ChemPubSoc Europe

DOI: 10.1002/ejoc.201600186

EurJOC European Journal of Organic Chemistry

Full Paper

Amidation of Isohexides

Bio-Based Amides from Renewable Isosorbide by a Direct and Atom-Economic Boric Acid Amidation Methodology

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Abstract: The functionalization of bio-sourced isohexides has proved challenging over the last number of years, especially in polymer and medicinal chemistry. We report herein the synthesis of bio-based amido-isohexides by the known boric acid catalysed amidation reaction. The coupling reaction was successfully performed with aliphatic and aromatic carboxylic acids. The extension of the scope of the reaction to eight Boc-protected amino acids is also described, the products being obtained in moderate to good yields. A preliminary screening of these new potential organocatalysts was carried out for the aldolization of isatin.

Introduction

Biomass represents an attractive renewable resource for an alternative production of chemicals and high-value-added molecules. As a continuation of on-going projects in the field of green and sustainable chemistry, the chemical transformation of bio-sourced molecules represents a challenge that still demands attention. Isosorbide, a chiral dianhydrohexitol, is a major product of the starch industry produced by Roquette Frères (Lestrem, France), which expanded its production to several thousands of tons in 2015. This renewable platform molecule is produced from D-sorbitol, following a double dehydration process.

The two hydroxy groups display different reactivity due to the geometry of the molecule. The hydroxy group at C-6 has an *exo* configuration, pointing outwards from the cycle, whereas the hydroxy group at C-3 with an *endo* configuration points inwards (Figure 1). A hydrogen bond between the *endo*-hydroxy group and the endocyclic oxygen atom also influences the geometry of the isosorbide, increasing the steric hindrance at the *endo*-hydroxy group. Two other diastereoisomers complete the family of 1,4:3,6-dianhydrohexitols: isomannide, the *endo*/*endo* isomer, and isoidide, the *exo*/*exo* isomer, derived from D-mannitol and L-iditol, respectively (Figure 1). Readily available and inexpensive isosorbide and isomannide have been used as starting materials for the preparation of monomers for the production of various copolymers[1] as well as pharmaceutical compounds[2] such as X_a inhibitors,[3] vasodilators or drugs treating vascular diseases, for example, isosorbide dinitrate, which is marketed under the trademark Isordil®.[4] The spatial arrangement combined with the intrinsic rigidity of isohexides make them attractive as chiral auxiliaries[5] or chiral ligands.[6] Challenging applications in organocatalysis have also been explored through the synthesis of chiral ammonium/imidazolium ionic liquids,[7] phase-transfer catalysts[8] and more recently thioureas or imines.[9]

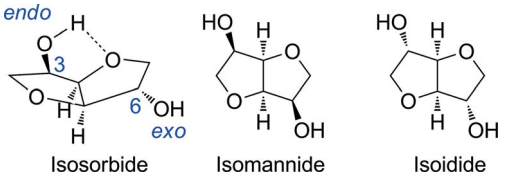

Figure 1. Structures of isosorbide and main diastereoisomers.

With our aim of inducing enantioselectivity mediated by isohexide derivatives as an alternative to other organocatalysts derived from the carbohydrate chiral pool,[10] the 1,2-diamino moiety appears to be a valuable target that could be introduced by the coupling of amino acids to amino isohexides. Nevertheless, there are only a few reports of the formation of an amide bond on an isohexide scaffold using β-amino acids (with DCC, DMAP or EDCI, HOBt),[11] acid chlorides (with triethylamine, DMAP),[12] symmetric anhydrides or oxazolones (by ring-opening in an Erlenmeyer–Plöchl reaction).[13] The amide bond, present in about 25 % of the top-selling pharmaceuticals, is largely formed by classical coupling reactions between amines and carboxylic acids or their derivatives (acyl chlorides, anhydrides or esters).[14] Recently, alternative strategies have been developed using alcohols or aldehydes (oxidative amidation)[15] and considerable effort is still being made to develop more convenient procedures suitable for industrial applications. Most of the well-established methods, which use a coupling agent (EDC, DCC, HOBt), are relatively inefficient with large quantities of potentially hazardous waste products being produced, leading to difficulties in the purification of the desired amide products.[16] More recently, the discovery of effective catalysts ($ZrCl_4$,[17] $[ZrCp_2Cl_2]$,[18] $[Hf(Cp)_2Cl_2]$,[19] silica gel,[20] triphenylphosphine[21]) for the direct amidation of carboxylic acids has

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201600186.

led to processes that offer increased efficiency.[22] All these catalysts have been used for the coupling of simple aliphatic carboxylic acids or benzoic acids with benzylamine, aniline and simple aliphatic amines. Adolfsson[17,19] and Mecinović[18] and their co-workers extended the methodology to amino acids. Notably, the work carried out by Adolfsson involved the use of $ZrCl_4$ in THF at reflux and more recently $[Hf(Cp)_2Cl_2]$ at room temperature.

The ability of boric acid or boronic acids to promote direct amidation reactions has also been known for a long time,[23] but it has become frequently used only in recent years.[24] Boric acid, as a cheap, readily available, stable reagent, has attracted our attention as a sustainable resource for amidation reactions. An additional benefit of the use of this substrate stems from a simple purification procedure with easy removal by basic aqueous workup. A literature survey of the reports from international laboratories disclosed a few examples of enantiopure substrates, but in most cases with laboratory-prepared synthetic catalysts, which thus require additional synthetic steps. As an example, the coupling of *N*-Boc-alanine with benzylamine was performed with $B(OMe)_3$ or synthetic $B(OCH_2CF_3)_3$ to give product yields of 49 and 81 %, respectively, with low levels of racemization.[24c] Hall and co-workers also reported the amidation of (*S*)-ibuprofen with benzylamine using substituted phenylboronic acids.[24d] Recent and efficient applications in dipeptide synthesis have been reported by Whiting and co-workers using the more expensive 3,4,5-trifluorophenylboronic acid.[24k] Today, economic and environmental guidelines and restrictions have had a significant influence on the evolution of synthetic strategies. Anticipation of the real chances of a potential industrialization is now, at least, considered earlier in the process, which argues in favour of the use of boric acid, albeit toxic, in the synthesis of active pharmaceutical ingredients.[24b]

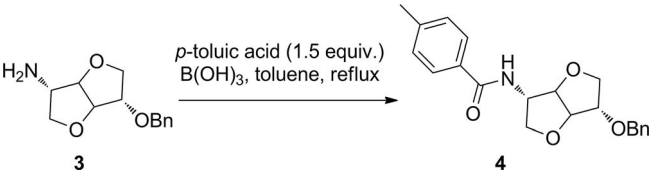
Considering all the criteria, we decided to combine the well-known boric acid methodology with the original reactivity of isohexide substrates for direct access to novel structures based on the isohexide skeleton with convenient purification procedures.

Results and Discussion

6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-amine (**3**) was first chosen as a model substrate, synthesized in four steps from isosorbide (Scheme 1). Following the conditions previously developed by Loupy and co-workers (CsOH, BnCl, 80 °C, water, 72 h),[25] isosorbide was converted into monobenzylated compound **1**, isolated in 28 % yield by simple crystallization on a 10 gram scale. After tosylation under classical conditions, displacement of the leaving group by sodium azide was performed efficiently despite requiring a high temperature and a long reaction time. Compound **2** was then submitted to hydrogenation under an atmospheric pressure of H_2 in the presence of 10 mol-% of Pd/C (10 %), allowing chemoselective hydrogenolysis to afford **3** in 98 % yield without any trace of the debenzylated product.

A mixture of the amine **3** and *p*-toluic acid (1.5 equiv.) was heated at reflux in toluene in a Dean–Stark apparatus with different amounts of boric acid ranging from 0 to 30 mol-% (Table 1). In the absence of catalyst, no trace of amide was detected, whereas an excellent isolated yield of 93 % was obtained for the highest load of boric acid.

Table 1. Optimization of the amount of boric acid required for the amidation of **3**.[a]



3 **4**

Entry	Boric acid [mol-%]	Reaction time [h]	Yield [%]
1	0	72	–
2	10	24	<10
3	20	24	78
4	30	24	93

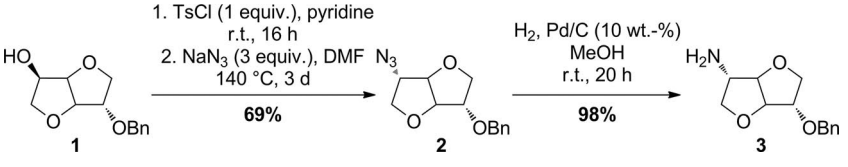
[a] Reagents and conditions: amine **3** (100 mg, 0.43 mmol, 1 equiv.), *p*-toluic acid (0.65 mmol, 1.5 equiv.), boric acid (*x* mol-%), toluene, azeotropic distillation in a Dean–Stark apparatus.

The relative stoichiometry of amine and carboxylic acid in the reaction was then investigated (Table 2). A molar equivalent of *p*-toluic acid only led to partial conversion and a modest isolated yield of 49 %. Using 1.2 equiv. increased the yield to 75 %, but the best results were still obtained with 1.5 equiv. of the carboxylic acid. As a simple basic workup allowed the easy removal of excess acid, the crude product could be obtained with quite good ^1H NMR purity.

Table 2. Optimization of the stoichiometric ratio of substrates in the amidation of **3**.[a]

Entry	*p*-Toluic acid [equiv.]	Yield [%]
1	1.0	49
2	1.2	75
1	1.5	93

[a] Reagents and conditions: amine **3** (100 mg, 0.43 mmol, 1 equiv.), *p*-toluic acid (*x* equiv.), boric acid (30 mol-%), toluene, azeotropic distillation in a Dean–Stark apparatus, 48 h.



1 **2** **3**

Scheme 1. Synthesis of amine model substrate **3**.

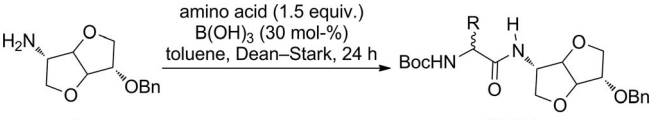
Other drying agents (magnesium sulfate, sodium sulfate or 4 Å molecular sieves) were tested instead of the Dean–Stark apparatus. Under these conditions the amide bond was barely or not detected. In some attempts, $MgSO_4$ did provide the expected compound, but there were significant problems with reproducibility.

The scope of the boric acid catalysed amidation was next investigated by studying the reaction of the model substrate **3** with a range of aliphatic and aromatic carboxylic acids; the corresponding amides **5**–**18** were obtained in isolated yields of 76–96 % (Figure 2).

The reaction conditions could be successfully applied to a wide range of benzoic acids substituted at the *ortho*, *meta* and *para* positions. The amidation was compatible with an aromatic halogen substituent (**7**–**9**) without a significant decrease in the yield. Poor electron-donating groups, such as methyl (**4**, **5**, **10**), and strong electron-withdrawing nitro groups (**11**), were well tolerated. However, 4-hydroxybenzoic acid was coupled with compound **3** to give an isolated yield of only 17 %. The reactions with benzyloxybenzoic acid and 2-amino-3-methylbenzoic acid were not successful, with only traces of the corresponding amides detected and conversions of less than 5 %, even after 48 h. According to these preliminary results, the use of strong electron-donating substituents on the phenyl ring seems to prevent the coupling reaction. Heteroaromatic indole-2-carboxylic acid and cinnamic acid were used to give **12** and **13** in yields of 77 and 85 %, respectively. The scope of the reaction was also successfully extended to aliphatic carboxylic acids. The treatment of **3** with butyric, isobutyric and isovaleric acids confirmed the robustness of the protocol with excellent isolated yields of **14–16** (86, 96 and 89 %, respectively). The reaction with cyclohexanecarboxylic acid or 4-phenylbutyric acid also afforded the amides **17** and **18** in excellent yields. Acrylic acid was coupled in a moderate yield of 39 %, but with an unsatisfactory purity, probably due to its well-known tendency to polymerize.

With the goal of designing original organocatalysts, we then focused on coupling reactions with amino acids (Table 3). This would offer access to original diamino derivatives based on the isohexide scaffold as promising candidates for amino organocatalysis. However, the methodology had to be tested for the possible racemization suffered by other classical methods.

Table 3. The boric acid-catalysed coupling of isohexide with *N*-Boc amino acids.



3 **19–27**

Entry	Amino acid	Product	Isolated yield [%]
1	Boc-L-proline	**19**	85
2	Boc-glycine	**20**	71
3	Boc-L-leucine	**21**	69
4	Boc-L-phenylalanine	**22**	72
5	Boc-D-serine	**23**	67
6	Boc-L-serine	**24**	64
7	Boc-L-valine	**25**	34
8	Boc-D-valine	**26**	38

Boc-L-proline was first introduced with an excellent 85 % yield (**19**). The methodology was then successfully extended to Boc-glycine, Boc-L-leucine, Boc-L-phenylalanine, Boc-D-serine and Boc-L-serine to yield **20**–**24**, respectively, with the yields ranging from 64 to 72 %. These lower yields could in part be explained by the difficult purification of the highly polar final products, as their crude yields were good. L- and D-Valine were also coupled with **3** to yield **25** and **26**, albeit in modest isolated yields of 34 and 38 %, respectively. This series of products

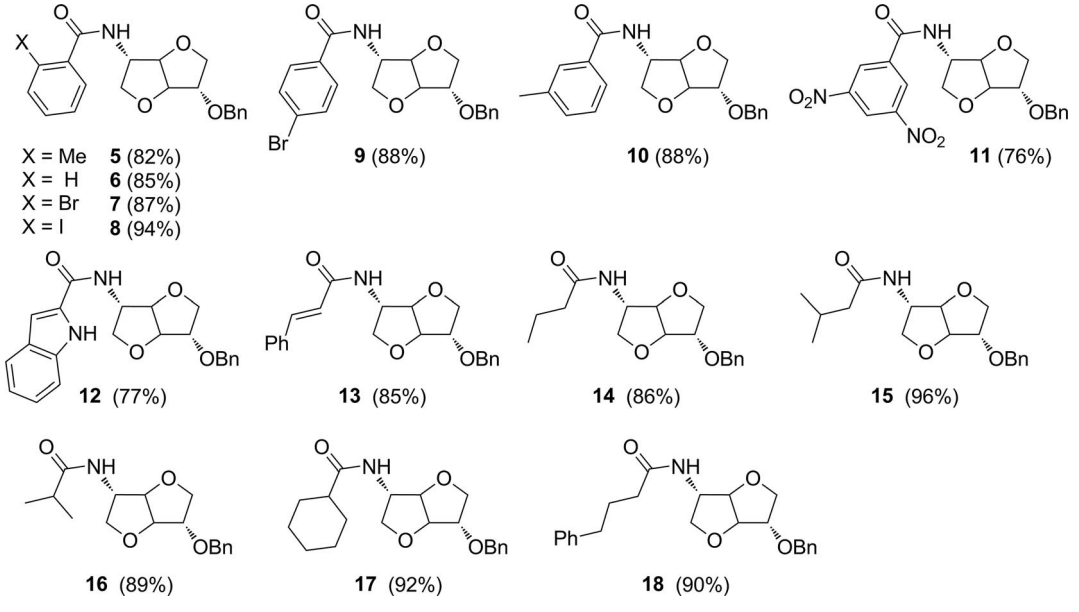


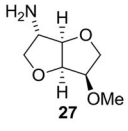
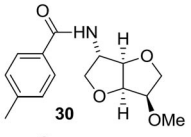
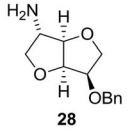
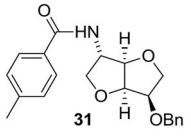
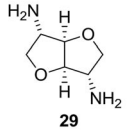
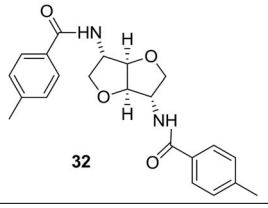
Figure 2. Scope of the boric acid catalysed amidation with respect to carboxylic acid structure.•Reagents and conditions: amine **3** (100 mg, 0.43 mmol, 1 equiv.), carboxylic acid (1.5 equiv.), boric acid (30 mol-%), toluene, azeotropic distillation in a Dean–Stark apparatus, 24 h.

offers a very interesting, diverse functionalization for future screening as organocatalysts precursors. As expected, a direct attempt to couple a non-protected amino acid led to the complete recovery of the starting material.

Careful examination of the NMR spectra did not show any evidence of racemization, except for compounds **23** and **24**, for which a splitting of signals is perceptible in their ^{13}C NMR spectra (in both cases, racemization was evaluated to be 10 %). In 2015, Lundberg and Adolfsson reported no reaction with Boc-protected valine, or isoleucine with the [$HfCp_2Cl_2$] catalyst, even after different modification of the reaction parameters.[19]

We then examined the influence of the substrate scaffold by investigating the reactions of the new and known mono amines **27** and **28**[11] and diamine **29**,[26] each synthesized from isomannide (in four steps for **27** and **28**, and in three steps for **29**). They were coupled with *p*-toluic acid under the optimized conditions to give the products **30**–**32** in moderate to good yields (61–80 %; Table 4).

Table 4. Influence of the isohexide configuration.[a]

Entry	Substrate	Product	Yield [%]
1	 **27**	 **30**	61
2	 **28**	 **31**	80
3	 **29**	 **32**	67

[a] Reagents and conditions: isohexide derivative (1 equiv.), *p*-toluic acid (1.5 or 3 equiv. for entry 3), boric acid (30 mol-%), toluene, azeotropic distillation in a Dean–Stark apparatus, 24 h.

Despite these encouraging results, some derivatives remained unreactive under our experimental conditions. *exo*/*endo*-Diamine **33**[26] reacted with *p*-toluic acid to give a poor yield of 18 %. No significant yield was obtained from the new mono amino ether **34** either. The presence of a hydrogen bond between the *endo* NH_2 and the endocyclic oxygen of the furanyl ring could explain this lack of reactivity. The starting compound **35**,[8] with a secondary amine, was completely recovered (Figure 3).

These laboratory-prepared organocatalysts were evaluated in an asymmetric aldol reaction, performed in accordance with the sustainable philosophy of our projects, targeting some of the 12 principles of green chemistry of Anastas and Warner:[28] the use of bio-sourced isohexides as organocatalyst (Principle 7), atom economy (Principle 2) and catalysis (Principle 9). Thus, we wished to explore for the first time the potential of highly functionalized isohexides in asymmetric synthesis

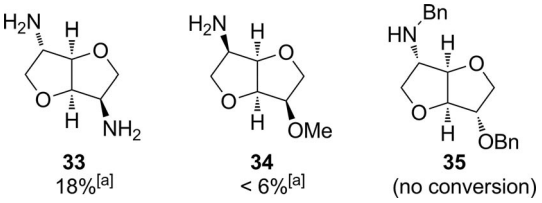
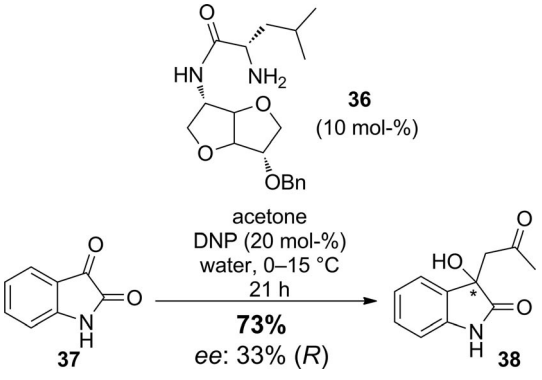


Figure 3. Less or unreactive substrates.[27] [a] Isolated yields in amide products.

through the reaction of acetone with isatin (**37**) (Scheme 2). Ten potential organocatalysts were evaluated under the following conditions, a mixture of acetone/water (80:20) with a 10 mol-% loading of organocatalyst in the presence of dinitrophenol (DNP) as additive (20 mol-%). The development of the boric acid methodology with the isohexide substrate **3** has provided a family of amido acids, which, upon deprotection (HCl, DCM), provided prospective organocatalysts quantitatively. The product of the reaction with leucinamide **36**, derived from **21**, was identified as the first promising hit, with the product obtained in 73 % yield and 33 % *ee* in favour of the *R* isomer. To confirm both the importance of the isohexide skeleton and the amide bond, the reaction of L-leucine was tested without success: the racemate was obtained in only 10 % yield. Studies specifically concerning asymmetric synthesis are currently under investigation.



Scheme 2. Preliminary result of the screening of the laboratory-prepared isohexide organocatalysts in the aldolization reaction of acetone with isatin.

Conclusions

We have proved the successful application of the boric acid catalysed peptidic coupling methodology to amino/diamino isohexide derivatives. A broad range of carboxylic acids and amino acids could thus be introduced into the isohexide skeleton in good to excellent yields, leading to a variety of new functionalized isohexide derivatives. This undoubtedly enriches the chemical library for this scaffold and opens the way for future investigation of its under-exploited potential as a chiral inducer. Some success has been achieved by using our organocatalyst **36** in asymmetric synthesis.

Experimental Section

General: Reagents and solvents were obtained from Aldrich, Acros, Lancaster, Alfa Aesar, Fluka or TCI and purchased at the highest commercial quality to be used without further purification. NMR spectra were recorded with Bruker 300 (^{1}H: 300 MHz; ^{13}C: 75 MHz), 400 (^{1}H: 400 MHz; ^{13}C: 100 MHz), or 500 (^{1}H: 500 MHz; ^{13}C: 125 MHz) spectrometers at 293 K using $CDCl_3$, CD_3OD and [D_6]DMSO as solvents. The chemical shifts (δ) are referenced to the residual solvent peak and coupling constants (J) are reported in the standard fashion. The following abbreviations are used to denote the multiplicities: s = singlet, d = doublet, t = triplet, q = quadruplet, quint. = quintuplet, sext = sextuplet, sept = septuplet, m = multiplet, br. = broad. Electrospray ionization (ESI) mass spectrometry (MS) was performed with a Thermo Finnigan LCQ Advantage mass spectrometer. High-resolution mass spectra (HRMS) were recorded with a Finnigan Mat 95xL mass spectrometer using the electrospray technique. Analytical TLC was carried out on silica gel Merck 60 D254 (0.25 mm). Flash chromatography was performed on Merck Si 60 silica gel (40–63 μm). IR spectra were recorded with an IRAffinity-1 Shimadzu spectrometer using attenuated total reflectance (ATRMiracle). Optical rotations were measured with a Perkin–Elmer 241 or Jasco P1010 polarimeter with a 10 cm cell (concentration c expressed as g/100 mL). Melting points were measured by using a Büchi B-540 apparatus.

(3*R*,3a*R*,6*S*,6a*R*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-ol (1): A solution of CsOH (50 % in water) (11.7 mL, 67 mmol, 1 equiv.), followed by benzyl chloride (7.72 mL, 67 mmol, 1 equiv.) after complete solubilization, were added to a solution of isosorbide (10 g, 67 mmol, 1 equiv.) in water (30 mL). The biphasic reaction mixture was stirred at 80 °C for 3 d. After completion, the pH was neutralized with 2 HCl N until pH 1. The aqueous phase was extracted with EtOAc (3 × 150 mL). The organic phases were combined, dried with Na_2SO_4, filtered and concentrated. The resulting yellow solid was washed with cold Et_2O and filtered to give compound **1** as a white solid (7.31 g, 28 %), m.p. 97–99 °C (Et_2O). $[\alpha]_D^{23}$ = +28.5 (c = 0.52, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3417, 2907, 1452, 1425, 1400, 1317, 1109, 1066, 1041, 738 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.70 (d, $^3J_{OH,3H}$ = 7.1 Hz, 1 H, OH), 3.55 (dd, $^3J_{2H,3H}$ = 5.9, ^2J = 9.4 Hz, 1 H, 2-H), 3.85 (dd, $^3J_{2'H,3H}$ = 5.9, ^2J = 9.4 Hz, 1 H, 2′-H), 3.89 (dd, $^3J_{5H,6H}$ = 3.9, ^2J = 10.1 Hz, 1 H, 5-H), 4.09 (br. d, ^2J = 10.1 Hz, 1 H, 5′-H), 4.12 (br. d, $^3J_{6H,5H}$ = 3.9 Hz, 6-H), 4.28 (m, 1 H, 3-H), 4.52 (d, $J_{6aH,3aH}$ = 4.5 Hz, 1 H, 6a-H), 4.58 (AB system, ^2J = 11.9 Hz, 2 H, CH_2Ph), 4.63 (app. t, $^3J_{3aH,6aH}$, $^3J_{3aH,3H}$ = 5 Hz, 1 H, 3a-H), 7.28–7.38 (m, 5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 71.7 (CH_2Ph), 72.3 (C-3), 73.5 (C-5), 73.7 (C-2), 81.9 (C-3a), 83.6 (C-6), 86.1 (C-6a), 127.8 (2 CH_{Ar}), 128.1 (CH_{Ar}), 128.6 (2 CH_{Ar}), 137.6 ($C_{q,Ar}$) ppm. HRMS (ESI): calcd. for $C_{13}H_{16}NaO_4$ [M + Na]$^+$ 259.0941; found 259.0936.

(3*S*,3a*R*,6*S*,6a*R*)-3-Azido-6-benzyloxyhexahydrofuro[3,2-*b*]furan (2): A solution of **1** (4.57 g, 19.33 mmol) and tosyl chloride (4.06 g, 21.3 mmol, 1.1 equiv.) in anhydrous pyridine (20 mL) was stirred at room temperature for 16 h under argon. After completion, the reaction mixture was acidified with HCl (2 M) until pH 1. After the addition of water (75 mL), the aqueous phase was extracted with EtOAc (3 × 150 mL). The combined organic phases were dried with Na_2SO_4, filtered and concentrated. The resulting colourless oil was purified by flash column chromatography in pentane/EtOAc (6:4) to give the tosylate intermediate as a white solid (6.84 g, 17.5 mmol, 94 %). Sodium azide (2.35 g, 36 mmol, 3 equiv.) was added to a solution of the tosylate (4.69 g, 12 mmol, 1 equiv.) in anhydrous DMF (40 mL) under argon and the suspension was stirred at 140 °C for 3 d. After completion, the mixture was cooled to room temperature, water was added (10 mL) and the mixture was concentrated under reduced pressure. The resulting oil was dissolved in water (100 mL) and EtOAc (150 mL). After extraction with EtOAc (4 × 150 mL), the combined organic phases were dried with Na_2SO_4, filtered and concentrated. The resulting yellow oil was purified by flash chromatography using petroleum ether/ethyl acetate (7:3) as eluent to give compound **2** as a colourless oil (2.29 g, 73 %). $[\alpha]_D^{23}$ = +39.5 (c = 1.12, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 2947, 2876, 2102, 1718, 1454, 1263, 1082 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (dd, $^3J_{5H,6H}$ = 4.1, ^2J = 10.1 Hz, 1 H, 5-H), 3.87 (dd, $^3J_{2H,3H}$ = 3.7, ^2J = 10.4 Hz, 1 H, 2-H), 3.93 (dd, $^3J_{2'H,3H}$ = 1.6, ^2J = 10.4 Hz, 1 H, 2′-H), 3.95 (dd, $^3J_{5'H,6H}$ = 1.7, ^2J = 10.1 Hz, 1 H, 5′-H), 4.03 (br. d, $^3J_{3H,2H}$ = 3.7 Hz, 1 H, 3-H), 4.08 (br. d, $^3J_{6H,5H}$ = 4.1 Hz, 1 H, 6-H), 4.59 (AB system, ^2J = 11.8 Hz, 2 H, CH_2Ph), 4.66 (d, $^3J_{3aH,6aH}$ = 3.9 Hz, 1 H, 3a-H), 4.69 (d, $^3J_{6aH,3aH}$ = 3.9 Hz, 1 H, 6a-H), 7.29–7.38 (m, 5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 65.8 (C-3), 71.5 and 71.7 (C-2, CH_2Ph), 72.8 (C-5), 82.9 (C-6), 85.8 (C-6a), 86.0 (C-3a), 127.9 (2 CH_{Ar}), 128.1 (CH_{Ar}), 128.7 (2 CH_{Ar}), 137.5 ($C_{q,Ar}$) ppm. HMRS (ESI): calcd. for $C_{13}H_{15}N_3NaO_3$ [M + Na]$^+$ 284.1006; found 284.1008.

(3*S*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-amine (3): Compound **2** (500 mg, 1.91 mmol) was dissolved in anhydrous methanol (40 mL) under argon before adding Pd/C (10 %) (50 mg, 0.1 mass. equiv.). After three vacuum–argon cycles and three vacuum–hydrogen cycles, the suspension was stirred at room temperature under an atmospheric pressure of H_2. After 20 h, the reaction mixture was filtered through Celite® and then washed three times (3 × 30 mL) with methanol. After concentration, the residue was purified by short-column flash chromatography using dichloromethane/methanol (9:1) as eluent to give **3** as a colourless oil (444 mg, 98 %). $[\alpha]_D^{22}$ = +15.9 (c = 1.00, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3356, 2933, 2870, 1670, 1454, 1365, 1072 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.68 (br. s, 2 H, NH_2), 3.52 (d, $^3J_{3H,2'H}$ = 4.1 Hz, 1 H, 3-H), 3.65 (dd, $^3J_{2H,3H}$ = 1.1, ^2J = 9.5 Hz, 1 H, 2-H), 3.86 (dd, $^3J_{2'H,3H} \approx {}^3J_{5H,6H}$ = 4.1, $^2J \approx {}^2J$ = 9.5 Hz, 2 H, 2′-H, 5-H), 3.91 (dd, $^3J_{5H,6H}$ = 2.4, ^2J = 10.1 Hz, 1 H, 5′-H), 4.06 (m, 1 H, 6-H), 4.42 (d, $^3J_{3aH,6aH}$ = 3.9 Hz, 1 H, 3a-H), 4.59 (AB system, ^2J = 11.9 Hz, 2 H, CH_2Ph), 4.71 (d, $^3J_{6aH,3aH}$ = 3.9 Hz, 1 H, 6a-H), 7.29–7.39 (m, 5 H, H_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 57.8 (C-3), 71.5 (CH_2Ph), 72.3 (C-5), 74.7 (C-2), 83.1 (C-6), 85.3 (C-6a), 89.3 (C-3a), 127.7 (2 CH_{Ar}), 127.9 (CH_{Ar}), 128.5 (2 CH_{Ar}), 137.6 ($C_{q,Ar}$) ppm. HRMS (ESI): calcd. for $C_{13}H_{18}NO_3$ [M + H]$^+$ 236.1281; found 236.1283.

Representative Procedure for Boric Acid Catalysed Amidation Reaction: Carboxylic acid (1.5 equiv.) and then boric acid (0.3 equiv.) were added to a 0.085 M solution of **3** (100 mg, 0.425 mmol) in toluene. After azeotropic distillation for 24 h in a Dean–Stark apparatus, the mixture was diluted in ethyl acetate (80 mL) and water (50 mL). After extraction with EtOAc (3 × 60 mL), the organic phase was washed with a saturated solution of $NaHCO_3$ (2 × 50 mL) and brine (50 mL), and then dried with Na_2SO_4. After filtration and concentration, the crude residue was purified by flash chromatography on silica gel.

***N*-[(3*S*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]-4-methylbenzamide (4):** The general procedure was followed using 4-methylbenzoic acid (87 mg, 0.638 mmol, 1.5 equiv.) to give a brown solid (144 mg, 96 % crude yield). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (1:1) as eluent to afford compound **4** as a white solid (140 mg, 93 %), m.p. 140–142 °C (Et_2O). $[\alpha]_D^{22}$ = +29.6, (c = 1.02, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3302, 2943, 2872, 1631, 1537, 1502, 1454, 1284, 1078 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, CH_3), 3.87 (dd, $^3J_{2H,3H}$ = 1.5, ^2J = 9.7 Hz, 1 H, 2-H), 3.94 (m, 2 H, 5-H, 5′-H), 4.00 (dd, $^3J_{2'H,3H}$ = 4.4, ^2J = 9.7 Hz, 1 H, 2′-H), 4.10 (t, $^3J_{6H,5H} \approx {}^3J_{6H,5'H}$ =

3.6 Hz, 1 H, 6-H), 4.58 (AB system, ^2J = 11.8 Hz, 2 H, CH_2Ph), 4.62 (m, 1 H, 3-H), 4.68 (dd, $^3J_{6aH,6H}$ = 1.0, $^3J_{6aH,3aH}$ = 4.2 Hz, 1 H, 6a-H), 4.70 (d, $^3J_{3aH,6aH}$ = 4.2 Hz, 1 H, 3a-H), 6.17 (d, $^3J_{NH,3H}$ = 7.1 Hz, 1 H, NH), 7.22–7.24 (d, ^3J = 7.9 Hz, 2 H, H_{Ar}), 7.27–7.38 (m, 5 H, H_{Ar}), 7.63–7.65 (d, ^3J = 7.9 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6 (CH_3), 56.7 (C-3), 71.7 (CH_2Ph), 72.4 and 72.5 (C-2, C-5), 83.3 (C-6), 86.0 (C-6a), 86.6 (C-3a), 127.1 (2 CH_{Ar}), 127.8 (2 CH_{Ar}), 128.0 (CH_{Ar}), 128.7 (2 CH_{Ar}), 129.4 (2 CH_{Ar}), 131.2 ($C_{q,Ar}$), 137.6 ($C_{q,Ar}$), 142.4 ($C_{q,Ar}$), 167.1 (C=O) ppm. HRMS (ESI): calcd. for $C_{21}H_{23}NNaO_4$ $[M + Na]^+$ 376.1519; found 376.1519.

***N*-[(3*S*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]-2-methylbenzamide (5):** The general procedure was followed using 2-methylbenzoic acid (87 mg, 0.638 mmol, 1.5 equiv.) to give a brown oil purified by flash chromatography using pentane/ethyl acetate (1:1) as eluent to give **5** (pale-yellow solid, 122 mg, 82 %), m.p. 104–106 °C (Et_2O). $[\alpha]_D^{22}$ = +30.1 (*c* = 0.99, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3277, 3258, 2926, 2854, 1633, 1532, 1453, 1325, 1205, 1099, 1079, 1057, 1047, 959, 904, 798, 758 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H, CH_3), 3.84 (dd, $^3J_{2H,3H}$ = 1.3, ^2J = 9.7 Hz, 1 H, 2-H), 3.90–3.94 (m, 2 H, 5-H, 5′-H), 3.98 (dd, $^3J_{2'H,3H}$ = 4.4, ^2J = 9.7 Hz, 1 H, 2′-H), 4.08 (app. t, $^3J_{6H,5H} \approx {}^3J_{6H,5'H}$ = 3.1 Hz, 1 H, 6-H), 4.58 (AB system, ^2J = 12.1 Hz, 2 H, CH_2Ph), 4.59–4.61 (m, 1 H, 3-H), 4.63 (d, $^3J_{6aH,3aH}$ = 4.1 Hz, 1 H, 6a-H), 4.68 (d, $^3J_{3aH,6aH}$ = 4.1 Hz, 1 H, 3a-H), 5.88 (d, $^3J_{NH,3H}$ = 7.2 Hz, 1 H, NH), 7.17–7.24 (m, 2 H, H_{Ar}), 7.28–7.38 (m, 7 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9 (CH_3), 56.6 (C-3), 71.8 (CH_2Ph), 72.4 and 72.5 (C-2, C-5), 83.3 (C-6), 86.0 (C-6a), 86.6 (C-3a), 125.9 (CH_{Ar}), 126.8 (CH_{Ar}), 127.9 (2 CH_{Ar}), 128.1 (CH_{Ar}), 128.7 (2 CH_{Ar}), 130.3 (CH_{Ar}), 131.3 (CH_{Ar}), 135.9 ($C_{q,Ar}$), 136.3 ($C_{q,Ar}$), 137.6 ($C_{q,Ar}$), 169.7 (C=O) ppm. HRMS (ESI): calcd. for $C_{21}H_{24}NO_4$ $[MH]^+$ 354.1700; found 354.1700.

***N*-[(3*S*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]benzamide (6):** The general procedure was followed using benzoic acid (78 mg, 0.638 mmol, 1.5 equiv.) to give a brown solid (144 mg, 99 % crude yield). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (1:1) as eluent to afford compound **6** (white solid, 122 mg, 85 %), m.p. 105–107 °C (Et_2O). $[\alpha]_D^{22}$ = +28.7 (*c* = 1.01, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3302, 2929, 2872, 1637, 1531, 1489, 1454, 1265, 1076 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87 (dd, $^3J_{2H,3H}$ = 1.5, ^2J = 9.7 Hz, 1 H, 2-H), 3.93 (m, 2 H, 5-H, 5′-H), 4.00 (dd, $^3J_{2'H,3H}$ = 4.5, ^2J = 9.7 Hz, 1 H, 2′-H), 4.09 (app. t, $^3J_{6H,5H} \approx {}^3J_{6H,5'H}$ = 3.4 Hz, 1 H, 6-H), 4.58 (AB system, ^2J = 11.9 Hz, 2 H, CH_2Ph), 4.62 (m, 1 H, 3-H), 4.68 (dd, $^3J_{6aH,6H}$ = 0.8, $^3J_{6aH,3aH}$ = 4.2 Hz, 1 H, 6a-H), 4.70 (d, $^3J_{3aH,6aH}$ = 4.2 Hz, 1 H, 3a-H), 6.33 (d, $^3J_{NH,3H}$ = 7.0 Hz, 1 H, NH), 7.28–7.37 (m, 5 H, H_{Ar}), 7.40–7.44 (m, 2 H, H_{Ar}), 7.48–7.52 (m, 1 H, H_{Ar}), 7.73–7.75 (m, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.9 (C-3), 71.7 (CH_2Ph), 72.3, 72.5 (C-2, C-5), 83.2 (C-6), 86.0 (C-6a), 86.6 (C-3a), 127.1 (2 CH_{Ar}), 127.8 (2 CH_{Ar}), 128.0 (CH_{Ar}), 128.6 (2 CH_{Ar}), 128.7 (2 CH_{Ar}), 131.9 (CH_{Ar}), 134.0, 137.6 (2 $C_{q,Ar}$), 167.3 (C=O) ppm. HRMS (ESI): calcd. for $C_{20}H_{21}NNaO_4$ $[M + Na]^+$ 362.1363; found 362.1362.

***N*-[(3*S*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]-2-bromobenzamide (7):** The general procedure was followed using 4-bromobenzoic acid (129 mg, 0.638 mmol, 1.5 equiv.) to give a brown oil (170 mg, 96 % crude yield). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (1:1) as eluent to afford **7** (white solid, 154 mg, 87 %), m.p. 93–94 °C (Et_2O). $[\alpha]_D^{25}$ = +10.3 (*c* = 1.18, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3321, 2930, 2866, 1725, 1644, 1519, 1333, 1285, 1097, 1074, 1044, 923, 909, 842, 737 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.88 (dd, $^3J_{2H,3H}$ = 1.2, ^2J = 9.8 Hz, 1 H, 2-H), 3.92–3.93 (m, 2 H, 5-H, 5′-H), 3.97 (dd, $^3J_{2'H,3H}$ = 4.3, ^2J = 9.8 Hz, 1 H, 2′-H), 4.09 (app. t, $^3J_{6H,5H} \approx {}^3J_{6H,5'H}$ = 3.0 Hz, 1 H, 6-H), 4.58 (app. s, 2 H, CH_2Ph), 4.62 (m, 1 H, 3-H), 4.65 (dd, $^3J_{6aH,6H}$ = 1.0, $^3J_{6aH,3aH}$ = 4.1 Hz, 1 H, 6a-H), 4.74 (app. d, $^3J_{3aH,6aH}$ = 4.1 Hz, 1 H, 3a-H), 6.14 (d, $^3J_{NH,3H}$ = 7.4 Hz, 1 H, NH), 7.25–7.37 (m, 7 H, H_{Ar}), 7.54 (dd, ^4J = 1.8, ^3J = 7.6 Hz, 1 H, $H_{Ar ortho\text{-}C=O}$), 7.58 (dd, ^4J = 1.1, ^3J = 8.0 Hz, 1 H, $H_{Ar ortho\text{-}Br}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.8 (C-3), 71.8 (CH_2Ph), 72.0 (C-2), 72.6 (C-5), 83.3 (C-6), 86.1 (C-6a), 86.3 (C-3a), 119.3 ($C_{q,Ar}$-Br), 127.8 (CH_{Ar}), 127.9 (2 CH_{Ar}), 128.1 (CH_{Ar}), 128.7 (2 CH_{Ar}), 130.0 (CH_{Ar}), 131.7 (CH_{Ar}), 133.5 (CH_{Ar}), 137.2 ($C_{q,Ar}$), 137.6 ($C_{q,Ar}$), 167.1 (C=O) ppm. HRMS (ESI): calcd. for $C_{20}H_{20}BrNNaO_4$ $[M + Na]^+$ 440.0468; found 440.0458.

***N*-[(3*S*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]-2-iodobenzamide (8):** The general procedure was followed using 2-iodobenzoic acid (158 mg, 0.638 mmol, 1.5 equiv.) to give a brown oil (198 mg, 99 % crude yield). The crude residue was purified by flash chromatography using pentane/ethyl acetate (1:1) as eluent to give **8** (white solid, 187 mg, 94 %), m.p. 91–92 °C (iPr_2O). $[\alpha]_D^{22}$ = +9.4 (*c* = 1.07, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3266, 2952, 2868, 1642, 1586, 1535, 1454, 1320, 1078, 1016, 909, 841, 734 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.90 (dd, $^3J_{2H,3H}$ = 1.4, ^2J = 9.8 Hz, 1 H, 2-H), 3.91–3.93 (m, 2 H, 5-H, 5′-H), 3.96 (dd, $^3J_{2'H,3H}$ = 4.2, ^2J = 9.8 Hz, 1 H, 2′-H), 4.08 (app. t, $^3J_{6H,5H} \approx {}^3J_{6H,5'H}$ = 3.3 Hz, 1 H, 6-H), 4.58 (s, 2 H, CH_2Ph), 4.60–4.63 (m, 1 H, 3-H), 4.67 (dd, $^3J_{6aH,6H}$ = 0.9, $^3J_{6aH,3aH}$ = 4.1 Hz, 1 H, 6a-H), 4.78 (app. d, $^3J_{3aH,6aH}$ = 4.1 Hz, 1 H, 3a-H), 5.92 (d, $^3J_{NH,3H}$ = 7.6 Hz, 1 H, NH), 7.08–7.12 (m, 1 H, H_{Ar}), 7.28–7.40 (m, 7 H, H_{Ar}), 7.84 (d, ^3J = 7.8 Hz, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.8 (C-3), 71.8 (CH_2Ph), 72.0 (C-2), 72.6 (C-5), 83.4 (C-6), 86.1, 86.2 (C-3a, C-6a), 92.5 ($C_{q,Ar}$), 127.9 (2 CH_{Ar}), 128.1 (CH_{Ar}), 128.4 (CH_{Ar}), 128.6 (CH_{Ar}), 128.7 (2 CH_{Ar}), 131.5 (CH_{Ar}), 137.6 ($C_{q,Ar}$), 140.0 (CH_{Ar}), 141.7 ($C_{q,Ar}$), 168.9 (C=O) ppm. HRMS (ESI): calcd. for $C_{20}H_{21}INO_4$ $[M + H]^+$ 466.0510; found 466.0507.

***N*-[(3*S*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]-4-bromobenzamide (9):** The general procedure was followed using 4-bromobenzoic acid (129 mg, 0.638 mmol, 1.5 equiv.) to afford a brown solid (173 mg, 98 % crude yield). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (1:1) as eluent to afford compound **9** as a white solid (155 mg, 88 %), m.p. 166–168 °C (Et_2O). $[\alpha]_D^{22}$ = +27.5 (*c* = 1.01, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3292, 2941, 2872, 1635, 1589, 1535, 1481, 1271, 1070, 735 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.86 (dd, $^3J_{2H,3H}$ = 1.4, ^2J = 9.8 Hz, 1 H, 2-H), 3.91 (dd, $^3J_{5H,6H}$ = 4.1, ^2J = 10.2 Hz, 1 H, 5-H), 3.94 (dd, $^3J_{5'H,6H}$ = 2.9, ^2J = 10.2 Hz, 1 H, 5′-H), 3.99 (dd, $^3J_{2'H,3H}$ = 4.5, ^2J = 9.8 Hz, 1 H, 2′-H), 4.09 (t, $^3J_{6H,5H} \approx {}^3J_{6H,5'H}$ = 3.3 Hz, 1 H, 6-H), 4.58 (AB system, ^2J = 11.8 Hz, 2 H, CH_2Ph), 4.60 (m, 1 H, 3-H), 4.67 (d, $^3J_{6aH,3aH}$ = 4.2 Hz, 1 H, 6a-H), 4.70 (d, $^3J_{3aH,6aH}$ = 4.2 Hz, 1 H, 3a-H), 6.34 (d, $^3J_{NH,3H}$ = 7.2 Hz, 1 H, NH), 7.27–7.37 (m, 5 H, H_{Ar}), 7.55 (m, 2 H, H_{Ar}), 7.61 (m, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.9 (C-3), 71.7 (CH_2Ph), 72.2 (C-2), 72.5 (C-5), 83.2 (C-6), 86.0 (C-6a), 86.5 (C-3a), 126.7 ($C_{q,Ar}$), 127.8 (2 CH_{Ar}), 128.1 (CH_{Ar}), 128.6 (2 CH_{Ar}), 128.8 (2 CH_{Ar}), 132.0 (2 CH_{Ar}), 132.8 ($C_{q,Ar}$), 137.6 ($C_{q,Ar}$), 166.4 (C=O) ppm. HRMS (ESI): calcd. for $C_{20}H_{20}BrNNaO_4$ $[M + Na]^+$ 440.0468; found 440.0461.

***N*-[(3*S*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]-3-methylbenzamide (10):** The general procedure was followed using 3-methylbenzoic acid (87 mg, 0.638 mmol, 1.5 equiv.) to give a brown oil (149 mg). The crude residue was purified by flash chromatography using pentane/ethyl acetate (1:1) as eluent to give **10** (white solid, 131 mg, 88 %), m.p. 99–101 °C (Et_2O). $[\alpha]_D^{22}$ = +27.5 (*c* = 1.01, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3346, 3286, 2940, 2862, 1643, 1630, 1524, 1333, 1296, 1209, 1091, 1081, 1042, 929, 813, 789, 747 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, CH_3), 3.87 (dd, $^3J_{2H,3H}$ = 1.5, ^2J = 9.7 Hz, 1 H, 2-H), 3.93–3.94 (m, 2 H, 5-H, 5′-H), 3.99 (dd, $^3J_{2'H,3H}$ = 4.4, ^2J = 9.7 Hz, 1 H, 2′-H), 4.09 (app. t, $^3J_{6H,5H} \approx {}^3J_{6H,5'H}$ = 3.4 Hz, 1 H, 6-H), 4.58 (AB system, ^2J = 11.9 Hz, 2 H, CH_2Ph), 4.62

(m, 1 H, 3-H), 4.68 (dd, $^3J_{6aH,6H}$ = 0.9, $^3J_{6aH,3aH}$ = 4.2 Hz, 1 H, 6a-H), 4.70 (d, $^3J_{3aH,6aH}$ = 4.2 Hz, 1 H, 3a-H), 6.28 (d, $J_{NH,3H}$ = 7.2 Hz, 1 H, NH), 7.27–7.37 (m, 7 H, H_{Ar}), 7.50–7.53 (m, 1 H, H_{Ar}), 7.55–7.58 (m, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4 (CH_3), 56.8 (C-3), 71.7 (CH_2Ph), 72.3 (C-2), 72.5 (C-5), 83.2 (C-6), 86.0 (C-6a), 86.6 (C-3a), 124.1 (CH_{Ar}), 127.8 (3 CH_{Ar}), 128.0 (CH_{Ar}), 128.6 (3 CH_{Ar}), 132.6 (CH_{Ar}), 134.0 ($C_{q,Ar}$), 137.6 ($C_{q,Ar}$), 138.6 ($C_{q,Ar}$), 167.5 (C=O) ppm. HRMS (ESI): calcd. for $C_{21}H_{24}NO_4$ $[M + H]^+$ 354.1700; found 354.1694.

***N*-[(3*S*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]-3,5-dinitrobenzamide (11):** The general procedure was followed using 3,5-dinitrobenzoic acid (135 mg, 0.638 mmol, 1.5 equiv.) to give a brown oil (206 mg). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (1:1) as eluent to afford **11** (white solid, 138 mg, 76 %), m.p. 157–159 °C (Et_2O). $[\alpha]_D^{22}$ = +26.1 (*c* = 0.99, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3304, 2970, 2881, 1647, 1535, 1342, 1078, 912 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (m, 2 H, 5-H, 5′-H), 3.94 (dd, $^3J_{2H,3H}$ = 1.6, ^2J = 10.1 Hz, 1 H, 2-H), 4.02 (dd, $^3J_{2'H,3H}$ = 4.5, ^2J = 10.1 Hz, 1 H, 2′-H), 4.09 (app. t, $^3J_{6H,5H} \approx {}^3J_{6H,5'H}$ = 3.3 Hz, 1 H, 6-H), 4.55 (s, 2 H, CH_2Ph), 4.62 (m, 1 H, 3-H), 4.69 (dd, $^3J_{6aH,6H}$ = 0.9, $^3J_{6aH,3aH}$ = 4.3 Hz, 1 H, 6a-H), 4.72 (d, $^3J_{3aH,6aH}$ = 4.3 Hz, 1 H, 3a-H), 7.09 (d, $^3J_{NH,3H}$ = 7.0 Hz, 1 H, NH), 7.25–7.35 (m, 5 H, H_{Ar}), 8.98 (d, *J* = 2.1 Hz, 2 H, H_{Ar}), 9.10 (t, *J* = 2.1 Hz, 1 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 57.6 (C-3), 71.8 (CH_2Ph, C-2), 72.6 (C-5), 83.1 (C-6), 86.1 (C-6a), 86.3 (C-3a), 121.5 (CH_{Ar}), 127.5 (2 CH_{Ar}), 127.8 (2 CH_{Ar}), 128.1 (CH_{Ar}), 128.6 (2 CH_{Ar}), 137.3 ($C_{q,Ar}$), 137.4 ($C_{q,Ar}$), 148.7 (2 $C_{q,Ar}$), 162.9 (C=O) ppm. HRMS (ESI): calcd. for $C_{20}H_{19}N_3NaO_8$ $[M + Na]^+$ 452.1064; found 452.1060.

***N*-[(3*S*,3a*R*,6*S*,6a*S*)-6-Benzyloxyhexahydrofuro[3,2-*b*]furan-3-yl]-1*H*-indole-2-carboxamide (12):** The general procedure was followed with indole-2-carboxylic acid (87 mg, 0.638 mmol, 1.5 equiv.) to give a yellow solid (160 mg, 99 % crude yield). The crude product was purified by flash chromatography using diethyl ether as eluent to afford **12** (white solid, 125 mg, 77 %), m.p. 152–153 °C (Et_2O). $[\alpha]_D^{25}$ = +72.4 (*c* = 1.03, MeOH). IR (ATR): $\tilde{\nu}$ = 3318, 3227, 2928, 1628, 1545, 1308, 1265, 1074, 1045, 817 cm^{-1}. ^{1}H NMR (400 MHz, $[D_6]$DMSO): δ = 3.80 (dd, $^3J_{2H,3H}$ = 2.8, ^2J = 9.3 Hz, 1 H, 2-H), 3.84 (dd, $^3J_{5H,6H}$ = 1.9, ^2J = 10.1 Hz, 1 H, 5-H), 3.88 (dd, $^3J_{5'H,6H}$ = 3.8, ^2J = 10.1 Hz, 1 H, 5′-H), 3.95 (dd, $J_{2'H,3H}$ = 5.3, ^2J = 9.3 Hz, 1 H, 2′-H), 4.07 (m, 1 H, 6-H), 4.35 (m, 1 H, 3-H), 4.57 (AB system, ^2J = 12.0 Hz, 2 H, CH_2Ph), 4.63 (dd, $^3J_{3aH,3H}$ = 0.7, $J_{3aH,6aH}$ = 4.1 Hz, 1 H, 3a-H), 4.68 (d, $J_{6aH,3aH}$ = 4.1 Hz, 1 H, 6a-H), 7.03 (ddd, *J* = 0.9, *J* = 7.0 Hz, *J* = 8.0 Hz, 1 H, H_{indole}), 7.18 (ddd, *J* = 1.1, *J* = 7.0 Hz, *J* = 8.0 Hz, 1 H, H_{indole}), 7.22–7.24 (m, 1 H, H_{indole}), 7.27–7.38 (m, 5 H, H_{Ar}), 7.43 (dd, *J* = 0.8, *J* = 8.3 Hz, 1 H, H_{indole}), 7.62 (d, *J* = 8.2 Hz, 1 H, H_{indole}), 8.58 (d, $^3J_{NH,3H}$ = 6.6 Hz, 1 H, NH), 11.59 (s, 1 H, NH_{indole}) ppm. ^{13}C NMR (100 MHz, $[D_6]$DMSO): δ = 56.3 (C-3), 70.4 (CH_2Ph), 71.6, 71.7 (C-2, C-5), 82.6 (C-6), 85.1 (C-6a), 86.2 (C-3a), 103.4 (CH_{indole}), 112.3 (CH_{indole}), 119.8 (CH_{indole}), 121.6 (CH_{indole}), 123.5 (CH_{indole}), 127.0 ($C_{q,indole}$), 127.6 (CH_{Ar}), 127.7 (2 CH_{Ar}), 128.3 (2 CH_{Ar}), 131.2 ($C_{q,indole}$), 136.5 ($C_{q,indole}$), 138.0 ($C_{q,Ar}$), 161.1 (C=O) ppm. HRMS (ESI): calcd. for $C_{22}H_{22}N_2NaO_4$ $[M + Na]^+$ 401.1472; found 401.1471.

(2*E*)-*N*-[(3*S*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]-3-phenylprop-2-enamide (13): The general procedure was followed using *trans*-cinnamic acid (95 mg, 0.638 mmol, 1.5 equiv.) to give a brown oil (161 mg). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (1:1) as eluent to afford **13** (white solid, 131 mg, 85 %), m.p. 146–147 °C (Et_2O). $[\alpha]_D^{22}$ = +32.5 (*c* = 1.00, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3269, 2968, 2879, 1654, 1618, 1541, 1450, 1338, 1211, 1076 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.83 (dd, $^3J_{2H,3H}$ = 1.6, ^2J = 9.7 Hz, 1 H, 2-H), 3.91–3.92 (m, 2 H, 5-H, 5′-H), 3.95 (dd, $^3J_{2'H,3H}$ = 4.4, ^2J = 9.7 Hz, 1 H, 2′-H), 4.08 (m, 1 H, 6-H), 4.57 (AB system, ^2J = 11.9 Hz, 2 H, CH_2Ph), 4.59 (m, 1 H, 3-H), 4.67 (app. s, 2 H, 6a-H, 3a-H), 6.05 (d, $^3J_{NH,3H}$ = 7.5 Hz, 1 H, NH), 6.40 (d, $^3J_{CH=CH,trans}$ = 15.6 Hz, 1 H, C=C-H), 7.27–7.36 (m, 8 H, H_{Ar}), 7.47–7.49 (m, 2 H, H_{Ar}), 7.65 (d, $^3J_{CH=CH,trans}$ = 15.6 Hz, 1 H, C=C-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.4 (C-3), 71.7 (CH_2Ph), 72.3 (C-2), 72.5 (C-5), 83.2 (C-6), 85.9, 86.6 (C-3a, C-6a), 120.0 (C=C), 127.8 (2 CH_{Ar}), 127.98 (2 CH_{Ar}), 128.02 (CH_{Ar}), 128.6 (2 CH_{Ar}), 129.0 (2 CH_{Ar}), 130.0 (CH_{Ar}), 134.7 ($C_{q,Ar}$), 137.7 ($C_{q,Ar}$), 142.0 (C=C), 165.6 (C=O) ppm. HRMS (ESI): calcd. for $C_{22}H_{23}NNaO_4$ $[M + Na]^+$ 388.1519; found 388.1526.

***N*-[(3*S*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]butanamide (14):** The general procedure was followed using butyric acid (59 µL, 0.638 mmol, 1.5 equiv.) to give a brown oil (127 mg, 98 % crude yield). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (3:7) as eluent to afford **14** (colourless oil, 111 mg, 86 %). $[\alpha]_D^{22}$ = +11.2 (*c* = 0.99, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3282, 2966, 2900, 1643, 1541, 1454, 1259, 1076 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, $^3J_{CH3,CH2CH3}$ = 7.4 Hz, 3 H, CH_3), 1.64 (app. sext, $^3J_{CH2CH3,CH3} \approx {}^3J_{CH2CH3,CH2CO}$ = 7.4 Hz, 2 H, CH_2CH_3), 2.14 (t, $^3J_{COCH2,CH2CH3}$ = 7.4 Hz, 2 H, $COCH_2$), 3.73 (dd, $^3J_{2H,3H}$ = 1.5, ^2J = 9.6 Hz, 1 H, 2-H), 3.85–3.92 (m, 3 H, 2′-H, 5-H, 5′-H), 4.05 (m, 1 H, 6-H), 4.42 (m, 1 H, 3-H), 4.53–4.56 (m, 3 H, CH_2Ph, 3a-H), 4.59 (d, $^3J_{6aH,3aH}$ = 3.1 Hz, 1 H, 6a-H), 5.70 (d, $^3J_{NH,3H}$ = 7.0 Hz, 1 H, NH), 7.27–7.37 (m, 5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8 (CH_3), 19.2 (CH_2CH_3), 38.6 ($COCH_2$), 56.2 (C-3), 71.7 (CH_2Ph), 72.4 (C-2, C-5), 83.2 (C-6), 85.9 (C-6a), 86.5 (C-3a), 127.8 (2 CH_{Ar}), 128.0 (CH_{Ar}), 128.6 (2 CH_{Ar}), 137.6 ($C_{q,Ar}$), 172.7 (C=O) ppm. HRMS (ESI): calcd. for $C_{17}H_{23}NNaO_4$ $[M + Na]^+$ 328.1519; found 328.1534; calcd. for $C_{17}H_{24}NO_4$ $[M + H]^+$ 306.1700; found 306.1705.

***N*-[(3*S*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]-3-methylbutanamide (15):** The general procedure was followed using isovaleric acid (70 µL, 0.638 mmol, 1.5 equiv.) to give a yellow oil (135 mg, 99 % crude yield). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (1:1) as eluent to afford **15** (white solid, 131 mg, 96 %), m.p. 77–78 °C (iPr_2O). $[\alpha]_D^{22}$ = +10.9 (*c* = 1.01, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3275, 2956, 2870, 1641, 1541, 1454, 1369, 1259, 1078 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 [d, ^3J = 6.5 Hz, 6 H, $CH(CH_3)_2$], 2.01 (d, $^3J_{CH2,CH}$ = 2.2 Hz, 2 H, CH_2CO), 2.10 [m, 1 H, $CH(CH_3)_2$], 3.73 (dd, $^3J_{2H,3H}$ = 1.4, ^2J = 9.6 Hz, 1 H, 2-H), 3.86–3.92 (m, 3 H, 2′-H, 5-H, 5′-H), 4.06 (app. t, $^3J_{6H,5H}$ = 3.3 Hz, 1 H, 6-H), 4.43 (m, 1 H, 3-H), 4.54–4.60 (m, 4 H, 3a-H, 6a-H, CH_2Ph), 5.57 (d, $^3J_{NH,3H}$ = 6.9 Hz, 1 H, NH), 7.29–7.37 (m, 5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6 (2 CH_3), 26.3 [$CH(CH_3)_2$], 46.0 (CH_2CO), 56.2 (C-3), 71.8 (CH_2Ph), 72.38, 72.40 (C-2, C-5), 83.3 (C-6), 86.0, 86.6 (C-3a, C-6a), 127.8 (2 CH_{Ar}), 128.1 (CH_{Ar}), 128.6 (2 CH_{Ar}), 137.6 ($C_{q,Ar}$), 172.2 (C=O) ppm. HRMS (ESI): calcd. for $C_{18}H_{25}NNaO_4$ $[M + Na]^+$ 342.1676; found 342.1679.

***N*-[(3*S*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]-2-methylpropanamide (16):** The general procedure was followed using isobutyric acid (88 µL, 0.638 mmol, 1.5 equiv.) to give a brown solid (137 mg). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (4:6) as eluent to afford **16** (white solid, 116 mg, 89 %), m.p. 84–86 °C (iPr_2O). $[\alpha]_D^{22}$ = +9.0 (*c* = 1.01, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3290, 2968, 2873, 1647, 1541, 1456, 1247, 1080 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 [d, $^3J_{CH3,CH}$ = 6.9 Hz, 6 H, $CH(CH_3)_2$], 2.32 [sept, $^3J_{CH,C3H}$ = 6.9 Hz, 1 H, $CH(CH_3)_2$], 3.73 (dd, $^3J_{2H,3H}$ = 1.5, ^2J = 9.6 Hz, 1 H, 2-H), 3.85–3.92 (m, 3 H, 2′-H, 5-H, 5′-H), 4.06 (m, 1 H, 6-H), 4.40 (m, 1 H, 3-H), 4.55 (d, $^3J_{6aH,3aH}$ = 3.8 Hz, 1 H, 3a-H), 4.57 (m, 2 H, CH_2Ph), 4.60 (d, $^3J_{6aH,3aH}$ = 3.8 Hz, 1 H, 6a-H), 5.67 (d, $^3J_{NH,3H}$ = 7.0 Hz, 1 H, NH), 7.27–7.36 (m, 5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6,

19.7 [CH(CH_3)$_2$], 35.6 [CH(CH$_3$)$_2$], 56.1 (C-3), 71.7 (CH_2Ph), 72.3 (C-2, C-5), 83.2 (C-6), 85.9 (C-6a), 86.6 (C-3a), 127.8 (2 CH_{Ar}), 128.0 (CH_{Ar}), 128.6 (2 CH_{Ar}), 137.6 ($C_{q,Ar}$), 176.7 (C=O) ppm. HRMS (ESI): calcd. for $C_{17}H_{23}NNaO_4$ [M + Na]$^+$ 328.1519; found 328.1512.

***N*-[(3*S*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]cyclohexanecarboxamide (17):** The general procedure was followed using cyclohexanecarboxylic acid (79 μL, 0.638 mmol, 1.5 equiv.) to give a rather pure brown solid (144 mg, 98 % crude yield). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (1:1) as eluent to afford **17** (white solid, 134 mg, 92 %), m.p. 113–115 °C (*i*Pr$_2$O). $[\alpha]_D^{22}$ = +13.4 (*c* = 1.00, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3308, 2983, 2900, 1647, 1521, 1454, 1265, 1078 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.25, 1.37–1.45, 1.64–1.66, 1.76–1.82 (m, 10 H, $CH_{2,cyclohexyl}$), 2.05 (tt, $^3J_{ax,eq}$ = 3.3, $^3J_{ax,ax}$ = 11.6 Hz, 1 H, $CH_{,cyclohexyl}$), 3.71 (dd, $^3J_{2H,3H}$ = 1.5, ^2J = 9.6 Hz, 1 H, 2-H), 3.84–3.91 (m, 3 H, 2′-H, 5-H, 5′-H), 4.05 (m, 1 H, 6-H), 4.39 (m, 1 H, 3-H), 4.54 (d, $^3J_{3aH,6aH}$ = 3.6 Hz, 1 H, 3a-H), 4.52–4.56 (m, 2 H, CH_2Ph), 4.59 (d, $^3J_{6aH,3aH}$ = 3.6 Hz, 1 H, 6a-H), 5.75 (d, $^3J_{NH,3H}$ = 7.4 Hz, 1 H, NH), 7.28–7.36 (m, 5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.70, 25.72, 29.6, 29.7 (5 $CH_{2,cyclohexyl}$), 45.3 ($CH_{,cyclohexyl}$), 56.0 (C-3), 71.6 (CH_2Ph), 72.29, 72.34 (C-2, C-5), 83.2 (C-6), 85.8 (C-6a), 86.6 (C-3a), 127.8 (2 CH_{Ar}), 128.0 (CH_{Ar}), 128.6 (2 CH_{Ar}), 137.6 ($C_{q,Ar}$), 175.9 (C=O) ppm. HRMS (ESI): calcd. for $C_{20}H_{27}NNaO_4$ [M + Na]$^+$ 368.1832; found 368.1827.

***N*-[(3*S*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]-4-phenylbutanamide (18):** The general procedure was followed using 4-phenylbutyric acid (105 mg, 0.638 mmol, 1.5 equiv.) to give a yellow oil (169 mg). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (4:6) as eluent to afford **18** (white solid, 145 mg, 90 %), m.p. 118–119 °C (Et$_2$O). $[\alpha]_D^{22}$ = +11.1 (*c* = 1.00, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3282, 2968, 2900, 1643, 1541, 1454, 1251, 1078 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.97 (app. quint, ^3J = 7.5 Hz, 2 H, $CH_2CH_2CH_2$), 2.16 (t, ^3J = 7.5 Hz, 2 H, $COCH_2$), 2.65 (t, ^3J = 7.5 Hz, 2 H, CH_2CH_2Ph), 3.71 (dd, $^3J_{2H,3H}$ = 1.4, ^2J = 9.6 Hz, 1 H, 2-H), 3.85–3.92 (m, 3 H, 2′-H, 5-H, 5′-H), 4.05 (m, 1 H, 6-H), 4.41 (m, 1 H, 3-H), 4.54 (d, $^3J_{3aH,6aH}$ = 4.0 Hz, 1 H, 3a-H), 4.57–4.60 (m, 3 H, 6a-H, CH_2Ph), 5.58 (d, $^3J_{NH,3H}$ = 7.3 Hz, 1 H, NH), 7.16–7.21 (m, 3 H, H_{Ar}), 7.26–7.37 (m, 7 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.0 ($CH_2CH_2CH_2$), 35.2 (CH_2CH_2Ph), 35.7 ($COCH_2$), 56.2 (C-3), 71.7 (CH_2Ph), 72.3, 72.4 (C-2, C-5), 83.2 (C-6), 85.9 (C-6a), 86.5 (C-3a), 126.2 (CH_{Ar}), 127.8 (2 CH_{Ar}), 128.0 (CH_{Ar}), 128.5 (2 CH_{Ar}), 128.61 (2 CH_{Ar}), 128.62 (2 CH_{Ar}), 137.6 ($C_{q,Ar}$), 141.4 ($C_{q,Ar}$), 172.4 (C=O) ppm. HRMS (ESI): calcd. for $C_{23}H_{27}NNaO_4$ [M + Na]$^+$ 404.1832; found 404.1840.

***tert*-Butyl (2*S*)-2-{[(3*S*,3a*R*,6*S*,6a*S*)-6-Benzyloxyhexahydrofuro[3,2-*b*]furan-3-yl]carbamoyl}pyrrolidine-1-carboxylate (19):** The general procedure was followed using *N*-Boc-L-proline (138 mg, 0.638 mmol, 1.5 equiv.) to give a brown oil (182 mg, 98 % crude yield). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (4:6) as eluent to afford **19** (colourless oil, 155 mg, 85 %). $[\alpha]_D^{25}$ = –40.5 (*c* = 0.99, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3296, 2974, 2874, 1682, 1661, 1543, 1395, 1366, 1161, 1082, 912 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 [s, 9 H, C(CH_3)$_3$], 1.75–2.45 (m, 4 H, CH_2CH_2), 3.20–3.42 (m, 2 H, NCH_2), 3.70 (app. d, ^2J = 9.4 Hz, 1 H, 2-H), 3.85–3.90 (m, 3 H, 2′-H, 5-H, 5′-H), 4.05 (m, 1 H, 6-H), 4.23 (m, 1 H, NCHCO), 4.38 (m, 1 H, 3-H), 4.50–4.65 (m, 4 H, CH_2Ph, 3a-H, 6a-H), 6.14 (br. s, 1 H, NH), 7.28–7.36 (m, 5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7 (CH_2CH_2), 27.6 (CH_2CH_2), 28.5 [C(CH_3)$_3$], 47.3 (NCH_2CH_2), 56.1 (C-3), 59.9 ($CHCH_2CH_2$), 71.7 (CH_2Ph), 72.3, 72.6 (C-2, C-5), 80.8 [C(CH$_3$)$_3$], 83.1 (C-6), 85.8, 86.5 (C-3a, C-6a), 127.8 (2 CH_{Ar}), 128.0 (CH_{Ar}), 128.6 (2 CH_{Ar}), 137.6 (C_{qAr}), 156.3 (NHCOO), 171.7 (NHCO) ppm. HRMS (ESI): calcd. for $C_{23}H_{32}N_2NaO_6$ [M + Na]$^+$ 455.2153; found 455.2144.

***tert*-Butyl (2-{[(3*S*,3a*R*,6*S*,6a*S*)-6-Benzyloxyhexahydrofuro[3,2-*b*]furan-3-yl]amino}-2-oxoethyl)carbamate (20):** The general procedure was followed using *N*-Boc glycine (112 mg, 0.638 mmol, 1.5 equiv.) to give a yellow oil (169 mg). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (2:8) as eluent to afford **20** (white solid, 118 mg, 71 %), m.p. 116–117 °C (Et$_2$O). $[\alpha]_D^{22}$ = +10.8 (*c* = 1.03, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3309, 2978, 1707, 1668, 1514, 1368, 1265, 1167, 1080, 1055, 1028 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.45 [s, 9 H, C(CH_3)$_3$], 3.73–3.76 (m, 3 H, CH_2NH, 2-H), 3.74–3.76 (m, 2 H, CH_2NH), 3.86–3.93 (m, 3 H, 2′-H, 5-H, 5′-H), 4.06 (m, 1 H, 6-H), 4.39–4.42 (m, 1 H, 3-H), 4.56 (AB system, ^2J = 12.0 Hz, 2 H, CH_2Ph), 4.56–4.57 (m, 1 H, 3a-H), 4.60–4.61 (m, 1 H, 6a-H), 5.27 (br. s, 1 H, NHCOO), 6.52 (br. s, 1 H, NHCO), 7.26–7.36 (m, 5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 [C(CH_3)$_3$], 44.6 (CH_2NH), 56.2 (C-3), 71.7 (CH_2Ph), 72.1 (C-2), 72.5 (C-5), 80.6 [C(CH$_3$)$_3$], 83.1 (C-6), 85.8 (C-6a), 86.4 (C-3a), 127.8 (2 CH_{Ar}), 128.0 (CH_{Ar}), 128.6 (2 CH_{Ar}), 137.6 ($C_{q,Ar}$), 156.4 (NHCOO), 169.5 (NHCO) ppm. HRMS (ESI): calcd. for $C_{20}H_{28}N_2NaO_6$ [M + Na]$^+$ 415.1840; found 415.1835.

***tert*-Butyl [(2*S*)-1-{[(3*S*,3a*R*,6*S*,6a*S*)-6-Benzyloxyhexahydrofuro[3,2-*b*]furan-3-yl]amino}-4-methyl-1-oxopentan-2-yl]carbamate (21):** The general procedure was followed using *N*-Boc-L-leucine (148 mg, 0.638 mmol, 1.5 equiv.) to give a brown oil (159 mg, 84 % crude yield). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (1:1) as eluent to afford **21** (pale-yellow oil, 130 mg, 69 %). $[\alpha]_D^{23}$ = –7.6 (*c* = 0.97, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3289, 2955, 2871, 1680, 1651, 1526, 1366, 1248, 1167, 1080, 1045, 910 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92, 0.94 [2 d, ^3J = 4.7 Hz, 6 H, CH(CH_3)$_2$], 1.44 [s, 9 H, C(CH_3)$_3$], 1.43–1.53 [m, 1 H, CH_2CH(CH$_3$)$_2$], 1.59–1.67 [m, 2 H, CH_2CH(CH$_3$)$_2$, CH(CH$_3$)$_2$], 3.72 (dd, $^3J_{2H,3H}$ = 1.3, ^2J = 9.6 Hz, 1 H, 2-H), 3.86–3.93 (m, 3 H, 2′-H, 5-H, 5′-H), 4.01–4.07 (m, 2 H, CHNHCOO, 6-H), 4.39 (m, 1 H, 3-H), 4.53–4.58 (m, 3 H, 3a-H, CH_2Ph), 4.60 (d, $^3J_{6aH,3aH}$ = 4.5 Hz, 1 H, 6a-H), 4.88 (d, $J_{NH,CH}$NH = 6.6 Hz, 1 H, NHCOO), 6.45 (br. s, 1 H, NHCO), 7.27–7.37 (m, 5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 23.1 [CH(CH_3)$_2$], 24.9 [CH(CH$_3$)$_2$], 28.4 [C(CH_3)$_3$], 40.9 [CH_2CH(CH$_3$)$_2$], 53.0 (CHNHCOO), 56.2 (C-3), 71.7 (CH_2Ph), 72.2 (C-2), 72.5 (C-5), 80.5 [C(CH$_3$)$_3$], 83.2 (C-6), 85.8 (C-6a), 86.5 (C-3a), 127.8 (2 CH_{Ar}), 128.1 (CH_{Ar}), 128.6 (2 CH_{Ar}), 137.6 ($C_{q,Ar}$), 156.0 (NHCOO), 172.4 (NHCO) ppm. HRMS (ESI): calcd. for $C_{24}H_{36}N_2NaO_6$ [M + Na]$^+$ 471.2466; found 471.2461.

***tert*-Butyl [(2*S*)-1-{[(3*S*,3a*R*,6*S*,6a*S*)-6-Benzyloxyhexahydrofuro[3,2-*b*]furan-3-yl]amino}-1-oxo-3-phenylpropan-2-yl]carbamate (22):** The general procedure was followed using *N*-Boc-L-phenylalanine (170 mg, 0.638 mmol, 1.5 equiv.) to give a brown oil (195 mg, 95 % crude yield). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (1:1) as eluent to afford **22** (pale-yellow oil, 148 mg, 72 %). $[\alpha]_D^{25}$ = +16.9 (*c* = 1.00, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3287, 3063, 2976, 2874, 1651, 1526, 1454, 1366, 1167, 1080, 910 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 [s, 9 H, C(CH_3)$_3$], 2.96, 3.07 (2 dd, ^3J = 6.2, 8.8, ^2J = 13.2 Hz, 2 H, $CHCH_2$Ph), 3.61 (app. dd, $^3J_{2H,3H}$ = 1.0, ^2J = 9.6 Hz, 1 H, 2-H), 3.76–3.88 (m, 3 H, 2′-H, 5-H, 5′-H), 3.97 (m, 1 H, 6-H), 4.16–4.27 (m, 3 H, 3a-H, 6a-H, $CHCH_2$Ph), 4.33 (m, 1 H, 3-H), 4.54 (AB system, ^2J = 11.9 Hz, 2 H, OCH_2Ph), 5.13 (m, 1 H, N$HCOO$), 5.72 (d, $J_{NH,3H}$ = 7.4 Hz, 1 H, $NHCO$), 7.20–7.23 (m, 3 H, H_{Ar}), 7.28–7.39 (m, 7 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 [C(CH_3)$_3$], 39.1 ($CHCH_2$Ph), 56.0 (C-3), 56.2 (NH$CHCO$), 71.6 (OCH_2Ph), 71.8 (C-2), 72.6 (C-5), 80.5 [C(CH$_3$)$_3$], 83.1 (C-6), 85.5, 86.2 (C-3a, C-6a), 127.3 (CH_{Ar}), 127.7 (2 CH_{Ar}), 128.0 (CH_{Ar}), 128.6 (2 CH_{Ar}), 129.0 (2 CH_{Ar}), 129.4 (2 CH_{Ar}),

136.8 ($C_{q,Ar}$), 137.7 ($C_{q,Ar}$), 155.5 (NHCOO), 170.8 (NHCO) ppm. HRMS (ESI): calcd. for $C_{27}H_{34}N_2NaO_6$ $[M + Na]^+$ 505.2309; found 505.2303.

***tert*-Butyl [(2*R*)-3-Hydroxy-1-{[(3*S*,3a*R*,6*S*,6a*S*)-6-benzyloxyhexahydrofuro[3,2-*b*]furan-3-yl]amino}-1-oxopropan-2-yl]carbamate (23):** The general procedure was followed using *N*-Boc-D-serine (131 mg, 0.638 mmol, 1.5 equiv.) to give a brown oil (207 mg). The crude product was purified by flash chromatography using diethyl ether/ethanol (96:4) as eluent to afford **23** (colourless oil, 121 mg, 67 %). $[\alpha]_D^{23}$ = +24.2 (*c* = 1.02, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3294, 2974, 2932, 2878, 1657, 1524, 1497, 1366, 1248, 1163, 1074, 1028, 908 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 [s, 9 H, C(CH_3)$_3$], 3.60–3.66 (m, 1 H, CH_2OH), 3.75 (dd, $^3J_{2H,3H}$ = 1.4, ^2J = 9.6 Hz, 1 H, 2-H), 3.85–3.94 (m, 3 H, 2′-H, 5-H, 5′-H), 4.05–4.12 (m, 3 H, 6-H, CH_2OH, NC*H*CH_2OH), 4.39 (m, 1 H, 3-H), 4.51–4.63 (m, 4 H, 3a-H, CH_2Ph, 6a-H), 5.61 (d, ^3J = 7.2 Hz, 1 H, N*H*COO), 6.99 (d, ^3J = 6.1 Hz, 1 H, N*H*CO), 7.27–7.37 (m, 5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 [C(CH_3)$_3$], 54.9 (*C*HCH$_2$OH), 56.2 (C-3), 62.6 (CH_2OH), 71.6 (CH_2Ph), 72.1 (C-2), 72.5 (C-5), 80.9 [*C*(CH_3)$_3$], 83.0 (C-6), 85.8 (C-6a), 86.5 (C-3a), 127.8 (2 CH_{Ar}), 128.0 (CH_{Ar}), 128.6 (2 CH_{Ar}), 137.6 ($C_{q,Ar}$), 156.6 (NH*C*OO), 171.5 (NH*C*O) ppm. HRMS (ESI): calcd. for $C_{21}H_{30}N_2NaO_7$ $[M + Na]^+$ 445.1945; found 445.1955.

***tert*-Butyl [(2*S*)-3-Hydroxy-1-{[(3*S*,3a*R*,6*S*,6a*S*)-6-benzyloxyhexahydrofuro[3,2-*b*]furan-3-yl]amino}-1-oxopropan-2-yl]carbamate (24):** The general procedure was followed using *N*-Boc-L-serine (131 mg, 0.638 mmol, 1.5 equiv.) to give a brown oil (179 mg). The crude product was purified by flash chromatography using ether/ethanol (98:2) as eluent to afford **24** (white solid, 115 mg, 64 %), m.p. 122–123 °C (*i*Pr_2O). $[\alpha]_D^{23}$ = –3.2 (*c* = 1.03, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3431, 3337, 2972, 2935, 2883, 1705, 1637, 1533, 1506, 1366, 1265, 1084, 1053, 912, 843 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.45 [s, 9 H, C(CH_3)$_3$], 2.04–2.17 (br. s, 1 H, OH), 3.63 (m, 1 H, CH_2OH), 3.73 (d, ^2J = 8.9 Hz, 1 H, 2-H), 3.86–3.93 (m, 3 H, 2′-H, 5-H, 5′-H), 4.05–4.12 (m, 3 H, 1 CH_2OH, 6-H, *C*HCH_2OH), 4.39 (m, 1 H, 3-H), 4.57 (AB system, ^2J = 12.0 Hz, 2 H, CH_2Ph), 4.59 (m, 1 H, 3a-H), 4.62 (m, 1 H, 6a-H), 5.59 (d, ^3J = 6.4 Hz, 1 H, N*H*COO), 6.99 (br. s, 1 H, N*H*CO), 7.28–7.36 (m, 5 H, H_{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.4 [C(CH_3)$_3$], 54.8 (NCHCH$_2$OH), 56.3 (C-3), 62.7 (CH_2OH), 71.7 (OCH_2Ph), 72.1 (C-2), 72.6 (C-5), 80.9 [*C*(CH_3)$_3$], 83.1 (C-6), 85.8 (C-6a), 86.5 (C-3a), 127.9 (2 CH_{Ar}), 128.1 (CH_{Ar}), 128.7 (2 CH_{Ar}), 137.6 ($C_{q,Ar}$), 156.6 (NH*C*OO), 171.4 (NH*C*O) ppm. HRMS (ESI): calcd. for $C_{21}H_{30}N_2NaO_7$ $[M + Na]^+$ 445.1945; found 445.1949.

***tert*-Butyl [(2*S*)-1-{[(3*S*,3a*R*,6*S*,6a*S*)-6-Benzyloxyhexahydrofuro[3,2-*b*]furan-3-yl]amino}-3-methyl-1-oxobutan-2-yl]carbamate (25):** The general procedure was followed using *N*-Boc-L-valine (139 mg, 0.638 mmol, 1.5 equiv.) to give a brown oil (139 mg, 75 % crude yield). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (1:1) as eluent to afford **25** (colourless oil, 63 mg, 34 %). $[\alpha]_D^{25}$ = +5.8 (*c* = 1.00, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3294, 2965, 2932, 2874, 1680, 1649, 1526, 1366, 1248, 1080, 1047, 910 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.91, 0.95 [2 d, ^3J = 6.8 Hz, 6 H, CH(C*H*$_3$)$_2$], 1.44 [s, 9 H, C(CH_3)$_3$], 2.04–2.17 [m, 1 H, C*H*(CH_3)$_2$], 3.73 (dd, $^3J_{2H,3H}$ = 1.4, ^2J = 9.6 Hz, 1 H, 2-H), 3.83 (dd, ^3J = 6.6, ^3J = 8.4 Hz, 1 H, NCH), 3.87–3.92 (m, 3 H, 2′-H, 5-H, 5′-H), 4.06 (m, 1 H, 6-H), 4.42 (m, 1 H, 3-H), 4.54–4.60 (m, 4 H, CH_2Ph, 3a-H, 6a-H), 5.04 (d, $J_{NH,CHNH}$ = 8.4 Hz, 1 H, *NH*COO), 6.17 (d, $J_{NHCO,3H}$ = 5.5 Hz, 1 H, *NH*CO), 7.27–7.37 (m, 5 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1, 19.5 [CH(*C*H$_3$)$_2$], 28.4 [C(CH_3)$_3$], 31.0 [CH(*C*H$_3$)$_2$], 56.2 (C-3), 60.1 (*C*HNH), 71.7 (CH_2Ph), 72.1 (C-2), 72.5 (C-5), 80.1 [*C*(CH_3)$_3$], 83.2 (C-6), 85.8 (C-6a), 86.5 (C-3a), 127.8 (2 CH_{Ar}), 128.0 (CH_{Ar}), 128.6 (2 CH_{Ar}), 137.6 ($C_{q,Ar}$), 156.1 (NH*C*OO), 171.6 (NH*C*O) ppm. HRMS (ESI): calcd. for $C_{23}H_{34}N_2NaO_6$ $[M + Na]^+$ 457.2309; found 457.2292.

***tert*-Butyl [(2*R*)-1-{[(3*S*,3a*R*,6*S*,6a*S*)-6-Benzyloxyhexahydrofuro[3,2-*b*]furan-3-yl]amino}-3-methyl-1-oxobutan-2-yl]carbamate (26):** The general procedure was followed using *N*-Boc-D-valine (139 mg, 0.638 mmol, 1.5 equiv.) to give a brown oil (195 mg, 95 % crude yield). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (1:1) as eluent to afford **26** (white solid, 69 mg, 38 %), m.p. 156–157 °C (*i*Pr_2O). $[\alpha]_D^{25}$ = +15.7 (*c* = 0.99, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3331, 3302, 2965, 2876, 1709, 1634, 1551, 1514, 1366, 1275, 1236, 1163, 1076, 1053, 1016, 916, 881 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.90, 0.94 [2 d, ^3J = 6.6 Hz, 6 H, CH(C*H*$_3$)$_2$], 1.43 [s, 9 H, C(CH_3)$_3$], 2.09–2.16 [m, 1 H, C*H*(CH_3)$_2$], 3.74 (app. d, ^2J = 9.6 Hz, 1 H, 2-H), 3.82 (app. t, ^3J = 7.6 Hz, 1 H, *CH*NH), 3.86–3.93 (m, 3 H, 2′-H, 5-H, 5′-H), 4.05–4.07 (m, 1 H, 6-H), 4.39–4.43 (m, 1 H, 3-H), 4.54–4.63 (m, 4 H, 6a-H, CH_2Ph, 3a-H), 5.03 (d, 1 H, $^3J_{NH,CHNH}$ = 8.5 Hz, N*H*COO), 6.21 (d, $^3J_{NHCO,3H}$ = 7.0 Hz, 1 H, N*H*CO), 7.28–7.36 (m, 5 H, H_{Ar}) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.9, 19.5 [CH(*C*H$_3$)$_2$], 28.4 [C(CH_3)$_3$], 30.6 [*C*H(CH_3)$_2$], 56.2 (C-3), 60.2 (*C*HNH), 71.7 (CH_2Ph), 72.1 (C-2), 72.5 (C-5), 80.3 [*C*(CH_3)$_3$], 83.0 (C-6), 85.7 (C-6a), 86.4 (C-3a), 127.9 (2 CH_{Ar}), 128.1 (CH_{Ar}), 128.6 (2 CH_{Ar}), 137.5 ($C_{q,Ar}$), 156.1 (NH*C*OO), 171.5 (NH*C*O) ppm. HRMS (ESI): calcd. for $C_{23}H_{34}N_2NaO_6$ $[M + Na]^+$ 457.2309; found 457.2310.

***N*-[(3*S*,3a*R*,6*R*,6a*S*)-6-Methoxyhexahydrofuro[3,2-*b*]furan-3-yl]-4-methylbenzamide (30):** The general procedure was followed using **27** (70 mg, 0.44 mmol), 4-methylbenzoic acid (90 mg, 0.66 mmol, 1.5 equiv.) and boric acid (8 mg, 0.132 mmol, 0.3 equiv.) in xylene (5 mL) to give a brown oil (87 mg, 71 % crude yield). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (2:8) as eluent to afford **30** (pale-yellow solid, 73 mg, 61 %), m.p. 122–123 °C (Et_2O). $[\alpha]_D^{25}$ = +79.3 (*c* = 1.07, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3289, 2941, 2878, 1636, 1535, 1503, 1325, 1138, 1096, 1055 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, CH_3), 3.47 (s, 3 H, OCH_3), 3.64–3.70 (m, 1 H, 5-H), 3.92–3.98 (m, 3 H, 2-H, 5′-H, 6-H), 4.11 (dd, $^3J_{2'H,3H}$ = 4.4, ^2J = 9.8 Hz, 1 H, 2′-H), 4.58–4.62 (m, 2 H, 3a-H, 3-H), 4.66–4.69 (m, 1 H, 6a-H), 6.28 (d, $^3J_{NHCO,3H}$ = 7.0 Hz, 1 H, NH), 7.20–7.22 (d, ^3J = 8.0 Hz, 2 H, H_{Ar}), 7.63–7.65 (d, ^3J = 8.0 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (CH_3), 57.6 (C-3), 58.5 (OCH_3), 70.6 (C-5), 73.7 (C-2), 80.2 (C-6a), 81.8 (C-6), 87.2 (C-3a), 127.1 (2 CH_{Ar}), 129.4 (2 CH_{Ar}), 131.1 ($C_{q,Ar}$), 142.4 ($C_{q,Ar}$), 167.2 (C=O) ppm. HRMS (ESI): calcd. for $C_{15}H_{19}NNaO_4$ $[M + Na]^+$ 300.1206; found 300.1210.

***N*-[(3*S*,3a*R*,6*R*,6a*S*)-6-(Benzyloxy)hexahydrofuro[3,2-*b*]furan-3-yl]-4-methylbenzamide (31):** The general procedure was followed using **28** (100 mg, 0.425 mmol), 4-methylbenzoic acid (87 mg, 0.638 mmol, 1.5 equiv.) and boric acid (8 mg, 0.128 mmol, 0.3 equiv.). The crude brown oil was purified by flash chromatography using petroleum ether/ethyl acetate (1:1) as eluent to afford **31** (white solid, 119 mg, 80 %), m.p. 130–131 °C (Et_2O). $[\alpha]_D^{22}$ = +75.8 (*c* = 1.03, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3296, 2972, 2856, 1631, 1531, 1506, 1334, 1160, 1070, 1042, 957, 839, 759, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, CH_3), 3.70 (dd, $^3J_{5H,6H}$ = 7.5, ^2J = 9.0 Hz, 1 H, 5-H), 3.88 (dd, $^3J_{5'H,6H}$ = 6.6, ^2J = 9.0 Hz, 1 H, 5′-H), 3.98 (app. d, $^2J'$ = 9.8 Hz, 1 H, 2-H), 4.08 (ddd, $^3J_{6H,6aH}$ = 4.9, $^3J_{6H,5H} \approx {}^3J_{6H,5'H}$ = 7.0 Hz, 1 H, 6-H), 4.15 (dd, $^3J_{2'H,3H}$ = 4.4, ^2J = 9.8 Hz, 1 H, 2′-H), 4.57 (AB system, ^2J = 11.8 Hz, 1 H, CH_2Ph), 4.55–4.62 (m, 2 H, 3a-H, 3-H), 4.66 (app. t, $J_{6aH,6H} \approx {}^3J_{6aH,3aH}$ = 4.6 Hz, 6a-H), 4.76 (AB system, ^2J = 11.8 Hz, 1 H, CH_2Ph), 6.35 (d, $^3J_{NH,3H}$ = 7.5 Hz, 1 H, NH), 7.21 (d, ^3J = 8.0 Hz, 2 H, H_{Ar}), 7.28–7.38 (m, 5 H, H_{Ar}), 7.65 (d, ^3J = 8.0 Hz, 2 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (CH_3), 57.6 (C-3), 70.9 (C-5), 72.7 (CH_2Ph), 73.6 (C-2), 79.2 (C-6), 80.5 (C-6a), 87.2 (C-3a), 127.1 (2 CH_{Ar}), 128.0 (2 CH_{Ar}), 128.1 (CH_{Ar}), 128.6 (2 CH_{Ar}), 129.4 (2 CH_{Ar}), 131.1 ($C_{q,Ar}$), 137.8 ($C_{q,Ar}$), 142.4 ($C_{q,Ar}$), 167.2 (C=O) ppm. HRMS (ESI): calcd. for $C_{21}H_{23}NaNO_4$ $[M + Na]^+$ 376.1519;

found 376.1511; calcd. for $C_{21}H_{24}NO_4$ $[M + H]^+$ 354.1700; found 354.1692.

***N,N′*-(3*S*,3a*R*,6*S*,6a*R*)-Hexahydrofuro[3,2-*b*]furan-3,6-diylbis(4-methylbenzamide) (32):** The general procedure was followed using **29** (100 mg, 0.693 mmol) and 4-methylbenzoic acid (283 mg, 2.08 mmol, 3 equiv.) and boric acid (26 mg, 0.416 mmol, 0.6 equiv.) in xylene (7 mL) to give a rather pure brown solid (226 mg, 86 % crude yield). The crude product was purified by flash chromatography using petroleum ether/ethyl acetate (3:7) as eluent to afford **32** (white solid, 175 mg, 67 %), m.p. 234–237 °C (Et_2O). $[\alpha]_D^{25}$ = +60.8 (*c* = 0.24, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3320, 2942, 1641, 1634, 1533, 1508, 1337, 1091, 1065, 910 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 6 H, 2 CH_3), 3.89 (dd, $^3J_{2H,3H} = {}^3J_{5H,6H}$ = 2.0, ^2J = 9.8 Hz, 2 H, 2-H, 5-H), 4.08 (dd, $^3J_{2'H,3H} = {}^3J_{5'H,6H}$ = 4.8, ^2J = 9.8 Hz, 2 H, 2′-H, 5′-H), 4.61–4.64 (m, 2 H, 3-H, 6-H), 4.72 (s, 2 H, 3a-H, 6a-H), 6.28 (d, $^3J_{NH,H}$ = 6.9 Hz, 2 H, 2 NH), 7.18 (d, ^3J = 8.0 Hz, 4 H, H_{Ar}), 7.62 (d, ^3J = 8.0 Hz, 4 H, H_{Ar}) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (2 CH_3), 57.3 (C-3, C-6), 72.7 (C-2, C-5), 86.7 (C-3a, C-6a), 127.2 (4 CH_{Ar}), 129.4 (4 CH_{Ar}), 131.3 (2 $C_{q,Ar}$), 142.4 (2 $C_{q,Ar}$), 167.4 (2 C=O) ppm. HRMS (ESI): calcd. for $C_{22}H_{24}NaN_2O_4$ $[M + Na]^+$ 403.1628; found 403.1619; calcd. for $C_{22}H_{25}N_2O_4$ $[M + H]^+$ 381.1809; found 381.1801.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra.

Acknowledgments

The Ministère de l'Enseignement Supérieur et de la Recherche is gratefully acknowledged for a grant to M. J.

Keywords: Organocatalysis · Carbohydrates · Amino acids · Amides

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Received: February 18, 2016
Published Online: April 13, 2016

