled to 0 °C. The solution was stirred at 0 °C for 10 min and then allowed to warm to rt. The reaction mixture was stirred for 1.5 h at rt and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 2 : 8 to 2 : 3). Traces of p-toluenesulfonyl isocyanate residues were still present. The residue was dissolved in 150 mL of cyclohexane and then 150 mL of H$_2$O were added. The solution was stirred at rt overnight. The two layers were separated and the organic layer was dried over MgSO$_4$, filtered and concentrated under reduced pressure to afford the desired N-tosylcarbamate **21** (405 mg, 87%) as a white solid.

R_f 0.25 (EtOAc/petroleum ether, 2 : 8), **IR** (film) 3241, 1740 cm^{-1}, ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.95 (d, J = 8.1 Hz, 2H, Ar), 7.36 (d, J = 8.2 Hz, 2H, Ar), 7.30–7.21 (m, 2H, Ar), 7.21–7.12 (m, 1H, Ar), 7.09–7.01 (m, 2H, Ar), 5.96–5.80 (m, 1H, H-1′), 5.04 (d, J = 7.9 Hz, 1H, H-3), 5.00–4.90 (m, 2H, H-2′), 3.08–2.92 (m, 1H, H-4), 2.46 (s, 3H, CH$_3$-Ph), 2.19 (t, J = 10.3 Hz, 1H, H-1a), 1.82 (t, J = 10.3 Hz, 1H, H-1b), 1.38 (s, 3H, CH$_3$-Ph), ^{13}C NMR (100 MHz, CDCl$_3$) δ 149.7 (NCO or Cq-Ar), 148.9 (NCO or Cq-Ar), 145.2 (NCO or Cq-Ar) 138.2 (C-1′), 135.8 (Cq-Ar), 129.8 (2 CH-Ar), 128.6 (2 CH-Ar), 128.4 (2 CH-Ar), 126.2 (CH-Ar), 124.9 (2 CH-Ar), 115.2 (C-2′), 80.4 (C-3), 45.6 (C-2), 42.3 (C-4), 32.5 (C-1), 24.6 (CH$_3$), 21.8 (CH$_3$), **HRMS** (ESI) m/z 408.126 ([M + Na]$^+$, calcd for C$_{21}$H$_{23}$NO$_4$SNa: 408.124).

(1R*,5R*,7R*)-7-Methyl-7-phenyl-4-tosyl-5-vinyl-2-oxa-4-azabicyclo[3.2.0]heptan-3-one (22)

Phenyl-benzoquinone[30] (48.3 mg, 0.26 mmol, 1.05 equiv.) and 1,2-bis(phenylsulfinyl)ethane palladium(II) acetate (12.6 mg, 0.025 mmol, 0.1 equiv.) were added to a solution of N-tosylcarbamate **21** (96.4 mg, 0.25 mmol, 1 equiv.) in degassed THF. The flask was sealed and the reaction mixture was stirred 66 h at 45 °C. The reaction mixture was diluted with CH$_2$Cl$_2$. The organic layer was washed with saturated aqueous NH$_4$Cl and then brine. The aqueous layer was extracted (4×) with CH$_2$Cl$_2$. The combined organic layer was dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1 : 9 to 15 : 85) to afford the desired product **21** (14 mg) contaminated with phenyl-benzoquinone. The yield of **21** (9%) was estimated by ^{1}H NMR analysis of the fraction containing **21** and PhBQ.

R_f 0.5 (EtOAc/petroleum ether, 1 : 9) **IR** (film) 1785 cm^{-1}, ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.98 (d, J = 8.3 Hz, 2H, Ar), 7.40–7.30 (m, 4H, Ar), 7.25–7.20 (m, 1H, Ar), 7.17 (d, J = 7.7 Hz, 2H, Ar), 6.04 (dd, J = 17.3, 10.6 Hz, 1H, H-1′), 5.39 (d, J = 10.2 Hz, 1H, H-2a′), 5.36 (d, J = 16.8 Hz, 1H, H-2a′), 4.87 (s, 1H, H-3), 3.00 (s, 2H, H-1), 2.45 (s, 3H, CH$_3$-Ph), 1.47 (s, 3H, CH$_3$-Ph), ^{13}C NMR (100 MHz, CDCl$_3$) δ 153.3 (NCO), 147.6 (Cq-Ar), 145.7 (Cq-Ar), 135.8 (C-1′), 135.6 (Cq-Ar), 130.3 (2 CH-Ar), 129.05 (2 CH-Ar), 129.0 (2 CH-Ar), 126.8 (CH-Ar), 125.1 (2 CH-Ar), 119.0 (C-2′), 84.1 (C-3), 65.6 (C-4), 45.3 (C-2), 40.9 (C-1), 26.3 (CH$_3$), 21.9 (CH$_3$), **HRMS** (m/z 406.109 ([M + Na]$^+$, calcd for C$_{21}$H$_{21}$NO$_4$SNa: 406.108).

(1R,2R,3S,4S)-2,3-Bis(benzyloxy)-4-vinylcyclobutyl carbamate (23a)

Trichloroacetyl isocyanate (0.20 mL, 1.72 mmol, 1.3 equiv.) was added to a solution of **17**[7a,8] (403 mg, 1.3 mmol, 1 equiv.) in CH$_2$Cl$_2$ (3.7 mL) at 0 °C. The solution was stirred at rt for 16 h and concentrated under reduced pressure. The residue was dissolved in MeOH (3.2 mL) and K$_2$CO$_3$ (18 mg, 0.13 mmol, 0.1 equiv.) was added. The solution was stirred at rt for 8 h. Saturated aqueous NH$_4$Cl (5 mL) was added and the product was extracted with CH$_2$Cl$_2$ (3×). The combined organic layer was washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1 : 3 to 1 : 1) to afford carbamate **23a** (431 mg, 94%) as a white solid.

R_f 0.46 (EtOAc/petroleum ether, 1 : 2), $[\alpha]_D^{20}$ +3 (c 1.0, CHCl$_3$), **IR** (film) 3354, 1718, 1326, 1087 cm^{-1}, ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.41–7.20 (m, 10H, Ph), 5.95 (ddd, J = 17.3, 10.2, 7.2 Hz, 1H, H-1′), 5.19 (d, J = 17.3 Hz, 1H, H-2′a), 5.09 (d, J = 10.2 Hz, 1H, H-2′b), 4.72–4.42 (m, 7H, 2 CH$_2$Ph, NH$_2$, H-1 or H-3), 3.95 (t, J = 5.9 Hz, 1H, H-2), 3.60 (m, 1H, H-1 or H-3), 2.48 (q, J = 7.5 Hz, 1H, H-4), ^{13}C NMR (75 MHz, CDCl$_3$) δ 156.0 (NCO), 137.84 (Cq-Ar), 137.82 (Cq-Ar), 136.3 (C-1′), 128.52 (2 CH-Ar), 128.50 (2 CH-Ar), 128.0 (2 CH-Ar), 127.9 (4 CH-Ar), 116.4 (C-2′), 82.6 (C-2), 77.1 (C-1 or C-3), 72.4 (C-1 or C-3),

71.62 (CH_2Ph), 71.57 (CH_2Ph), 46.3 (C-4), **HRMS** (ESI) m/z 376.148 ([M + Na]$^+$, calcd for $C_{21}H_{23}NO_4$Na: 376.152).

Debenzylation of 23a

BCl_3 (1 M in CH_2Cl_2, 14 mL, 14 mmol, 12 equiv.) was added to a solution of carbamate **23a** (411 mg, 1.16 mmol, 1 equiv.) in CH_2Cl_2 (12 mL) at −60 °C. The solution was allowed to warm slowly to rt overnight. MeOH/H_2O (20 : 1, 50 mL) was added and the solution was concentrated under reduced pressure. The process was repeated once. The crude product was purified by flash chromatography (MeOH/CH_2Cl_2, 10 : 90 to 15 : 85) to afford (1R,2R,3S,4S)-2,3-dihydroxy-4-vinylcyclobutyl carbamate (169 mg, 84%) as a white solid.[8]

(1S,2R,3R,4S)-3-(Carbamoyloxy)-4-vinylcyclobutane-1,2-diyl diacetate (23b)

Ac_2O (0.31 mL, 3.30 mmol, 6 equiv.) and DMAP (136 mg, 1.11 mmol, 2 equiv.) were added to a solution of (1R,2R,3S,4S)-2,3-dihydroxy-4-vinylcyclobutyl carbamate[8] (96 mg, 0.55 mmol, 1 equiv., obtained by debenzylation of **23a**) in pyridine (5.5 mL). The solution was stirred at rt for 17 h. Et_2O (38 mL) was added and the organic layer was washed successively with 1% aqueous HCl (22 mL), saturated aqueous $NaHCO_3$ (38 mL) and brine (38 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/ petroleum ether, 1 : 2 to 1 : 1) to afford **23b** (115 mg, 81%) as a colorless oil.

R_f 0.33 (EtOAc/petroleum ether, 1 : 1), $[\alpha]_D^{20}$ −9 (c 1.0, $CHCl_3$), **IR** (film) 3374, 1728, 1220 cm^{-1}, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.95 (ddd, J = 17.2, 10.4, 6.7 Hz, 1H, H-1′), 5.22 (d, J = 17.2, H-2′a), 5.15 (d, J = 10.4 Hz, 1H, H-2′b), 5.09 (t, J = 6.3 Hz, 1H, H-2), 4.99–4.86 (br s, 2H, NH_2), 4.73 (m, 1H, H-1 or H-3), 4.68 (m, 1H, H-1 or H-3), 2.65 (q, J = 7.5 Hz, 1H, H-4), 2.06 (s, 6H, CH_3), **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.13 (CO), 170.10 (CO), 155.6 (NCO), 134.2 (C-1′), 117.3 (C-2′), 75.2 (C-2), 70.7 (C-1 or C-3), 69.9 (C-1 or C-3), 45.1 (C-4), 20.84 (CH_3), 20.80 (CH_3), **HRMS** (ESI) m/z 280.078 ([M + Na]$^+$, calcd for $C_{11}H_{15}NO_6$Na: 280.079).

(1S,2R,3R,4S)-3-(Carbamoyloxy)-4-vinylcyclobutane-1,2-diyl dibenzoate (23c)

BzCl (0.19 mL, 1.64 mmol, 4.6 equiv.) was added to a solution of (1R,2R,3S,4S)-2,3-dihydroxy-4-vinylcyclobutyl carbamate[8] (62 mg, 0.36 mmol, 1 equiv., obtained by debenzylation of **23a**) in pyridine (3.6 mL) at 0 °C. The solution was stirred at 0 °C for 1 h. MeOH was added and the solution was diluted in EtOAc. The organic layer was washed with water and 1 N HCl, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1 : 2 to 1 : 1) to afford cyclobutane **23c** (118 mg, 87%) as a white solid.

R_f 0.25 (silica gel, EtOAc/petroleum ether, 1 : 2), $[\alpha]_D^{20}$ +48 (c 1.0, $CHCl_3$), **IR** (film) 3374, 1721, 1275 cm^{-1}, **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.07 (d, J = 8.1 Hz, 4H, Ph), 7.62–7.53 (m, 2H, Ph), 7.49–7.40 (m, 4H, Ph), 6.12 (ddd, J = 17.2, 10.5,

6.5 Hz, 1H, H-1′), 5.53 (t, J = 6.3 Hz, 1H, H-2), 5.34 (dt, J = 17.2, 1.7 Hz, 1H, H-2′a), 5.23 (dt, J = 10.4, 1.2 Hz, 1H, H-2′b), 5.16 (dd, J = 7.9, 6.3 Hz, 1H, H-1 or H-3), 4.96 (dd, J = 8.1, 6.3 Hz, 1H, H-1 or H-3), 4.76 (br s, 2H, NH_2), 2.90 (q, J = 7.6 Hz, 1H, H-4), **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.72 (CO), 165.67 (CO), 155.4 (NCO), 134.3 (C-1′), 133.5 (2 CH-Ar), 130.1 (3 CH-Ar), 130.0 (3 CH-Ar), 129.5 (Cq-Ar), 129.4 (Cq-Ar), 128.55 (CH-Ar), 128.54 (CH-Ar), 117.5 (C-2′), 75.6 (C-2), 71.0 (C-1 or C-3), 70.6 (C-1 or C-3), 45.8 (C-4), **HRMS** (ESI) m/z 404.109 ([M + Na]$^+$, calcd for $C_{21}H_{19}NO_6$Na: 404.110).

(1S,2R,3R,4S)-3-(Carbamoyloxy)-4-vinylcyclobutane-1,2-diyl bis(4-methoxybenzoate) (23d)

p-Anisoyl chloride (0.22 mL, 1.59 mmol, 4.6 equiv.) was added to a solution of (1R,2R,3S,4S)-2,3-dihydroxy-4-vinylcyclobutyl carbamate[8] (60 mg, 0.35 mmol, 1 equiv., obtained by debenzylation of **23a**) in pyridine (3.5 mL) cooled at 0 °C. The solution was stirred at 0 °C for 2 h. The reaction mixture was quenched with ice and diluted with Et_2O. The product was extracted with Et_2O (4×). The combined organic layer was washed with 1 N HCl until pH 5, water, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 2 : 3) to afford the desired cyclobutane **23d** (110 mg, 72%) as a white solid.

R_f 0.19 (EtOAc/petroleum ether, 2 : 3), $[\alpha]_D^{20}$ +85 (c 1.0, $CHCl_3$), **IR** (film) 1712, 1604, 1251, 1167, 1095 cm^{-1}, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.3 Hz, 4H, Ph), 6.95–6.87 (m, 4H, Ph), 6.11 (ddd, J = 17.1, 10.5, 6.5 Hz, 1H, H-1′), 5.49 (t, J = 6.3 Hz, 1H, H-2), 5.33 (d, J = 17.2 Hz, 1H, H-2′a), 5.22 (d, J = 10.4 Hz, 1H, H-2′b), 5.12 (m, 1H, H-1 or H-3), 4.93 (m, 1H, H-1 or H-3), 4.80 (br s, 2H, NH_2), 3.86 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 2.85 (m, 1H, H-4), **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.42 (Cq-OCH_3 or CO), 165.36 (Cq-OCH_3 or CO), 163.8 (2 Cq-OCH_3 or CO), 155.5 (NCO), 134.4 (C-1′), 132.2 (2 CH-Ar), 132.1 (2 CH-Ar), 121.83 (Cq-Ar), 121.77 (Cq-Ar), 117.3 (C-2′), 113.80 (2 CH-Ar), 113.78 (2 CH-Ar), 75.3 (C-1 or C-2 or C-3), 71.1 (C-1 or C-2 or C-3), 70.3 (C-1 or C-2 or C-3), 55.59 (OCH_3), 55.58 (OCH_3), 45.9 (C-4), **HRMS** (ESI) m/z 464.130 ([M + Na]$^+$, calcd for $C_{23}H_{23}NO_8$Na: 464.132).

(1R,5R,6S,7R)-6,7-Bis(benzyloxy)-5-vinyl-2-oxa-4-azabicyclo-[3.2.0]heptan-3-one (24a) and (1R,5R,6S,7S)-5,6-bis(benzyloxy)-7-vinyl-2-oxa-4-azabicyclo[3.2.0]heptan-3-one (25a) (Table 3, entry 1)

According to general procedure A, compounds **25a** and **24a** were obtained as pale yellow oils after flash chromatography (EtOAc/petroleum ether, 1 : 5 to 1 : 2).

Compound 25a. R_f 0.48 (EtOAc/toluene, 1 : 3), $[\alpha]_D^{20}$ −7 (c 0.6, $CHCl_3$), **IR** (film) 3272, 1760 cm^{-1}, **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41–7.26 (m, 10H, Ph), 5.86 (m, 1H, H-1′), 5.57 (br s, 1H, NH), 5.17 (d, J = 1.0 Hz, 1H, H-2′a), 5.14 (d, J = 6.6 Hz, 1H, H-2′b), 4.63 (d, J = 11.9 Hz, 1H, CH_2Ph), 4.57 (d, J = 11.5 Hz, 1H, CH_2Ph), 4.50 (d, J = 11.9 Hz, 1H, CH_2Ph), 4.44 (d, J = 11.5 Hz, 1H, CH_2Ph), 4.30 (d, J = 4.7 Hz, 1H, H-1 or H-3), 4.02 (dd, J = 7.2, 1.0 Hz, 1H, H-1 or H-3), 2.68 (m, 1H, H-4),

2792 | *Org. Biomol. Chem.*, 2016, **14**, 2780–2796

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^{13}**C NMR** (100 MHz, CDCl$_3$) δ 158.2 (NCO), 137.2 (Cq-Ar), 136.8 (Cq-Ar), 134.3 (C-1′), 128.76 (2 CH-Ar), 128.72 (2 CH-Ar), 128.4 (CH-Ar), 128.3 (CH-Ar), 128.2 (2 CH-Ar), 127.9 (2 CH-Ar), 117.4 (C-2′), 91.1 (C-2), 81.0 (C-1 or C-3), 76.4 (C-1 or C-3), 72.5 (CH$_2$Ph), 65.9 (CH$_2$Ph), 49.0 (C-4), **HRMS** (ESI) *m/z* 374.136 ([M + Na]$^+$, calcd for C$_{21}$H$_{21}$NO$_4$Na: 374.136).

Compound 24a. R_f 0.45 (EtAc/petroleum ether, 1 : 2), $[\alpha]_D^{20}$ +54 (*c* 1.0, CHCl$_3$), **IR** (film) 3279, 1755 cm^{-1}, ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 7.40–7.24 (m, 10H, Ph), 5.81 (dd, *J* = 17.3, 10.6 Hz, 1H, H-1′), 5.71 (br s, 1H, NH), 5.24 (d, *J* = 17.6 Hz, 1H, H-2′a), 5.22 (d, *J* = 10.6 Hz, 1H, H-2′b), 4.57 (d, *J* = 11.5 Hz, 1H, CH$_2$Ph), 4.56 (d, *J* = 11.9 Hz, 1H, CH$_2$Ph), 4.51 (d, *J* = 11.8 Hz, 1H, CH$_2$Ph), 4.47 (d, *J* = 12.0 Hz, 1H, CH$_2$Ph), 4.32 (d, *J* = 2.1 Hz, 1H, H-1 or H-3), 4.11 (dd, *J* = 5.3, 3.5 Hz, 1H, H-2), 3.96 (d, *J* = 5.5 Hz, 1H, H-1 or H-3), ^{13}**C NMR** (100 MHz, CDCl$_3$) δ 159.2 (NCO), 137.1 (Cq-Ar), 136.9 (Cq-Ar), 136.2 (C-1′), 128.74 (2 CH-Ar), 128.73 (2 CH-Ar), 128.4 (CH-Ar), 128.3 (CH-Ar), 128.24 (2 CH-Ar), 128.21 (2 CH-Ar), 116.7 (C-2′), 84.2 (C-2), 81.3 (C-1 or C-3), 78.9 (C-1 or C-3), 72.22 (CH$_2$Ph), 72.21 (CH$_2$Ph), 62.1 (C-4), **HRMS** (ESI) *m/z* 374.148 ([M + Na]$^+$, calcd for C$_{21}$H$_{21}$NO$_4$Na: 374.136).

(1*R*,5*R*,6*S*,7*R*)-3-Oxo-5-vinyl-2-oxa-4-azabicyclo[3.2.0]heptane-6,7-diyl diacetate (24b) (Table 3, entry 3)

According to general procedure A, compound **24b** was obtained as a colorless oil after purification by flash chromatography (EtAc/petroleum ether, 1 : 5 to 2 : 1).

R_f 0.46 (Et$_2$O/CH$_2$Cl$_2$, 1 : 1), $[\alpha]_D^{20}$ +57 (*c* 1.0, CHCl$_3$), **IR** (film) 3293, 1747, 1220 cm^{-1}, ^{1}**H NMR** (300 MHz, CDCl$_3$) δ 6.03 (dd, *J* = 17.3, 10.6 Hz, 1H, H-1′), 5.99 (s, 1H, NH), 5.43 (d, *J* = 14.4 Hz, 1H, H-2′a), 5.38 (d, *J* = 7.6 Hz, 1H, H-2′b), 5.15 (dd, *J* = 5.8, 3.5 Hz, 1H, H-2), 5.08 (dd, *J* = 5.8, 1.7 Hz, 1H, H-1), 4.62 (dd, *J* = 3.5, 1.7 Hz, 1H, H-3), 2.14 (s, 3H, CH$_3$), 2.12 (s, 3H, CH$_3$), ^{13}**C NMR** (75 MHz, CDCl$_3$) δ 170.0 (CO), 169.4 (CO), 158.8 (NCO), 134.9 (C-1′), 118.1 (C-2′), 78.4 (C-3), 76.9 (C-2), 74.4 (C-1), 62.6 (C-4), 20.7 (CH$_3$), 20.6 (CH$_3$), **HRMS** (ESI) *m/z* 278.063 ([M + Na]$^+$, calcd for C$_{11}$H$_{13}$NO$_6$Na: 278.064).

(1*R*,5*R*,6*S*,7*R*)-3-Oxo-5-vinyl-2-oxa-4-azabicyclo[3.2.0]heptane-6,7-diyl dibenzoate (24c) (Table 3, entries 5 and 6)

According to general procedure A, compound **24c** was obtained as a colorless oil after purification by flash chromatography (EtAc/toluene, 1 : 7 to 1 : 6).

R_f 0.48 (EtAc/toluene, 1 : 3), $[\alpha]_D^{20}$ +97 (*c* 1.0, CHCl$_3$), **IR** (film) 3321, 1762, 1722, 1248 cm^{-1}, ^{1}**H NMR** (300 MHz, CDCl$_3$) δ 8.12–8.04 (m, 4H, Ph), 7.65–7.56 (m, 2H, Ph), 7.51–7.43 (m, 4H, Ph), 6.20 (dd, *J* = 17.3, 10.7 Hz, 1H, H-1′), 5.96–5.90 (br s, 1H, NH), 5.54 (d, *J* = 17.3 Hz, 1H, H-2′a), 5.50–5.43 (m, 3H, H-1, H-2, H-2′b), 4.85 (dd, *J* = 2.8, 2.0 Hz, 1H, H-3), ^{13}**C NMR** (75 MHz, CDCl$_3$) δ 165.6 (CO), 165.2 (CO), 158.8 (NCO), 135.0 (C-1′), 134.0 (CH-Ar), 133.9 (CH-Ar), 130.2 (2 CH-Ar), 130.1 (2 CH-Ar), 128.82 (Cq-Ar), 128.78 (2 CH-Ar), 128.7 (2 CH-Ar), 128.6 (Cq-Ar), 118.2 (C-2′), 78.7 (C-3), 77.6 (C-1 or C-2), 75.1 (C-1 or C-2), 63.0 (C-4), **HRMS** (ESI) *m/z* 402.094 ([M + Na]$^+$, calcd for C$_{21}$H$_{17}$NO$_7$Na: 402.095).

(1*R*,5*R*,6*S*,7*R*)-3-Oxo-5-vinyl-2-oxa-4-azabicyclo[3.2.0]heptane-6,7-diyl bis(4-methoxybenzoate) (24d) (Table 1, entry 4)

According to general procedure A, compound **24d** was obtained as a colorless oil after purification by flash chromatography (EtAc/toluene, 1 : 4).

R_f 0.27 (EtAc/toluene, 1 : 4), $[\alpha]_D^{20}$ = +144 (*c* 1.0, CHCl$_3$), **IR** (film) 3326, 1761, 1716, 1605, 1250, 1168, 1100 cm^{-1}, ^{1}**H NMR** (400 MHz, CDCl$_3$) δ 8.03 (d, *J* = 6.7 Hz, 2H, Ph), 8.01 (d, *J* = 6.6 Hz, 2H, Ph), 6.93 (d, *J* = 6.6 Hz, 4H, Ph), 6.19 (dd, *J* = 17.3, 10.7 Hz, 1H, H-1′), 5.88 (br s, 1H, NH), 5.53 (d, *J* = 17.2 Hz, 1H, H-2′a), 5.47–5.38 (m, 3H, H-1 or H-3, H-2, H-2′b), 4.82 (dd, *J* = 3.1, 1.5 Hz, 1H, H-1 or H-3), 3.87 (s, 3H, OCH$_3$), 3.86 (s, 3H, OCH$_3$), ^{13}**C NMR** (100 MHz, CDCl$_3$) δ 165.3 (Cq-OCH$_3$ or CO), 164.9 (Cq-OCH$_3$ or CO), 164.2 (Cq-OCH$_3$ or CO), 164.1 (Cq-OCH$_3$ or CO), 158.8 (NCO), 135.2 (C-1′), 132.3 (2 CH-Ar), 132.2 (2 CH-Ar), 121.1 (Cq-Ar), 120.8 (Cq-Ar), 118.0 (C-2′), 114.04 (2 CH-Ar), 113.96 (2 CH-Ar), 78.8 (C-1 or C-2 or C-3), 77.4 (C-1 or C-2 or C-3), 75.0 (C-1 or C-2 or C-3), 63.0 (C-4), 55.65 (OCH$_3$), 55.64 (OCH$_3$), **HRMS** (ESI) *m/z* 462.110 ([M + Na]$^+$, calcd for C$_{23}$H$_{21}$NO$_8$Na: 462.116).

(1*R**,5*R**,7*R**)-4-Allyl-7-methyl-7-phenyl-5-vinyl-2-oxa-4-azabicyclo[3.2.0]heptan-3-one (26)

NaH (60% in oil, 11.5 mg, 0.29 mmol, 1.2 equiv.) was added to a solution of carbamate **20** (55 mg, 0.24 mmol, 1 equiv.) in DMF (0.9 mL) cooled at 0 °C. The solution was stirred for 30 min at 0 °C and then 1 h at rt. An additional portion of DMF (0.4 mL) was added and allyl bromide (42 μL, 0.48 mmol, 2 equiv.) was added and the solution was stirred at rt for 2.5 h. Saturated aqueous NH$_4$Cl was added, the solution was diluted with Et$_2$O and the product was extracted with Et$_2$O (4×). The combined organic layer was washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtAc/petroleum ether, 8 : 92 to 10 : 90) to afford diene **26** (60 mg, 93%) as a colorless oil.

R_f 0.65 (EtAc/petroleum ether, 3 : 7), **IR** (film) 1748 cm^{-1}, ^{1}**H NMR** (300 MHz, CDCl$_3$) δ 7.40–7.30 (m, 2H, Ph), 7.35–7.15 (m, 3H, Ph), 6.01–5.85 (m, 1H, H-2′), 5.83 (dd, *J* = 17.3, 10.6 Hz, 1H, H-1″), 5.34 (d, *J* = 10.6 Hz, 1H, H-2″a), 5.31–5.15 (m, 3H, H-2″b, H-3′), 4.84 (s, 1H, H-3), 4.07 (ddt, *J* = 15.5, 5.6, 1.4 Hz, 1H, H-1′a), 3.70 (dd, *J* = 15.4, 7.6 Hz, 1H, H-1′b), 2.82 (d, *J* = 12.9 Hz, 1H, H-1a) 2.47 (d, *J* = 13.0 Hz, 1H, H-1b), 1.49 (s, 3H, CH$_3$), ^{13}**C NMR** (100 MHz, CDCl$_3$) δ 157.8 (NCO), 147.4 (Cq-Ar), 135.7 (C-1″), 132.7 (C-2′), 127.9 (2 CH-Ar), 125.5 (CH-Ar), 124.3 (2 CH-Ar), 118.0 (C-3′ or C-2″), 117.7 (C-3′ or C-2″), 82.7 (C-3), 62.2 (C-4), 44.1 (C-2), 43.5 (C-1′), 39.1 (C-1), 25.3 (CH$_3$), **HRMS** *m/z* 292.129 ([M + Na]$^+$, calcd for C$_{17}$H$_{19}$NO$_2$Na: 292.131).

(2*R**,2a*R**,8a*R**)-2-Methyl-2-phenyl-2,2a-dihydro-1*H*-cyclobuta[*d*]pyrrolo[1,2-*c*]oxazol-4(6*H*)-one (27)

A solution of Grubbs II catalyst (7.9 mg, 93 μmol, 0.05 equiv.) in degassed CH$_2$Cl$_2$ (0.5 mL) was added to a solution of diene **26** (50 mg, 0.186 mmol, 1 equiv.) in degassed CH$_2$Cl$_2$ (2.5 mL). The solution was refluxed for 7 h. After cooling, the solution

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Org. Biomol. Chem., 2016, **14**, 2780–2796 | **2793**

was concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1 : 4) to afford compound **27** (42 mg, 94%) as a light brown cream solid.

R_f 0.32 (EtOAc/petroleum ether, 1 : 4), **IR** (film), 1756, 1343, 1044, 703 cm^{-1}, **^{1}H NMR** (300 MHz, CDCl$_3$) δ 7.43–7.34 (m, 2H, Ph), 7.29–7.21 (m, 3H, Ph), 5.95 (dt, J = 6.1, 1.7 Hz, 1H, H-3′), 5.80 (dt, J = 6.0, 2.3 Hz, 1H, H-2′), 5.26 (s, 1H, H-3), 4.41 (dt, J = 16.0, 2.1 Hz, 1H, H-1′a), 3.99–3.88 (m, 1H, H-1′b), 2.64 (d, J = 13.0 Hz, 1H, H-1a) 2.45 (d, J = 13.0 Hz, 1H, H-1b), 1.50 (s, 3H, CH$_3$), **^{13}C NMR** (100 MHz, CDCl$_3$) δ 164.9 (NCO), 148.5 (Cq-Ar), 129.9 (C-3′), 129.7 (C-2′), 128.9 (2 CH-Ar), 126.5 (CH-Ar), 125.4 (2 CH-Ar), 86.5 (C-3), 74.3 (C-4), 54.6 (C-1′), 45.6 (C-2), 42.9 (C-1), 25.5 (CH$_3$), **HRMS** m/z 264.096 ([M + Na]$^+$, calcd for C$_{15}$H$_{15}$NO$_2$Na: 264.099).

(1S,2R,2aR,8aR)-4-oxo-2,2a,4,6-tetrahydro-1H-cyclobuta[d]pyrrolo[1,2-c]oxazole-1,2-diyl dibenzoate (28)

NaH (60%, 17 mg, 0.43 mmol, 1.05 equiv.) was added to a solution of compound **24c** (156 mg, 0.41 mmol 1 equiv.) in DMF (1.6 mL) at 0 °C. The solution was stirred for 30 min at 0 °C and then 1 h at rt. Allyl bromide (72 µL, 0.82 mmol, 2 equiv.) was added and the solution was stirred at rt for 2 h. Saturated aqueous NH$_4$Cl was added and the product was extracted with Et$_2$O (7×). The combined organic layer was washed with brine, dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 1 : 4) to afford the corresponding diene (96 mg, 55%) as a colorless oil.[8] A solution of Grubbs II catalyst (5 mg, 57 µmol, 0.05 equiv.) in degassed CH$_2$Cl$_2$ (1 mL) was added to a solution of the diene (48 mg, 0.11 mmol, 1 equiv.) in degassed CH$_2$Cl$_2$ (3.6 mL). The solution was refluxed for 5 h. After cooling, the solution was concentrated under reduced pressure. The crude product was purified by flash chromatography (EtOAc/petroleum ether, 3 : 7 to 2 : 3) to afford compound **28** (40 mg, 89%) as a cream solid.[8]

R_f 0.17 (EtOAc/petroleum ether, 1 : 4), $[\alpha]_D^{20}$ +127 (c 1.0, CHCl$_3$), **IR** (film) 1765, 1721, 1247, 1066 cm^{-1}, **^{1}H NMR** (400 MHz, CDCl$_3$) δ 8.08 (d, J = 7.2 Hz, 2H, Ph), 8.04 (d, J = 7.2 Hz, 2H, Ph), 7.64–7.56 (m, 2H, Ph), 7.51–7.42 (m, 4H, Ph), 6.17–6.09 (m, 2H, H-2′, H-3′), 5.61 (dd, J = 6.2, 1.4 Hz, 1H, CH–O), 5.47 (dd, J = 6.1, 3.4 Hz, 1H, CH–O), 5.15 (dd, J = 3.2, 1.5 Hz, 1H, CH–O), 4.47 (d, J = 15.9 Hz, 1H, H-1′a), 3.85 (d, J = 16.2 Hz, 1H, H-1′b), **^{13}C NMR** (100 MHz, CDCl$_3$) δ 165.5 (CO), 165.3 (CO), 163.4 (NCO), 133.9 (2 CH-Ar), 132.8 (C-2′ or C-3′), 130.11 (2 CH-Ar), 130.10 (2 CH-Ar), 128.9 (2 Cq-Ar), 128.74 (2 CH-Ar), 128.71 (2 CH-Ar), 126.8 (C-2′ or C-3′), 78.5 (CH–O), 77.9 (CH–O), 77.1 (C-4), 74.4 (CH–O), 55.7 (C-1), **HRMS** (ESI) m/z 414.093 ([M + Na]$^+$, calcd for C$_{22}$H$_{17}$NO$_6$Na: 414.095).

Iodide efflux

The F508del-CFTR Cl$^-$ channel activity was assayed by measuring the rate of iodide (^{125}I) efflux from HeLa cells stably transfected with F508del-CFTR as previously described.[31] Time-dependent rates of ^{125}I efflux were calculated from the following: $\ln(^{125}\text{I}_{t1}/^{125}\text{I}_{t2})/(t_1 - t_2)$, where $^{125}\text{I}_t$ is the intracellular ^{125}I at time t, and t_1 and t_2 successive time points. Curves were constructed by plotting the rates of ^{125}I versus time. All comparisons were based on maximal values for the time-dependent rates (k = peak rates, min^{-1}), excluding the points used to establish the baseline (k peak–k basal, min^{-1}) (for more details see ref. 24).

Enzymatic inhibition assay

The enzyme used was Cerezyme™, the recombinant enzyme of the β-glucocerebrosidase commercialized by Genzyme. The enzyme activity was measured in a 96-well plate: 13 µL of BTT buffer (pH 5.2), 2 µL of inhibitor solution in DMSO and 25 µL of enzyme solution in BTT buffer (pH 5.2, 0.1 mg mL^{-1}) containing 0.2% sodium taurocholate and 0.1% TX-100 were added. The plate was incubated at 37 °C for 30 min. Then 60 µL of substrate solution of 4-methylumbelliferyl-β-D-glucoside in McIlvaine buffer (pH 5.2, 4 mM) were added and the plate was incubated at 37 °C for 10 min. The reaction was stopped by the addition of glycine/NaOH buffer (pH 10.6, 100 mM, 150 µL), and the fluorescence of the released 4-methylumbelliferone was measured by the use of an excitation wavelength of 355 nm and an emission wavelength of 460 nm. Inhibition constants were generated for Cerezyme™ using 2.4 mM substrate concentration for IC$_{50}$ determinations. The percentage of inhibition was plotted as a function of the logarithm of the inhibitor concentration. By means of a linear regression, the IC$_{50}$ value for each compound was calculated from the value of the log of the inhibitor concentration corresponding to an inhibition of 50% of the enzyme activity.

Acknowledgements

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