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Asymmetric synthesis of homo-apioneplanocin A from D-ribose

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Abstract—Homo-apioneplanocin A was efficiently synthesized via stereoselective hydroxymethylation, regio- and chemoselective hydroboration, and chemoselective oxidation as key steps from D-ribose.

1. Introduction

(−)-Neplanocin A (NPA), originally isolated from the culture filtrate of the soil fungus *Ampullariella regularis*,[1] is a carbocyclic nucleoside in which a methylene group replaces the oxygen atom in the furanose ring and one of the most potent *S*-adenosylhomocysteine (AdoHcy) hydrolase inhibitors.[2] NPA has been reported to possess a significant antiviral effect[3] correlating with the inhibition of AdoHcy hydrolase, but it was too cytotoxic to be a clinically useful antiviral agent.[2b,4]

Moreover, it is known to undergo deamination by adenosine deaminase to the biologically inactive compound, the inosine congener.[5]

Apionucleoside has a unique sugar moiety, in that the 4′-hydroxymethyl group of the sugar is shifted to the C3′-position.[6–9] Apio-ddA has been reported to show potent anti-AIDS activity comparable to that of the parent nucleoside, 2′,3′-dideoxyadenosine (ddA) and better stability of the glycosidic bond under acidic conditions than ddA.[8b] In order to search for potent inhibitors of AdoHcy hydrolase, we have recently synthesized the apioneplanocin A (apio-NPA),[10] which combines the structural characteristics of NPA and apionucleoside, but this compound showed neither a significant antiviral activity nor inhibitory activity against AdoHcy hydrolase.

However, since another NPA-modified compound, 6′-homoneplanocin A[11] was reported to have a significant inhibitory activity against AdoHcy hydrolase, we designed the homo-apioneplanocin A (HANPA, **1**), which combined apioneplanocin A and 6′-homoneplanocin A as a potential inhibitor of AdoHcy hydrolase (Fig. 1). Herein, we wish to describe the asymmetric synthesis of HANPA (**1**) from D-ribose via stereoselective hydroxymethylation, regio- and chemoselective hydroboration, and chemoselective oxidation as key steps.

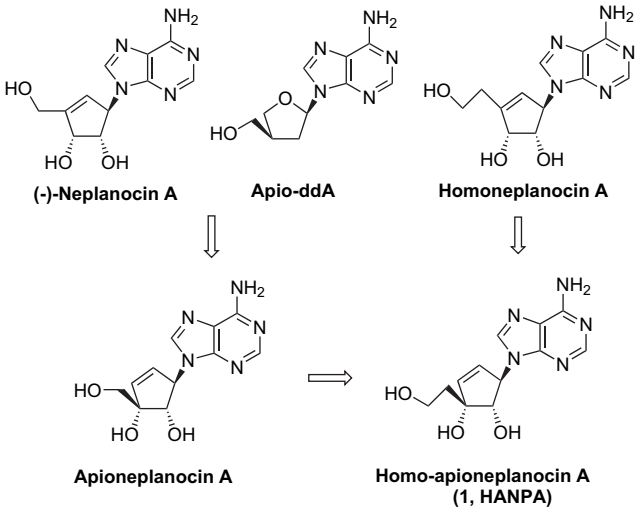

Figure 1. The rational for the design of the desired nucleoside, HANPA (**1**).

2. Results and discussion

The synthetic strategy of the target compound **1** is outlined in Scheme 1. It was envisioned that dienyl diols **4**[10] could

Keywords: Homo-apioneplanocin A; Stereoselective hydroxymethylation; Chemoselective hydroboration; Chemoselective oxidation.
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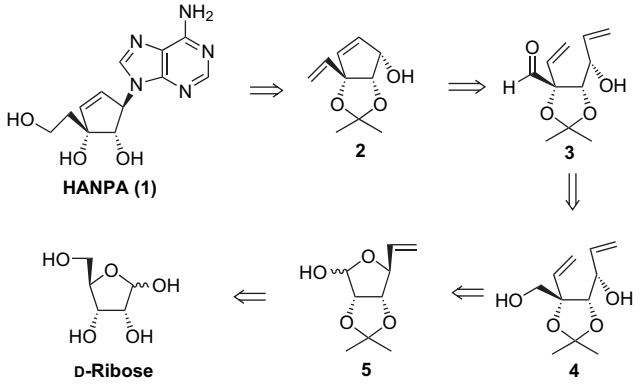
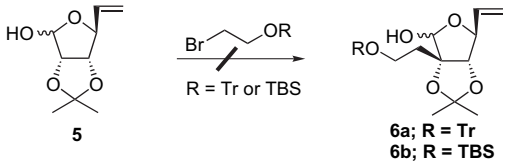
be an appropriate intermediate, efficiently synthesized by our laboratory, for the final compound.



Scheme 1. Retrosynthetic analysis of the desired nucleoside, HANPA (**1**).

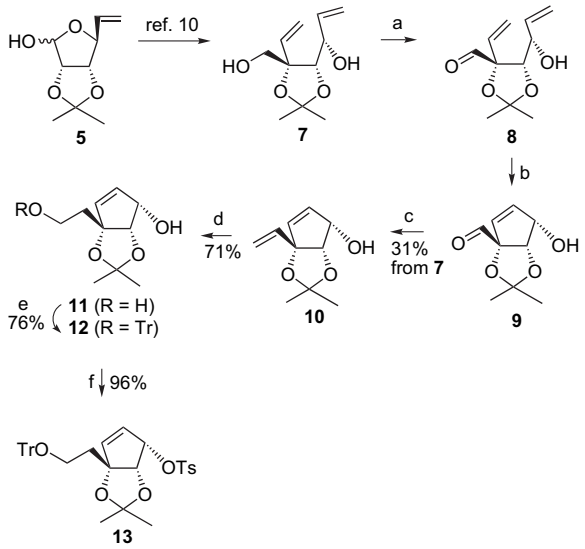
Our initial approach was to introduce the hydroxyethyl group at C3-position of **5** directly in the stereoselective manner, as depicted in Scheme 2. Treatment of **5** with 2-trityloxyethyl bromide and 2-*tert*-butyldimethylsilyloxyethyl bromide in the presence of various bases such as LDA, LiHMDS, and K_2CO_3 at various temperatures such as −78 and 80 °C in THF failed to produce the desired product **6** or afforded **6** in less than 5% yield.



Scheme 2. Attempted methods for the direct introduction of hydroxyethyl functional group.

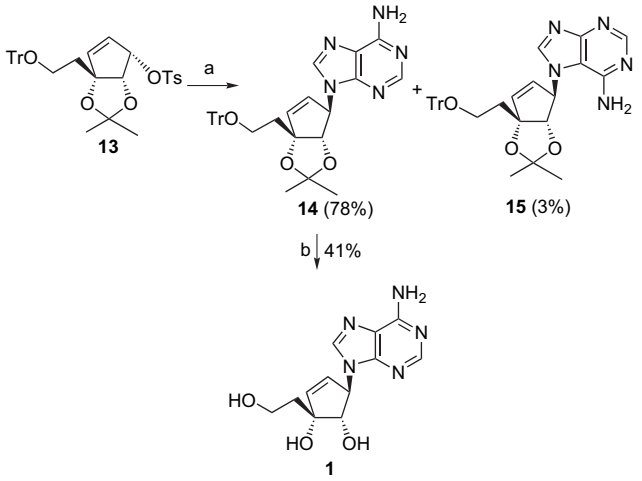
Thus, another route including stereoselective hydroxymethylation, regioselective oxidation, Wittig reaction, and chemoselective hydroboration was employed to introduce hydroxyethyl group stereoselectively at C3-position (Scheme 3). Lactol **5** was converted to diol **7** as a single diastereoisomer according to our previously reported procedure.[10]

Chemoselective oxidation of diol **7** to aldehyde **8** was achieved by treating with TEMPO, TBACl, and NCS under pH 8.6.[12] Ring-closing metathesis (RCM)[13] of **8** with second generation Grubbs catalyst afforded cyclopentenal **9**. However, RCM reaction of **7** gave the cyclopentene diol in good yield, but chemoselective oxidation of the diol failed to give the desired product **9**. Wittig reaction of **9** under the standard conditions gave vinylcyclopentenol **10**. Various hydroboration reagents were attempted to accomplish regio- and chemoselective hydroboration. Hydroboration of **10** using catecholborane and Wilkinson catalyst $Rh(PPh_3)_3Cl$ (rhodium-catalyzed olefin hydroboration) in THF[14] or 9-BBN in THF did not give the desired alcohol **11**, while treatment with Sia_2BH gave the desired product **11** in good yield (71%) after oxidation with sodium perborate. Selective protection of the primary hydroxyl group of **11** with a bulky trityl group followed by tosylation of the resulting **12** gave the glycosyl donor **13**.



Scheme 3. Reagents and conditions: (a) TEMPO, TBACl, NCS, aqueous $NaHCO_3$ and K_2CO_3 (pH=8.6), CH_2Cl_2, rt, 3 h; (b) second generation Grubbs catalyst, CH_2Cl_2, rt, 5 h; (c) $MePh_3PBr$, KO*t*-Bu, THF, rt, 12 h; (d) (i) Sia_2BH, THF, from 0 °C to rt, 16 h; (ii) $NaBO_3 \cdot H_2O$, rt, 12 h; (e) TrCl, pyridine, DMAP, rt, 24 h; (f) TsCl, DMAP, CH_2Cl_2, rt, 24 h.

Condensation of **13** with adenine in the presence of K_2CO_3 and 18-crown-6 in DMF afforded the N-9 isomer **14** as a major product (78%) along with its N-7 isomer **15** (3%) after the separation by silica gel column chromatography (Scheme 4). The regio-isomers **14** and **15** were easily assigned based on the comparison with UV literature data.[15] Removal of the protecting groups of **14** under acidic conditions produced the desired product **1**.



Scheme 4. Reagents and conditions: (a) adenine, K_2CO_3, 18-crown-6, DMF, 80 °C, 12 h; (b) 1% HCl, MeOH, rt, 12 h.

Inhibitory activity of AdoHcy hydrolase by compound **1** was measured using pure recombinant enzyme obtained from human placenta. Compound **1** did not exhibit significant inhibitory activity against AdoHcy hydrolase, although we expected the hydroxyethyl side chain of **1** to induce the favorable binding to AdoHcy hydrolase. This lack of enzyme inhibitory activity might be attributed to the presence of the tertiary hydroxyl group at the C3-position, which should be oxidized by cofactor-bound NAD^+.

3. Conclusions

Asymmetric synthesis of homo-apioneplanocin A (**1**, HANPA) was efficiently achieved using stereoselective hydroxylation, chemoselective oxidation, and regio- and chemoselective hydroboration as key steps from D-ribose. To our best knowledge, homo-apioneplanocin A is the first example of carbocyclic nucleosides with unnatural homo-apio carbasugar.

4. Experimental

4.1. General

Melting points are uncorrected. NMR data were recorded on a 300, 400, and 500 MHz NMR spectrometer using tetramethylsilane (TMS) as an internal standard, and the chemical shifts are reported in parts per million (δ). Coupling constants are reported in Hertz. The abbreviations used are as follows: s (singlet), d (doublet), m (multiplet), dd (doublet of doublet), and br s (broad singlet). All the reactions described below were performed under argon or nitrogen atmosphere and monitored by thin layer chromatography (TLC, Silica gel 60 F_{254}). All anhydrous solvents were distilled over CaH_2 or Na/benzophenone prior to use.

4.1.1. (−)-(1*S*,2*S*,3*R*)-2,3-*O*-Isopropylidene-3-vinyl-4-cyclopentenol (10). A solution of diol **7** (3.09 g, 14.47 mmol), TEMPO (226 mg, 1.45 mmol), and tetrabutylammonium chloride (403 mg, 1.45 mmol) in methylene chloride (100 mL) and an aqueous solution (100 mL) of 0.5 M $NaHCO_3$ and 0.05 M K_2CO_3 were vigorously stirred at room temperature. After adding *N*-chlorosuccinimide (2.125 g, 15.9 mmol) to the mixture, the mixture was stirred at room temperature for 3 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate=3:1) to give **8** as a colorless oil, which was immediately used for the next step. To a stirred solution of **8** in CH_2Cl_2 (25 mL) was added second generation Grubbs catalyst (7 mg, 0.07 mmol) at room temperature and the reaction mixture was stirred at room temperature for 5 h and evaporated to give a brown residue. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate=1:3) to give cyclopentenal **9** as a colorless oil, which was immediately used for the next step. To a stirred suspension of CH_3PPh_3Br (6.058 g, 16.62 mmol) in THF (80 mL) was added potassium *tert*-butoxide (16.6 mL, 16.60 mmol, 1 M solution in THF) at 0 °C and the mixture was stirred at room temperature for 1 h . To this stirred solution was added a solution of cyclopentenal **9** in THF (30 mL) through a cannula at 0 °C, and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was partitioned between water and ethyl acetate and the organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate=3:1) to give diene **10** (826 mg, 31% over three steps) as a colorless oil: $[\alpha]_D^{25}$ −32.9 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.94 (dd, 1H, *J*=10.6, 17.3 Hz), 5.8 (td, 1H, *J*=0.8, 5.7 Hz), 5.75 (ddd, 1H, *J*=0.6, 1.6, 5.7 Hz), 5.24 (dd, 1H, *J*=1.1, 17.3 Hz), 5.15 (dd, 1H, *J*=1.1, 10.6 Hz), 4.61 (tdd, 1H, *J*=1.6, 5.1, 10.6 Hz), 4.43 (d, 1H, *J*=5.1 Hz), 2.64 (d, 1H, *J*=10.6 Hz), 1.42 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 137.9, 135.6, 134.0, 115.6, 112.6, 94.0, 82.6, 74.6, 27.8, 27.5; LRMS (ESI) *m/z* 205 $[M+Na]^+$; Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 66.04; H, 7.60.

4.1.2. (+)-(1*S*,2*S*,3*R*)-2,3-*O*-Isopropylidene-3-(2-hydroxy)-ethyl-4-cyclopentenol (11). 2-Methyl-2-butene (9.2 mL, 18.4 mmol, 2 M solution in THF) was added to borane–dimethyl sulfide (4.6 mL, 9.2 mmol, 2 M solution in THF) and the reaction mixture was stirred at 0 °C for 2.5 h. The resulting solution was added dropwise through a cannula to a stirred solution of **10** (712 mg, 3.91 mmol) in THF (5 mL) at 0 °C and the mixture was stirred at room temperature for 16 h. $NaBO_3 \cdot H_2O$ (1.512 g, 15.15 mmol) and H_2O (8 mL) were added carefully, and the mixture was stirred at room temperature for 12 h. The mixture was partitioned between water and CH_2Cl_2. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate=1:3) to give **11** (559 mg, 71%) as a white solid; mp 81.9 °C; $[\alpha]_D^{25}$ +20.1 (*c* 1.52, MeOH); ^{1}H NMR ($CDCl_3$) δ 5.84 (d, 1H, *J*=5.9 Hz), 5.81 (d, 1H, *J*=5.9 Hz), 4.62 (s, 1H), 4.49 (d, 1H, *J*=4.9 Hz), 3.79 (m, 1H), 3.71 (m, 1H), 2.87 (s, 1H), 2.74 (s, 1H), 1.97 (m, 2H), 1.44 (s, 3H), 1.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 135.0, 134.7, 111.9, 93.8, 82.1, 74.3, 59.2, 38.2, 27.9, 27.9; IR (KBr): 3395, 2922, 1646, 1372, 1105, 893, 615 cm^{-1}; LRMS (FAB) *m/z* 201 $[M+H]^+$; HRMS calcd for $C_{10}H_{17}O_4$ $[M+H]^+$: 201.1129, found: 201.1126; Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.61; H, 8.19.

4.1.3. (+)-(1*S*,2*S*,3*R*)-2,3-*O*-Isopropylidene-3-(2-triphenylmethyloxy)ethyl-4-cyclopentenol (12). A solution of cyclopentenol **11** (482 mg, 2.4 mmol), trityl chloride (1.338 g, 4.8 mmol), and 4-(dimethylamino)pyridine (61 mg, 0.5 mmol) in pyridine (15 mL) was stirred at room temperature for 24 h. The reaction mixture was partitioned between water and ethyl acetate and the organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate=5:1) to give **12** (807 mg, 76%) as a white solid; mp 135.8 °C; $[\alpha]_D^{25}$ +17.1 (*c* 2.57, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 15H), 5.64 (d, 1H, *J*=5.8 Hz), 5.58 (d, 1H, *J*=5.8 Hz), 4.55 (d, 1H, *J*=5.0 Hz), 4.47 (tdd, 1H, *J*=1.3, 5.0, 10.4 Hz), 3.23 (td, 1H, *J*=5.8, 11.4 Hz), 2.97 (m, 1H), 2.62 (d, 1H, *J*=10.4 Hz), 2.12 (ddd, 1H, *J*=6.0, 7.9. 14.1 Hz), 1.97 (td, 1H, *J*=5.6, 14.2 Hz), 1.33 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 144.0, 135.1, 135.1, 128.5, 127.8, 127.0, 111.4, 96.1, 93.3, 87.2, 82.1, 74.5, 60.0, 36.6, 28.0, 28.0; IR (KBr) 3543, 2986, 2931, 1489, 1448, 1376, 1221, 1066 cm^{-1}; LRMS (ESI) *m/z* 465 $[M+Na]^+$; Anal. Calcd for $C_{29}H_{30}O_4$: C, 78.71; H, 6.83. Found: C, 78.45; H, 6.81.

4.1.4. (−)-(1*S*,2*S*,3*R*)-2,3-*O*-Isopropylidene-3-(2-triphenylmethyloxy)ethyl-4-cyclopentenyl *p*-toluenesulfonate (13). To a stirred solution of **12** (473 mg, 1.07 mmol) and 4-(dimethylamino)pyridine (395 mg, 3.23 mmol) in CH_2Cl_2 (15 mL) was added TsCl (416 mg, 2.18 mmol). After being stirred at room temperature for 24 h, the reaction mixture was partitioned between water and CH_2Cl_2. The

organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate=3:1) to give tosylate **13** (614 mg, 96%) as a white solid; mp 133.4 °C; $[\alpha]_D^{25}$ −0.6 (*c* 1.18, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.41 (m, 19H), 5.67 (dd, 1H, *J*=1.6, 5.8 Hz), 5.42 (dd, 1H, *J*=0.9, 5.8 Hz), 5.16 (td, 1H, *J*=1.6, 5.4 Hz), 4.71 (d, 1H, *J*=4.9 Hz), 3.22 (td, 1H, *J*=4.9, 9.9 Hz), 2.80 (dt, 1H, *J*=3.9, 9.5 Hz), 2.48 (s, 3H), 2.15 (qd, 1H, *J*=4.6, 14.4 Hz), 1.89 (td, 1H, *J*=4.1, 14.4 Hz), 1.28 (s, 3H), 1.27 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 144.3, 143.7, 138.4, 129.7, 129.5, 128.4, 128.0, 127.9, 127.0, 111.8, 93.1, 87.3, 81.5, 81.5, 59.7, 36.1, 28.0, 27.6, 21.6; IR (KBr): 2927, 1597, 1449, 1368, 1179, 1073, 997 cm^{-1}; LRMS (ESI) *m/z* 619 $[M+Na]^+$.

4.1.5. (−)-(3*R*,4*S*,5*S*)-3,4-*O*-Isopropylidene-3-(2-triphenylmethyloxy)ethyl-5-(adenin-9-yl)-cyclopentene (14) and its N-7 isomer (15). A stirred suspension of adenine (36 mg, 0.26 mmol), 18-crown-6 (69 mg, 0.26 mmol), and K_2CO_3 (54 mg, 0.39 mmol) in DMF (2 mL) was heated at 80 °C for 30 min. To this clear solution was added a solution of tosylate **13** (77 mg, 0.13 mmol) in DMF (3 mL) at 80 °C and the reaction mixture was heated at 80 °C for 12 h. The reaction mixture was cooled to room temperature and partitioned between water and CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol=30:1) to give **14** (57 mg, 78%) as a white solid and **15** (2 mg, 3%).

Compound **14**: mp 77.1 °C; $[\alpha]_D^{25}$ −52.9 (*c* 0.1, $CHCl_3$); UV ($CHCl_3$) λ_{max} 260 nm; ^1H NMR ($CDCl_3$) δ 8.44 (s, 1H), 7.62 (s, 1H), 7.24 (m, 15H), 6.29 (dd, 1H, *J*=1.2, 5.7 Hz), 5.94 (dd, 1H, *J*=2.0, 5.7 Hz), 5.64 (br s, 2H), 5.57 (s, 1H), 4.49 (s, 1H), 3.29 (t, 2H, *J*=6.4 Hz), 2.05 (t, 2H, *J*=6.5 Hz), 1.39 (s, 3H, CH_3), 1.22 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 155.3, 153.4, 150.0, 143.9, 143.2, 138.1, 128.5, 127.7, 127.0, 126.7, 112.2, 93.8, 87.5, 87.2, 65.5, 59.7, 37.9, 28.0, 27.8; IR (KBr) 2922, 1728, 1642, 1462, 1285, 1072, 615 cm^{-1}; LRMS (ESI) *m/z* 560 $[M+H]^+$; Anal. Calcd for $C_{34}H_{33}N_5O_3$: C, 72.97; H, 5.94; N, 12.51. Found: C, 72.74; H, 5.87; N, 12.81.

Compound **15**: UV ($CHCl_3$) λ_{max} 279 nm; ^1H NMR ($CDCl_3$) δ 8.17 (s, 1H), 7.89 (s, 1H), 7.22 (m, 15H), 6.41 (d, 1H, *J*=5.0 Hz), 5.93 (m, 2H), 4.56 (s, 1H), 3.29 (t, 2H, *J*=6.2 Hz), 1.99 (t, 2H, *J*=6.0 Hz), 1.25 (s, 6H).

4.1.6. (−)-(1*R*,2*S*,3*S*)-1-(2-Hydroxy)ethyl-3-(adenin-9-yl)-4-cyclopentene-1,2-diol (1). A solution of **14** (59 mg, 0.11 mmol) in a mixture of MeOH (15 mL) and acetyl chloride (0.2 mL) was stirred at room temperature for 12 h. The reaction mixture was neutralized with Et_3N and evaporated. The resulting residue was purified by silica gel column chromatography (methylene chloride/methanol=5:1) to give **1** (12 mg, 41%) as a white solid; mp 198.5 °C; $[\alpha]_D^{25}$ −25.8 (*c* 0.1, MeOH); UV ($CHCl_3$) λ_{max} 260 nm; ^1H NMR (MeOH-d_4) δ 8.17 (s, 1H), 8.14 (s, 1H), 6.22 (dd, 1H, *J*=2.4, 6.3 Hz), 6.06 (dd, 1H, *J*=1.7, 6.3 Hz), 5.50 (td, 1H, *J*=2.0, 6.4 Hz), 4.28 (d, 1H, *J*=6.5 Hz), 3.83 (t, 2H, *J*=6.6 Hz), 1.97 (m, 2H); ^{13}C NMR (MeOH-d_4) δ 41.8, 59.3, 66.9, 80.9, 82.5, 120.8, 132.4, 139.8, 141.6, 150.9, 153.8, 157.5; LRMS (EI) *m/z* 277 $[M]^+$; HRMS calcd for $C_{12}H_{12}N_5O_3$: 277.1175, found: 277.1178.

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