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Carbohydrate templates for the synthesis of prototype renin inhibitors

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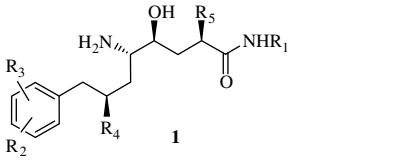
ABSTRACT

A concise synthesis of a prototype renin inhibitor and its 7-epimer has been accomplished starting from readily available D-glucose.

1. Introduction

Renin inhibitors have proven efficacy in ameliorating hypertension and cardiovascular disorders. A variety of stable peptide-like analogues that can inhibit renin have been developed; intravenous administration of these results in a dramatic lowering of blood pressure.[1,2] More recently, a new class of non-peptidic renin inhibitors has been synthesized. Various analogues of non-peptidic renin inhibitors **1** carrying different substituents at the aromatic ring, at the amide nitrogen, and at 2,7-alkyls have shown unique binding affinities to renin (Fig. 1)[2,3] and have therefore, attracted attention from synthetic process chemists wanting to prepare significant quantities for bioavailability and related pharmacological evaluation.

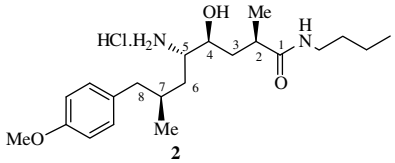


1

R_1 = alkyl, amidoalkyl, etc.

R_2, R_3 = methoxy and methoxy ethoxy, etc.

R_4, R_5 = methyl, isopropyl



2

Figure 1. General structure **1**[2] and our target molecule **2**.

Herein, we report a simple synthesis of a prototype analogue **2** and its 7-epimer **19** that could afford divergent entries into the synthesis of related analogues that differ in the *para* substituents. Some of them have been very potent, for example, *p*-phenyl and *p*-*tert*-butyl analogues of **2** have shown binding affinities (IC_{50}, μM at pH 7.2) of 3 and 2, respectively.[4] Recently, Hanessian et al. have also reported the synthesis of the 2,7-diisopropyl analogue of **18**.[2]

2. Results and discussion

Retrosynthetic analysis of the target analogue **2** envisages D-glucose as an appropriate starting point (Scheme 1). The inherent stereochemical centers at C-2 and C-3 of D-glucose correlate with those at C-4 and C-5 of **2** via routine transformations. In addition, the D-glucofuranose ring system was expected to provide necessary off-template stereo control,[5] particularly at C-5 of the glucofuranose ring. The aromatic moiety and the C-7 methyl could be installed by Wittig olefination, followed by stereoselective hydrogenation. The C-2 stereocenter could be obtained by methylation of the enolate of the butyrolactone moiety. Finally, the target molecule **2** could be elaborated from the butyrolactone **3** by replacing the hydroxyl group with an amine equivalent, followed by aminolysis of the lactone ring with *n*-butylamine.

The known 5-ulose[6] derivative **9** was made from compound **8** by a sequence of oxidative cleavage, methyl Grignard followed by Swern oxidation. Ketone **9** upon treatment with *p*-methoxybenzylidene-triphenylphosphorane[7] at room temperature yielded an inseparable mixture (4:1, from ^{1}H NMR) of geometrical isomers **10**, which on hydrogenation in the presence of 10% Pd/C at 50 psi afforded compound **11** as a mixture of C-5 methyl epimers in a 7:3 ratio. Although the furanose ring normally gives good off-template selectivity in the hydrogenation of the double bond at C-5 and C-6,[8] we obtained rather low stereoselectivity (7:3) presumably due to the absence of functionalities responsible for the stability of the rotamers. To introduce the amino group with retention of stereochemistry at a later stage, the C3 hydroxyl group of

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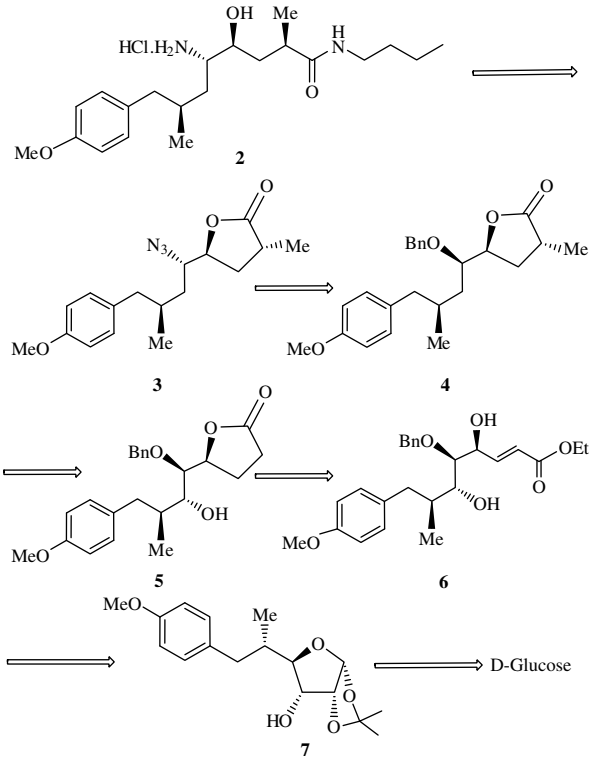


Scheme 1. Retrosynthetic scheme for **2**.

compound **11** was oxidized to a mixture of 3-ulose derivatives, which were separated by chromatography. Both the ketones **12a** (major isomer) and **12b** (minor isomer) were separately reduced using $NaBH_4$ in MeOH to obtain stereochemically inverted C_3–OH derivatives **7** and **13** as crystalline solids (Scheme 2). Stereochemistry at the methyl center in compound **7** was deduced to be (*S*) by single crystal X-ray studies[9] (Fig. 2).

Our next concern was to design the synthesis of the right half of the molecule, which includes a methyl stereogenic center and an alkyl amide. For this, the hydroxyl group in compound **7** was first protected as its benzyl ether. Cleavage of the isopropylidene group, two-carbon Wittig homologation with (ethoxycarbonylmethylene)

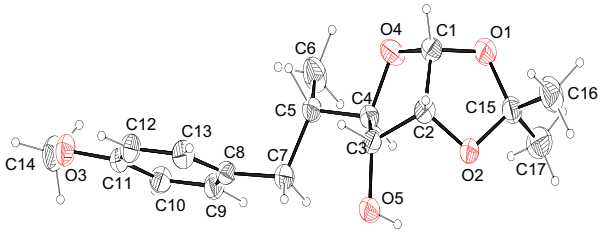


Figure 2. ORTEP diagram of **7**.

triphenylphosphorane yielded the (*E*)-α,β-unsaturated ester **6** exclusively. The olefinic protons appeared at 6.13 ppm (dd, J = 15.7, 1.9 Hz) and at 7.15 ppm (dd, J = 15.66, 4.42 Hz). Reduction of the double bond with Raney nickel and treatment with *p*-TSA yielded the γ-butyrolactone derivative **5** in preference to the 7-membered lactone. Regioselective formation of the 5-membered lactone ensures the protection of the γ-hydroxyl group, leaving the other hydroxyl group unaffected without necessitating any further protecting group manipulation. The unwanted hydroxyl group in compound **5** was removed by using the Barton–McCombie radical deoxygenation protocol.[10] This transformation was confirmed by the disappearance of the signal for the methine proton at 3.52 ppm. For the introduction of the C-2 methyl stereocenter, the enolate derived from compound **15** by treatment with LiHMDS was reacted with MeI at −78 °C. Exclusive formation of compound **4** was established by NOE studies. As depicted in Figure 3, 3a-H (1.80 ppm) shows strong NOE interactions with both H_4 (4.40 ppm) and the methyl protons (1.22 ppm). Relevant NOE interactions were also observed between 2b-H (2.72 ppm) and 3b-H (2.44 ppm) confirming the *syn* relationship of the methyl group with H_4. To introduce the amino functionality at C-5, the

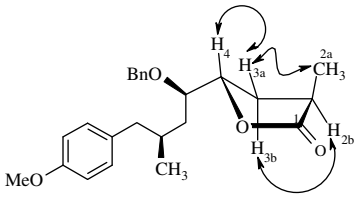
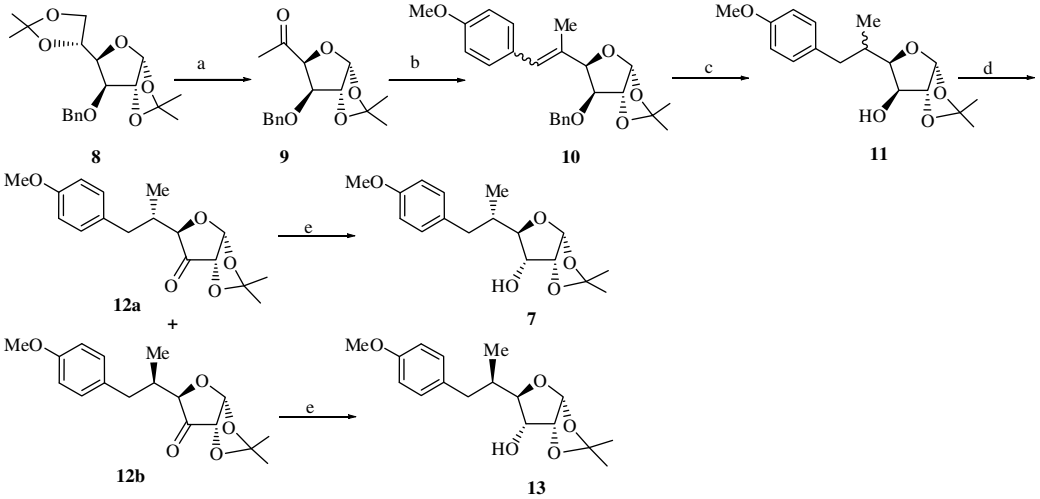
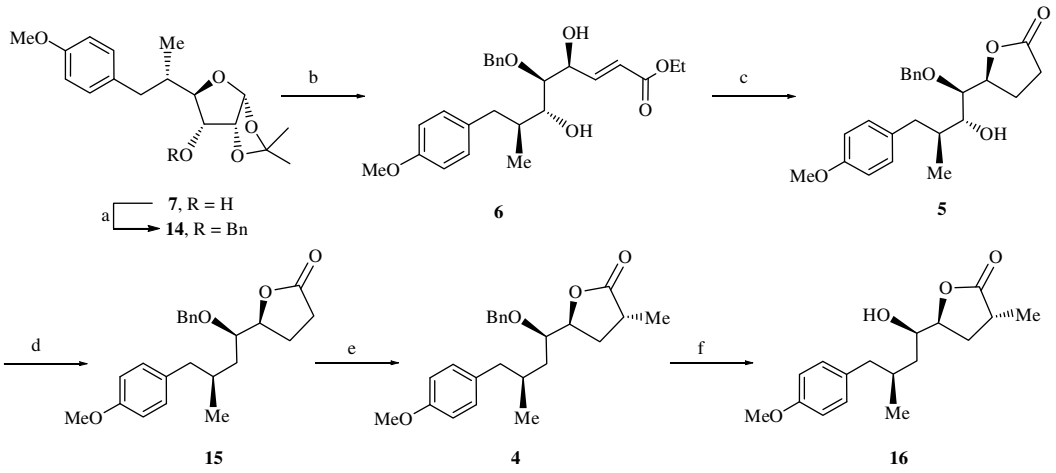


Figure 3. NOE studies of **4**.



Scheme 2. Reagents and conditions: (a) (i) $HIO_4{\cdot}2H_2O$, EtOAc, rt, 20 min; (ii) CH_3MgI, THF, 0 ° to rt, 2 h, 87% (for two steps); (iii) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −78 °C, 1 h, 85%; (b) *p*-$OMeC_6H_4CH{=}PPh_3$, C_6H_6, rt, 4 h, 70%; (c) Pd/C, H_2 (50 psi), rt, 2 h, 95%; (d) PDC, CH_2Cl_2, 4 Å molecular sieves, Ac_2O (cat.), rt, 2 h, 87%, SiO_2 chromatography; (e) $NaBH_4$, MeOH, rt, 2 h, 84%.



Scheme 3. Reagents and conditions: (a) NaH, BnBr, THF, 0 °C to rt, 3 h, 94%; (b) (i) 6 M HCl, THF/H_2O (3:1), H_2SO_4 (cat.), reflux, 30 min, 92%; (ii) PPh_3=CHCOOEt, toluene, reflux, 2 h, 88%; (c) Raney Ni, MeOH, 2 h, then filtration, *p*-TSA, 2 h, 85%; (d) Im_2CS, toluene, reflux, 6 h; then Bu_3SnH, AIBN, degassing, reflux, 2 h, 80%; (e) LiHMDS, THF, −78 °C, MeI, 2 h, 84%; (f) 10% Pd/C, H_2 (50 psi), MeOH, 1 h, 92%.

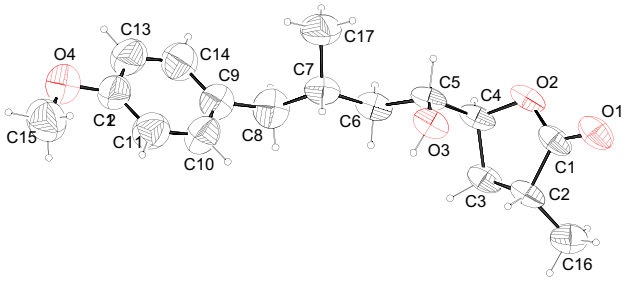


Figure 4. ORTEP diagram of **16**.

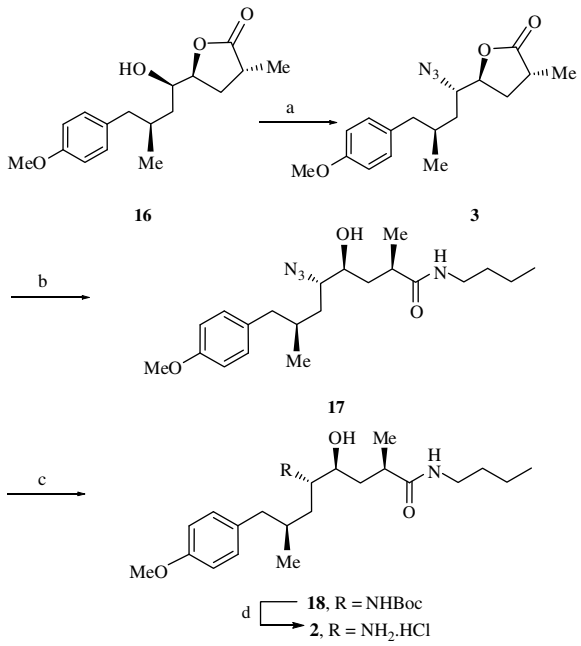
benzyl ether was cleaved by hydrogenolysis over 10% Pd/C (Scheme 3). At this juncture the single crystal X-ray crystallographic study of alcohol **16** assures[11] the newly generated stereocenter beyond doubt (Fig. 4).

Compound **16** was subsequently mesylated, and S_N2 displacement with LiN_3 in DMF at 60 °C gave **3** (marked by appearance of a characteristic peak at 2108 cm^{-1} in IR spectroscopy for the azide group), which on treatment with *n*-$BuNH_2$ in ethanol[12] yielded **17**. Finally hydrogenation of the azide using 10% Pd/C and in situ Boc-protection afforded the compound **18**, which was characterized by NMR, IR, and elemental analysis. Treatment of compound **18** with dry HCl gas in ether/CH_2Cl_2 culminated in the total synthesis of the target molecule **2** (Scheme 4).

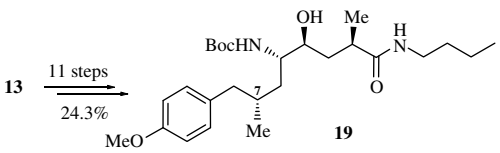
Similarly, the diastereomer **13** was taken through all the 11 steps as described above for **7**, leading to the formation of another diastereomer **19** (Scheme 5). The structure and the absolute configuration of **19** were confirmed by single crystal X-ray crystallography (Fig. 5).[13]

3. Conclusions

In conclusion, we have successfully achieved the synthesis of a prototype 2,7-dimethyl analogue (8.1% from **7** over 16 steps) of a renin inhibitor and its 7-*epi* isomer in a practical, concise, and stereoselective manner starting from D-glucose with high yielding steps. The absolute stereochemistry of some key intermediates and the 7-*epi* isomer of the target molecule have been established by X-ray crystallography. The syntheses of different analogues are currently in progress in our laboratory for biological investigations and will be reported in due course.



Scheme 4. Reagents and conditions: (a) (i) MsCl, Et_3N, CH_2Cl_2, rt, 1 h, (ii) LiN_3, DMF, 60 °C, 4 h, 82% over two steps; (b) *n*-$BuNH_2$, EtOH, rt, 2 h, 83%; (c) 10% Pd/C, H_2 (1 atm), MeOH, $(Boc)_2O$, 4 h, 95%; (d) dry HCl gas, CH_2Cl_2/Et_2O, 15 min, 92%.



Scheme 5. Synthesis of the 7-*epi* compound **19**.

4. Experimental

4.1. General

Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in an oven/

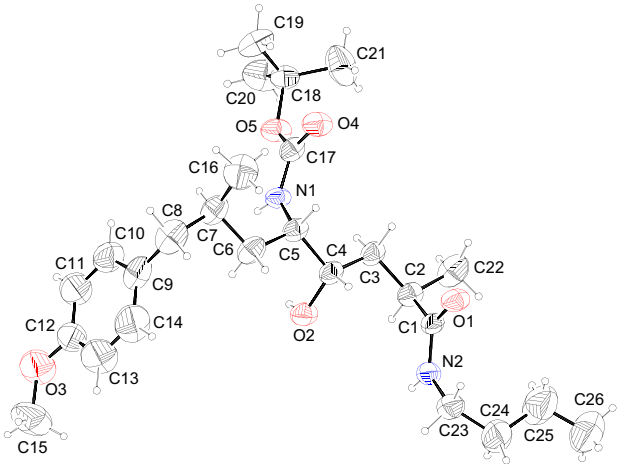


Figure 5. ORTEP diagram of **19**.

flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, benzene, toluene, and diethyl ether from Na and benzophenone; CH_2Cl_2 and *N*-methyl pyrolidinone from CaH_2; MeOH and EtOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out by using Spectrochem Silica Gel (60–120 mesh). Specific optical rotations $[\alpha]_D$ are given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded in $CHCl_3$/neat (as mentioned) and reported in wave number (cm^{-1}). ^{1}H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane, and coupling constants (*J*) are reported in Hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

4.1.1. (3′*R*,5*R*,6*S*,6′*R*)-6-(Benzyloxy)-5-(1-(4-methoxyphenyl)prop-1-en-2-yl)-2,2-dimethyltetrahydrofuro[3,2-*d*][1,3]dioxole 10

To a suspension of *p*-methoxybenzyltriphenylphosphonium chloride (5.74 g, 13.7 mmol) in dry benzene (50 mL) was added *n*-BuLi (6.4 mL, 1.6 M in hexane, 10.3 mmol) dropwise at 0 °C under an argon atmosphere. After 4 h at room temperature, the supernatant was then slowly cannulated to a solution of ketone **9** (2.0 g, 6.9 mmol) in dry benzene (10 mL) under an argon atmosphere. The reaction mixture was stirred for 4 h at room temperature, quenched with saturated aqueous ammonium chloride solution, and the organic layer was separated. The organic layer was washed with water, brine, dried over Na_2SO_4, and concentrated to give the crude product, which upon purification by silica gel column chromatography using ethyl acetate/light petroleum (1:19) afforded **10** (1.9 g, 70%) as a yellow liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.28 (s, 3H), 1.33 (s, 3H), 1.82 (d, 0.7H, *J* = 1.0 Hz), 2.08 (d, 2.3H, *J* = 1.4 Hz), 3.77 (s, 2.3H), 3.8 (s, 0.7H), 3.95 (d, 1H, *J* = 3.4 Hz), 4.58 (m, 3H), 5.06 (d, 1H, *J* = 3.4 Hz), 5.97 (d, 0.78H, *J* = 4.1 Hz), 6.03 (d, 0.22H, *J* = 4.1 Hz), 6.49 (s, 0.78H), 6.63 (s, 0.22H), 6.78–6.96 (ABq, 4H, *J* = 8.8 Hz), 7.30 (m, 5H). Anal. Calcd for $C_{24}H_{28}O_5$: C, 72.71; H, 7.12. Found: C, 72.51; H, 7.40.

4.1.2. (3′*R*,5*R*,6*S*,6′*R*)-5-(1-(4-Methoxyphenyl)propan-2-yl)-2,2-dimethyl-tetrahydrofuro[3,2-*d*][1,3]dioxol-6-ol 11

A solution of **10** (5.6 g, 14.3 mmol), 10% Pd/C (100 mg), and methanol (20 mL) was hydrogenated at 50 psi for 2 h. The reaction mixture was filtered through a bed of Celite, and the clear filtrate was evaporated. The residue was purified on silica gel column chromatography by using ethyl acetate/light petroleum (1:6) to obtain **11** (4.2 g, 95%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.82 (d, 0.9H, *J* = 6.8 Hz), 1.03 (d, 2.1H, *J* = 6.5 Hz), 1.29–1.30 (2s, 3H), 1.47–1.49 (2s, 3H), 2.09 (m, 1H), 2.32 (dd, 0.7H, *J* = 8.4, 13.5 Hz), 2.50 (dd, 0.3H, *J* = 8.6, 13.5 Hz), 2.70 (dd, 0.7H, *J* = 5.4, 13.5 Hz), 2.97 (dd, 0.3H, *J* = 3.3, 13.5 Hz), 3.72 (m, 1H), 3.77 (s, 3H), 4.03 (d, 1H, *J* = 1.9 Hz), 4.45–4.48 (2d, 1H, *J* = 3.9 Hz), 5.84 (d, 0.7H, *J* = 3.9 Hz), 5.92 (d, 0.3H, *J* = 3.9 Hz), 6.79–7.10 (2ABq, 4H, *J* = 8.8 Hz). Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.05; H, 8.01.

4.1.3. (3′*R*,5*R*,6′*S*)-5-((*S*)-1-(4-Methoxyphenyl)propan-2-yl)-2,2-dimethylfuro[3,2-*d*][1,3]dioxol-6(3′*H*,5*H*,6′*H*)-one 12a and (3′*R*,5*R*,6′*S*)-5-((*R*)-1-(4-methoxyphenyl)propan-2-yl)-2,2-dimethylfuro[3,2-*d*][1,3]dioxol-6(3′*H*,5*H*,6′*H*)-one 12b

A suspension of **11** (3.0 g, 9.7 mmol), 4 Å molecular sieves (7.5 g), PDC (4.4 g, 11.7 mmol), and Ac_2O (0.5 mL) in dichloromethane (60 mL) was stirred for 2 h at room temperature. It was filtered through a pad of Celite, concentrated, and purified on silica gel using ethyl acetate/light petroleum (1:19) to afford **12a** (1.8 g, 61%) as a light yellow liquid. $[\alpha]_D^{25} = +153.3$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.82 (d, 3H, *J* = 6.7 Hz), 1.40 (s, 3H), 1.42 (s, 3H), 2.14 (m, 1H), 2.52 (dd, 1H, *J* = 7.5, 13.5 Hz), 2.72 (dd, 1H, *J* = 8.2, 13.5 Hz), 3.78 (s, 3H), 4.22 (m, 2H), 6.03 (d, 1H, *J* = 4.3 Hz), 6.80–7.08 (ABq, 4H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.1 (q), 27.2 (q), 27.3 (q), 37.6 (d), 38.6 (t), 55.1 (q), 76.7 (d), 80.4 (d), 102.6 (d), 113.7 (s), 113.8 (d), 130.1 (d), 131.5 (s), 158.1 (s), 211.4 (s). Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.49; H, 7.37. Further elution gave **12b** (0.78 g, 26%) as a light yellow liquid. $[\alpha]_D^{25} = +109.9$ (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.02 (d, 3H, *J* = 6.8 Hz), 1.38 (s, 3H), 1.42 (s, 3H), 2.32 (m, 1H), 2.57 (m, 2H), 3.77 (s, 3H), 3.93 (dd, 1H, *J* = 0.9, 4.6 Hz), 4.18 (d, 1H, *J* = 3.4 Hz), 5.98 (d, 1H, *J* = 4.6 Hz), 6.78–7.03 (ABq, 4H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 16.7 (q), 27.2 (q), 27.3 (q), 36.9 (t), 37.7 (d), 55.1 (q), 76.4 (d), 81.5 (d), 102.5 (d), 113.3 (s), 113.7 (d), 130.5 (d), 131.1 (s), 158.2 (s), 211.1 (s). Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.84; H, 7.12.

4.1.4. (3′*R*,5*R*,6*R*,6′*R*)-5-((*S*)-1-(4-Methoxyphenyl)propan-2-yl)-2,2-dimethyl-tetrahydrofuro[3,2-*d*][1,3]dioxol-6-ol 7

A solution of **12a** (4.2 g, 13.7 mmol) and $NaBH_4$ (0.62 g, 16.5 mmol) in MeOH (30 mL) at 0 °C was stirred for 2 h. The reaction mixture was then quenched with water and methanol was removed. The aqueous phase was extracted with ethyl acetate, washed with water, brine, dried over Na_2SO_4, concentrated, and purified on silica gel column chromatography by using ethyl acetate/light petroleum (1:6) to give **7** (3.56 g, 84%) as a white solid. Mp 94.5 °C; $[\alpha]_D^{25} = +48.4$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.91 (d, 3H, *J* = 6.8 Hz), 1.35 (s, 3H), 1.48 (s, 3H), 1.99 (m, 1H), 2.21 (d, 1H, *J* = 10.2 Hz), 2.43 (dd, 1H, *J* = 8.6, 13.4 Hz), 2.82 (dd, 1H, *J* = 6.6, 13.4 Hz), 3.57 (dd, 1H, *J* = 3.9, 8.9 Hz), 3.77 (s, 3H), 3.81 (m, 1H), 4.51 (t, 1H, *J* = 4.6 Hz), 5.77 (d, 1H, *J* = 3.9 Hz), 6.79–7.09 (ABq, 4H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.0 (q), 26.4 (q), 26.8 (q), 35.9 (d), 38.8 (t), 55.1 (q), 72.7 (d), 78.7 (d), 81.8 (d), 103.6 (d), 112.2 (s), 113.6 (d), 130.1 (d), 132.5 (s), 157.8 (s). Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 65.97; H, 8.03.

4.1.5. (3′*R*,5*R*,6*R*,6′*R*)-5-((*R*)-1-(4-Methoxyphenyl)propan-2-yl)-2,2-dimethyl-tetrahydrofuro[3,2-*d*][1,3]dioxol-6-ol 13

Following the above procedure, **12b** (3.7 g, 12.1 mmol) was reduced with $NaBH_4$ (0.54 g, 14.6 mmol) in MeOH (30 mL) to the corresponding alcohol **13** (3.21 g, 86%) as a white solid. Mp 117.1 °C; $[\alpha]_D^{25} = +37.7$ (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.92 (d, 3H, *J* = 6.9 Hz), 1.37 (s, 3H), 1.54 (s, 3H), 1.95 (m, 1H), 2.34 (d, 1H, *J* = 10.4 Hz), 2.43 (dd, 1H, *J* = 9.2, 13.6 Hz), 2.89 (dd, 1H, *J* = 4.1, 13.6 Hz), 3.52 (m, 1H), 3.78 (s, 3H), 3.80 (m, 1H), 4.55 (t,

1H, J = 4.8 Hz), 5.81 (d, 1H, J = 4.0 Hz), 6.80–7.10 (ABq, 4H, J = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.4 (q), 26.4 (q), 26.7 (q), 37.6 (d), 38.2 (t), 55.1 (q), 73.7 (d), 78.9 (d), 83.0 (d), 103.4 (d), 112.2 (s), 113.5 (d), 130.3 (d), 132.1 (s), 157.8 (s). Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.04; H, 7.97.

4.1.6. (3′*R*,5*R*,6*R*,6′*R*)-6-(Benzyloxy)-5-((*S*)-1-(4-methoxyphenyl)propan-2-yl)-2,2-dimethyl-tetrahydrofuro-[3,2-*d*][1,3]dioxole 14

Sodium hydride (0.74 g, 60% in mineral oil, 18.7 mmol) was added to a stirred solution of **13** (4.8 g, 15.6 mmol) in THF (40 mL) at 0 °C under nitrogen. After 2 h, BnBr (4.32 mL, 17.0 mmol) was introduced and stirring continued at room temperature for an additional 1 h, at which time cold water was added and layers separated. The organic layer was dried over Na_2SO_4, concentrated, and the crude product was purified on silica gel by using ethyl acetate/light petroleum (1:9) to afford **14** (5.88 g, 94%) as a colorless liquid. $[\alpha]_D^{25} = +72.4$ (c 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.74 (d, 3H, J = 6.8 Hz), 1.35 (s, 3H), 1.54 (s, 3H), 1.91 (m, 1H), 2.39 (dd, 1H, J = 9.0, 13.6 Hz), 2.76 (dd, 1H, J = 6.4, 13.6 Hz), 3.57 (dd, 1H, J = 4.4, 9.1 Hz), 3.78 (s, 3H), 3.97 (dd, 1H, J = 3.5, 9.1 Hz), 4.51–4.78 (ABq, 2H, J = 12.2 Hz), 4.54 (t, 1H, J = 4.0 Hz), 5.68 (d, 1H, J = 4.0 Hz), 6.80–7.07 (ABq, 4H, J = 8.4 Hz), 7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.4 (q), 26.7 (q), 35.7 (d), 39.0 (t), 55.0 (q), 71.6 (t), 77.2 (d), 78.2 (d), 79.5 (d), 103.6 (d), 112.5 (s), 113.5 (d), 127.9 (d), 128.3 (d), 130.0 (d), 132.5 (s), 137.5 (s), 157.7 (s). Anal. Calcd for $C_{24}H_{30}O_5$: C, 72.34; H, 7.59. Found: C, 72.38; H, 7.77.

4.1.7. (4*S*,5*R*,6*R*,7*S*,*E*)-Ethyl-5-(benzyloxy)-4,6-dihydroxy-8-(4-methoxyphenyl)-7-methyloct-2-enoate 6

A stirred solution of **14** (2.0 g, 5.03 mmol) in THF/H_2O (3:1, 20 mL), 6 M HCl (15 mL), and catalytic amount of H_2SO_4 (2 drops) was heated at reflux for 30 min. Solid $NaHCO_3$ was added to quench the reaction. THF was removed, partitioned between ethyl acetate (70 mL) and water (30 mL). The organic layer was separated, washed with water, brine, dried over Na_2SO_4, and concentrated to give a colorless viscous liquid (1.66 g, 92%), which was used as such for the next reaction. The crude lactol (1.66 g, 4.2 mmol) was dissolved in anhydrous toluene (30 mL) and to it was added (ethoxycarbonylmethylene)-triphenylphosphorane (2.77 g, 5.57 mmol) in toluene (25 mL). The reaction mixture was refluxed for 2 h. The solvent was evaporated and purified on silica gel by using ethyl acetate/light petroleum (1:4) to give **6** (1.75 g, 88%) as a viscous liquid. $[\alpha]_D^{25} = +14.9$ (c 3.3, MeOH); IR (neat, cm^{-1}) 3449, 3064, 3030, 2964, 2934, 1782, 1717, 1655, 1611, 1583, 1512, 1456, 1247, 1178, 1037, 755, 699; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.83 (d, 3H, J = 6.7 Hz), 1.28 (t, 3H, J = 7.1 Hz), 2.17 (m, 1H), 2.49 (m, 1H), 2.64 (m, 1H), 3.04 (br, 1H), 3.45 (dd, 1H, J = 5.1, 8.2 Hz), 3.71 (m, 1H), 3.78 (s, 3H), 4.18 (q, 2H, J = 7.2 Hz), 4.59–4.60 (ABq, 2H, J = 11.1 Hz), 4.54 (merged, 1H), 6.13 (dd, 1H, J = 1.9, 15.7 Hz), 6.78–7.04 (ABq, 4H, J = 8.6 Hz), 7.08 (dd, 1H, J = 4.4, 15.7), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 12.4 (q), 14.0 (q), 35.9 (d), 39.4 (t), 54.9 (q), 60.2 (t), 72.6 (d), 73.5 (t), 74.7 (d), 81.9 (d), 113.6 (d), 120.8 (d), 127.7 (d), 127.9 (d), 128.1 (d), 128.2 (d), 129.8 (d), 132.6 (s), 137.6 (s), 147.5 (d), 157.7 (s), 166.5 (s). Anal. Calcd for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 69.88; H, 7.67.

4.1.8. (*S*)-5-((1*R*,2*R*,3*S*)-1-(Benzyloxy)-2-hydroxy-4-(4-methoxyphenyl)-3-methylbutyl)-dihydrofuran-2(3*H*)-one 5

Compound **6** (1.6 g, 3.7 mmol) in MeOH (15 mL) was hydrogenated at balloon pressure using Raney Ni. After 2 h, the reaction mixture was filtered through a short bed of Celite and treated with catalytic amount of p-TSA (0.05 g). After 2 h, the reaction mixture was neutralized with solid $NaHCO_3$, concentrated, and partitioned between ethyl acetate (70 mL) and water (30 mL). The organic layer was separated, dried over Na_2SO_4, concentrated, and purified on silica gel column chromatography using ethyl acetate/light petroleum (1:6) to afford **5** (1.22 g, 85%) as a colorless liquid. $[\alpha]_D^{25} = -4.8$ (c 3.6, MeOH); IR (neat, cm^{-1}) 3480, 3032, 2962, 2934, 2837, 1771, 1611, 1584, 1512, 1456, 1247, 1179, 1036, 752, 700, 682. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.84 (d, 3H, J = 6.8 Hz), 1.84 (m, 1H), 2.12 (m, 2H), 2.28 (m, 1H), 2.47 (m, 3H), 2.63 (dd, 1H, J = 6.7, 13.7 Hz), 3.51 (m, 1H), 3.77 (s, 3H), 3.83 (m, 1H), 4.52–4.68 (ABq, 2H, J = 10.9 Hz), 4.93 (ddd, 1H, J = 2.4, 6.7, 8.2 Hz), 6.80–7.04 (ABq, 4H, J = 8.6 Hz), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 12.5 (q), 21.2 (t), 28.4 (t), 35.8 (d), 39.3 (t), 54.9 (q), 72.7 (d), 74.5 (t), 79.4 (d), 81.5 (d), 113.7 (d), 127.5 (d), 127.7 (d), 127.9 (d), 128.1 (d), 128.2 (d), 129.7 (d), 132.2 (s), 137.6 (s), 157.8 (s), 177.6 (s). Anal. Calcd for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.83; H, 7.39.

4.1.9. (*S*)-5-((1*R*,3*S*)-1-(Benzyloxy)-4-(4-methoxyphenyl)-3-methylbutyl)-dihydrofuran-2(3*H*)-one 15

A solution of **5** (1.1 g, 2.9 mmol) and 1,1′-thiocarbonyl diimidazole (0.62 g, 3.4 mmol) in toluene (20 mL) was heated at reflux for 6 h. After completion of the reaction, the reaction mixture was brought to room temperature. TBTH (1 mL, 3.4 mmol) and catalytic amount of AIBN (0.02 g) were added to the reaction mixture, degassed with argon, and heated at reflux again for 2 h. The reaction mixture was concentrated, and partitioned between ethyl acetate (50 mL) and water (20 mL). The organic layer was separated, washed with water, brine, dried over Na_2SO_4, concentrated and purified on silica gel by using ethyl acetate/light petroleum (1:9) to give **15** (0.85 g, 80%) as a colorless liquid. $[\alpha]_D^{25} = +7.5$ (c 1.25, MeOH); IR (neat, cm^{-1}) 3064, 3018, 2956, 2929, 2871, 1774, 1612, 1583, 1512, 1456, 1248, 1276, 1179, 1036, 756, 698, 667; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.83 (d, 3H, J = 6.5 Hz), 1.09 (ddd, 1H, J = 3.8, 9.3, 13.5 Hz), 1.59 (ddd, 1H, J = 4.0, 9.3, 13.5 Hz), 1.89 (m, 1H), 2.17 (m, 2H), 2.38–2.59 (m, 4H), 3.77 (s, 3H), 3.84 (m, 1H), 4.45 (m, 1H), 4.50–4.62 (ABq, 2H, J = 11.24 Hz), 6.79–7.10 (ABq, 4H, J = 8.61 Hz), 7.3 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.3 (q), 21.5 (t), 28.2 (t), 31.2 (d), 37.9 (t), 43.0 (t), 54.9 (q), 73.7 (t), 77.4 (d), 82.6 (d), 113.6 (d), 127.6 (d), 127.8 (d), 128.2 (d), 129.8 (d), 132.3 (s), 138.1 (s), 157.8 (s), 176.6 (s). Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.86; H, 7.68.

4.1.10. (3*R*,5*S*)-5-((1*R*,3*S*)-1-(Benzyloxy)-4-(4-methoxyphenyl)-3-methylbutyl)-3-methyl-dihydrofuran-2(3*H*)-one 4

To a stirred solution of **15** (0.76 g, 2.06 mmol) in THF (20 mL) at −78 °C, was added LiHMDS (2.06 mL, 1 M solution in THF, 2.06 mmol). After 1 h, MeI (0.13 mL, 2.06 mmol) was added and the reaction mixture was stirred for an additional 1 h at −78 °C. The reaction was quenched by saturated aqueous NH_4Cl solution (5 mL) and extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, concentrated, and the crude product was purified on silica gel using ethyl acetate/light petroleum (1:9) to afford **4** (0.66 g, 84%) as a colorless liquid. $[\alpha]_D^{25} = +13.3$ (c 1, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.85 (d, 3H, J = 6.6 Hz), 1.09 (ddd, 1H, J = 3.9, 9.4, 13.4 Hz), 1.23 (d, 3H, J = 7.4 Hz), 1.60 (ddd, 1H, J = 4.1, 9.0, 13.4 Hz), 1.80 (ddd, 1H, J = 8.6, 12.8, 17.2 Hz), 1.88 (m, 1H), 2.38 (dd, 1H, J = 7.9, 13.5 Hz), 2.43 (ddd, 1H, J = 3.8, 9.6, 12.9 Hz), 2.53 (dd, 1H, J = 6.4, 13.5 Hz), 2.72 (m, 1H), 3.77 (s, 3H), 3.81 (dt, 1H, J = 3.4, 6.6, 9.0 Hz), 4.40 (dt, 1H, J = 3.4, 6.4, 8.6 Hz), 4.47–4.58 (ABq, 2H, J = 11.2 Hz), 6.79–7.00 (ABq, 4H, J = 8.5 Hz), 7.3 (m, 5H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 16.5 (q), 19.5 (q), 30.0 (t), 31.4 (d), 34.2 (d), 38.2 (t), 43.2 (t), 55.1 (q), 74.1 (t), 77.8 (d), 80.5 (d), 113.6 (d), 127.8 (d), 128.1 (d), 128.4 (d), 129.9 (d), 132.4 (s), 138.0 (s), 157.9 (s), 180.0 (s). Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.48; H, 8.02.

4.1.11. (3*R*,5*S*)-5-((1*R*,3*S*)-1-Hydroxy-4-(4-methoxy-phenyl)-3-methylbutyl)-3-methyl-dihydrofuran-2(3*H*)-one 16

Compound **4** (0.6 g, 1.57 mmol) in MeOH (10 mL) was hydrogenated by a catalytic amount of 10% Pd/C (0.03 g) at 50 psi. After 1 h, the reaction mixture was filtered through a small bed of Celite, concentrated, and purified on silica gel column chromatography using ethyl acetate/light petroleum (1:4) to obtain **16** (0.42 g, 92%) as a white solid which on recrystallization (ethyl acetate/petroleum ether) gave a crystalline solid. Mp 80.5°; $[\alpha]_D^{25} = +38.0$ (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 0.88 (d, 3H, *J* = 6.6 Hz), 1.07 (ddd, 1H, *J* = 2.7, 10.2, 13.2 Hz), 1.23 (d, 3H, *J* = 7.3 Hz), 1.48 (ddd, 1H, *J* = 3.7, 10.6, 13.2 Hz), 1.78 (ddd, 1H, *J* = 8.2, 12.8, 16.2 Hz), 2.00 (m, 1H), 2.34–2.62 (m, 3H), 2.65 (m, 1H), 3.04 (br s, 1H), 3.77 (s, 3H), 4.00 (d, 1H, *J* = 10.5 Hz), 4.31 (m, 1H), 6.79–7.04 (ABq, 4H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 16.3 (q), 18.8 (q), 29.6 (t), 31.0 (d), 34.4 (d), 38.9 (t), 43.3 (t), 55.0 (q), 69.4 (d), 81.2(d), 113.6 (d), 129.9 (d), 132.6 (s), 157.8 (s), 180.6 (s). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.75; H, 8.15.

4.1.12. (3*R*,5*S*)-5-((1*S*,3*S*)-1-Azido-4-(4-methoxyphenyl)-3-methylbutyl)-3-methyl-dihydrofuran-2(3*H*)-one 3

A solution of **16** (0.4 g, 1.4 mmol), Et_3N (0.23 mL, 1.6 mmol), and MsCl (0.13 mL, 1.6 mmol) in CH_2Cl_2 (10 mL) was stirred under nitrogen at 0 °C. After 1 h, the reaction mixture was partitioned between CH_2Cl_2 and water. The organic layer was separated, washed with water, brine, dried over Na_2SO_4, and concentrated to afford the mesylated product as a brownish liquid. The crude compound was taken with LiN_3 (0.27 g, 5.6 mmol) in DMF (5 mL), and the reaction mixture was heated at 60 °C for 4 h. After completion of the reaction, the reaction mixture was partitioned between diethyl ether and water. The organic layer was separated, washed with water, brine, dried over Na_2SO_4, concentrated, and purified on silica gel using ethyl acetate/light petroleum (1:9) to give **3** (0.36 g, 82%) as a light yellow liquid. $[\alpha]_D^{25} = +53.6$ (*c* 1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) 2932, 2851, 2108, 1778, 1612, 1583, 1513, 1457, 1380, 1248, 1178, 1034, 920, 807, 754; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.92 (d, 3H, *J* = 6.6 Hz), 1.27 (d, 3H, *J* = 7.4 Hz), 1.61 (m, 2H), 1.94 (m, 2H), 2.29 (m, 2H), 2.75 (m, 2H), 3.33 (m, 1H), 3.78 (s, 3H), 4.42 (p, 1H, *J* = 4.3, 4.0, 8.3 Hz), 6.80–7.04 (ABq, 4H, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 16.4 (q), 20.0 (q), 32.1 (d), 32.8 (t), 33.7 (d), 37.2 (t), 42.2 (t), 55.1 (q), 63.0 (d), 78.5 (d), 113.8 (d), 130.0 (d), 132.0 (s), 158.1 (s), 179.0 (s). Anal. Calcd for $C_{17}H_{23}N_3O_3$: C, 64.33; H, 7.30; N, 13.24. Found: C, 64.52; H, 7.57; N, 13.20.

4.1.13. (2*R*,4*S*,5*S*,7*S*)-5-Azido-N-butyl-4-hydroxy-8-(4-methoxyphenyl)-2,7-dimethyloctanamide 17

Compound **3** (0.15 g, 0.47 mmol) was treated with a 33% w/v solution of *n*-$BuNH_2$ in dry ethanol (1.7 g. *n*-$BuNH_2$ in 5 mL dry ethanol) under nitrogen. After 2 h, the reaction mixture was concentrated, partitioned between ethyl acetate and water. The organic layer was washed with water, brine, dried over Na_2SO_4, concentrated, and purified on silica gel column by using ethyl acetate/light petroleum (1:6) to afford **17** (0.153 g, 83%) as a colorless liquid. $[\alpha]_D^{25} = -10.5$ (*c* 1, $CHCl_3$); IR (neat, cm^{-1}) 3316, 2931, 2873, 2105, 1634, 1549, 1512, 1463, 1376, 1247, 1178, 1037, 850, 805, 754; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.89 (d, 3H, *J* = 6.6 Hz), 0.92 (t, 3H, *J* = 7.0 Hz), 1.19 (d, 3H, *J* = 6.9 Hz), 1.33 (m, 3H), 1.45 (m, 2H), 1.62 (m, 4H), 1.88 (m, 1H), 2.28 (dd, 1H, *J* = 8.6, 13.4 Hz), 2.57 (m, 1H), 2.70 (dd, 1H, *J* = 5.3, 13.4 Hz), 3.20 (m, 3H), 3.55 (m, 1H), 3.79 (s, 3H), 5.91 (br s, 1H), 6.83–7.07 (ABq, 4H, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 13.7 (q), 18.1 (q), 20.0 (t), 20.1 (q), 31.6 (t), 32.2 (d), 37.7 (d), 37.8 (t), 38.3 (t), 39.2 (t), 41.9 (t), 55.2 (q), 65.4 (d), 71.1 (d), 113.7 (d), 130.0 (d), 132.6 (s), 157.8 (s), 176.4 (s). Anal. Calcd for $C_{21}H_{34}N_4O_3$: C, 64.59; H, 8.78; N, 14.35. Found: C, 64.46; H, 8.95; N, 14.19.

4.1.14. *tert*-Butyl (2*S*,4*S*,5*S*,7*R*)-8-(butylamino)-5-hydroxy-1-(4-methoxyphenyl)-2,7-dimethyl-8-oxooctan-4-ylcarbamate 18

Compound **17** (0.065 g, 0.17 mmol) in methanol (5 mL) was hydrogenated by catalytic amount of 10% Pd/C (0.01 g) at 1 atm for 3 h. After completion of the reaction, Boc_2O (0.05 mL, 0.2 mmol) was added to the reaction mixture and stirred at room temperature for 1 h. The reaction mixture was passed through a short Celite plug, concentrated, and purified on silica gel column chromatography (1:9) to give **18** (0.071 g, 95%) as a viscous liquid. $[\alpha]_D^{25} = -17.6$ (*c* 1, $CHCl_3$); IR (neat, cm^{-1}) 3438, 3346, 3017, 2964, 2933, 1696, 1646, 1512, 1456, 1367, 1247, 1216, 1176, 1039, 756, 668; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.78 (2d, 3H, *J* = 6.8 Hz), 0.86 (2t, 3H, *J* = 7.3 Hz), 1.10 (d, 3H, *J* = 6.9 Hz), 1.2 (m, 2H), 1.27 (m, 2H), 1.39 (s, 9H), 1.40 (m, 4H), 1.59 (m, 2H), 1.68 (br, 1H), 2.10 (dd, 0.8H, *J* = 9.3, 13.4 Hz), 2.24 (m, 0.2H), 2.33 (m, 0.2H), 2.48 (m, 0.8H), 2.63 (m, 0.2H), 2.72 (dd, 0.8H, *J* = 4.5, 13.4 Hz), 2.92 (m, 0.2H), 3.09 (m, 0.8H), 3.19 (m, 1H), 3.55 (m, 0.8H), 3.61 (m, 0.8H), 3.70 (2s, 3H), 3.78 (m, 0.2H), 3.88 (m, 0.2H), 4.43 (d, 0.2H, *J* = 9.6 Hz), 4.78 (d, 0.8H, *J* = 9.6 Hz), 6.03 (br s, 1H), 6.72–6.98 (ABq, 4H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): Major rotamer: δ 13.7 (q), 17.1 (q), 19.8 (q), 20.0 (t), 28.4 (q), 31.6 (t), 32.1 (d), 37.6 (d), 38.5 (t), 39.2 (t), 40.0 (t), 41.7 (t), 52.0 (d), 55.1 (q), 70.2 (d), 79.2 (s), 113.4 (d), 130.1 (d), 133.2 (s), 156.5 (s), 157.6 (s), 176.9 (s); Minor rotamer: δ 13.4 (q), 16.6 (q), 19.7 (q), 19.9 (t), 28.3 (q), 32.4 (t), 34.3 (d), 37.0 (d), 38.7 (t), 39.4 (t), 40.1 (t), 41.5 (t), 51.3 (d), 58.9 (q), 70.5 (d), 80.0 (s), 113.5 (d), 130.0 (d), 132.7 (s), 156.0 (s), 157.7 (s), 174.6 (s). Anal. Calcd for $C_{26}H_{44}N_2O_5$: C, 67.21; H, 9.54; N, 6.03. Found: C, 67.14; H, 9.59; N, 6.10.

4.1.15. Hydrochloride salt of (2*R*,4*S*,5*S*,7*S*)-5-amino-*N*-butyl-4-hydroxy-8-(4-methoxyphenyl)-2,7-dimethyloctanamide 2

To a stirred solution of **18** (0.028 g, 0.07 mmol) in CH_2Cl_2/Et_2O (2:2 mL) at rt, dry HCl gas was passed for 15 min. The suspension was filtered and the residue was washed with CH_2Cl_2. The compound was dried to get compound **2** as a white solid. (0.022 g, 92%) $[\alpha]_D^{25} = +6.2$ (*c* 0.5, H_2O). ^1H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, 3H, *J* = 7.4 Hz), 0.93 (d, 3H, *J* = 6.5 Hz), 1.18 (d, 3H, *J* = 7.0 Hz), 1.33 (m, 2H), 1.48 (m, 4H), 1.79 (m, 2H), 2.52 (dd, 1H, *J* = 7.5, 13.6 Hz), 2.64 (m, 2H), 3.21 (m, 3H), 3.52 (ddd, 1H, *J* = 2.3, 4.5, 10.54 Hz), 3.86 (s, 3H), 7.00–7.25 (ABq, 4H, *J* = 8.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.7 (q), 19.7 (q), 20.3 (q), 21.1 (t), 32.3 (t), 32.9 (d), 37.9 (t), 39.2 (t), 39.3 (d), 40.6 (t), 43.2 (t), 56.1 (d), 57.1 (q), 69.4 (d), 115.7 (d), 132.3 (d), 134.9 (s), 158.9 (s), 179.9 (s). Anal. Calcd for $C_{21}H_{37}N_2O_3Cl$ (400.99): Calcd. C, 62.90; H, 9.30, N, 6.99, Cl, 8.84. Found C, 62.76; H, 9.59, N, 7.16, Cl, 8.69.

4.1.16. *tert*-Butyl (2*R*,4*S*,5*S*,7*R*)-8-(butylamino)-5-hydroxy-1-(4-methoxyphenyl)-2,7-dimethyl-8-oxooctan-4-ylcarbamate 19

Following the same sequence of reaction procedures as of **7**, 7-*epi* isomer **19** was obtained from **13** in 11 steps (24.3% over all yield). $[\alpha]_D^{25} = -17.9$ (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 0.90 (d, 3H, *J* = 6.4 Hz), 0.91 (t, 3H, *J* = 7.3 Hz), 1.17 (d, 3H, *J* = 6.9 Hz), 1.26 (m, 2H), 1.33 (m, 2H), 1.43 (s, 9H), 1.48 (m, 2H), 1.59 (m, 1H), 1.66 (m, 1H), 1.77 (m, 1H), 2.39 (dd, 1H, *J* = 7.7, 13.3 Hz), 2.53 (dd, 1H, *J* = 6.3, 13.3 Hz), 3.17 (m, 1H), 3.26 (m, 1H), 3.57 (m, 2H), 3.79 (s, 3H), 4.64 (d, 1H, *J* = 9.5 Hz), 6.01 (b, 1H), 6.81–7.05 (ABq, 4H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.7 (q), 17.2 (q), 19.1 (q), 20.0 (t), 28.3 (q), 31.6 (t), 31.8 (d), 37.6 (d), 38.5 (t), 39.2 (t), 39.4 (t), 43.0 (t), 52.4 (d), 55.2 (q), 71.3 (d), 79.2 (s), 113.6 (d), 130.2 (d), 133.0 (s), 156.7 (s), 157.7 (s), 176.9 (s). Anal. Calcd for $C_{26}H_{44}N_2O_5$: C, 67.21; H, 9.54; N, 6.03. Found: C, 67.15; H, 9.65; N, 6.12.

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9. Crystal data for **7**: $C_{17}H_{24}O_5$, $M = 308.36$, crystal dimensions: $0.82 \times 0.26 \times 0.08$ mm, crystal system: monoclinic, space group: $P21$, $a = 10.2759(19)$, $b = 5.7656(11)$, $c = 14.152(3)$ Å, $\beta = 97.622\ (3)^\circ$, $V = 831.0(3)$ Å^3, $Z = 2$, $D_c = 1.232$ g cm^{-3}, $\mu = 0.090$ mm^{-1}, $F(000) = 332$, $2\theta_{max} = 51.00^\circ$, max. and min. transmission 0.9931 and 0.9299, 4337 reflections collected, 2635 unique 2444 observed $[I > 2\sigma(I)]$ reflection, 295 refined parameters, $S = 1.050$, R value 0.0380, $wR_2 = 0.0926$ (all data $R = 0.0411$, $wR_2 = 0.0944$), max. and min. residual electron densities +0.172 and −0.123 e Å^{-3}. Additional crystallographic details CCDC 269453 (atomic co-ordinates and equivalent isotropic displacement coefficients) have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
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11. Crystal data for **16**: $C_{17}H_{24}O_4$, $M = 292.36$, crystal dimensions: $0.67 \times 0.60 \times 0.10$ mm, crystal system: orthorhombic, space group: $P212121$, $a = 5.5146(12)$, $b = 9.2177(19)$, $c = 33.537(7)$ Å, $V = 1704.8(6)$ Å^3, $Z = 4$, $D_c = 1.139$ g cm^{-3}, $\mu = 0.080$ mm^{-1}, $F(000) = 632$, $2\theta_{max} = 51.00^\circ$, max. and min. transmission 0.9917 and 0.9481, 8848 reflections collected, 3165 unique 1931 observed $[I > 2\sigma(I)]$ reflection, 194 refined parameters, $S = 1.044$, R value 0.0502, $wR_2 = 0.1294$ (all data $R = 0.0887$, $wR_2 = 0.1453$), max. and min. residual electron densities +0.127 and −0.119 e Å^{-3}. Additional crystallographic details CCDC 269454 (atomic co-ordinates and equivalent isotropic displacement coefficients) have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.
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13. Crystal data for **19**: $C_{26}H_{44}N_2O_5$, $M = 464.63$, crystal dimensions: $0.87 \times 0.09 \times 0.08$ mm, crystal system: orthorhombic, space group: $P212121$, $a = 9.474(4)$, $b = 10.893(5)$, $c = 27.787(12)$ Å, $V = 2867(2)$ Å^3, $Z = 4$, $D_c = 1.076$ g cm^{-3}, $\mu = 0.074$ mm^{-1}, $F(000) = 1016$, $2\theta_{max} = 50.00^\circ$, max. and min. transmission 0.9943 and 0.9389, 12,036 reflections collected, 5031 unique, 2029 observed $[I > 2\sigma(I)]$ reflection, 307 refined parameters, $S = 0.957$, R value 0.0670, $wR_2 = 0.1246$ (all data $R = 0.1949$, $wR_2 = 0.1575$), maximum and minimum residual electron densities +0.190 and −0.126 e Å^{-3}. Additional crystallographic details CCDC 269452 (atomic co-ordinates and equivalent isotropic displacement coefficients) have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. All the data were corrected for Lorentzian, polarization and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97 (G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Gottingen, Germany, 1997) was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model.