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A convenient and highly stereoselective method for synthesis of octahydropyrano[3,2-*b*]pyrrole derivatives

Xiaofeng Ma [a,c], Qin Tang [a,c], Jun Ke [a,c], Haibo Wang [a,c], Wei Zou [b], Huawu Shao [a,*]

[a] Natural Product Research Center, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, PR China
[b] Institute for Biological Sciences, National Research Council of Canada, 100 Sussex Drive, Ottawa, Ontario, Canada K1A 0R6
[c] Graduate School of Chinese Academy of Sciences, Beijing 100039, PR China

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ABSTRACT

The octahydropyrano[3,2-*b*]pyrrole derivatives are synthesized by a double reductive amination from pyranose derivatives of nono-2,5-diuloses and octos-4-uloses and various amines. The cyclization proceeded smoothly in the presence of sodium triacetoxyborohydride to produce a series of novel fused *N*-heterobicyclic compounds with high stereoselectivity.

1. Introduction

Polyhydroxylated 2-*N*-acetamidosugar are potential glycosidase inhibitors, castanospermine and swainsonine are the two examples that are mostly studied. In contrast, octahydropyrano[3,2-*b*]pyrroles have so far attracted less interest as glycosidase inhibitors, probably due to lack of effective synthetic methods. 2-Acetamido-2-deoxy-D-glycopyranosides subunits constitute the core structural elements prevalent in a large number of living organisms as oligosaccharides and glycoconjugates, and could serve as metabolic substrates for cell surface engineering.[1] To understand these biological processes, considerable studies on the modification of 2-*N*-acetamidosugar residues were performed during the last decade[2] and change O-glycoside to C-glycoside attracted more attention in glycochemistry[3] and glycobiology,[4] since these carbohydrate mimics possess an improved stability towards acid, base and enzymatic hydrolysis, and display interesting biological activity.[4] However, nitrogen-based groups such as amides, carbamates and azides are incompatible under conventional C-glycosylation conditions, so C-glycosylation of 2-amino sugar has been regarded as one of the most difficult modifications.[4,5] The strategies for the construction of 2-amino-C-glycosides include Wittig reactions with sugar lactols,[6] radical coupling between glycosyl Se[5d–f,7] or X (Br, Cl)[8] and activated alkenes, or Ramberg–Bäcklund rearrangement using glycosyl sulfones[3a,9] and conjugate addition of carbanions to 2-nitroglycals.[5a,10]

Octahydropyrano[3,2-*b*]pyrrole, which combines a pyrrole segment to 2-amino-C-glycoside backbone, is a potential glycosidase inhibitor. Actually, castanospermine is the analogue of octahydropyrano[3,2-*b*]pyrrole and an efficient glycosidase inhibitors (Figure 1a)[11] and a variety of analogues of castanospermine (Fig. 1b) have been identified as specific inhibitors of β-D-galactosidase.[12]

Octahydropyrano[3,2-*b*]pyrrole derivatives were often synthesized by radical cyclization reaction using glycosyl Se as radical precursors,[7] or intramolecular hydrogen atom transfer reaction promoted by *N*-radicals via C-glycosides phosphoramidates.[13] In 2005, Wang and co-workers developed an alternative method via 1,5-anhydro-6-bromo-4-*O*-methyl-sulfonyl-D-glucitol through 12 steps.[14] In 2007, Schweizer and co-workers reported a simpler method via 2-amino-2-deoxy-C-glycoside.[15] Furthermore, 2-nitro-β-C-glycosides, which were obtained by conjugate addition of carbanions to 2-nitroglycals, can be converted to trans-fusion of bicyclic lactam analogue, but this conjugate addition reaction only given the mixture C-glycosides of anomeric isomers.[5a] Vankar and cooperators have recently obtained bicyclic pyrrolidines via sequential intermolecular and intramolecular nucleophilic substitutions.[16] However, only four different bicyclic products were afforded by this procedure.

Reductive amination is an efficient method for C–N bond formation and has been successfully used in synthesis of 2 and 3-*N*-pyrrolidine derivatives of glycosides.[12,17] However, there are no

* Corresponding author.
E-mail address: shaohw@cib.ac.cn (H. Shao).

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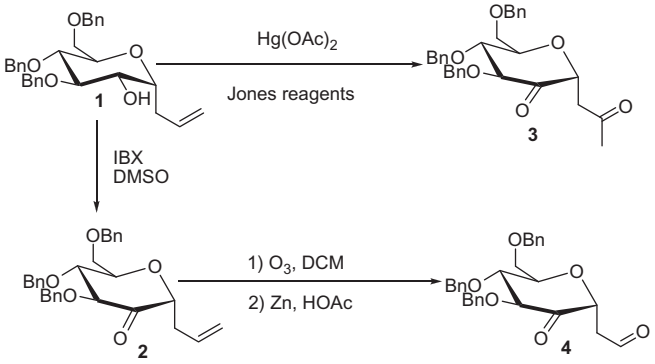
Figure 1. The structures of castanospermine (a) and previous compound (b).



Scheme 1. Synthesis of glycosyl-1,4-dicarbonyl compounds **3** and **4**.

reports on the synthesis of octahydropyrano[3,2-*b*]pyrrole using reductive amination. Therefore, it is necessary to develop a highly stereoselective and convenient method for the synthesis of octahydropyrano[3,2-*b*]pyrrole derivatives. As part of our continuing interest in the development of new synthetic methodologies,[18,19] we disclose our results on the highly stereoselective synthesis of octahydropyrano[3,2-*b*]pyrrole derivatives via double reductive amination of glycosyl-1,4-dicarbonyl compounds using $NaBH(OAc)_3$ in dichloromethane at room temperature.

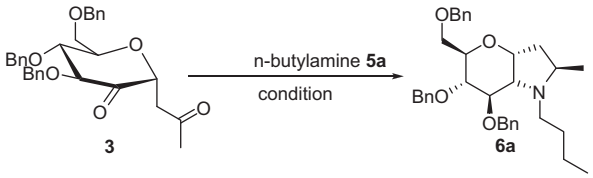
2. Results and discussion

1,4-Dicarbonyl compound **3** was prepared by oxidization of 2-OH and C=C bond of alkene **1**, using $Hg(OAc)_2$ and Jones reagent in 76% yield and 1,4-dicarbonyl compound **4** was obtained in two steps by oxidization of 2-OH of alkene **1** using IBX to afford alkene ketone **2** followed by ozonolysis and in situ reduction of the ozonide using Zn powder and HOAc in 72% total yield (Scheme 1). With compounds **3** and **4** in hand, the construction of octahydropyrano[3,2-*b*]pyrrole via reductive amination was carried out.

Initial studies were performed with $NaCNBH_3$ in MeOH using *n*-butylamine as aminating reagent at 0 °C,[17a] but the reaction was so complex that no major product could be detected by TLC. Then, $NaBH(OAc)_3$, which is a powerful and versatile reducing reagent for the reductive amination, was used (Table 1). In order to find a suitable condition for our experiments, an optimization on the solvent, the amounts of $NaBH(OAc)_3$ and HOAc were executed. Fortunately, the reaction could proceed smoothly in all solvents including dichloroethane, dichloromethane, acetonitrile and tetrahydrofuran. Dichloromethane was the best solvent (Table 1, entry 4), and dichloroethane was also efficient (Table 1, entry 1), while the acetonitrile (Table 1, entry 3) and tetrahydrofuran (Table 1, entry2) were not as good as the former solvents. After variation of the amount of reducing agent and acetic acid, it was found that the double reductive amination could be proceeded smoothly with 3.0 equiv of $NaBH(OAc)_3$ and 2.0 equiv of HOAc in CH_2Cl_2 at room temperature (Table 1, entry 6).

The stereochemistry of new stereocenters in compound **6a** was confirmed by ^1H NMR and NOESY spectra. The cyclization leads to the less strained *cis*-fused bicycle with the newly formed C–N bond in equatorial orientation, while the methyl group at C-2 adopts an exo-disposition on the bicyclic system by steric reasons. This is confirmed by NOESY interactions between methyl group and H-7a, H-3a in compound **6a** as shown in Figure 2.

Table 1
Conditions optimization of the double reductive amination[a]



Entry	Reductant (equiv)	HOAc (equiv)	Solvent	Yield[b] (%)
1	4	2	$ClCH_2CH_2Cl$	62
2	4	2	THF	50
3	4	2	CH_3CN	48
4	4	2	CH_2Cl_2	70
5	3.5	2	CH_2Cl_2	67
6	3	2	CH_2Cl_2	70
7	2.5	2	CH_2Cl_2	23
8	2	2	CH_2Cl_2	Trace
9	3	1	CH_2Cl_2	NR
10	3	0	CH_2Cl_2	Trace

[a] All reactions were performed with diketone **3** (0.20 mmol), *n*-butylamine **5a** (0.22 mmol) under a N_2 atmosphere, in solvent (0.7 mL) at room temperature overnight.
[b] Isolated yield.

Encouraged by the initial success, we decided to explore the applicability of the double reductive amination to a number of amines including aliphatic amines such as benzylamine (**5b**), 2-aminoethanol (**5c**), octylamine (**5d**), hexylamine (**5e**) and 4-fluoro-phenethylamine (**5f**) (Table 2, entries 1–5), and aromatic amine including aniline (**5g**), *p*-toluidine (**5h**) and *o*-toluidine (**5i**) (Table 2, entries 6–8). To our delight, the expected octahydropyrano[3,2-*b*]pyrrole derivatives were obtained in 53–76% yields. Surprisingly, in all product only one diastereoisomer was obtained as a major product except for 2-aminoethanol (Table 2, entry 2), aniline (Table 2, entry 6) and p-toluidine (Table 2, entry 7).[20]

In order to obtain better results for synthesis of pyrrole derivatives and expand molecular libraries of these compounds, the feasibility was further studied with keto-aldehyde derivative **4**. Logically, keto-aldehyde **4** was subjected to the double reductive amination procedure using a range of primary amines, and a series of other octahydropyrano[3,2-*b*]pyrrole derivatives were prepared in 42–67% yields (Table 2, entries 9–15).

In summary, we have developed a mild and efficient method for the stereoselective synthesis of octahydropyrano[3,2-*b*]pyrrole derivatives from C-glycosides. The method is applied to the synthesis of castanospermine analogues. Further investigations of the scope of this reaction and of the biological activities of these compounds will be undertaken.

3. Experimental

All reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. Reactions were monitored by thin layer chromatography using silica gel HSGF254 plates (0.20–0.25 mm thickness) with a fluorescent indicator. Visualization on TLC was achieved by UV light (254 nm) and a typical TLC indicator solution (5% sulfuric acid/ethanol solution). Column chromatography was performed on silica gel 90, 200–300 mesh. Optical rotations were measured with a

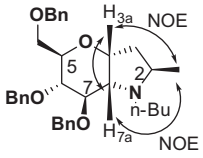


Figure 2. The NOEs of compound **6a**.

Perkin Elmer-341 Digital Polarimeter. ^{1}H NMR and ^{13}C NMR (600 and 150 MHz, respectively) spectra were recorded with a Bruker Avance 600 spectrometer. ^{1}H NMR chemical shifts are reported in ppm (δ) relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$, δ = 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz) and integration. ^{13}C NMR chemical shifts are reported in ppm from tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$, δ = 77.0 ppm). ESI-HRMS spectra were recorded on BioTOF Q.

3.1. 4,8-Anhydro-6,7,9-tri-*O*-benzyl-1,3-dideoxy-D-*manno*-nono-2,5-diulose (3)

To a solution of **1** (1.0 g, 2.11 mmol) and $Hg(OAc)_2$ (236 mg, 0.74 mmol) in acetone/water (4:1, 10 mL) was added dropwise at 0 °C a solution of Jones reagent (2 M, 5.9 mL). The dark greenish-brown mixture was stirred for 4 h at 0 °C and 2 mL *i*-propanol was added and the reaction mixture was kept stirring until the dark greenish-brown mixture became deep green, and then the reaction mixture poured into water (10 mL). The aqueous mixture was extracted with EtOAc (3 × 15 mL). Usual workup and chromatography (Petroleum ether/EtOAc = 3:1) afforded **3** as a colourless syrup (0.78 g, 1.60 mmol, 76%).

$[\alpha]_D^{20}$ +20.4 (*c* 0.6, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.49–7.20 (m, 15H), 5.03 (d, *J* = 11.5 Hz, 1H), 4.85 (d, *J* = 11.5 Hz, 1H), 4.79 (d, *J* = 9.7 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.55 (t, *J* = 4.9 Hz, 1H), 4.51 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 12.0 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.07–4.00 (m, 1H), 3.95 (dd, *J* = 9.6, 7.1 Hz, 1H), 3.60 (dd, *J* = 10.6, 2.6 Hz, 1H), 3.54 (dd, *J* = 10.6, 4.4 Hz, 1H), 2.94 (d, *J* = 5.0 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 209.8, 204.4, 137.9, 137.8, 137.7 128.4(3), 128.3, 128.2, 127.9, 127.8, 127.7, 84.5, 77.3, 76.1, 75.5, 74.2, 74.0, 73.4, 70.0, 45.4, 30.0; ESI-HRMS: *m*/*z* calcd for $C_{30}H_{32}NaO_6$ $[M+Na]^+$: 511.2097, found 511.2091.

3.2. 3,7-Anhydro-5,6,8-tri-*O*-benzyl-2-deoxy-D-*manno*-octos-4-ulose (4)

To a stirred solution of **1** (7.6 g, 15.9 mmol) in DMSO (20 mL) was added IBX in DMSO (9.0 g, 32.0 mmol, 20 mL). The reaction mixture was allowed to stir at room temperature for 2.5 h. The mixture was diluted with CH_2Cl_2 (60 mL), extracted with water (40 mL) and filtered over celit. The organic layer was collected, and the aqueous layer was re-extracted with further CH_2Cl_2 (2 × 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and concentrated to give colourless syrup (7.0 g) **2**. To a solution of ketone **2** in CH_2Cl_2 (150 mL) was cooled in −78 °C. A stream of ozone was passed into the solution through a sintered-glass sprayer. When the starting material disappeared (about 30 min), the solution was concentrated to a residue. To the above residue in glacial acetic acid (151 mL) was added zinc dust (3.2 g, 49.0 mmol) and the mixture was stirred at room temperature overnight. Usual workup and chromatographic purification (Petroleum ether/EtOAc 3:1) afforded **4** as a white solid (5.43 g, 11.4 mmol, 72%).

$[\alpha]_D^{20}$ +55.7 (*c* 0.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.67 (s, 1H), 7.47–7.11 (m, 15H), 5.00 (d, *J* = 11.5 Hz, 1H), 4.83 (d, *J* = 11.4 Hz, 2H), 4.69 (d, *J* = 11.6 Hz, 3H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.45 (d, *J* = 11.9 Hz, 1H), 4.35 (d, *J* = 12.0 Hz, 1H), 4.00 (d, *J* = 8.2 Hz, 1H), 3.62 (d, *J* = 10.4 Hz, 1H), 3.55 (d, *J* = 10.5 Hz, 1H), 2.97–2.79 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 209.0, 197.9, 138.0, 137.8, 137.6(2), 128.5, 128.4(2), 128.3, 128.2, 128.1, 127.9(2), 127.8, 127.7(2), 84.1, 76.0, 74.7, 74.2, 74.1, 73.4, 70.0, 45.1; ESI-HRMS: *m*/*z* calcd for $C_{29}H_{30}NaO_6$ $[M+Na]^+$: 497.1935, found 497.1940.

3.3. General procedure for synthesis of octahydropyrano[3,2-*b*]pyrrole derivatives

To a solution of diketone **3** (98.0 mg, 0.201 mmoL) or keto-aldehyde **4** (95.0 mg, 0.2 mmoL) in CH_2Cl_2 (0.7 mL) were successively added AcOH (23 μL, 0.4 mmoL), and primary amine (0.22 mmoL) and $NaBH(OAc)_3$ (138 mg, 0.60 mmoL). The mixture was stirred at room temperature under a N_2 atmosphere until the reactants were consumed as determined by TLC analysis. The reaction mixture was concentrated and purified by silica gel column chromatography (Petroleum ether/EtOAc/TEA = 80:20:1–50:50:1).

3.4. (2*R*,3a*R*,5*R*,6*S*,7*R*,7a*S*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)-methyl]-1-butyl-2-methyl-octahydropyrano[3,2-*b*]pyrrole (6a)

Yield: 74.1 mg, 0.14 mmol, 70%. Light red syrup: $[\alpha]_D^{20}$ +41.2 (*c* 0.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39–7.19 (m, 15H), 4.88 (d, *J* = 11.4 Hz, 1H), 4.84 (d, *J* = 11.4 Hz, 1H), 4.72 (d, *J* = 11.1 Hz, 1H), 4.56 (d, *J* = 12.2 Hz, 1H), 4.47 (dd, *J* = 17.7, 11.7 Hz, 2H), 4.40 (dd, *J* = 15.0, 7.5 Hz, 1H), 3.86–3.80 (m, 1H), 3.69 (t, *J* = 7.5 Hz, 1H), 3.65–3.55 (m, 3H), 2.84 (t, *J* = 6.8 Hz, 1H), 2.74–2.59 (m, 3H), 2.13–2.05 (m, 1H), 1.72–1.57 (m, 1H), 1.47–1.36 (m, 2H), 1.19 (dd, *J* = 14.3, 6.9 Hz, 2H), 1.13 (d, *J* = 5.9 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.9, 138.3, 128.3(2), 128.0, 127.8, 127.7, 127.6, 127.5, 127.4, 83.9, 77.9, 74.3, 74.2, 73.9, 73.7, 73.4, 70.0, 67.2, 56.9, 53.1, 37.7, 29.7, 21.2, 20.7, 14.1; ESI-HRMS: *m*/*z* calcd for $C_{34}H_{44}NO_4$ $[M+H]^+$: 530.3270, found 580.3292.

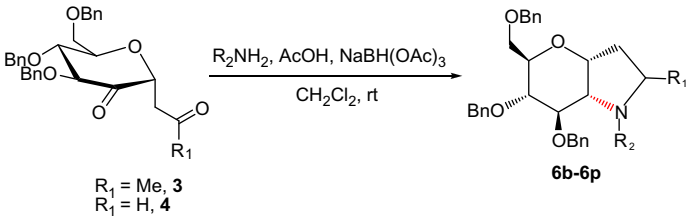
3.5. (2*R*,3a*R*,5*R*,6*S*,7*R*,7a*S*)-1-Benzyl-6,7-bis(benzyloxy)-5-[(benzyloxy)methyl]-2-methyl-octahydropyrano[3,2-*b*]pyrrole (6b)

Yield: 69.8 mg, 0.124 mmol, 62%. Light red syrup: $[\alpha]_D^{20}$ +30.0 (*c* 0.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (m, 20H), 4.81 (d, *J* = 11.4 Hz, 1H), 4.67 (d, *J* = 11.4 Hz, 1H), 4.63 (d, *J* = 11.3 Hz, 1H), 4.55 (d, *J* = 12.3 Hz, 1H), 4.48 (d, *J* = 12.3 Hz, 1H), 4.39 (dd, *J* = 9.0, 6.1 Hz, 2H), 4.00 (d, *J* = 14.6 Hz, 1H), 3.95–3.90 (m, 1H), 3.81 (t, *J* = 6.6 Hz, 1H), 3.73 (d, *J* = 14.6 Hz, 1H), 3.63–3.58 (m, 3H), 2.92 (t, *J* = 6.6 Hz, 1H), 2.61 (dd, *J* = 15.9, 6.1 Hz, 1H), 2.23–2.09 (m, 1H), 1.61 (dd, *J* = 21.4, 8.6 Hz, 1H), 1.00 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 139.2, 138.7, 138.3(2), 129.1, 128.3, 128.0, 127.9, 127.8, 127.8, 127.7, 127.6, 126.7, 82.4, 77.8, 73.7, 73.7, 73.6, 73.5, 73.4, 70.2, 67.4, 58.0, 57.0, 38.6, 20.6; ESI-HRMS: *m*/*z* calcd for $C_{37}H_{42}NO_4$ $[M+H]^+$: 564.3114, found 564.3116.

3.6. (3a*R*,5*R*,6*S*,7*R*,7a*S*)-1-Hydroxyethyl-6,7-bis(benzyloxy)-5-[(benzyloxy)-methyl]-2-methyl-octahydropyrano[3,2-*b*]pyrrole (6c)

Yield: 54.8 mg, 0.106 mmol, 53%, major:minor = 3:1. Light red syrup: $[\alpha]_D^{20}$ +27.8 (*c* 0.7, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57–6.99 (m, 15H), 4.75 (d, *J* = 11.7 Hz, 1H), 4.66 (d, *J* = 11.7 Hz, 1H), 4.65–4.57(m, 1H), 4.52 (t, *J* = 11.4 Hz, 2H), 4.50–4.44 (m, 2H), 4.41 (t, *J* = 11.5 Hz, 1H), 3.92–3.86 (m, 1H), 3.70 (dd, *J* = 14.7,

Table 2
Synthesis of octahydropyrano[3,2-*b*]pyrrole derivatives from glycosyl-1,4-dicarbonyl compounds[a]



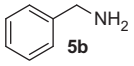
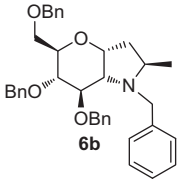
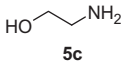
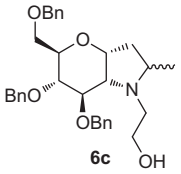
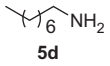
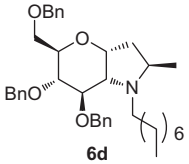
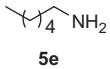
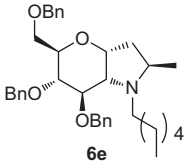
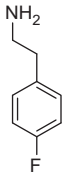
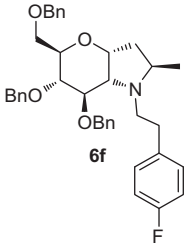
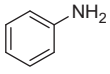
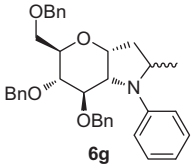
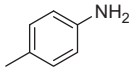
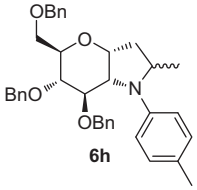
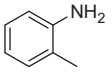
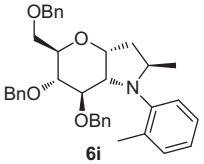
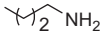
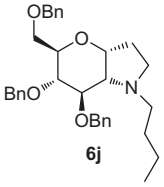
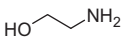
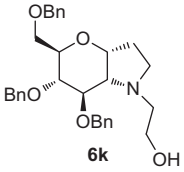
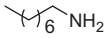
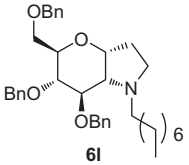
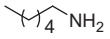
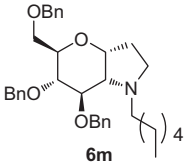
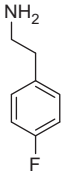
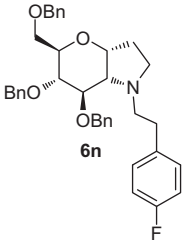
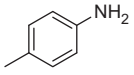
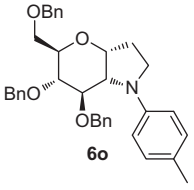
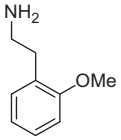
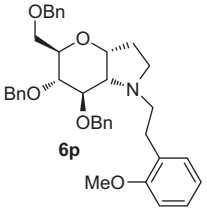
Entry	R_1	R_2NH_2	Products	Time (h)	Yield[b] (%)
1	Me	 **5b**	 **6b**	26	62
2	Me	 **5c**	 **6c**	20	53[c]
3	Me	 **5d**	 **6d**	16	55
4	Me	 **5e**	 **6e**	16	63
5	Me	 **5f**	 **6f**	16	59
6	Me	 **5g**	 **6g**	26	64[d]
7	Me	 **5h**	 **6h**	20	76[e]

Table 2 (*continued*)

Entry	R_1	R_2NH_2	Products	Time (h)	Yield[b] (%)
8	Me	 **5i**	 **6i**	16	58
9	H	 **5a**	 **6j**	11	55
10	H	 **5c**	 **6k**	11	64
11	H	 **5d**	 **6l**	11	42
12	H	 **5e**	 **6m**	11	54
13	H	 **5f**	 **6n**	11	53
14	H	 **5h**	 **6o**	13	62
15	H	 **5j**	 **6p**	11	67

[a] Reaction conditions: In all cases, the productwas obtained by using : dicarbonyl compounds **3** or **4** (0.20 mmol), AcOH (23 μL, 0.4 mmol), amine (0.22 mmol), $NaBH(OAc)_3$ (138 mg, 0.60 mmol), 0.7 mL CH_2Cl_2.

[b] Isolated yield.

[c] Major/Minor = 3:1 (values were determined by ^1H NMR).

[d] Major/Minor = 3:2 (values were determined by ^1H NMR).

[e] Major/Minor = 1:1 (Values were determined by ^1H NMR).

9.2 Hz, 1H), 3.62–3.47 (m, 4H), 2.83 (t, J = 6.3 Hz, 1H), 2.75 (d, J = 9.2 Hz, 1H), 2.66–2.55 (m, 1H), 2.18 (dd, J = 13.3, 7.0 Hz, 1H), 1.65 (dd, J = 18.6, 11.4 Hz, 1H), 1.26 (s, 1H), 1.16 (d, J = 6.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.1, 137.6, 128.4(2), 128.3(2), 128.1, 127.9(2), 127.8, 127.7, 127.6(2), 79.9, 77.6, 73.5, 73.4, 73.2, 72.3, 69.8, 67.6, 62.0, 61.2, 59.4, 57.5, 37.5, 21.6; ESI-HRMS: m/z calcd for $C_{32}H_{40}NO_5$ $[M+H]^+$: 518.2906, found 518.2918.

3.7. (2*R*,3a*R*,5*R*,6*S*,7*R*,7a*S*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)-methyl]-2-methyl-1-octyl-octahydropyrano[3,2-*b*]pyrrole (6d)

Yield: 64.4 mg, 0.11 mmol, 55%. Light red syrup: $[\alpha]_D^{20}$ +38.1 (c 0.6, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44–7.18 (m, 15H), 4.88 (d, J = 11.4 Hz, 1H), 4.84 (d, J = 11.4 Hz, 1H), 4.71 (t, J = 10.0 Hz, 1H), 4.58–4.53 (m, 1H), 4.48 (dt, J = 15.5, 8.8 Hz, 2H), 4.39 (q, J = 7.5 Hz, 1H), 3.83 (dd, J = 7.9, 3.5 Hz, 1H), 3.69 (t, J = 7.7 Hz, 1H), 3.65–3.57 (m, 3H), 2.84 (t, J = 6.9 Hz, 1H), 2.72–2.60 (m, 3H), 2.13–2.04 (m, 1H), 1.61 (dd, J = 21.3, 9.4 Hz, 1H), 1.48–1.37 (m, 2H), 1.27 (dd, J = 12.6, 5.8 Hz, 2H), 1.20 (s, 8H), 1.13 (d, J = 6.0 Hz, 3H), 0.86 (dt, J = 11.1, 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 139.0, 138.3(2), 128.3(2), 128.0, 127.9, 127.8, 127.6(2), 127.4, 84.0, 77.9, 74.3, 74.2, 73.9, 73.8, 73.4, 70.0, 67.2, 56.8, 53.3, 37.8, 31.9, 29.6, 29.4, 27.7, 26.4, 22.7, 21.2, 14.11; ESI-HRMS: m/z calcd for $C_{38}H_{52}NO_4$ $[M+H]^+$: 586.3896, found 586.3916.

3.8. (2*R*,3a*R*,5*R*,6*S*,7*R*,7a*S*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)-methyl]-1-hexyl-2-methyl-octahydropyrano[3,2-*b*]pyrrole (6e)

Yield: 70.2 mg, 0.126 mmol, 63%. Light red syrup: $[\alpha]_D^{20}$ +42.6 (c 0.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39–7.22 (m, 15H), 4.88 (d, J = 11.3 Hz, 1H), 4.83 (d, J = 11.4 Hz, 1H), 4.72 (d, J = 11.0 Hz, 1H), 4.56 (d, J = 12.2 Hz, 1H), 4.47 (dd, J = 16.4, 11.9 Hz, 2H), 4.39 (dd, J = 14.6, 7.4 Hz, 1H), 3.85–3.80 (m, 1H), 3.69 (t, J = 7.3 Hz, 1H), 3.66–3.56 (m, 3H), 2.84 (t, J = 6.6 Hz, 1H), 2.73–2.59 (m, 3H), 2.13–2.04 (m, 1H), 1.73 (s, 1H), 1.61 (dd, J = 20.4, 9.7 Hz, 1H), 1.48–1.37 (m, 2H), 1.28–1.06 (m, 8H), 0.84 (t, J = 6.9 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.9, 138.3(2), 128.3(2), 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 84.0, 77.9, 74.3, 74.2, 73.9, 73.8, 73.4, 70.0, 67.2, 56.8, 53.3, 37.8, 31.9, 27.3, 26.3, 22.7, 21.1, 14.1; ESI-HRMS: m/z calcd for $C_{36}H_{48}NO_4$ $[M+H]^+$: 558.3583, found 558.3593.

3.9. (2*R*,3a*R*,5*R*,6*S*,7*R*,7a*S*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)methyl]-1-[2-(4-fluorophenyl)ethyl]-2-methyl-octahydropyrano[3,2-*b*]pyrrole (6f)

Yield: 70.2 mg, 0.118 mmol, 59%. Light red syrup: $[\alpha]_D^{20}$ +34.7 (c 0.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35–7.23 (m, 13H), 7.19–7.13 (m, 2H), 6.92 (dd, J = 8.2, 5.7 Hz, 2H), 6.85 (t, J = 8.7 Hz, 2H), 4.95 (d, J = 11.5 Hz, 1H), 4.78 (d, J = 11.6 Hz, 1H), 4.73 (t, J = 7.8 Hz, 1H), 4.57 (d, J = 12.2 Hz, 1H), 4.48 (d, J = 10.9 Hz, 2H), 4.43 (dd, J = 14.8, 7.5 Hz, 1H), 3.87–3.82 (m, 1H), 3.76–3.71 (m, 1H), 3.67–3.58 (m, 3H), 3.00–2.86 (m, 3H), 2.83–2.73 (m, 1H), 2.72–2.61 (m, 2H), 2.15 (dt, J = 13.2, 6.6 Hz, 1H), 1.69–1.57 (m, 1H), 1.17 (d, J = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.0, 160.4, 138.8, 138.3, 138.2, 136.2, 130.0(2), 128.4, 128.0, 127.8, 127.7, 127.6, 127.5, 115.1, 114.9, 83.9, 77.9, 74.3(2), 74.2, 73.8, 73.4, 70.0, 66.9, 56.6, 54.3, 38.0, 31.7, 20.7; ESI-HRMS: m/z calcd for $C_{38}H_{43}FNO_4$ $[M+H]^+$: 596.3176, found 596.3171.

3.10. (3a*R*,5*R*,6*S*,7*R*,7a*S*)-6,7-bis(benzyloxy)-5-[(benzyloxy)-methyl]-2-methyl-1-phenyl-octahydropyrano[3,2-*b*]pyrrole (6g)

Yield: 70.3 mg, 0.128 mmol, 64%, major:minor = 3:2. Red syrup: $[\alpha]_D^{20}$ −19.2 (c 0.6, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38–7.15 (m, 28H), 7.12 (t, J = 7.9 Hz, 2H), 7.10–7.07 (m, 2H), 6.94 (d, J = 8.3 Hz, 2H), 6.92–6.87 (m, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.73 (t, J = 7.2 Hz, 1H), 6.66 (t, J = 7.2 Hz, 1H), 4.87 (d, J = 10.7 Hz, 1H), 4.76–4.72 (m, 1H), 4.71 (d, J = 8.1 Hz, 2H), 4.68 (d, J = 1.8 Hz, 1H), 4.60 (d, J = 12.2 Hz, 2H), 4.56 (dd, J = 11.5, 5.4 Hz, 3H), 4.51 (d, J = 10.2 Hz, 1H), 4.46 (d, J = 11.0 Hz, 1H), 4.38 (dt, J = 11.8, 7.2 Hz, 1H), 4.23 (t, J = 7.3 Hz, 1H), 4.18 (d, J = 9.8 Hz, 1H), 3.89–3.77 (m, 4H), 3.78–3.65 (m, 5H), 3.60 (dt, J = 17.5, 9.1 Hz, 2H), 2.53 (dd, J = 21.3, 9.8 Hz, 1H), 2.30–2.14 (m, 1H), 2.05 (td, J = 11.9, 9.2 Hz, 1H), 1.76 (dd, J = 11.4, 7.6 Hz, 1H), 1.34 (d, J = 6.0 Hz, 3H), 1.15 (d, J = 6.1 Hz, 2H), 0.92–0.72 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 147.6, 145.8, 138.2(3), 138.1, 138.0(2), 129.1, 128.8, 128.6, 128.4, 128.2, 128.1, 127.9, 127.7, 127.6, 127.5, 116.9, 116.2, 112.8, 85.7, 83.5, 77.6, 77.5, 75.4, 75.2, 75.0, 74.5, 74.1, 73.6, 73.6, 73.5, 73.2, 73.0, 69.5(2), 69.3, 63.9, 60.0, 52.5, 51.0, 33.8, 33.6, 22.1, 19.6; ESI-HRMS: m/z calcd for $C_{36}H_{39}NNaO_4$ $[M+Na]^+$: 572.2777, found 572.2798.

3.11. (3a*R*,5*R*,6*S*,7*R*,7a*S*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)-methyl]-2-methyl-1-(4-methylphenyl)octahydropyrano[3,2-*b*]pyrrole (6h)

Yield: 85.6 mg, 0.152 mmol, 76%, major:minor = 1:1. Light red syrup: $[\alpha]_D^{20}$ +34.7 (c 0.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36–7.21 (m, 21H), 7.17 (dd, J = 15.1, 7.2 Hz, 5H), 7.10–7.06 (m, 2H), 7.02 (d, J = 8.2 Hz, 2H), 6.93 (d, J = 8.0 Hz, 2H), 6.87 (t, J = 8.8 Hz, 4H), 6.74 (d, J = 8.2 Hz, 2H), 4.86 (d, J = 10.8 Hz, 1H), 4.74 (t, J = 7.9 Hz, 2H), 4.71–4.65 (m, 2H), 4.60 (d, J = 12.2 Hz, 2H), 4.55 (d, J = 11.7 Hz, 3H), 4.51 (d, J = 10.1 Hz, 1H), 4.45 (d, J = 10.9 Hz, 1H), 4.36 (dt, J = 13.9, 7.0 Hz, 1H), 4.19 (t, J = 7.3 Hz, 1H), 4.15 (d, J = 10.3 Hz, 2H), 3.80 (dd, J = 16.4, 8.8 Hz, 4H), 3.70 (ddd, J = 29.3, 15.9, 9.2 Hz, 6H), 3.59 (dt, J = 17.1, 9.0 Hz, 2H), 2.50 (dd, J = 21.0, 9.8 Hz, 1H), 2.26 (s, 3H), 2.24–2.18 (m, 3H), 2.09–1.99 (m, 1H), 1.79–1.72 (m, 1H), 1.33 (d, J = 5.9 Hz, 3H), 1.26 (s, 3H), 1.13 (d, J = 6.0 Hz, 2H), 0.87 (dd, J = 18.4, 11.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 145.6, 143.5, 138.3, 138.2, 138.1(2), 138.0, 128.6, 128.4, 128.3, 128.2, 128.0, 127.9(2), 127.8, 127.7(2), 127.6(2), 127.5, 126.1, 116.7, 112.9, 85.8, 83.2, 77.6, 77.5, 75.3, 75.1, 74.9, 74.4, 74.1, 73.6, 73.6, 73.1, 73.0, 69.6, 69.3, 64.4, 60.5, 52.7, 51.0, 33.9, 29.7, 22.1, 20.4, 20.2, 19.7; ESI-HRMS: m/z calcd $C_{37}H_{42}NO_4$ $[M+H]^+$: 564.3114, found 564.3113.

3.12. (2*R*,3a*R*,5*R*,6*S*,7*R*,7a*S*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)-methyl]-2-methyl-1-(*o*-tolyl)-octahydropyrano[3,2-*b*]pyrrole (6i)

Yield: 65.3 mg, 0.116 mmol, 58%. Light red syrup: $[\alpha]_D^{20}$ +33.4 (c 0.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 (d, J = 19.6 Hz, 5H), 7.29–7.20 (m, 7H), 7.19–7.10 (m, 4H), 7.06 (dd, J = 6.9, 2.3 Hz, 2H), 6.80 (dd, J = 7.3, 1.7 Hz, 1H), 4.69 (dd, J = 12.3, 7.6 Hz, 1H), 4.58 (d, J = 12.3 Hz, 1H), 4.49 (d, J = 12.2 Hz, 1H), 4.34 (d, J = 11.4 Hz, 1H), 4.27 (d, J = 11.0 Hz, 1H), 4.20 (d, J = 11.4 Hz, 1H), 4.13 (d, J = 11.0 Hz, 1H), 4.07 (ddd, J = 9.1, 5.2, 2.4 Hz, 1H), 3.65 (dd, J = 10.5, 2.4 Hz, 1H), 3.63–3.58 (m, 2H), 3.54 (dd, J = 5.9, 4.0 Hz, 1H), 3.45 (dd, J = 6.8, 4.0 Hz, 1H), 3.01–2.89 (m, 1H), 2.53–2.42 (m, 1H), 2.32 (s, 3H), 1.73–1.63 (m, 1H), 0.96 (d, J = 6.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 147.6, 139.2, 138.5, 138.3, 138.1, 130.8, 128.3, 128.2, 128.1, 127.8, 127.7, 127.5, 126.8, 125.7, 124.5, 80.0, 77.7(2), 73.3, 72.7(2), 72.2, 70.4, 69.4, 62.1, 40.3, 18.7, 18.5; ESI-HRMS: m/z calcd for $C_{37}H_{41}NNaO_4$ $[M+Na]^+$: 586.2933, found 586.2946.

3.13. (3a*R*,5*R*,6*S*,7*R*,7a*S*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)-methyl]-1-butyl-octahydropyrano[3,2-*b*]pyrrole (6j)

Yield: 55.7 mg, 0.110 mmol, 55%. Light red syrup: $[\alpha]_D^{20}$ +24.1 (c 0.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36–7.17 (m, 15H), 4.88 (d, J = 10.4 Hz, 1H), 4.81–4.67 (m, 2H), 4.63–4.37 (m, 5H), 3.91–

3.83 (m, 1H), 3.68 (s, 1H), 3.59 (d, J = 3.2 Hz, 2H), 3.19 (s, 1H), 2.92 (s, 1H), 2.58 (s, 1H), 2.28 (s, 1H), 2.11 (s, 2H), 1.90 (s, 1H), 1.49 (s, 2H), 1.31–1.20 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.6, 128.3(2), 128.4(2), 127.9, 127.8, 127.7, 127.6, 77.7, 74.6, 73.8, 73.3, 70.2, 68.5, 55.6, 51.5, 30.1, 29.7, 20.7, 14.0; ESI-HRMS: m/z calcd for $C_{33}H_{42}NO_4$ $[M+H]^+$: 516.3114, found 516.3108.

3.14. (3a*R*,5*R*,6*S*,7*R*,7a*S*)- 6,7-Bis(benzyloxy)-5-[(benzyloxy)-methyl]- 1-hydroxyethyl-octahydropyrano[3,2-*b*]pyrrole (6k)

Yield: 64.4 mg, 0.128 mmol, 64%. Colourless syrup: $[\alpha]_D^{20}$ +22.3 (c 0.9, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35–7.18 (m, 15H), 4.70 (d, J = 11.7 Hz, 1H), 4.64–4.55 (m, 3H), 4.49 (d, J = 12.2 Hz, 1H), 4.47–4.44 (m, 1H), 4.40–4.36 (m, 1H), 3.91 (dt, J = 8.1, 4.2 Hz, 1H), 3.79 (s, 1H), 3.67–3.61 (m, 1H), 3.59 (dd, J = 7.7, 4.9 Hz, 1H), 3.55–3.49 (m, 3H), 3.37 (s, 1H), 2.99 (t, J = 9.8 Hz, 1H), 2.82–2.73 (m, 1H), 2.46 (d, J = 12.7 Hz, 1H), 2.21 (dd, J = 17.6, 8.5 Hz, 1H), 2.15 (dtd, J = 11.0, 7.8, 3.0 Hz, 1H), 1.99–1.91 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.3, 138.2, 137.7, 129.7, 128.5(2), 128.4, 128.3(2), 127.9(2), 127.8, 127.6, 77.6, 76.3, 75.6, 74.3, 73.3, 72.9, 72.8, 72.7, 70.2, 59.7, 57.2, 52.7, 30.0; ESI-HRMS: m/z calcd for $C_{31}H_{38}NO_5$ $[M+H]^+$: 504.2750, found 504.2744.

3.15. (3a*R*,5*R*,6*S*,7*R*,7a*S*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)-methyl]-1-octyl-octahydropyrano[3,2-*b*]pyrrole (6l)

Yield: 48.0 mg, 0.084 mmol, 42%. Light red syrup: $[\alpha]_D^{20}$ +20.2 (c 0.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38–7.17 (m, 15H), 4.87 (s, 1H), 4.70 (d, J = 18.9 Hz, 3H), 4.50 (dd, J = 32.4, 11.4 Hz, 4H), 3.89–3.84 (m, 1H), 3.67 (s, 1H), 3.58 (d, J = 2.7 Hz, 2H), 3.16 (s, 1H), 2.88 (s, 1H), 2.56 (s, 1H), 2.26 (s, 1H), 2.10 (s, 1H), 1.83 (d, J = 36.8 Hz, 1H), 1.49 (s, 1H), 1.26 (dd, J = 24.0, 14.9 Hz, 12H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 141.0, 138.6, 138.2, 128.9, 128.6, 128.4, 127.9, 127.7, 127.6, 127.0, 77.6, 74.5, 73.8, 73.3, 70.1, 68.4, 65.3, 55.8, 51.5, 31.8, 29.3, 27.5, 22.6, 14.1; ESI-HRMS: m/z calcd for $C_{37}H_{50}NO_4$ $[M+H]^+$: 572.3740, found 572.3734.

3.16. (3a*R*,5*R*,6*S*,7*R*,7a*S*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)-methyl]-1-hexyl-octahydropyrano[3,2-*b*]pyrrole (6m)

Yield: 58.7 mg, 0.108 mmol, 54%. Light red syrup: $[\alpha]_D^{20}$ +20.8 (c 0.6, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41–7.21 (m, 15H), 4.92 (d, J = 10.4 Hz, 1H), 4.84–4.70 (m, 2H), 4.62–4.53 (m, 2H), 4.50 (t, J = 11.7 Hz, 2H), 3.95–3.88 (m, 1H), 3.72 (d, J = 7.6 Hz, 1H), 3.63 (d, J = 2.4 Hz, 2H), 3.22 (s, 1H), 2.94 (s, 1H), 2.61 (s, 1H), 2.30 (s, 1H), 2.14 (s, 1H), 1.93 (s, 1H), 1.54 (s, 2H), 1.28 (dd, J = 20.9, 7.5 Hz, 8H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.6, 138.3, 128.4, 127.9, 127.8, 127.7(2), 127.6, 127.5, 81.9, 77.7, 74.6, 73.8, 73.3, 70.2, 68.5, 55.8, 51.4, 31.8, 30.1, 27.9, 27.2, 22.6, 14.0; ESI-HRMS: m/z calcd for $C_{35}H_{46}NO_4$ $[M+H]^+$: 544.3427, found 544.3421.

3.17. (3a*R*,5*R*,6*S*,7*R*,7a*S*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)-methyl]-1-(4-fluorophenethyl)-octahydropyrano[3,2-*b*]pyrrole (6n)

Yield: 61.6 mg, 0.106 mmol, 53%. Light red syrup: $[\alpha]_D^{20}$ +21.0 (c 0.7, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38–6.85 (m, 19H), 4.89 (d, J = 11.1 Hz, 1H), 4.71 (d, J = 11.3 Hz, 2H), 4.62–4.43 (m, 5H), 3.90–3.85 (m, 1H), 3.68 (t, J = 8.1 Hz, 1H), 3.60 (d, J = 2.7 Hz, 2H), 3.29 (s, 1H), 3.17 (s, 1H), 2.78 (s, 2H), 2.63 (d, J = 62.0 Hz, 2H), 2.28 (s, 1H), 2.14 (s, 1H), 1.92 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 162.2, 160.6, 138.5, 138.2(2), 130.0(2), 128.4, 128.0, 127.7, 127.6(2), 115.1, 115.0, 77.7, 74.9, 74.5, 74.0(2), 73.3, 70.2, 68.2, 57.2, 51.5, 33.7, 30.1, 29.7; ESI-HRMS: m/z calcd for $C_{37}H_{41}FNO_4$ $[M+H]^+$: 582.3020, found 582.3014.

3.18. (3a*R*,5*R*,6*S*,7*R*,7a*S*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)-methyl]-1-(*p*-tolyl)-octahydropyrano[3,2-*b*]pyrrole (6o)

Yield: 68.1 mg, 0.124 mmol, 62%. Red syrup: $[\alpha]_D^{20}$ −19.8 (c 1.2, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38–6.98 (m, 19H), 4.79 (d, J = 11.0 Hz, 1H), 4.62 (d, J = 10.4 Hz, 1H), 4.58 (t, J = 8.8 Hz, 2H), 4.52 (d, J = 4.0 Hz, 1H), 4.50 (s, 1H), 3.93 (s, 1H), 3.83 (d, J = 9.0 Hz, 2H), 3.71–3.63 (m, 3H), 3.28 (d, J = 8.4 Hz, 1H), 2.41–2.29 (m, 2H), 2.26 (s, 3H), 2.10 (s, 1H), 1.57 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 138.1, 138.0(2), 129.9, 129.8, 129.7, 128.6, 128.4(2), 128.2, 128.1, 128.0, 127.8, 127.7, 127.5, 74.9, 74.8, 74.7(2), 74.4, 73.5, 69.7, 69.6, 63.8, 29.7, 20.5, 20.4; ESI-HRMS: m/z calcd for $C_{36}H_{39}NNaO_4$ $[M+Na]^+$: 572.2777, found 572.2771.

3.19. (3a*R*,5*R*,6*S*,7*R*,7a*S*)-6,7-Bis(benzyloxy)-5-[(benzyloxy)-methyl]-1-(2-methoxy-phenethyl)-octahydropyrano[3,2-*b*]pyrrole (6p)

Yield: 79.5 mg, 0.134 mmol, 67%. Light red syrup: $[\alpha]_D^{20}$ +14.3 (c 0.5, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41–6.67 (m, 19H), 4.82 (d, J = 11.0 Hz, 1H), 4.71 (d, J = 11.3 Hz, 1H), 4.53 (d, J = 12.1 Hz, 2H), 4.46 (d, J = 11.2 Hz, 2H), 3.87 (dt, J = 7.7, 3.7 Hz, 1H), 3.84–3.76 (m, 1H), 3.72–3.63 (m, 4H), 3.63–3.55 (m, 2H), 3.32 (s, 1H), 3.20 (s, 1H), 2.85 (s, 2H), 2.65 (s, 1H), 2.56 (s, 1H), 2.30 (s, 1H), 2.12 (s, 1H), 1.93 (s, 1H), 1.78 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 157.5, 138.6, 138.3, 130.3, 129.7, 128.4, 128.3, 127.9, 127.8, 127.7(2), 127.6, 127.5, 127.3, 120.4, 110.2, 77.6, 74.7, 73.9, 73.3, 70.1, 68.3, 55.7, 55.1, 51.3, 30.1, 29.1; ESI-HRMS: m/z calcd for $C_{38}H_{44}NO_5$ $[M+H]^+$: 584.3219, found 584.3214.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.carres.2012.11.016.

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20. The same result of inequal mixture of diastereomers was obtained by reductive amination of the diketone. See Ref. 12.