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Note

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Diastereoselective Iridium-Catalyzed Amination of Biosourced Isohexides Through Borrowing Hydrogen Methodology

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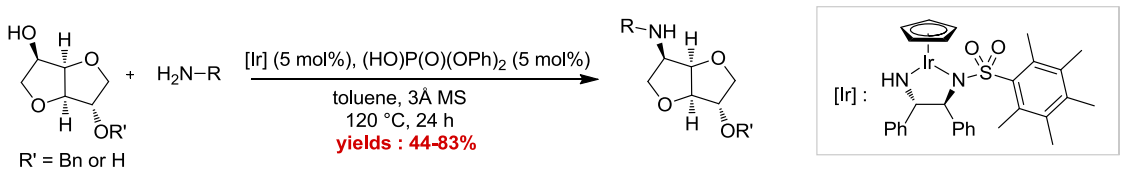
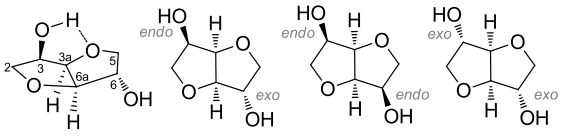
ABSTRACT: A novel direct and diastereoselective amination of biosourced monobenzylated isohexides has been developed through borrowing hydrogen methodology using a cooperative catalysis between an iridium complex and a phosphoric acid. We also report herein the first regio- and diastereoselective direct amination of isosorbide.



Isosorbide, a major product of the starch industry,[1] is a renewable platform chemical able to significantly contribute to the future replacement of fossil resource-based products.[2] This isohexide is a V-shaped chiral molecule of two *cis*-connected tetrahydrofuran rings with secondary hydroxyl groups in C-3 and C-6 positions with *endo* and *exo* configurations respectively. Isomannide (*endo*/*endo*), produced from D-mannitol, and non-commercial isoidide (*exo*/*exo*) are two other diastereoisomers (Figure1).

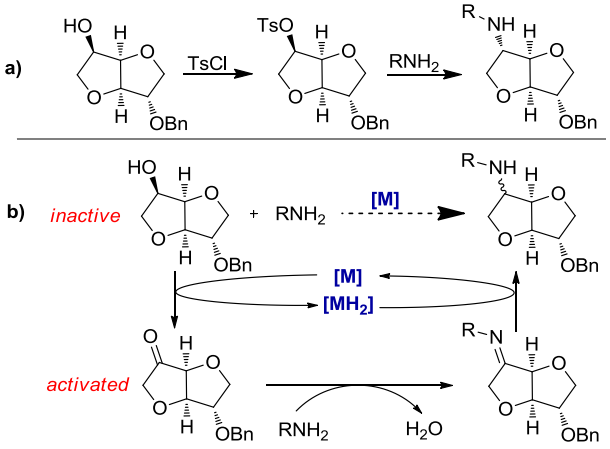
Figure 1. Chemical structure of bio-based isohexides



Isosorbide and isomannide have been used for the synthesis of biogenic polymers[3] as well as pharmaceutical compounds[4] such as isosorbide dinitrate (Isordil®).[5] Over the last decades, functionalization of these biosourced isohexides into corresponding amines has also attracted considerable interest for polymer applications[6] and for asymmetric induction in organic synthesis[7] (auxiliaries,[8] ligands[9] and organocatalysts[10]).

Reported synthesis of isohexide-based amines involved the use of highly reactive leaving groups, such as tosylates as a given example (Scheme 1, a). Although effective, this process has low atom efficiency and high amount of waste is generated. The advent of green chemistry has promoted innovative methodologies considering atom economy parameter. With respect to this point, borrowing hydrogen (BH) methodology has emerged as an important tool in organic chemistry for the construction of C-C and C-N bonds.[11] In the case of amination of alcohols, a first step of catalytic dehydrogenation converts an unreactive alcohol into the corresponding carbonyl compound. Subsequent reaction with an amine leads to the imine *in situ* which upon hydrogenation affords the desired product. This one pot strategy benefits from metal catalysis and affords water as the sole by-product. We thus proposed to apply this atom-efficient transformation for the synthesis of isohexide-based amines as an alternative to classical reported methods (Scheme 1, b).

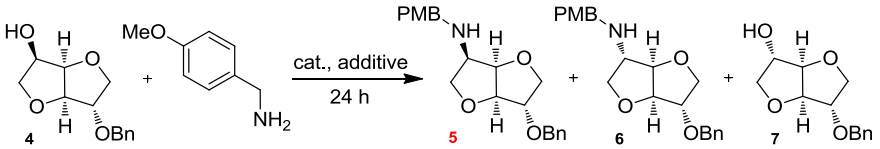
Scheme 1. Two-step reported amination of isohexides (a) and proposed catalytic amination using BH methodology (b)



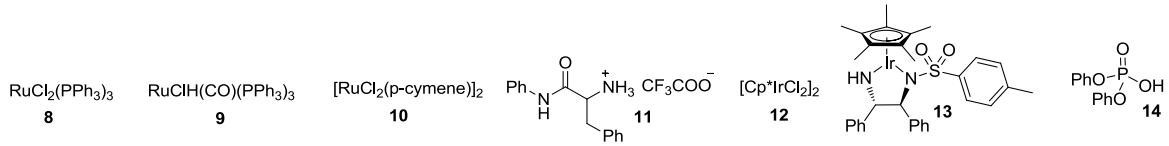
Already used for homogeneous catalyzed diamination of isosorbide and isomannide with ammonia,[12] this approach led to diamines with excellent conversions but as a mixture of three diastereoisomers (in an optimal distribution *endo*/*exo*, *endo*/*endo*, *exo*/*exo* 45:15:35 when determined).

The *exo*-monobenzylated isosorbide **4** was first chosen as a model substrate. The number of possible products, inherent to the involved mechanism, should be limited and the analysis of the reaction outcome be simplified. This choice was also consistent with calculations reporting that the oxidation of the hydroxyl group in *endo* position was slightly favored towards the one in *exo* position ($\Delta(\Delta G^{\#}) = 2$ kcal.mol^{-1}).[13]

Table 1. Preliminary screening for reactions conditions



Entry	Cat. (mol%)	T (°C)	additive (mol%)	solvent	**ratio 4 : 5 : 6 : 7**[a]	**5** (%)[b]
1	**8** (5)	140	KOH (20)	^{t}amyl alcohol	**25 : 0 : 0 : 75**	-
2	**9** (5)	120	Xantphos (5)	toluene	**100 : 0 : 0 : 0**	-
3	**9** (10)	170[c]	Xantphos (10)	^{t}amyl alcohol	**22 : 8 : 8 : 62**	**nd**
4	**9** (10)	170	Xantphos (10)	xylene	**20 : 30 : 30 : 20**	**17**[d]
5	**10** (5)	120	DPE-phos (10)	toluene	**100 : 0 : 0 : 0**	-
6	**10** (5)	120	**11** (10), ^{t}BuOK (30)	toluene	**100 : 0 : 0 : 0**	-
7	**12** (1.5)	120	$NaHCO_3$ (5)	toluene	**55 : 45 : 0 : 0**	**34**
8	**12** (1.5)	120	-	toluene	**62 : 38 : 0 : 0**	**nd**
9	**12** (1.5)	120	$NaHCO_3$ (50)	toluene	**57 : 11 : 0 : 31**	**nd**
10	**12** (1.5)	120	K_2CO_3 (5)	toluene	**62 : 0 : 0 : 38**	-
11[e]	**12** (1.5)	120	$NaHCO_3$ (5)	toluene	**20 : 18 : 0 : 62**	**nd**
12	**13** (5)	120	**14** (5)	toluene	**40 : 60 : 0 : 0**	**50**



Reaction conditions: **4** (1 equiv), amine (1 equiv), catalyst, additive, solvent [2M], 24 h. a) conversion rate and diastereoisomeric ratio were determined by ^{1}H NMR b) isolated yields, c) reaction was also performed at 140 °C and same results were obtained, d) isolated yield of **6** : 16%, e) with 3Å MS - nd : not determined

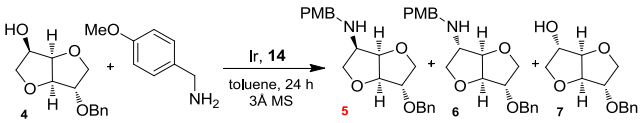
We started our investigations with $RuCl_2(PPh_3)_3$ **8** and KOH catalytic system for the reaction from **4**, taking advantage of the recent results obtained in our group using a borrowing hydrogen reaction between 4-hydroxycoumarin and benzylic alcohol[14] (Table 1, entry 1). Despite a 75% conversion rate, no amination product was detected and only epimerized isohexide **7** was observed. The use of the previously reported catalytic system by Beller *et al.* using $RuClH(CO)(PPh_3)_3$ / Xantphos[12a] was then shown to be strongly dependent from the solvent. (Table 1, entries 2-4). While no reaction occurred in toluene at 120 °C, the formation of a diastereoisomeric mixture of amines **5** and **6** in a 1:1 ratio[15] was observed in ^{t}amyl alcohol or xylene at 140-170 °C, along with the isomer **7** in non negligible amount (20 to 62%). Amines **5** and **6** were isolated with 17 and 16% yields respectively (Table 1, entry 4).[16] No conversion was observed using the

dimeric $[RuCl_2(p\text{-cymene})]_2$ catalyst **10** either with oxydi-2,1-phenylene)bis(diphenylphosphine (DPE-Phos) or phenyl phenyl alaninamide trifluoroacetic acid as additive (Table 1, entries 5 and 6).

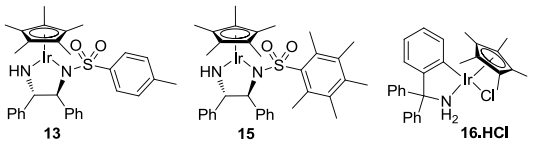
Because of the disappointing results obtained with ruthenium complexes, we decided to radically switch to iridium catalysts. $[Cp^*IrCl_2]_2$ **12** has specially proven to be efficient for amination of primary or secondary alcohols using borrowing hydrogen methodology under basic conditions.[17] The use of 1.5 mol% of **12** and 5 mol% of sodium bicarbonate in toluene at 120 °C led to the formation of a single diastereoisomer **5** with 45% conversion rate and 34% isolated yield (Table 1, entry 7). Following this very promising result, optimization of the reaction parameters was pursued. The absence of base did not seem to influence conversion rate (about 40%, entries 7-10) but the use of either 50 mol% of $NaHCO_3$ (Table 1, entry 9) or 5 mol% of K_2CO_3 (Table 1, entry 10) mainly led to the formation of compound **7**. The obtention of this epimerized product *via* the formation of the intermediate ketone led us to speculate that the limiting step was the imine formation. To displace the equilibrium, the reaction was thus performed with molecular sieves that unfortunately promoted epimerization (Table 1, entry 11). In the work reported by Zhao on enantioselective amination of secondary alcohols,[18] phosphoric acids proved to promote the condensation of ketones with aniline using iridium catalyst **13**. Gratifyingly, the combination of diphenylphosphate **14** (5 mol%) with **13** (5 mol%) in toluene at 120 °C improved indeed significantly the results. Conversion rate reached 60% and amine **5** was isolated in 50% yield (Table 1, entry 12). It is noticeable that without acid, 28% of epimerized isohexide **7** was formed with only 2% of expected compound **5**.

To investigate more thoroughly the cooperative catalysis between Ir^{III} complex and phosphoric acid, a new optimization of iridium catalysis was carried out (Table 2). First, a slightly positive synergistic effect of molecular sieves was noticed as conversion rate increased to 70% (Table 2, entry 2). Replacing the organometallic catalyst **13** by its pentamethyl analog **15** led satisfyingly to the formation of **5** with 95% conversion and 67% isolated yield (Table 2, entry 4). Zhao *et al*. had also reported the use of a racemic iridacycle **16** as an efficient catalyst for the synthesis of tetrahydroquinolines by borrowing hydrogen methodology under acidic conditions.[19]

Table 2. Optimization of the iridium-based catalysis



Entry	Ir	T (°C)	ratio 4 : 5 : 6 : 7	5 (%)[a]
1[b]	**13**	120	**40 : 60 : 0 : 0**	**50**
2	**13**	120	**30 : 70 : 0 : 0**	**52**
3[b]	**15**	120	**26 : 74 : 0 : 0**	**51**
4	**15**	120	**5 : 95 : 0 : 0**	**67**
5[c]	**16**	120	**18 : 1 : 0 : 81**	**-**
6	**16**	120	**0 : 90 : 0 : 0**	**71**
7	**16**	90	**45 : 55 : 0 : 0**	**nd**
8	**16**	140	**0 : 60 : 0 : 0**	**nd**

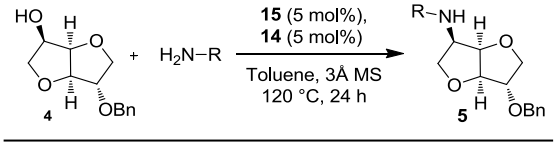


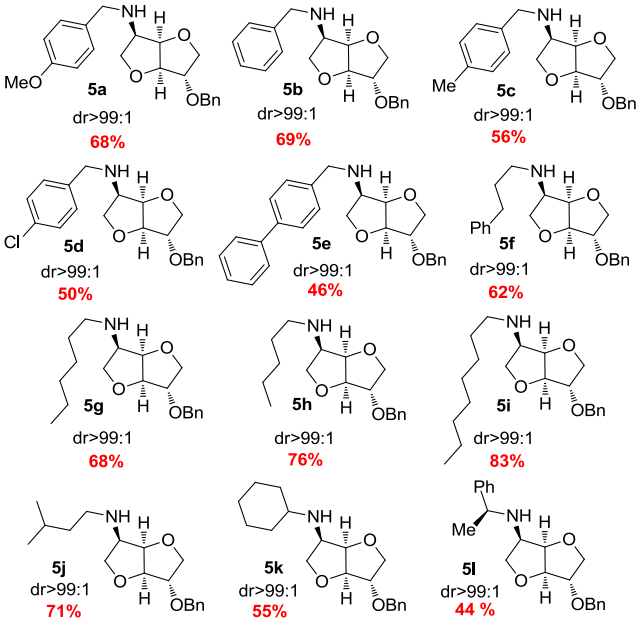
Reaction conditions: **4** (1 equiv), amine (1 equiv), metal catalyst (5 mol%), **14** (5 mol%), toluene, 24 h. a) isolated yields b) without 3Å MS c) without phosphoric acid

We thus decided to examine the reactivity of **16.HCl** simply obtained in one step from $[Cp^*IrCl_2]_2$ and tritylamine. When performing the reaction with **16.HCl**, released HCl was not sufficient to promote the formation of imine and led to **7** as the major compound after 82% conversion (Table 2, entry 5). When 5 mol% of acid **14** was added, total conversion led to a 9/1 mixture of **5** and **7** and **5** was isolated with 71% yield (Table 2, entry 6). Interestingly, reaction temperature had a strong influence on the selectivity: at 90 °C, conversion into **5** decreased to 55% but no epimerized isohexide **7** was formed (Table 2, entry 7) while at 140 °C, total conversion led to a mixture of **5**/**7** in a 3/2 ratio (Table 2, entry 8). Best results were thus obtained with 5 mol% of iridium catalyst (**15** or **16.HCl**), 5 mol% of phosphoric acid **14** with molecular sieves in toluene at 120 °C for 24 h. The conversion was slightly better with catalyst **16.HCl**, whereas catalyst **15** offered a total selectivity without epimerization product. The isolated yields were also roughly in the same range.

The scope of the reaction was examined and first studied with various amines using optimized conditions combining **15** and phosphoric acid **14** (Scheme 2).[20]

Scheme 2. Scope of amines reacting with **4**

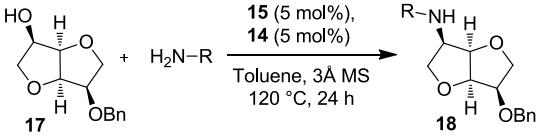


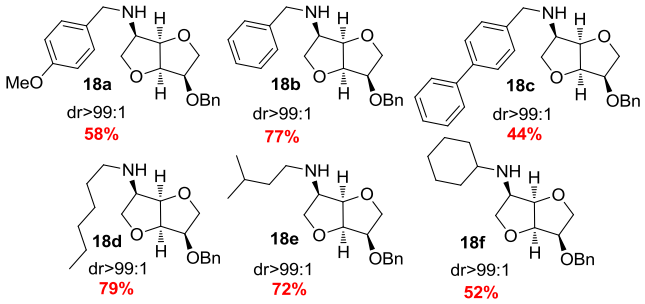


Reactions with benzylamine and *p*-methylbenzylamine provided the corresponding amines in yields of 69% (**5b**) and 56% (**5c**) respectively. With less nucleophilic benzylamines, such as chloro and phenyl electronwithdrawing groups in *para* position, some epimerization of starting material (10-20%) and moderate conversion rates into amines **5d** and **5e** (60-70%) were observed. More hindered amines such as cyclohexylamine and α-methylbenzylamine provided the expected compounds in 55 and 44 % respectively. Unfortunately, no reaction occurred with aniline. In the case of ^{tert}butylamine, only epimerized isohexide **7** was formed with a conversion rate of 50%.

To better understand the scope of application of the reaction, it was interesting to study the influence of the unreacted C-6 position. The amination *via* borrowing hydrogen methodology was thus also studied on monobenzylated isomannide **17** which differs from **4** only by the orientation of the benzyloxy group. Under the above optimized conditions, reacting **17** with *p*-methoxybenzylamine also provided a single diastereoisomer **18a** with an excellent conversion rate and a 58% isolated yield (Scheme 3).

Scheme 3. Scope of amines reacting with **17**

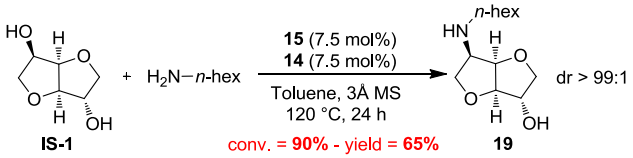




Confirming the robustness of the process, this result also pointed out the non-assistance of the C-6 position in the control of the diastereoselectivity. A scope of benzylic and aliphatic amines was then investigated. The use of benzylamine afforded chiral amine **18b** with an excellent conversion rate and 77% isolated yield. The less nucleophilic 4-phenylbenzylamine provided **18c** in 44% isolated yield (*vs* 46% for **5e**). Using aliphatic amines gave very satisfying results. Indeed, total conversions were observed affording amines **18d** and **18e** in 79% and 72% yield respectively. As from **4**, the amination with cyclohexylamine also led to the concurrent formation of the isomerized by-product and expected amine isolated in a more moderate yield of 52%. The same range of yields was globally measured for amines obtained from **4** or **17**, only differing from the stereocenter in C-6 position.

Considering Gibbs free energies calculated for oxidation of isohexides,[13] oxidation of the hydroxyl in *exo* position appeared to be disfavoured. This was confirmed by submitting *endo*-benzyloxy-isosorbide (with an *exo* alcohol) to our amination reaction using our optimized conditions. No amination product was formed and starting material was recovered. To take benefit from this selectivity, we then envisaged the direct and more challenging transformation of isosorbide into a chiral amino-alcohol. Our optimised conditions using iridium complex **15** / acid cooperative catalysis were first tested. We were delighted to observe the formation of a single stereoisomer with 70% conversion (Scheme 4).[21] Increasing the catalytic loading to 7.5 mol% made the conversion rate reach 90% and the chiral amino-alcohol **19** was isolated in 65% yield in one step from isosorbide.

Scheme 4. Regio- and diastereoselective amination of IS-1



To conclude, we developed an efficient methodology for the diastereoselective direct amination of biobased isohexides. In each case examined, the sense of diastereoselectivity corresponds to an *exo* attack of the [Ir]-H species onto an imine intermediate. Optimized conditions allowed very good conversion rates and excellent selectivity towards the formation of valuable chiral amino-isohexides. Moreover, the regioselectivity of the oxidation step was proved and we could propose the first regio- and diastereoselective direct amination of the biosourced unprotected isosorbide using BH methodology. The scope of application of this approach is currently being further explored in conjunction with mechanistic investigations.

EXPERIMENTAL SECTION

Reagents and solvents were supplied by Aldrich, Acros or Alfa Aesar and purchased at the highest commercial quality to be used without further purification. NMR spectra were recorded on a Bruker DPX-300 (^{1}H: 300 or 400 MHz; ^{13}C: 75 or 100 MHz) spectrometer using $CDCl_3$. The chemical shifts (δ ppm) and coupling constants (Hz) are reported in the standard fashion. The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. NMR peak assignments was performed for each compound using classical 1D and 2D NMR (COSY, HSQC, HMBC and NOESY). For better clarity, a mean of close measured coupling constants for correlated protons are displayed in NMR assignments. High-resolution mass spectra (HRMS) were recorded on a Bruker MicrOTOF-Q II XL spectrometer using ESI as ionization source. Analytical thin-layer chromatographies were carried out on silica gel Merck 60 D254 (0.25 mm). Flash chromatographies were performed on Merck Si 60 silica gel (40–63 μm). Infra-red (IR) spectra were recorded with an IRAffinity-1 Shimadzu spectrometer using attenuated total reflectance (ATRMiracle), and the wavenumbers were expressed in cm^{-1}. Optical rotations were measured with a Perkin–Elmer 241 polarimeter with a 10 cm cell (concentration *c* expressed in g/100 mL).

General procedure for isohexide amination. To a solution of isohexide **4** or **17** (60 mg, 0.25 mmol, 1 equiv), diphenylphosphate **14** (3.1 mg, 0.0125 mmol, 0.05 equiv), iridium catalyst **15** (9.3 mg, 0.0125 mmol, 0.05 equiv) and 3Å molecular sieves in anhydrous toluene (130 μL) was added amine (0.25 mmol, 1 equiv). The vial was sealed and the reaction mixture was stirred under heating at 120 °C for 24 h. After cooling down to rt, the mixture was filtered through Celite® and the solvent was evaporated. After NMR analyses of the

crude mixture, purification by column chromatography on silica gel (EtOAc/Pentane as eluent) afforded the targeted amines as yellow oils.

(3*R*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)-*N*-(4-methoxybenzyl)hexahydrofuro[3,2-*b*]furan-3-amine (**5a**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 7/3 as eluent affording **5a** (60 mg, **68%**) as a pale yellow oil. **^{1}H NMR ($CDCl_3$, 300 MHz)** δ 3.26 (dd, *J* = 7.8 and 10.0, 1H, H_2), 3.30-3.41 (m, 1H, H_3), 3.72 (d, *J* = 13.0, 1H, CH_2N), 3.79 (s, 3H, OMe), 3.87 (d, *J* = 13.0, 1H, CH_2N), 3.83-3.89 (m, 1H, H_5), 3.96-4.01 (m, 2H, H_2 and H_5), 4.06-4.07 (m, 1H, H_6), 4.52-4.62 (m, 3H, H_{6a} and CH_2O), 4.64 (app. t, *J* = 4.0, 1H, H_{3a}), 6.86 (d, *J* = 8.3, 2H, 2 H_c), 7.27 (d, *J* = 8.3, 2H, 2 H_b), 7.31-7.40 (m, 5H, H_{Ar}); **^{13}C NMR ($CDCl_3$, 75 MHz)** δ 51.7 (CH_2N), 55.2 (OMe), 61.7 (C_3), 71.1 (C_2), 71.5 (CH_2O), 73.0 (C_5), 79.9 (C_{3a}), 84.2 (C_6), 86.4 (C_{6a}), 113.7 (2 C_c), 127.6 (2 C_{Ar}), 127.8 (C_{Ar}), 128.4 (2 C_{Ar}), 129.3 (2 C_b), 132.0 (C_a), 137.6 (C_{qAr}), 158.7 (C_d); **IR (ATR)** ν 2953, 2932, 1611, 1510, 1456, 1244, 1076, 1032, 820, 733 cm^{-1} ; $[\alpha]_D^{21}$ = +42.3° (*c* 1.35 $CHCl_3$); **HRMS (ESI)** $[M+Na]^+$: calcd for $C_{21}H_{25}NNaO_4$: 378.1676; found 378.1695; $[M+H]^+$: calcd for $C_{21}H_{26}NO_4$: 356.1856 ; found 356.1842

(3*R*,3a*R*,6*S*,6a*S*)-*N*-Benzyl-6-(benzyloxy)hexahydrofuro[3,2-*b*]furan-3-amine (**5b**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 6/4 as eluent affording **5b** (56 mg, **69%**) as a pale yellow oil. **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 3.28 (dd, *J* = 8.0 and 10.0, 1H, H_2), 3.34-3.39 (m, 1H, H_3), 3.78 (d, *J* = 12.9, 1H, CH_2N), 3.88 (dd, *J* = 4.2 and 10.0, 1H, H_5), 3.94 (d, *J* = 12.9, 1H, CH_2N), 3.98-4.02 (m, 2H, H_2 and H_5), 4.06-4.08 (m, 1H, H_6), 4.57 and 4.60 (2 d, *J* = 11.9, 2H, CH_2O), 4.60 (d, *J* = 4.1, 1H, H_{6a}), 4.65 (app. t, *J* = 4.1, 1H, H_{3a}), 7.24-7.38 (m, 10H, H_{Ar}); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 52.3 (CH_2N), 61.8 (C_3), 71.1 (C_2), 71.5 (CH_2O), 73.0 (C_5), 79.9 (C_{3a}), 84.2 (C_6), 86.5 (C_{6a}), 127.1 (C_{Ar}), 127.7 (2 C_{Ar}), 127.8 (C_{Ar}), 128.1 (2 C_{Ar}), 128.4 (2 C_{Ar}), 128.4 (2 C_{Ar}), 137.6 (C_{qAr}), 139.9 (C_{qAr}); $[\alpha]_D^{21}$ = +29.9° (*c* 0.936 $CHCl_3$); **IR (ATR)** ν 2932, 2864, 1454, 1080, 1067, 733 cm^{-1}; **HRMS (ESI)** $[M+Na]^+$: calcd for $C_{20}H_{23}NNaO_3$: 348.1570; found 348.1564; $[M+H]^+$: calcd for $C_{20}H_{24}NO_3$: 326.1751; found 326.1738

(3*R*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)-*N*-(4-methylbenzyl)hexahydrofuro[3,2-*b*]furan-3-amine (**5c**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 6/4 as eluent affording **5c** (48 mg, **56%**) as a pale yellow oil. **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 2.34 (s, 3H, Me), 3.27 (dd, *J* = 8.1 and 9.9,

1H, H_2), 3.32-341 (m, 1H, H_3), 3.75 (d, *J* = 12.7, 1H, CH_2N), 3.85-3.93 (m, 2H, H_5 and CH_2N), 3.96-4.03 (m, 2H, H_2 and H_5), 4.04-4.09 (m, 1H, H_6), 4.57 (d, *J* = 12.0, 1H, CH_2O), 4.59 (d, *J* = 4.2, 1H, H_{6a}), 4.60 (d, *J* = 12.0, 1H, CH_2O), 4.65 (app. t, *J* = 4.2, 1H, H_{3a}), 7.14 (d, *J* = 7.8, 2H, H_{Ar}), 7.25 (d, *J* = 8.0, 2H, H_{Ar}), 7.28-7.39 (m, 5H, H_{Ar}); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 21.1 (Me), 52.0 (CH_2N), 61.7 (C_3), 71.1 (C_2), 71.5 (CH_2O), 73.0 (C_5), 79.9 (C_{3a}), 84.2 (C_6), 86.5 (C_{6a}), 127.7 (2 C_{Ar}), 127.8 (C_{Ar}), 128.1 (2 C_b), 128.4 (2 C_{Ar}), 129.1 (2 C_c), 136.7 (C_d), 136.8 (C_a), 137.7 (C_{qAr}); $[\alpha]_D^{21}$ = +49.7° (*c* 1.11 $CHCl_3$); **IR (ATR)** ν 2924, 2866, 1456, 1078, 733 cm^{-1}; **HRMS (ESI)** $[M+H]^+$: calcd for $C_{21}H_{26}NO_3$: 340.1907; found 340.1903

(3*R*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)-*N*-(4-chlorobenzyl)hexahydrofuro[3,2-*b*]furan-3-amine (**5d**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 7/3 to 8/2 as eluent affording **5d** (45 mg, 50**%**) as a pale yellow oil. **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 3.26 (dd, *J* = 7.8 and 10.0, 1H, H_2), 3.30-3.37 (m, 1H, H_3), 3.74 (d, *J* = 13.1, 1H, CH_2N), 3.87 (dd, *J* = 4.2 and 10.0, 1H, H_5), 3.89 (d, *J* = 13.1, 1H, CH_2N), 3.96-4.02 (m, 2H, H_2 and H_5), 4.05-4.08 (m, 1H, H_6), 4.56 (d, *J* = 11.9, 1H, CH_2O), 4.59 (d, *J* = 4.2, 1H, H_{6a}), 4.60 (d, *J* = 11.9, 1H, CH_2O), 4.63 (app. t, *J* = 4.2, 1H, H_{3a}), 7.26-7.37 (m, 9H, H_{Ar}); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 51.6 (CH_2N), 61.9 (C_3), 71.1 (C_2), 71.6 (CH_2O), 73.1 (C_5), 79.8 (C_{3a}), 84.2 (C_6), 86.5 (C_{6a}), 127.7 (2 C_{Ar}), 127.8 (C_{Ar}), 128.5 (2 C_{Ar}), 128.5 (2 C_c), 129.4 (2 C_b), 132.7 (C_d), 137.6 (C_{qAr}), 138.5 (C_a); $[\alpha]_D^{21}$ = +47.7° (*c* 0.99 $CHCl_3$); **IR (ATR)** ν 2924, 2870, 1456, 1265, 1080, 700 cm^{-1}; **HRMS (ESI)** $[M+Na]^+$: calcd for $C_{20}H_{22}ClNNaO_3$: 382.1180; found 382.1180; $[M+H]^+$: calcd for $C_{20}H_{23}ClNO_3$: 360.1361; found 360.1349

(3*R*,3a*R*,6*S*,6a*S*)-*N*-([1,1'-Biphenyl]-4-ylmethyl)-6-(benzyloxy)hexahydrofuro[3,2-*b*]furan-3-amine (**5e**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 6/4 as eluent affording **5e** (46 mg, 46**%**) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 3.30 (dd, *J* = 8.2 and 10.0, 1H, H_2), 3.37-3.44 (m, 1H, H_3), 3.83 (d, *J* = 13.1, 1H, CH_2N), 3.90 (dd, *J* = 4.2 and 10.0, 1H, H_5), 3.98 (d, *J* = 13.1, 1H, CH_2N), 4.00-4.05 (m, 2H, H_2 and H_5), 4.07-4.10 (m, 1H, H_6), 4.57 and 4.60 (2 d, *J* = 11.9, 2H, CH_2O), 4.62 (d, *J* = 4.1, 1H, H_{6a}), 4.68 (app. t, *J* = 4.1, 1H, H_{3a}), 7.27-7.67 (m, 14H, H_{Ar}); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 52.0 (CH_2N), 61.9 (C_3), 71.2 (C_2), 71.6 (CH_2O), 73.1 (C_5), 79.9 (C_{3a}), 84.2 (C_6), 86.5 (C_{6a}), 127.0 (2 C_{Ar}), 127.2 (3 C_{Ar}), 127.7 (2 C_{Ar}), 127.8 (C_{Ar}), 128.5 (2 C_{Ar}), 128.6 (2 C_{Ar}), 128.7 (2 C_{Ar}), 137.6 (C_{qAr}), 139.0 (C_{qAr}), 140.0 (C_{qAr}), 140.9 (C_{qAr}); **IR (ATR)** ν 2926, 2870, 1456, 1265, 1076, 733 cm^{-1}; $[\alpha]_D^{21}$ = +45.7°

(*c* 1.09 $CHCl_3$); **HRMS (ESI)** $[M+Na]^+$: calcd for $C_{26}H_{27}NNaO_3$: 424.1883; found 424.1890; $[M+H]^+$: calcd for $C_{26}H_{28}NO_3$: 402.2064; found 402.2053

(3*R*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)-*N*-(3-phenylpropyl)hexahydrofuro[3,2-*b*]furan-3-amine (**5f**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 7/3 as eluent affording **5f** (55 mg, 62%) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 1.77-1.88 (m, 2H, $H_{2'}$), 2.60 (dt, *J* = 7.2 and 11.3, 1H, $H_{1'}$), 2.67 (t, *J* = 7.5, 2H, $H_{3'}$), 2.80 (dt, *J* = 7.2 and 11.3, 1H, $H_{1'}$), 3.25 (dd, *J* = 7.7 and 10.0, 1H, H_2), 3.28-3.35 (m, 1H, H_3), 3.87 (dd, *J* = 4.2 and 10.0, 1H, H_5), 3.96-4.04 (m, 2H, H_5 and H_2), 4.05-4.09 (m, 1H, H_6), 4.56 and 4.59 (2 d, *J* = 11.9, 2H, CH_2O), 4.60 (d, *J* = 3.9, 1H, H_{6a}), 4.63 (app. t, *J* = 3.9, 1H, H_{3a}), 7.16-7.37 (m, 10H, H_{Ar}); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 32.0 ($C_{2'}$), 33.5 ($C_{3'}$), 48.0 ($C_{1'}$), 62.7 (C_3), 71.1 (C_2), 71.5 (CH_2O), 73.0 (C_5), 80.1 (C_{3a}), 84.2 (C_6), 86.5 (C_{6a}), 125.7 (C_{Ar}), 127.7 (2 C_{Ar}), 127.8 (C_{Ar}), 128.3 (2 C_{Ar}), 128.3 (2 C_{Ar}), 128.4 (2 C_{Ar}), 137.6 (C_{qAr}), 141.9 (C_{qAr}); **IR (ATR)** ν 2928, 2862, 1454, 1084, 733 cm^{-1}; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = +27.1° (*c* 0.92 $CHCl_3$); **HRMS (ESI)** $[M+H]^+$: calcd for $C_{22}H_{28}NO_3$: 354.2064; found 354.2053

(3*R*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)-*N*-hexylhexahydrofuro[3,2-*b*]furan-3-amine (**5g**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 7/3 to 8/2 as eluent affording **5g** (54 mg, 68%) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 0.88 (t, *J* = 6.9, 3H, $H_{6'}$), 1.23-1.36 (m, 6H, $H_{5'}$, $H_{4'}$ and $H_{3'}$), 1.42-1.56 (m, 2H, $H_{2'}$), 2.55 and 2.74 (2 ddd, *J* = 6.4, 8.3 and 11.1, 2H, $H_{1'}$), 3.24 (dd, *J* = 7.7 and 10.1, 1H, H_2), 3.28-3.35 (m, 1H, H_3), 3.86 (dd, *J* = 4.2 and 10.0, 1H, H_5), 3.97 (dd, *J* = 2.0 and 10.0, 1H, H_5), 4.01 (dd, *J* = 7.1 and 7.7, 1H, H_2), 4.04-4.08 (m, 1H, H_6), 4.55 and 4.58 (2 d, *J* = 11.9, 2H, CH_2O), 4.60 (d, *J* = 4.0, 1H, H_{6a}), 4.62 (app. t, *J* = 4.0, 1H, H_{3a}), 7.26-7.36 (m, 5H, H_{Ar}); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 14.0 ($C_{6'}$), 22.5 ($C_{4'}$ or $C_{5'}$), 26.9 ($C_{3'}$), 30.4 ($C_{2'}$), 31.7 ($C_{4'}$ or $C_{5'}$), 48.6 ($C_{1'}$), 62.8 (C_3), 71.1 (C_2), 71.5 (CH_2O), 73.0 (C_5), 80.0 (C_{3a}), 84.2 (C_6), 86.5 (C_{6a}), 127.6 (2 C_{Ar}), 127.8 (C_{A}r), 128.4 (2 C_{Ar}), 137.6 (C_{qAr}); **IR (ATR)** ν 2953, 2926, 2857, 1456, 1084, 737 cm^{-1}; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{21}}$ = +46.9° (*c* 0.96 $CHCl_3$); **HRMS (ESI)** $[M+Na]^+$: calcd for $C_{19}H_{29}NNaO_3$: 342.2040; found 342.2048; $[M+H]^+$: calcd for $C_{19}H_{30}NO_3$: 320.2220; found 320.2208

(3*R*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)-*N*-pentylhexahydrofuro[3,2-*b*]furan-3-amine (**5h**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 7/3 as eluent affording **5h** (58 mg, 76%) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 0.89 (t, *J* = 6.9 Hz, 3H, $H_{5'}$), 1.25-1.37 (m, 4H, $H_{3'}$ and $H_{4'}$), 1.44-1.56 (m, 2H, $H_{2'}$), 1.75 (bs, NH), 2.55 and 2.74 (2 ddd, *J* = 6.2, 8.4 and 11.1, 2H, $H_{1'}$), 3.24 (dd, *J* = 7.5 and 10.4, 1H, H_2), 3.32 (dd, *J* = 7.5 and 10.4, 1H, H_3), 3.86 (dd, *J* = 4.2 and 10.0, 1H, H_5), 3.98 (dd, *J* = 1.9 and 10.0, 1H, H_5), 4.02 (app. t, *J* = 7.5, 1H, H_2), 4.05-4.07 (m, 1H, H_6), 4.56 and 4.59 (2 d, *J* = 11.9, 2H, CH_2O), 4.61 (d, *J* = 4.0, 1H, H_{6a}), 4.63 (app. t, *J* = 4.0, 1H, H_{3a}), 7.26-7.38 (m, 5H, H_{Ar}); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 14.0 ($C_{5'}$), 22.5 ($C_{3'}$), 29.4 ($C_{4'}$), 30.1 ($C_{2'}$), 48.6 ($C_{1'}$), 62.8 (C_3), 71.1 (C_2), 71.5 (CH_2O), 73.0 (C_5), 80.0 (C_{3a}), 84.1 (C_6), 86.5 (C_{6a}), 127.7 (2 C_{Ar}), 127.8 (C_{Ar}), 128.4 (2 C_{Ar}), 137.6 (C_{qAr}); **IR (ATR)** ν 2953, 2928, 2860, 1456, 1084, 735 cm^{-1}; $[\alpha]_D^{21}$ = +50.1° (*c* 1.00 $CHCl_3$); **HRMS (ESI)** $[M+H]^+$: calcd for $C_{18}H_{28}NO_3$: 306.2064; found 306.2053

(3*R*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)-*N*-octylhexahydrofuro[3,2-*b*]furan-3-amine (**5i**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 7/3 as eluent affording **5i** (72 mg, 83%) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 0.87 (t, *J* = 6.9 Hz, 3H, $H_{8'}$), 1.16-1.33 (m, 10H, $H_{7'}$, $H_{6'}$, $H_{5'}$, $H_{4'}$ and $H_{3'}$), 1.41-1.54 (m, 2H, $H_{2'}$), 1.78 (bs, NH), 2.55 and 2.73 (2 ddd, *J* = 6.4, 8.3 and 11.1, 2H, $H_{1'}$), 3.24 (dd, *J* = 7.5 and 10.5, 1H, H_2), 3.31 (ddd, *J* = 3.9, 7.5 and 10.5, 1H, H_3), 3.86 (dd, *J* = 4.2 and 10.0, 1H, H_5), 3.97 (dd, *J* = 1.9 and 10.0, 1H, H_5), 4.01 (app. t, *J* = 7.5, 1H, H_2), 4.04-4.07 (m, 1H, H_6), 4.55 and 4.59 (2d, J = 11.9, 2H, CH_2O), 4.60 (d, *J* = 3.9, 1H, H_{6a}), 4.63 (app. t, *J* = 3.9, 1H, H_{3a}), 7.27-7.36 (m, 5H, H_{Ar}); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 14.1 ($C_{8'}$), 22.7 ($C_{6'}$ or $C_{7'}$), 27.3 ($C_{3'}$), 29.3 ($C_{4'}$ or $C_{5'}$), 29.5 ($C_{4'}$ or $C_{5'}$), 30.5 ($C_{2'}$), 31.8 ($C_{6'}$ or $C_{7'}$), 48.7 ($C_{1'}$), 62.8 (C_3), 71.2 (C_2), 71.6 (CH_2O), 73.1 (C_5), 80.1 (C_{3a}), 84.2 (C_6), 86.5 (C_{6a}), 127.7 (2 C_{Ar}), 127.9 (C_{Ar}), 128.5 (2 C_{Ar}), 137.6 (C_{qAr}); **IR (ATR)** ν 2924, 2855, 1456, 1084, 737 cm^{-1}; $[\alpha]_D^{21}$ = +43.3° (*c* 0.95 $CHCl_3$); **HRMS (ESI)** $[M+H]^+$: calcd for $C_{21}H_{34}NO_3$: 348.2533; found 348.2523.

(3*R*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)-*N*-isopentylhexahydrofuro[3,2-*b*]furan-3-amine (**5j**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 7/3 as eluent affording **5j** (54 mg, 71%) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 0.91 (2 d, *J* = 6.6 Hz, 6H, $H_{4'}$), 1.41 (app. q, *J* = 7.3, 2H, $H_{2'}$), 1.57-1.71 (m, 1H, $H_{3'}$), 1.81 (bs, NH), 2.59 and 2.78 (2 dt, *J* = 7.3 and 11.1, 2H, $H_{1'}$), 3.26 (dd, *J* = 7.7 and 10.1, 1H, H_2), 3.30-3.38 (m, 1H, H_3), 3.88 (dd, *J* = 3.9 and 10.0, 1H, H_5), 3.99 (dd, *J* = 1.9 and 10.0, 1H, H_5), 4.03 (app. t, J = 7.7, 1H, H_2), 4.07 (dd, *J* = 1.9 and 3.9, 1H, H_6), 4.57 and 4.61 (2 d, *J* = 11.9, 2H, CH_2O), 4.62 (d, *J* = 4.0, 1H, H_{6a}), 4.65 (app. t, *J* = 4.0, 1H, H_{3a}), 7.26-7.37 (m, 5H, H_{Ar}); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 22.4 ($C_{4'}$), 22.8 ($C_{4'}$), 26.1 ($C_{3'}$), 39.4 ($C_{2'}$), 46.7 ($C_{1'}$), 62.8 (C_3), 71.1 (C_2), 71.5 (CH_2O), 73.0 (C_5), 80.0 (C_{3a}), 84.2 (C_6), 86.5 (C_{6a}), 127.7 (2 C_{Ar}), 127.8 (C_{Ar}), 128.4 (2 C_{Ar}), 137.6 (C_{qAr}); **IR (ATR)** ν 2953, 2926, 2888, 1456, 1366, 1082, 1051, 735 cm^{-1}; $[\alpha]_D^{21}$ = +44.8° (*c* 1.01 $CHCl_3$) ; **HRMS (ESI)** $[M+H]^+$: calcd for $C_{18}H_{28}NO_3$: 306.2064; found 306.2052

(3*R*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)-*N*-cyclohexylhexahydrofuro[3,2-*b*]furan-3-amine (**5k**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 7/3 as eluent affording **5k** (44 mg, 55%) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 1.00-1.65 (m, 6H, CH_2-cyclohexyl), 1.68-1.77 (m, 2H, CH_2-cyclohexyl), 1.80-1.88 (m, 2H, CH_2-cyclohexyl), 2.52 (tt, *J* = 3.7 and 10.4, 1H, CH-cyclohexyl), 3.22 (dd, *J* = 8.2 and 10.3, 1H, H_2), 3.41-3.49 (m, 1H, H_3), 3.86 (dd, *J* = 4.2 and 10.0, 1H, H_5), 3.94-4.03 (m, 2H, H_2 and H_5), 4.03-4.07 (m, 1H, H6), 4.55 and 4.58 (2 d, *J* = 11.9, 2H, CH_2O), 4.57-4.61 (m, 2H, H_{6a} and H_{3a}), 7.27-7.39 (m, 5H, H_{Ar}); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 24.9 (CH_2-cyclohexyl), 25.0 (CH_2-cyclohexyl), 26.0 (CH_2-cyclohexyl), 33.4 (CH_2-cyclohexyl), 34.1 (CH_2-cyclohexyl), 55.3 (CH-cyclohexyl), 59.4 (C_3), 71.4 (C_2), 71.5 (CH_2O), 72.9 (C_5), 80.5 (C_{3a}), 84.2 (C_6), 86.4 (C_{6a}), 127.7 (2 C_{Ar}), 127.8 (C_{Ar}), 128.4 (2 C_{Ar}), 137.6 (C_{qAr}); **IR (ATR)** ν 2924, 2853, 1456, 1084, 1051, 737 cm^{-1}; $[\alpha]_D^{21}$ = +49.2° (*c* 0.93 $CHCl_3$); **HRMS (ESI)** $[M+H]^+$: calcd for $C_{19}H_{28}NO_3$: 318.2064; found 318.2051

(3*R*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)-*N*-((*S*)-1-phenylethyl)hexahydrofuro[3,2-*b*]furan-3-amine (**5l**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 6/4 to 7/3 as eluent affording **5l** (37 mg, 44**%**) as a pale yellow oil. **^{1}H NMR ($CDCl_3$, 400 MHz)** δ 1.36 (d, *J* = 6.5, 3H, Me), 1.89 (bs, NH), 3.10-3.17 (m, 1H, H_3), 3.21 (dd, 7.5 and 10.4, 1H, H_2), 3.81 (app. t, *J* = 7.5, 1H, H_2), 3.89 (dd, 4.2 and 10.0, 1H, H_5), 3.96 (q, *J* = 6.5, 1H, CHN), 4.00 (dd, *J* = 1.8 and 10.0, 1H, H_5), 4.03-4.06 (m, 1H, H_6), 4.51 (d, *J* = 3.9, 1H, H_{6a}), 4.54 and 4.57 (2 d, *J* = 11.9, 2H, CH_2O), 4.59 (app. t, *J* = 3.9, 1H, H_{3a}), 7.23-7.37 (m, 10H, H_{Ar}); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 25.2 (Me), 56.6 (CHN), 60.2 (C_3), 70.9 (C_2), 71.5 (CH_2O), 73.0 (C_5), 79.6 (C_{3a}), 84.3 (C_6), 86.5 (C_{6a}), 126.7 (2 C_{Ar}), 127.1 (C_{Ar}), 127.7 (2 C_{Ar}), 127.8 (C_{Ar}), 128.4 (2 C_{Ar}), 128.5 (2 C_{Ar}), 137.6 (C_{qAr}), 145.2 (C_{qAr}); **IR (ATR)** ν 2955, 2928, 2864, 1456, 1090, 1055, 764, 739; $[\alpha]_D^{21}$ = +103.8° (*c* 0.87 $CHCl_3$); **HRMS (ESI)** $[M+Na]^+$: calcd for $C_{21}H_{25}NNaO_3$: 362.1727; found 362.1722; $[M+H]^+$: calcd for $C_{21}H_{26}NO_3$: 340.1907; found 340.1893.

(3*R*,3a*R*,6*R*,6a*S*)-6-(Benzyloxy)-*N*-(4-methoxybenzyl)hexahydrofuro[3,2-*b*]furan-3-amine (**18a**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 6/4 to 8/2 as eluent affording **18a** (52 mg, 58**%**) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 3.33-3.40 (m, 1H, H_3), 3.44 (dd, *J* = 8.0 and 10.3, 1H, H_2) ; 3.64 (dd, *J* = 8.3 and 8.5, 1H, H_5), 3.71 (d, *J* = 12.7, 1H, CH_2N), 3.79 (s, 3H, OMe), 3.83 (d, *J* = 12.7, 1H, CH_2N), 3.92 (dd, *J* = 6.7 and 8.5, 1H, H_5), 4.05-4.14 (m, 2H, H_2 and H_6), 4.45 (app. t, *J* = 4.4, 1H, H_{3a}), 4.54 (d, *J* = 11.9, 1H, CH_2O), 4.59 (app. t, *J* = 4.4, 1H, H_{6a}), 4.75 (d, *J* = 11.9, 1H, CH_2O), 6.85 (d, *J* = 8.7, 2H, H_c), 7.26 (d, *J* = 8.7, 2H, H_b), 7.29-7.36 (m, 5H, H_{Ar}); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 51.8 (CH_2N), 55.2 (OMe), 62.0 (C_3), 71.2 (C_5), 72.4 (CH_2O), 72.7 (C_2), 79.9 (C_6), 80.3 (C_{3a}), 81.1 (C_{6a}), 113.8 (2 C_c), 127.8 (C_{Ar}), 127.9 (2 C_{Ar}), 128.4 (2 C_{Ar}), 129.3 (2 C_b), 132.1 (C_a), 137.8 (C_{qAr}), 158.7 (C_d); **IR (ATR)** ν 2932, 2870, 1512, 1456, 1248, 1136, 1082, 1072, 1030, 826, 741 cm^{-1} $[\alpha]_D^{21}$ = +112.2° (*c* 0.93 $CHCl_3$) ; **HRMS (ESI)** $[M+Na]^+$: calcd for $C_{21}H_{25}NNaO_4$: 378.1676; found 378.1676; $[M+H]^+$: calcd for $C_{21}H_{26}NO_4$: 356.1856; found 356.1848

(3*R*,3a*R*,6*R*,6a*S*)-*N*-Benzyl-6-(benzyloxy)hexahydrofuro[3,2-*b*]furan-3-amine (**18b**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 7/3 to 8/2 as eluent affording **18b** (63 mg, 77**%**) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 3.34-3.42 (m, 1H, H_3), 3.46 (dd, *J* = 7.8 and 10.3, 1H, H_2), 3.65 (app. t, *J* = 8.3, 1H, H_5), 3.77 (d, *J* = 12.9, 1H, CH_2N), 3.87-3.97 (m, 2H, CH_2N and H_5), 4.04-4.10 (m, 1H, H_6), 4.13 (dd, *J* = 7.4 and 7.8, 1H, H_2), 4.46 (app. t, *J* = 4.4, 1H, H_{3a}), 4.55 (d, *J* = 11.9, 1H, CH_2O), 4.59 (app. t, *J* = 4.4, 1H, H_{6a}), 4.75 (d, *J* = 11.9, 1H, CH_2O), 7.21-7.42 (m, 10H, H_{Ar}); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 52.3 (CH_2N), 62.1 (C_3), 71.2 (C_5), 72.4 (CH_2O), 72.7 (C_2), 79.8 (C_6), 80.3 (C_{3a}), 81.1 (C_{6a}), 127.0 (C_{Ar}), 127.8 (C_{Ar}), 127.9 (2 C_{Ar}), 128.1 (2 C_{Ar}), 128.4 (2 C_{Ar}), 128.4 (2 C_{Ar}), 137.7 (C_{qAr}), 140.0 (C_{qAr}); **IR (ATR)** ν 2928, 2870, 1454, 1134, 1070, 1026, 737 cm^{-1}; $[\alpha]_D^{21}$ = +83.0° (*c* 0.96 $CHCl_3$); **HRMS (ESI)** $[M+Na]^+$: calcd for $C_{20}H_{23}NNaO_3$: 348.1570; found 348.1582; $[M+H]^+$: calcd for $C_{20}H_{24}NO_3$: 326.1751; found 326.1755

(3*R*,3a*R*,6*R*,6a*S*)-*N*-([1,1'-Biphenyl]-4-ylmethyl)-6-(benzyloxy)hexahydrofuro[3,2-*b*]furan-3-amine (**18c**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 7/3 as eluent affording **18c** (44 mg, 44**%**) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 3.39-3.46 (m, 1H, H_3), 3.49 (dd, *J* = 7.7 and 10.2, 1H, H_2), 3.67 (app. t, *J* = 8.3, 1H, H_5), 3.82 (d, *J* = 13.0, 1H, CH_2N), 3.93-3.96 (m, 2H, CH_2N and H_5), 4.07-4.13 (m, 1H, H_6), 4.16 (app. t, *J* = 7.7, 1H, H_2), 4.49 (app. t, *J* = 4.4, 1H, H_{3a}), 4.56 (d, *J* = 11.9, 1H, CH_2O), 4.61 (app. t, *J* = 4.4, 1H, H_{6a}), 4.76 (d, *J* = 11.9, 1H, CH_2O), 7.30-7.60 (m, 14 H_{Ar}) ; **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 52.0 (CH_2N), 62.1 (C_3), 71.2 (C_5), 72.4 (CH_2O), 72.7 (C_2), 79.8 (C_6), 80.3 (C_{3a}), 81.2 (C_{6a}), 127.0 (2 C_{Ar}), 127.1 (3 C_{Ar}), 127.8 (C_{Ar}), 127.9 (2 C_{Ar}), 128.4 (2 C_{Ar}), 128.5 (2 C_{Ar}), 128.7 (2 C_{Ar}), 137.7 (C_{qAr}), 139.0 (C_{qAr}), 140.0 (C_{qAr}), 140.9 (C_{qAr}); **IR (ATR)** ν 2934, 2870, 1487, 1454, 1134, 1071, 1026, 827, 760, 737 cm^{-1}; $[\alpha]_D^{21}$ = +93.5° (*c* 1.17 $CHCl_3$); **HRMS (ESI)** $[M+H]^+$: calcd for $C_{26}H_{28}NO_3$ 402.2064; found 402.2055.

(3*R*,3a*R*,6*R*,6a*S*)-6-(Benzyloxy)-*N*-hexylhexahydrofuro[3,2-*b*]furan-3-amine (**18d**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 7/3 to 8/2 as eluent affording **18d** (63 mg, 79%) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 0.86 (t, *J* = 6.8, 3H, $H_{6'}$), 1.20-1.37 (m, 6H, $H_{3'}$, $H_{4'}$ and $H_{5'}$), 1.41-1.51 (m, 2H, $H_{2'}$), 1.87 (bs, NH), 2.54 and 2.69 (2 ddd, *J* = 6.5, 8.1 and 11.1, 2H, $H_{1'}$), 3.29-3.36 (m, 1H, H_3), 3.41 (dd, *J* = 7.8 and 10.4, 1H, H_2), 3.63 (dd, *J* = 8.2 and 8.5, 1H, H_5), 3.90 (dd, *J* = 6.7 and 8.5, 1H, H_5), 4.04-4.10 (m, 1H, H_6), 4.13 (app. t, *J* = 7.8, 1H, H_2), 4.46 (app. t, *J* = 4.4, 1H, H_{3a}), 4.53 (d, *J* = 11.9, 1H, CH_2O), 4.60 (app. t, *J* = 4.4, 1H, H_{6a}), 4.74 (d, *J* = 11.9, 1H, CH_2O), 7.25-7.40 (m, 5H, H_{Ar}); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 14.0 ($C_{6'}$), 22.5 ($C_{4'}$), 26.9 ($C_{3'}$), 30.4 ($C_{2'}$), 31.7 ($C_{5'}$), 48.6 ($C_{1'}$), 63.0 (C_3), 71.2 (C_5), 72.4 (CH_2O), 72.7 (C_2), 79.8 (C_6), 80.4 (C_{3a}), 81.1 (C_{6a}), 127.8 (C_{Ar}), 127.9 (2 C_{Ar}), 128.4 (2 C_{Ar}), 137.7 (C_{qAr}); **IR (ATR)** ν 2928, 2957, 1454, 1141, 1084, 1072, 1026, 737 cm^{-1}; $[\alpha]_D^{21}$ = +106.4° (*c* 0.97 $CHCl_3$); **HRMS (ESI)** $[M+Na]^+$: calcd for $C_{19}H_{29}NNaO_3$342.2040; found 342.2036; $[M+H]^+$: calcd for $C_{19}H_{30}NO_3$: 320.2220; found 320.2206

(3*R*,3a*R*,6*R*,6a*S*)-6-(Benzyloxy)-*N*-isopentylhexahydrofuro[3,2-*b*]furan-3-amine (**18e**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 8/2 as eluent affording **18e** (55 mg, 72%) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 0.88 (2 d, *J* = 6.6, 6H, $H_{4'}$), 1.39 (app. q, *J* = 7.4, 2H, $H_{2'}$), 1.56-1.65 (m, 1H, $H_{3'}$), 2.13 (bs, NH), 2.56 and 2.72 (2 dt, *J* = 7.4 and 11.0, 2H, $H_{1'}$), 3.30-3.38 (m, 1H, H_3), 3.42 (d, *J* = 7.8 and 10.3, 1H, H_2), 3.63 (dd, *J* = 8.2 and 8.6, 1H, H_5), 3.91 (dd, *J* = 6.7 and 8.6, 1H, H_5), 4.04-4.11 (m, 1H, H_6), 4.14 (app. t, *J* = 7.8, 1H, H_2), 4.47 (app. t, *J* = 4.4, 1H, H_{3a}), 4.54 (d, *J* = 11.9, 1H, CH_2O), 4.61 (app. t, *J* = 4.4, 1H, H_{6a}), 4.75 (d, *J* = 11.9, 1H, CH_2O), 7.27-7.37 (m, 5H, H_{Ar}); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 22.4 ($C_{4'}$), 22.7 ($C_{4'}$), 26.0 ($C_{3'}$), 39.4 ($C_{2'}$), 46.6 ($C_{1'}$), 63.0 (C_3), 71.2 (C_5), 72.4 (CH_2O), 72.7 (C_2), 79.8 (C_6), 80.4 (C_{3a}), 81.2 (C_{6a}), 127.8 (C_{Ar}), 127.9 (2 C_{Ar}), 128.4 (2 C_{Ar}), 137.7 (C_{qAr}); **IR (ATR)** ν 2951, 2924, 2868, 1456, 1134, 1082, 1026, 737 cm^{-1}; $[\alpha]_D^{21}$ = +99.7° (*c* 1.07 $CHCl_3$); **HRMS (ESI)** $[M+Na]^+$: calcd for $C_{18}H_{27}NNaO_3$ 328.1883; found 328.1882; $[M+H]^+$: calcd for $C_{18}H_{28}NO_3$ 306.2064; found 306.2055.

(3*R*,3a*R*,6*S*,6a*S*)-6-(Benzyloxy)-*N*-cyclohexylhexahydrofuro[3,2-*b*]furan-3-amine (**18f**). The crude product was purified by column chromatography on silica gel using EtOAc/Pentane 6/4 to 7/3 as eluent affording **18f** (41 mg, 52%) as a pale yellow oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 1.00-1.29 (m, 5H, CH_2-cyclohexyl), 1.57-1.64 (m, 1H, CH_2-cyclohexyl), 1.67-1.76 (m, 2H, CH_2-cyclohexyl), 1.79-1.91 (m, 3H, CH_2-cyclohexyl and NH), 2.47 (tt, *J* = 3.7 and 10.4, 1H, CH-cyclohexyl), 3.39 (dd, *J* = 7.8 and 10.5, 1H, H_2), 3.47 (m, 1H, H_3), 3.62 (dd, *J* = 8.3 and 8.6, 1H, H_5), 3.90 (dd, *J* = 6.8 and 8.6, 1H, H_5), 4.02-4.10 (m, 1H, H_6), 4.12 (app. t, *J* = 7.8, 1H, H_2), 4.42 (app. t, *J* = 4.4, 1H, H_{3a}), 4.54 (d, *J* = 11.9, 1H, CH_2O), 4.60 (app. t, *J* = 4.4, 1H, H_{6a}), 4.74 (d, *J* = 11.9, 1H, CH_2O), 7.27-7.41 (m, 5H, H_{Ar}); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 24.8 (CH_2-cyclohexyl), 24.9 (CH_2-cyclohexyl), 25.9 (CH_2-cyclohexyl), 33.5 (CH_2-cyclohexyl), 34.0 (CH_2-cyclohexyl), 55.2 (CH-cyclohexyl), 59.6 (C_3), 71.2 (C_5), 72.4 (CH_2O), 73.0 (C_2), 79.8 (C_6), 80.9 (C_{3a}), 81.0 (C_{6a}), 127.8 (C_{Ar}), 127.9 (2 C_{Ar}), 128.4 (2 C_{Ar}), 137.7 (C_{qAr}); **IR (ATR)** ν 2926, 2853, 1452, 1134, 1083, 1070, 1026, 737 cm^{-1}; $[\alpha]_D^{21}$ = +121.7° (*c* 0.92 $CHCl_3$) ; **HRMS (ESI)** $[M+H]^+$: calcd for $C_{19}H_{28}NO_3$: 318.2064; found 318.2068

(3*S*,3a*R*,6*R*,6a*R*)-6-(Hexylamino)hexahydrofuro[3,2-b]furan-3-ol (**19**)**.** To a solution of isosorbide **IS-1** (36.5 mg, 0.25 mmol, 1 equiv), diphenylphosphate **14** (4.8 mg, 0.019 mmol, 0.075 equiv), iridium catalyst **15** (14.2 mg, 0.019 mmol, 0.075 equiv) and 3Å molecular sieves in anhydrous toluene (250 µL) was added *n*-hexylamine (33 µL, 0.25 mmol, 1 equiv). The vial was sealed and the reaction mixture was stirred and heated to 120 °C for 24 h. After cooling down to rt, the mixture was filtered through Celite® and the solvent was evaporated. After NMR analyses of the crude mixture, purification by column chromatography on silica gel using Et_2O/acetone 1/1 as eluent afforded **19** as a pale yellow oil in 65% yield (37 mg). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 0.86 (t, *J* = 6.8, 3H, $H_{6'}$), 1.19-1.34 (m, 6H, $H_{3'}$, $H_{4'}$ and $H_{5'}$), 1.40-1.57 (m, 2H, $H_{2'}$), 2.54 (ddd, *J* = 6.7, 8.2 and 11.1, 1H, $H_{1'}$), 2.54 (bs, 1H, NH), 2.71 (ddd, *J* = 6.7, 8.2 and 11.1, 1H, $H_{1'}$), 3.21 (dd, *J* = 7.8 and 10.1, 1H, H_2), 3.24-3.37 (m, 1H, H_3), 3.79-3.91 (m, 2H, H_5), 4.01 (app. t, *J* = 7.8, 1H, H_2), 4.18-4.33 (m, 1H, H_6), 4.44 (d, *J* = 3.8, 1H, H_{6a}), 4.64 (app. t, *J* = 3.8, 1H, H_{3a}); **^{13}C NMR ($CDCl_3$, 100 MHz)** δ 14.0 ($C_{6'}$), 22.5 ($C_{4'}$ or $C_{5'}$), 26.9 ($C_{3'}$), 30.3 ($C_{2'}$), 31.7 ($C_{4'}$ or $C_{5'}$), 48.6 ($C_{1'}$), 62.7 (C_3), 71.2 (C_2), 75.5 (C_5), 76.9 (C_6), 79.8 (C_{3a}), 88.6 (C_{6a}); **IR (ATR)** ν 3362, 3285, 2953, 2926, 2857, 1458, 1078, 1049, 775, 735 cm^{-1}; $[\alpha]_D^{21}$ = +48.9° (*c* 0.94 $CHCl_3$) ; **HRMS (ESI)** $[M+Na]^+$: calcd for $C_{12}H_{23}NNaO_3$: 252.1570; found 252.1574; $[M+H]^+$: calcd for $C_{12}H_{24}NO_3$: 230.1751; found 230.1743

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. NMR spectra for all compounds are provided.

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(20) The scope of the reaction with catalyst **16.HCl** is depicted in supporting information - page S6.

(21) Analytical standard was synthesized according procedure reported in the thesis of Dr M. Janvier.