Supporting Information

Synthesis of C-4-Substituted Steviol Derivatives and Their Inhibitory Effects against Hepatitis B Virus

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Contents

Synthesis of C-4 ureido derivatives 3–5 and 7–19

*ent-13-Hydroxykaur-16-ene-19-N-methylureide (**3**):* Following the general procedure described for method A, compound **3** was prepared from **2** (60 mg, 0.19 mmol), using methylamine (93 mg, 3 mmol); white crystals (36 mg, 54.6%); mp 253–257 °C; $[\alpha]^{28}_{D}$ –75.7 (*c* 1.05, $CHCl_3$); R_f 0.38 [CH_2Cl_2-CH_3OH (30:1)]; ^{1}H NMR (C_5D_5N, 500 MHz) δ 0.75 (1H, t, *J* = 11.4 Hz), 0.86 (1H, d, *J* = 12.0 Hz), 0.92 (1H, d, *J* = 7.8 Hz), 1.14 (3H, s), 1.24 (1H, m), 1.36-1.44 (4H, m), 1.58 (3H, s), 1.63-1.86 (7H, m), 1.98 (1H, m), 2.11-2.21 (3H, m), 2.87 (3H, d, *J* = 4.0 Hz), 3.33 (1H, d, *J* = 13.5 Hz), 4.80 (1H, s), 4.98 (1H, s), 5.40 (1H, s), 6.37 (1H, br s, OH); 6.73 (1H, d, *J* = 3.5 Hz); ^{13}C NMR (C_5D_5N, 125 MHz) δ 159.1, 157.5, 103.1, 79.9, 56.8, 55.0, 54.6, 48.2, 47.7, 41.6, 41.4, 40.8, 40.5, 39.3, 37.3, 28.4, 26.8, 20.4, 19.8, 18.5, 17.9; HRESIMS *m/z* 347.2700 $[M + H]^+$ (calcd for $C_{21}H_{35}N_2O_2$, 347.2699).

*ent-13-Hydroxykaur-16-ene-19-N-ethylureide (**4**).* Following the general procedure described for method A, compound **4** was prepared from **2** (60 mg, 0.19 mmol), using ethylamine (135 mg, 3 mmol); white crystals (45.0 mg, 65.6%); mp 234–236 °C; $[\alpha]^{28}_{D}$ –72.1 (*c* 1.0, $CHCl_3$); R_f 0.40 [CH_2Cl_2-CH_3OH (30:1)]; ^{1}H NMR (C_5D_5N, 500 MHz) δ 0.73 (1H, td, *J* = 13.0, 3.0 Hz), 0.84 (1H, d, *J* = 11.5 Hz), 0.90 (1H, d, *J* = 8.0 Hz), 1.07 (3H, t, *J* = 7.0 Hz), 1.12 (1H, m), 1.15 (3H, s), 1.27 (1H, m), 1.35-1.37 (3H, m), 1.42 (1H, d, *J* = 10.5 Hz), 1.56 (3H, s), 1.58-1.84 (7H, m), 1.96 (1H, m), 2.09-2.20 (2H, m), 3.31-3.42 (3H, m), 4.85 (1H, s), 4.97 (1H, s), 5.39 (1H, s), 6.49 (1H, br s, OH), 6.78 (1H, t, *J* = 5.0 Hz); ^{13}C NMR (C_5D_5N, 125 MHz) δ 158.3, 157.3, 103.0, 79.9, 56.7, 54.9, 54.5, 48.0, 47.6, 41.5, 41.3, 40.6, 40.4, 39.2, 37.1, 34.9, 28.3, 20.2, 19.7, 18.4, 17.8, 15.9; HRESIMS *m/z* 361.2867 $[M + H]^+$ (calcd for $C_{22}H_{37}N_2O_2$, 361.2855).

*ent-13-Hydroxykaur-16-ene-19-N-propylureide (**5**).* Following the general procedure described for method A, compound **5** was prepared from **2** (60 mg, 0.19 mmol), using propylamine (178 mg, 3 mmol); white crystals (40 mg, 56.1%); mp 144–146 °C; $[\alpha]^{28}_{D}$ –64.3 (*c* 1.05, $CHCl_3$); R_f 0.46 [CH_2Cl_2-CH_3OH (30:1)]; ^{1}H NMR (C_5D_5N, 500 MHz) δ 0.74 (1H, td, *J* = 13.0, 3.0 Hz), 0.80-0.86 (4H, m), 0.91 (1H, d, *J* = 8.5 Hz), 1.09 (1H, dd, *J* = 13.5, 4.0 Hz), 1.14 (3H, s), 1.23 (1H, m),

1.34-1.45 (4H, m), 1.48 (2H, m), 1.57 (3H, s), 1.59-1.87 (6H, m), 1.98 (1H, m), 2.11-2.20 (3H, m), 3.25-3.39 (3H, m), 4.84 (1H, s), 4.98 (1H, s), 5.40 (1H, s), 6.43 (1H, s, OH); 6.80 (1H, t, J = 5.0 Hz); ^{13}C NMR (C_5D_5N, 125 MHz) δ 158.4, 157.4, 103.0, 79.9, 56.7, 54.9, 54.5, 48.1, 47.6, 42.0, 41.5, 41.4, 40.6, 40.4, 39.2, 37.2, 28.3, 24.1, 20.3, 19.8, 18.5, 17.8, 11.7; HRESIMS *m/z* 375.3020 $[M + H]^+$ (calcd for $C_{23}H_{39}N_2O_2$, 375.3012)

*ent-13-Hydroxykaur-16-ene-19-N,N-dimethylureide (**7**).* Following the general procedure described for method B, compound **7** was prepared from **2** (60 mg, 0.19 mmol), using dimethylamine (135 mg, 3 mmol); white powder (27.3 mg, 39.8%); $[\alpha]^{28}_D$ −70.2 (*c* 1.0, $CHCl_3$); R_f 0.50 [CH_2Cl_2-CH_3OH (30:1)]; ^{1}H NMR (C_5D_5N, 500 MHz) δ 0.73 (1H, td, J = 13.0, 3.0 Hz), 0.87 (1H, d, J = 11.5 Hz), 0.94 (1H, d, J = 8.0 Hz), 1.05 (1H, td, J = 13.5, 3.5 Hz), 1.15 (3H, s), 1.30-1.53 (5H, m), 1.54 (3H, s), 1.60-1.75 (5H, m), 1.86 (1H, m), 2.03 (1H, m), 2.12-2.25 (3H, m), 2.83 (6H, s), 3.19 (1H, d, J = 12.5 Hz), 4.40 (1H, s), 4.99 (1H, s), 5.45 (1H, s), 6.29 (1H, br s, OH); ^{13}C NMR (C_5D_5N, 125 MHz) δ 157.4, 157.4, 103.1, 79.8, 56.6, 55.3, 54.6, 48.0, 47.6, 41.5, 41.3, 40.7, 40.1, 39.0, 36.2, 36.1, 36.1, 28.0, 20.2, 19.6, 18.3, 18.1; HRESIMS *m/z* 361.2853 $[M + H]^+$ (calcd for $C_{22}H_{37}N_2O_2$, 361.2855).

*ent-13-Hydroxykaur-16-ene-19-N,N-diethylureide (**8**):* Following the general procedure described for method B, compound **8** was prepared from **2** (60 mg, 0.19 mmol), using diethylamine (310 μL, 3 mmol); white powder (16.6 mg, 22.4%); $[\alpha]^{28}_D$ −60.0 (*c* 1.0, $CHCl_3$); R_f 0.60 [*n*-hexane-EtOAc (1:5)]; ^{1}H NMR (C_5D_5N, 500 MHz) δ 0.74 (1H, m, H-1), 0.89 (1H, d, J = 12.0 Hz,), 0.95 (1H, d, J = 8.0 Hz), 1.03-1.10 (6H, m), 1.18 (3H, s), 1.28-1.54 (5H, m), 1.57 (3H, s), 1.58-1.77 (6H, m), 1.86 (1H, m), 2.04 (1H, m), 2.11-2.27 (3H, m), 3.19-3.31 (5H, m), 4.34 (1H, s), 5.00 (1H, s), 5.46 (1H, s), 6.30 (1H, br s, OH); ^{13}C NMR (C_5D_5N, 125 MHz) δ 157.4, 156.5,103.1, 79.8, 56.7, 55.4, 54.6, 48.0, 47.6, 41.5, 41.5, 41.5, 41.3, 40.7, 40.1, 39.0, 36.5, 28.1, 20.3, 19.7, 18.4, 18.0, 14.3, 14.3; HRESIMS *m/z* 389.3173 $[M + H]^+$ (calcd for $C_{24}H_{41}N_2O_2$, 389.3168).

*ent-13-Hydroxykaur-16-ene-19-N-isopropylureide (**9**).* Following the general procedure described for method A, compound **9** was prepared from **2** (60 mg, 0.19 mmol), using

isopropylamine (178 mg, 3 mmol); white powder (42 mg, 59.0%); mp 265–267°C (H_2O–CH_3OH); $[\alpha]^{26}_D$ –68.6 (*c* 1.05, CH_3OH); R_f 0.46 [CH_2Cl_2-CH_3OH (30:1)]; ^{1}H NMR (C_5D_5N, 500 MHz) δ 0.76 (1H, m), 0.86 (1H, d, *J* = 12.0 Hz), 0.92 (1H, d, *J* = 8.0 Hz), 1.09-1.17 (10H, m), 1.27 (1H, m), 1.38-1.46 (4H, m), 1.59 (3H, s), 1.61-1.86 (5H, m), 1.99 (1H, m), 2.04 (1H, m), 2.11-2.21 (3H, m), 3.37 (1H, d, *J* = 13.0 Hz), 4.19 (1H, m), 4.81 (1H, s), 4.99 (1H, s), 5.41 (1H, s), 6.50 (1H, br s, OH); 6.60 (1H, d, *J* = 7.5 Hz); ^{13}C NMR (C_5D_5N, 125 MHz) δ 158.0, 157.4, 103.2, 80.1, 56.9, 55.0, 54.6, 48.2, 47.8, 41.7, 41.6, 41.5, 40.7, 40.5, 39.3, 37.4, 28.4, 23.8, 23.8, 20.4, 19.9, 18.6, 17.9; HRESIMS *m/z* 375.3026 $[M + H]^+$ (calcd for $C_{23}H_{39}N_2O_2$, 375.3012).

*ent-13-Hydroxykaur-16-ene-19-N-phenylureide (**10**).* Following the general procedure described for method A, compound **10** was prepared from **2** (60 mg, 0.19 mmol), using aniline (275 μL, 3 mmol); white crystals (30 mg, 38.6%); mp 149–151 °C; $[\alpha]^{28}_D$ –102.9 (*c* 1.0, $CHCl_3$); R_f 0.20 [CH_2Cl_2-CH_3OH (60:1)]; ^{1}H NMR (C_5D_5N, 500 MHz) δ 0.72 (1H, td, *J* = 13.0, 3.0 Hz), 0.84 (1H, dd, *J* = 12.0, 1.5 Hz), 0.89 (1H, d, *J* = 8.0 Hz), 1.06 (3H, s), 1.08-1.21 (2H, m), 1.33-1.41 (4H, m), 1.56 (3H, s), 1.57-1.82 (6H, m), 1.94 (1H, td, *J* = 13.0, 6.0 Hz), 2.04-2.20 (3H, m), 3.32 (1H, d, *J* = 13.5 Hz), 4.97 (1H, s), 5.19 (1H, s), 5.42 (1H, s), 6.50 (1H, br s, OH); 6.95 (1H, m), 7.28 (2H, td, *J* = 7.0, 2.0 Hz), 7.88 (2H, dd, *J* = 9.0, 2.0 Hz), 9.60 (1H, s); ^{13}C NMR (C_5D_5N, 125 MHz) δ 157.2, 155.3, 142.1, 129.1, 129.1, 121.4, 118.4, 118.4, 103.1, 79.9, 56.5, 55.2, 54.4, 48.0, 47.6, 41.4, 41.2, 40.6, 40.2, 39.1, 36.9, 27.9, 20.2, 19.7, 18.3, 17.7; HRESIMS *m/z* 409.2857 $[M + H]^+$ (calcd for $C_{26}H_{37}N_2O_2$, 409.2855).

*ent-13-Hydroxykaur-16-ene-19-N-benzylureide (**11**).* Following the general procedure described for method B, compound **11** was prepared from **2** (60 mg, 0.19 mmol), using benzylamine (328 μL, 3 mmol); white powder (30 mg, 60.0%); $[\alpha]^{28}_D$ –67.4 (*c* 1.05, $CHCl_3$); R_f 0.50 [CH_2Cl_2-CH_3OH (20:1)]; ^{1}H NMR (C_5D_5N, 500 MHz) δ 0.74 (1H, t, *J* = 11.5 Hz), 0.84 (1H, d, *J* = 12.0 Hz), 0.90 (1H, d, *J* = 8.0 Hz), 1.06-1.20 (4H, m), 1.23-1.43 (5H, m), 1.56 (3H, s), 1.58-1.88 (6H, m), 1.95 (1H, td, *J* = 12.5, 6.0 Hz), 2.07-2.20 (3H, m), 3.35 (1H, d, *J* = 13.5 Hz), 4.56 (1H, dd, *J* = 15.0, 5.5 Hz), 4.66 (1H, dd, *J* = 15.0, 6.0 Hz), 4.93 (1H, s), 5.03 (1H, s), 5.30 (1H,

br s), 7.18 (1H, m), 7.27 (2H, t, *J* = 7.5 Hz), 7.39 (1H, t, *J* = 5.5 Hz), 7.45 (2H, d, *J* = 7.5 Hz); ^{13}C NMR (C_5D_5N, 125 MHz) δ 158.3, 157.1, 141.8, 128.7, 128.7, 127.7, 127.7, 126.9, 103.0, 79.9, 56.6, 55.0, 54.4, 48.0, 47.6, 44.0, 41.5, 41.3, 40.5, 40.3, 39.2, 37.1, 28.2, 20.2, 19.7, 18.4, 17.9; HRESIMS *m/z* 423.3023 $[M + H]^+$ (calcd for $C_{27}H_{39}N_2O_2$, 423.3012).

ent-13-Hydroxykaur-16-ene-19-N-(4′-fluorophethyl)ureide ***(12).*** Following the general procedure described for method B, compound **12** was prepared from **2** (60 mg, 0.19 mmol), using 4-fluoroaniline (284 μL, 3 mmol); white powder (19 mg, 23.4%); $[\alpha]^{28}_D$ −84.9 (*c* 1.05, $CHCl_3$); R_f 0.44 [CH_2Cl_2-CH_3OH (50:1)]; ^{1}H NMR (C_5D_5N, 500 MHz) δ 0.72 (1H, td, *J* = 13.0, 3.0 Hz), 0.84 (1H, d, *J* = 11.0 Hz), 0.89 (1H, d, *J* = 8.0 Hz), 1.03 (3H, s), 1.05-1.20 (2H, m), 1.31-1.39 (4H, m), 1.57 (3H, s), 1.59-1.81 (6H, m), 1.95 (1H, m), 2.00 (1H, d, *J* = 12.0 Hz), 2.16 (2H, m), 3.28 (1H, d, *J* = 14.0 Hz), 4.98 (1H, s), 5.10 (1H, s), 5.42 (1H, d, *J* = 1.0 Hz), 6.30 (1H, br s, OH), 7.07 (2H, t, *J* = 9.0 Hz), 7.79 (2H, dd, *J* = 7.0, 2.5 Hz), 9.65 (1H, s); ^{13}C NMR (C_5D_5N, 125 MHz) δ 158.8, 157.3, 156.9, 155.3, 138.3, 119.7, 119.7, 119.8, 119.8, 115.5, 115.5, 115.4, 115.4, 103.1, 79.8, 56.5, 55.3, 54.4, 48.0, 47.6, 41.5, 41.2, 40.7, 40.2, 39.2, 36.9, 28.0, 20.3, 19.7, 18.3, 17.6; HRESIMS *m/z* 427.2746 $[M + H]^+$ (calcd for $C_{26}H_{36}FN_2O_2$, 427.2761).

ent-13-Hydroxykaur-16-ene-19-N-(4′-chlorophenyl)ureide ***(13).*** Following the general procedure described for method B, compound **13** was prepared from **2** (60 mg, 0.19 mmol), using 4-chloroaniline (385.5 mg, 3 mmol); white powder (25 mg, 29.7%); $[\alpha]^{28}_D$ −112.3 (*c* 0.6, $CHCl_3$); R_f 0.50 [CH_2Cl_2-CH_3OH (20:1)]; ^{1}H NMR (C_5D_5N, 500 MHz) δ 0.71 (1H, td, *J* = 13.0, 3.0 Hz), 0.84 (1H, dd, *J* = 12.5, 1.5 Hz), 0.87 (1H, d, *J* = 8.0 Hz), 0.97 (3H, s), 1.05 (1H, m), 1.14 (1H, m), 1.23-1.38 (4H, m), 1.56 (3H, s), 1.57-1.82 (6H, m), 1.88-1.95 (2H, m), 2.07-2.19 (2H, m), 3.25 (1H, d, *J* = 13.5 Hz), 4.97 (1H, s), 5.06 (1H, s), 5.42 (1H, s), 6.29 (1H, br s, OH), 7.29 (2H, d, *J* = 9.0 Hz), 7.78 (2H, d, *J* = 9.0 Hz), 9.77 (1H, s); ^{13}C NMR (C_5D_5N, 125 MHz) δ 157.3, 155.1, 141.0, 129.0, 129.0, 125.7, 119.6, 119.6, 103.1, 79.7, 56.5, 55.4, 54.4, 48.1, 47.6, 41.5, 41.2, 40.8, 40.2, 39.1, 36.9, 27.9, 20.3, 19.7, 18.3, 17.6; HRESIMS *m/z* 443.2474 $[M + H]^+$ (calcd for $C_{26}H_{36}ClN_2O_2$, 443.2465).

*ent-13-Hydroxykaur-16-ene-19-N-(4′-bromophenyl)ureide (**14**).* Following the general procedure described for method B, compound **14** was prepared from **2** (60 mg, 0.19 mmol), using 4-bromoaniline (516 mg, 3 mmol); white powder (16 mg, 17.3%); $[\alpha]^{28}_{D}$ –78.7 (*c* 0.55, $CHCl_3$); R_f 0.32 [CH_2Cl_2-CH_3OH (60:1)]; ^{1}H NMR (C_5D_5N, 500 MHz) δ 0.72 (1H, td, *J* = 13.0, 3.5 Hz, H-1), 0.85 (1H, d, *J* = 9.0 Hz), 0.88 (1H, d, *J* = 8.0 Hz), 1.00 (3H, s), 1.02-1.17 (2H, m), 1.32-1.45 (4H, m), 1.55 (3H, s), 1.60-1.81 (6H, m), 1.89-2.00 (2H, m), 2.15 (2H, m), 3.27 (1H, d, *J* = 13.5 Hz), 4.98 (1H, s), 5.09 (1H, s), 5.41 (1H, s), 6.43 (1H, br s, OH),7.43 (2H, dd, *J* = 7.0, 2.0 Hz), 7.74 (2H, dd, *J* = 7.0.0, 2.0 Hz), 9.73 (1H, s); ^{13}C NMR (C_5D_5N, 125 MHz) δ 157.2, 155.0, 141.4, 131.9, 131.9, 113.3, 120.1, 120.1, 103.1, 79.8, 56.5, 55.4, 54.4, 48.0, 47.6, 41.5, 41.2, 40.7, 40.2, 39.1, 36.8, 27.9, 20.2, 19.7, 18.3, 17.6; HRESIMS *m/z* 487.1973 $[M + H]^+$ (calcd for $C_{26}H_{36}BrN_2O_2$, 487.1960).

*ent-13-Hydroxykaur-16-ene-19-N-(4′-tolyl)ureide (**15**).* Following the general procedure described for method B, compound **15** was prepared from **2** (60 mg, 0.19 mmol), using *p*-toluidine (321 mg, 3 mmol); white powder (26.8 mg, 33.3%); $[\alpha]^{28}_{D}$ –98.0 (*c* 1.05, $CHCl_3$); R_f 0.38 [CH_2Cl_2-CH_3OH (40:1)]; ^{1}H NMR (C_5D_5N, 500 MHz) δ 0.72 (1H, td, *J* = 13.5, 3.5 Hz, H-1), 0.84 (1H, d, *J* = 11.0 Hz,), 0.89 (1H, d, *J* = 8.0 Hz), 1.04 (3H, s), 1.05-1.16 (2H, m), 1.32-1.40 (4H, m), 1.57 (3H, s), 1.59-1.82 (6H, m), 1.93 (1H, m), 2.01-2.20 (5H, m), 3.33 (1H, d, *J* = 13.5 Hz), 4.98 (1H, s), 5.10 (1H, s), 5.42 (1H, s), 6.42 (1H, br s, OH), 7.09 (2H, d, *J* = 8.5 Hz), 7.79 (2H, d, *J* = 8.5 Hz), 9.51 (1H, s); ^{13}C NMR (C_5D_5N, 125 MHz) δ 157.3, 155.5, 139.6, 130.5, 129.6, 129.6, 118.6, 118.6, 103.1, 79.8, 56.6, 55.2, 54.4, 48.0, 47.6, 41.5, 41.2, 40.7, 40.2, 39.2, 37.0, 28.0, 20.6, 20.2, 19.7, 18.4, 17.7; HRESIMS *m/z* 423.3019 $[M + H]^+$ (calcd for $C_{27}H_{39}N_2O_2$, 423.3012).

*ent-13-Hydroxykaur-16-ene-19-N-(4′-methoxyphenyl)ureide (**16**).* Following the general procedure described for method B, compound **16** was prepared from **2** (60 mg, 0.19 mmol), using 4-methoxyaniline (370 mg, 3 mmol); white powder (30 mg, 36.0%); $[\alpha]^{28}_{D}$ –81.2 (*c* 1.0, $CHCl_3$); R_f 0.56 [CH_2Cl_2-CH_3OH (30:1)]; ^{1}H NMR (C_5D_5N, 500 MHz) δ 0.73 (1H, td, *J* = 13.0, 3.0 Hz), 0.84 (1H, d, *J* = 11.5 Hz), 0.89 (1H, d, *J* = 8.0 Hz), 1.04 (3H, s), 1.09-1.17 (2H, m), 1.33-1.40 (4H, m),

1.58 (3H, s), 1.59-1.82 (6H, m), 1.94 (1H, m), 2.02 (1H, d, *J* = 12.5 Hz), 2.16 (2H, m), 3.33 (1H, d, *J* = 13.5 Hz), 3.58 (3H, s), 4.98 (1H, s), 5.06 (1H, s), 5.42 (1H, s), 6.41 (1H, br s, OH), 6.96 (2H, d, *J* = 9.0 Hz), 7.78 (2H, d, *J* = 9.0 Hz), 9.44 (1H, s); ^{13}C NMR (C_5D_5N, 125 MHz) δ 157.3, 155.7, 154.9, 135.8, 120.2, 120.2, 114.5, 114.5, 103.1, 79.8, 56.6, 55.3, 55.2, 54.4, 48.0, 47.6, 41.5, 41.3, 40.7, 40.2, 39.2, 37.0, 28.0, 20.2, 19.7, 18.4, 17.7; HRESIMS *m/z* 439.2979 $[M + H]^+$ (calcd for $C_{27}H_{39}N_2O_3$, 439.2961).

*ent-13-Hydroxykaur-16-ene-19-N-(3′,4′-dimethoxyphenyl)ureide (**17**).* Following the general procedure described for method B, compound **17** was prepared from **2** (60 mg, 0.19 mmol), using 3,4-dimethoxyaniline (459 mg, 3 mmol); white powder (35 mg, 38.8%); $[\alpha]^{28}_D$ −82.2 (*c* 1.05, $CHCl_3$); R_f 0.34 [CH_2Cl_2-CH_3OH (30:1)]; ^{1}H NMR (C_5D_5N, 500 MHz) δ 0.73 (1H, td, *J* = 12.5, 3.5 Hz), 0.85 (1H, dd, *J* = 12.5, 1.5 Hz), 0.89 (1H, d, *J* = 8.0 Hz), 1.07 (3H, s), 1.08-1.23 (2H, m), 1.32-1.40 (4H, m), 1.60 (3H, s), 1.61-1.82 (6H, m), 1.93 (1H, m), 2.03-2.33 (3H, m), 3.32 (1H, d, *J* = 13.5 Hz), 3.68 (3H, s), 3.70 (3H, s), 4.98 (1H, s), 5.15 (1H, s), 5.42 (1H, s), 6.34 (1H, br s, OH), 6.87 (1H, d, *J* = 8.5 Hz), 7.15 (1H, dd, *J* = 8.5, 2.5 Hz), 7.86 (1H, s), 9.50 (1H, s); ^{13}C NMR (C_5D_5N, 125 MHz) δ 157.3, 155.6, 150.2 , 144.6, 136.2, 113.6, 110.3, 104.7, 103.0, 79.7, 56.6, 56.5, 55.7, 55.2, 54.4, 48.0, 47.6, 41.5, 41.2, 40.7, 40.2, 39.2, 37.0, 28.0, 20.3, 19.7, 18.4, 17.6; HRESIMS *m/z* 469.3071 $[M + H]^+$ (calcd for $C_{28}H_{41}N_2O_4$, 469.3066).

*ent-13-Hydroxykaur-16-ene-19-N-(3′,4′,5′-trimethoxyphenyl)ureide (**18**).* Following the general procedure described for method B, compound **18** was prepared from **2** (60 mg, 0.19 mmol), using 3,4,5-trimethoxyaniline (549.6 mg, 3 mmol); white powder (6 mg, 6.3%); $[\alpha]^{28}_D$ −101.5 (*c* 1.05, $CHCl_3$); R_f 0.34 [*n*-hexane-EtOAc (1:2)]; ^{1}H NMR (C_5D_5N, 600 MHz) δ 0.75 (1H, m, H-1), 0.81-0.91 (2H, m), 1.06 (3H, s), 1.08-1.22 (2H, m), 1.33-1.42 (4H, m), 1.61 (3H, s), 1.62-1.85 (6H, m), 1.95 (1H, m), 2.02-2.21 (3H, m), 3.32 (1H, d, *J* = 11.0 Hz), 3.66 (6H, s), 3.85 (3H, s), 4.98 (1H, s), 5.13 (1H, s), 5.43 (1H, s), 6.38 (1H, br s, OH), 7.21 (2H, s), 9.48 (1H, s); ^{13}C NMR (C_5D_5N, 125 MHz) δ 157.3, 155.4, 154.0, 154.0, 138.3, 133.5, 103.1, 96.5, 96.5, 79.8, 60.8, 56.5, 56.5, 55.9, 55.3, 54.4, 48.0, 47.6, 41.5, 41.2, 40.8, 40.2, 39.2, 37.0, 28.0, 20.3, 19.8, 18.4, 17.7; HRESIMS *m/z*

499.3186 $[M + H]^+$ (calcd for $C_{29}H_{43}N_2O_5$, 499.3172)。

*ent-13-Hydroxykaur-16-ene-19-N-(3′-acetylphenyl)ureide (**19**).* Following the general procedure described for method B, compound **19** was prepared from **2** (60 mg, 0.19 mmol), using 1-(3-aminophenyl)ethanone (405 mg, 3 mmol); white powder (12 mg, 14.0%); $[\alpha]^{28}_D$ −84.8 (*c* 1.0, $CHCl_3$); R_f 0.28 [CH_2Cl_2-CH_3OH (30:1)]; ^{1}H NMR (C_5D_5N, 500 MHz) δ 0.73 (1H, td, *J* = 13.0, 3.5 Hz), 0.85-0.90 (2H, m), 1.08 (3H, s), 1.11-1.23 (2H, m), 1.32-1.40 (4H, m), 1.58 (3H, s), 1.59-1.83 (6H, m), 1.93 (1H, m), 2.02 (1H, m), 2.16 (2H, m), 2.46 (3H, s), 3.30 (1H, d, *J* = 13.5 Hz), 4.98 (1H, s), 5.24 (1H, d), 5.43 (1H, s), 6.39 (1H, br s, OH), 7.32 (1H, t, *J* = 8.0 Hz), 7.61 (1H, d, *J* = 8.0 Hz), 7.97 (1H, dd, *J* = 8.0, 2.0 Hz), 8.61 (1H, s), 9.86 (1H, s); ^{13}C NMR (C_5D_5N, 125 MHz) δ 197.9, 157.3, 155.2, 142.5, 138.3 , 129.2, 122.7, 121.4, 117.9, 103.1, 79.8, 56.5, 55.4, 54.4, 48.0, 47.6, 41.5, 41.2, 40.7, 40.2, 39.2, 36.9, 27.9, 26.6, 20.2, 19.7, 18.3, 17.6; HRESIMS *m/z* 451.2967 $[M + H]^+$ (calcd for $C_{28}H_{39}N_2O_3$, 451.2961).

Synthesis of C-4 amides derivatives 21–36

*N-(Ethylcarbonyl)-4α-amino-19-nor-ent-13-hydroxykaur-16-ene (**21**).* Following the general procedure, compound **21** was prepared from **20** (60 mg, 0.19 mmol), using acetyl chloride (57.0 μL, 0.8 mmol); white powder (27.5 mg, 40.0%); $[\alpha]^{26}_{D}$ –66.1 (*c* 1.05, CH_3OH); R_f 0.20 [*n*-hexane-EtOAc (1:2)]; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.81 (1H, td, *J* = 12.6, 3.6 Hz), 0.90-1.05 (3H, m, H-3, H-5, H-9), 1.12 (3H, s), 1.22-1.37 (2H, m), 1.38 (3H, s), 1.41 (1H, m), 1.49-1.61 (5H, m), 1.74-1.84 (4H, m), 1.90 (3H, s), 2.05-2.10 (2H, m), 2.21 (1H, m), 2.78 (1H, d, *J* = 14.4 Hz), 4.81 (1H, s), 4.97 (1H, s), 5.15 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.1, 155.7, 103.2, 80.2, 56.0, 56.0, 54.3, 47.4, 47.3, 41.4, 40.8, 39.9, 39.3, 38.9, 35.6, 27.0, 24.9, 20.0, 19.5, 17.8, 17.3; HRESIMS *m/z* 332.2600 $[M + H]^+$ (calcd for $C_{21}H_{34}NO_2$, 332.2590).

*N-(Propylcarbonyl)-4α-amino-19-nor-ent-13-hydroxykaur-16-ene (**22**).* Following the general procedure, compound **22** was prepared from **20** (60 mg, 0.19 mmol), using propionyl chloride (69.5 μL, 0.8 mmol); white powder (25 mg, 34.9%); $[\alpha]^{28}_{D}$ –83.8 (*c* 1.05, $CHCl_3$); R_f 0.30 [*n*-hexane-EtOAc (1:1)]; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.82 (1H, td, *J* = 13.2, 4.2 Hz), 0.91-1.07 (3H, m), 1.09 (3H, t, *J* = 7.2), 1.12 (3H, s), 1.26 (1H, m), 1.31-1.42 (2H, m), 1.38 (3H, s), 1.49-1.60 (5H, m), 1.74-1.84 (4H, m), 2.05-2.14 (4H, m), 2.19 (1H, *J* = 14.5, 2.5 Hz), 2.79 (1H, d, *J* = 14.4 Hz), 4.81 (1H, s), 4.97 (1H, s), 5.17 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.7, 155.7, 103.2, 80.2, 56.1, 55.8, 54.3, 47.4, 47.3, 41.4, 40.8, 39.9, 39.3, 38.9, 35.7, 31.0, 27.1, 20.0, 19.5, 17.8, 17.5, 9.9; HRESIMS *m/z* 346.2762 $[M + H]^+$ (calcd for $C_{22}H_{36}NO_2$, 346.2746).

*N-(Butylcarbonyl)-4α-amino-19-nor-ent-13-hydroxykaur-16-ene (**23**).* Following the general procedure, compound **23** was prepared from **20** (60 mg, 0.19 mmol), using butyryl chloride (82.5 μL, 0.8 mmol); white powder (21 mg, 24.8%); $[\alpha]^{28}_{D}$ –88.4 (*c* 1.05, $CHCl_3$); R_f 0.44 [*n*-hexane-EtOAc (1:1)]; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.82 (1H, td, *J* = 13.2, 3.6 Hz), 0.90 (1H, m), 0.93 (3H, t, *J* = 7.2 Hz), 0.97-1.16 (2H, m), 1.12 (3H, s), 1.26-1.36 (2H, m), 1.38 (3H, s), 1.40 (1H, m), 1.49-1.64 (7H, m), 1.74-1.84 (4H, m), 2.03-2.22 (5H, m), 2.80 (1H, d, *J* = 12.6 Hz), 4.81 (1H, s), 4.97 (1H, s), 5.16 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.0, 155.7, 103.2, 80.2, 56.1,

55.9, 54.3, 47.4, 47.3, 41.4, 40.8, 40.2, 39.9, 39.3, 38.9, 35.7, 27.1, 20.0, 19.5, 19.2, 17.9, 17.4, 13.7; HRESIMS *m/z* 360.2917 $[M + H]^+$ (calcd for $C_{23}H_{38}NO_2$, 360.2903).

*N-(Pentylcarbonyl)-4α-amino-19-nor-ent-13-hydroxykaur-16-ene (**24**).* Following the general procedure, compound **24** was prepared from **20** (60 mg, 0.19 mmol), using pentanoyl chloride (95 μL, 0.8 mmol); white powder (59.0 mg, 76.2%); $[\alpha]^{28}_D$ −85.8 (*c* 1.0, $CHCl_3$); R_f 0.32 [*n*-hexane-EtOAc (2:1)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.81 (1H, td, *J* = 13.0, 3.5 Hz), 0.90 (3H, t, *J* = 7.0 Hz), 0.91 (1H, m), 0.98-1.12 (2H, m), 1.12 (3H, s), 1.22-1.43 (5H, m), 1.38 (3H, s), 1.49-1.62 (7H, m), 1.70-1.84 (4H, m), 2.04-2.11 (4H, m), 2.20 (1H,dt, *J* = 17.5, 2.5 Hz), 2.78 (1H, m), 4.81 (1H, t, *J* = 2.0 Hz), 4.97 (1H, t, *J* = 2.0 Hz), 5.15 (1H, s, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.1, 155.7, 103.2, 80.2, 56.1, 55.9, 54.3, 47.4, 47.3, 41.4, 40.8, 39.9, 39.3, 38.9, 37.9, 35.7, 27.9, 27.1, 22.3, 20.0, 19.5,17.9, 17.4, 13.8; HRESIMS *m/z* 374.3050 $[M + H]^+$ (calcd for $C_{24}H_{40}NO_2$, 374.3059).

*N-(Hexylcarbonyl)-4α-amino-19-nor-ent-13-hydroxykaur-16-ene (**25**).* Following the general procedure, compound **25** was prepared from **20** (60 mg, 0.19 mmol), using hexanoyl chloride (112 μL, 0.8 mmol); white powder (49.2 mg, 61.2%); $[\alpha]^{28}_D$ −76.4 (*c* 1.1, $CHCl_3$); R_f 0.36 [*n*-hexane-EtOAc (2:1)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.81 (1H, td, *J* = 13.3, 3.5 Hz), 0.88 (3H, t, *J* = 7.0 Hz), 0.90 (1H, m), 0.93-1.06 (2H, m), 1.12 (3H, s), 1.23-1.42 (7H, m), 1.38 (3H, s), 1.49-1.68 (7H, m), 1.75-1.84 (4H, m), 2.05-2.11 (4H, m), 2.20 (1H, d, *J* = 17.5 Hz), 2.79 (1H, d, *J* = 14.0 Hz), 4.81 (1H, s), 4.97 (1H, s), 5.15 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.1, 155.7, 103.2, 80.2, 56.1, 55.9, 54.3, 47.4, 47.3, 41.5, 40.8, 39.9, 39.3, 38.9, 38.2, 35.7, 31.4, 27.1, 25.5, 22.4, 20.0, 19.5, 17.9, 17.4, 13.9; HRESIMS *m/z* 388.3222 $[M + H]^+$ (calcd for $C_{25}H_{42}NO_2$, 388.3216).

*N-(Phenylcarbonyl)-4α-amino-19-nor-ent-13-hydroxykaur-16-ene (**26**).* Following the general procedure, compound **26** was prepared from **20** (60 mg, 0.19 mmol), using benzoyl chloride (93 μL, 0.8 mmol); white powder (21.7 mg, 26.6%); $[\alpha]^{28}_D$ −77.2 (*c* 0.55, $CHCl_3$); R_f 0.80 [*n*-hexane-EtOAc (3:1)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (1H, td, *J* = 13.0, 3.5 Hz), 1.02-1.09

(2H, m), 1.14 (1H, td, *J* = 13.5, 4.0 Hz), 1.24 (3H, s), 1.31 (1H, dd, *J* = 10.5, 2.0 Hz), 1.40-1.48 (2H, m), 1.51 (3H, s), 1.53-1.66 (5H, m), 1.76-1.80 (2H, m), 1.81-1.88 (2H, m), 2.05-2.16 (2H, m), 2.21 (1H, dt, *J* = 17.0, 3.0 Hz), 2.96 (1H, d, *J* = 14.0 Hz), 4.82 (1H, s), 4.99 ((1H, t, *J* = 2.0 Hz), 5.96 (1H, s), 7.39-7.43 (2H, m), 7.46 (1H, m), 7.67-7.70 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.2, 155.6, 136.0, 131.1, 128.6, 128.6, 126.4, 126.4, 103.2, 80.2, 56.4, 56.3, 54.3, 47.4, 47.3, 41.5, 40.8, 39.8, 39.3, 38.9, 35.6, 27.1, 20.0, 19.6, 17.9, 17.9; HRESIMS *m/z* 394.2733 $[M + H]^+$ (calcd for $C_{26}H_{36}NO_2$, 394.2746)。

*N-(4′-Fluorophenylcarbonyl)-4α-amino-19-nor-ent-13-hydroxykaur-16-ene (**27**).* Following the general procedure, compound **27** was prepared from **20** (60 mg, 0.19 mmol), using 4-fluorobenzoyl chloride (96.1 μL, 0.8 mmol); white powder (54.0 mg, 63.3%); $[\alpha]^{28}_D$ –95.0 (*c* 1.05, $CHCl_3$); R_f 0.40 [*n*-hexane-EtOAc (3:1)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (1H, m), 1.03-1.08 (2H, m), 1.14 (1H, td, *J* = 13.5, 4.0 Hz), 1.23 (3H, s), 1.30 (1H, dd, *J* = 11.0, 2.5 Hz), 1.42-1.49 (2H, m), 1.50 (3H, s), 1.54-1.65 (5H, m), 1.71-1.81 (2H, m), 1.85-1.88 (2H, m), 2.08-2.26 (3H, m), 2.93 (1H, d, *J* = 13.5 Hz), 4.82 (1H, s), 4.99 (1H, t, *J* = 2.5 Hz), 5.87 (1H, s), 7.08 (2H, m), 7.68 (2H, m); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.5, 155.6, 132.2, 165.2, 165.5, 128.6, 128.7, 115.5, 115.7, 103.3, 80.2, 56.5, 56.3, 54.3, 47.4, 47.4, 41.5, 40.8, 39.8, 39.3, 38.9, 35.6, 27.1, 20.0, 19.6, 17.9, 17.9; HRESIMS *m/z* 412.2657 $[M + H]^+$ (calcd for $C_{26}H_{35}FNO_2$, 412.2652).

*N-(4′-Chlorophenylcarbonyl)-4α-amino-19-nor-ent-13-hydroxykaur-16-ene (**28**).* Following the general procedure, compound **28** was prepared from **20** (60 mg, 0.19 mmol), using 4-chlorobenzoyl chloride (102.2 μL, 0.8 mmol); white powder (50.0 mg, 56.4%); $[\alpha]^{28}_D$ –92.9 (*c* 1.05, $CHCl_3$); R_f 0.40 [*n*-hexane-EtOAc (3:1)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (1H, m, H-1), 1.03-1.07 (2H, m), 1.14 (1H, td, *J* = 13.5, 4.0 Hz), 1.22 (3H, s), 1.30 (1H, dd, *J* = 11.0, 2.0 Hz), 1.37-1.48 (2H, m), 1.50 (3H, s), 1.52-1.65 (5H, m), 1.76-1.81 (2H, m), 1.85-1.88 (2H, m), 2.08-2.15 (2H, m), 2.24 (1H, dt, *J* = 17.0, 2.5 Hz), 2.92 (1H, d, *J* = 14.0 Hz), 4.83 (1H, s), 4.98 (1H, t, *J* = 2.5 Hz), 5.88 (1H, s), 7.38 (2H, dt, *J* = 8.5, 2.5 Hz), 7.61 (2H, dt, *J* = 8.5, 2.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.2, 155.6, 137.3, 134.4, 128.9, 128.9, 127.9, 127.9, 103.3, 80.2, 56.6, 56.3, 54.3,

47.4, 47.4, 41.5, 40.8, 39.8, 39.3, 38.9, 35.6, 27.1, 20.0, 19.6, 17.9, 17.9; HRESIMS *m/z* 428.2350 $[M + H]^+$ (calcd for $C_{26}H_{35}ClNO_2$, 428.2356).

*N-(4′-Bromophenylcarbonyl)-4α-amino-19-nor-ent-13-hydroxykaur-16-ene (**29**).* Following the general procedure, compound **29** was prepared from **20** (60 mg, 0.19 mmol), using 4-bromobenzoyl chloride (105.7 μL, 0.8 mmol); white powder (47.4 mg, 48.5%); $[\alpha]^{28}_D$ −89.5 (*c* 1.0, $CHCl_3$); R_f 0.40 [*n*-hexane-EtOAc (3:1)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (1H, m), 1.03-1.07 (2H, m), 1.15 (1H, td, *J* = 14.0, 4.5 Hz), 1.21 (3H, s), 1.30 (1H, dd, *J* = 11.0, 2.0 Hz), 1.38-1.48 (2H, m), 1.49 (3H, s), 1.53-1.64 (5H, m), 1.76-1.81 (2H, m), 1.85-1.88 (2H, m), 2.06-2.15 (2H, m), 2.24 (1H, dt, *J* = 17.0, 3.0 Hz), 2.93 (1H, d, *J* = 14.0 Hz, H-3), 4.83 (1H, s), 4.99 (1H, t, *J* = 2.5 Hz), 7.52-7.54 (4H, m), 5.89 (1H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.2, 155.6, 125.7, 134.8, 131.8, 131.8, 128.1, 128.1, 103.3, 80.2, 56.6, 56.2, 54.3, 47.4, 47.4, 41.5, 40.8, 39.8, 39.3, 38.9, 35.6, 27.0, 20.0, 19.6, 17.9, 17.9; HRESIMS *m/z* 472.1854 $[M + H]^+$ (calcd for $C_{26}H_{35}BrNO_2$, 472.1851)

*N-(4′-Iodophenylcarbonyl)-4α-amino-19-nor-ent-13-hydroxykaur-16-ene (**30**).* Following the general procedure, compound **30** was prepared from **20** (60 mg, 0.19 mmol), using 4-iodobenzoyl chloride (110.4 μL, 0.8 mmol); yellow powder (57.0 mg, 52.9%); $[\alpha]^{28}_D$ −85.3 (*c* 1.1, $CHCl_3$); R_f 0.40 [*n*-hexane-EtOAc (3:1)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (1H, td, *J* = 13.0, 3.5 Hz), 1.02-1.05 (2H, m), 1.14 (1H, td, *J* = 13.5, 4.5 Hz), 1.21 (3H, s), 1.21-1.32 (1H, dd, *J* = 10.5, 1.5 Hz), 1.37-1.48 (2H, m), 1.49 (3H, s), 1.53-1.63 (5H, m), 1.75-1.80 (2H, m), 1.84-1.88 (2H, m), 2.07-2.14 (2H, m), 2.23 (1H, dt, *J* = 17.0, 2.5 Hz), 2.91 (1H, d, *J* = 14.5 Hz), 4.82 (1H, s, H-17), 4.98 (1H, t, *J* = 2.5 Hz, H-17), 5.89 (1H, s), 7.39 (2H, d, *J* = 8.5 Hz), 7.75 (2H, d, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.4, 155.6, 137.8, 137.8, 135.4, 128.1, 128.1, 103.3, 97.9, 80.2, 56.5, 56.2, 54.2, 47.4, 47.3, 41.4, 40.8, 39.8, 39.3, 38.9, 35.6, 27.0, 20.0, 19.6, 17.9, 17.9; HRESIMS *m/z* 520.1721 $[M + H]^+$ (calcd for $C_{26}H_{35}INO_2$, 520.1712).

*N-(4′-Methylphenylcarbonyl)-4α-amino-19-nor-ent-13-hydroxykaur-16-ene (**31**).* Following the general procedure, compound **31** was prepared from **20** (60 mg, 0.19 mmol), using

4-methylbenzoyl chloride (105.8 μL, 0.8 mmol); white powder (43.2 mg, 51.1%); $[\alpha]^{28}_{D}$ –87.4 (*c* 1.1, $CHCl_3$); R_f 0.64 [CH_2Cl_2-CH_3OH (40:1)]; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.86 (1H, td, *J* = 12.6, 3.6 Hz), 1.02-1.07 (2H, m), 1.14 (1H, td, *J* = 13.5, 4.0 Hz), 1.23 (3H, s), 1.32 (1H, m), 1.42-1.47 (2H, m), 1.50 (3H, s), 1.54-1.64 (5H, m), 1.77-1.81 (2H, m), 1.85-1.88 (2H, m), 2.08-2.22 (3H, m), 2.37 (3H, s), 2.95 (1H, d, *J* = 13.8 Hz), 4.83 (1H, s), 4.98 (1H, t, *J* = 2.4 Hz), 5.93 (1H, s), 7.20 (2H, d, *J* = 7.0 Hz), 7.57 (2H, d, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.2, 155.6, 141.5, 133.1, 126.4, 126.4, 129.3, 129.3, 103.2, 80.2, 56.3, 56.2, 54.3, 47.4, 47.3, 41.5, 40.8, 39.9, 39.3, 38.9, 35.7, 27.1, 21.4, 20.0, 19.6, 17.9, 17.9; HRESIMS *m/z* 408.2907 $[M + H]^+$ (calcd for $C_{27}H_{38}NO_2$, 408.2903).

*N-(4′-Ethylphenylcarbonyl)-4α-amino-19-nor-ent-13-hydroxykaur-16-ene (**32**).* Following the general procedure, compound **32** was prepared from **20** (60 mg, 0.19 mmol), using 4-ethylbenzoyl chloride (117.6 μL, 0.8 mmol); white powder (51.0 mg, 58.4%); $[\alpha]^{28}_{D}$ –90.9 (*c* 1.1, $CHCl_3$); R_f 0.44 [*n*-hexane-EtOAc (3:1)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (1H, td, *J* = 13.5, 3.5 Hz), 1.02-1.05 (2H, m, H-5, H-9), 1.14 (1H, td, *J* = 14.0, 4.0 Hz), 1.21-1.24 (6H, m), 1.30 (1H, dd, *J* = 11.0, 2.0 Hz), 1.40-1.48 (2H, m), 1.50 (3H, s), 1.52-1.64 (5H, m), 1.77-1.88 (4H, m), 2.08-2.25 (3H, m), 2.67 (2H, q, *J* = 7.5 Hz), 2.96 (1H, d, *J* = 14.0 Hz), 4.82 (1H, s), 4.98 (1H, t, *J* = 2.0 Hz), 5.93 (1H, s), 7.23 (2H, d, *J* = 8.0 Hz), 7.60 (2H, dt, *J* = 8.0, 2.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 166.2, 155.7, 147.7, 133.4, 128.1, 126.5, 103.2, 80.2, 56.4, 56.3, 54.3, 47.4, 47.4, 41.5, 40.9, 39.9, 39.3, 38.9, 35.7, 28.7, 27.1, 20.0, 19.6, 17.9, 17.9, 15.3; HRESIMS *m/z* 422.3062 $[M + H]^+$ (calcd for $C_{28}H_{40}NO_2$, 422.3059).

*N-(4′-Methoxyphenylcarbonyl)-4α-amino-19-nor-ent-13-hydroxykaur-16-ene (**33**).* Following the general procedure, compound **33** was prepared from **20** (60 mg, 0.19 mmol), using 4-methoxybenzoyl chloride (108.3 μL, 0.8 mmol); white powder (44.3 mg, 50.5%); $[\alpha]^{28}_{D}$ –90.4 (*c* 1.1, $CHCl_3$); R_f 0.30 [*n*-hexane-EtOAc (2:1)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (1H, td, *J* = 13.5, 4.0 Hz), 1.02-1.09 (2H, m), 1.13 (1H, td, *J* = 13.5, 4.0 Hz), 1.24 (3H, s), 1.30 (1H, dd, *J* = 10.5, 2.0 Hz), 1.42-1.48 (2H, m), 1.49 (3H, s), 1.55-1.62 (5H, m), 1.76-1.89 (4H, m), 2.06-2.17 (2H, m), 2.23

(1H, dt, *J* = 17.0, 2.5 Hz), 2.94 (1H, d, *J* = 14.5 Hz), 3.83 (3H, s), 4.82 (1H, s), 4.98 (1H, t, *J* = 2.5 Hz), 5.87 (1H, s), 6.90 (2H, d, *J* = 8.5 Hz), 7.64 (2H, d, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.8, 161.9, 155.7, 128.3, 128.2, 128.2, 113.8, 113.8, 103.2, 80.2, 56.4, 56.2, 55.4, 54.3, 47.4, 47.4, 41.5, 40.8, 39.9, 39.3, 38.9, 35.7, 27.2, 20.0, 19.6, 17.9, 17.9; HRESIMS *m/z* 424.2842 $[M + H]^+$ (calcd for $C_{27}H_{38}NO_3$, 424.2852).

*N-(4′-Ethoxyphenylcarbonyl)-4α-amino-19-nor-ent-13-hydroxykaur-16-ene (**34**).* Following the general procedure, compound **34** was prepared from **20** (60 mg, 0.19 mmol), using 4-ethoxybenzoyl chloride (94.3 μL, 0.8 mmol); yellow powder (48.8 mg, 53.8%); $[\alpha]^{28}_D$ –95.7 (*c* 1.15, $CHCl_3$); R_f 0.38 [*n*-hexane-EtOAc (2:1)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (1H, td, *J* = 13.0, 3.5 Hz), 1.01-1.05 (2H, m), 1.12 (1H, td, *J* = 14.0, 4.0 Hz), 1.24 (3H, s), 1.30 (1H, dd, *J* = 11.0, 2.0 Hz), 1.41 (3H, t, *J* = 7.0 Hz), 1.45-1.48 (2H, m), 1.49 (3H, s), 1.54-1.63 (5H, m), 1.77-1.88 (4H, m), 2.02-2.17 (2H, m), 2.24 (1H, dt, *J* = 17.0, 2.5 Hz, H-15), 2.94 (1H, d, *J* = 14.0 Hz), 4.06 (2H, q, *J* = 7.0 Hz), 4.82 (1H, s), 4.98 (1H, t, *J* = 2.5 Hz), 5.87 (1H, s), 6.88 (2H, d, *J* = 8.5 Hz), 7.62 (2H, d, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 165.8, 161.3, 155.7, 128.1, 128.1, 128.1, 114.2, 114.2, 103.2, 80.2, 63.6, 56.4, 56.2, 54.3, 47.4, 47.4, 41.5, 40.8, 39.9, 39.3, 38.9, 35.7, 27.2, 20.0, 19.6, 17.9, 17.9, 14.7; HRESIMS *m/z* 438.2995 $[M + H]^+$ (calcd for $C_{28}H_{40}NO_3$, 438.3008).

*N-(4′-Cyanophenylcarbonyl)-4α-amino-19-nor-ent-13-hydroxykaur-16-ene (**35**).* Following the general procedure, compound **35** was prepared from **20** (60 mg, 0.19 mmol), using 4-cyanobenzoyl chloride (100.4 μL, 0.8 mmol); white powder (53.0 mg, 61.1%); $[\alpha]^{28}_D$ –94.5 (*c* 1.1, $CHCl_3$); R_f 0.20 [*n*-hexane-EtOAc (2:1)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.87 (1H, m), 1.04-1.07 (2H, m), 1.16 (1H, td, *J* = 14.0, 4.5 Hz), 1.22 (3H, s), 1.31 (1H, m), 1.37-1.47 (2H, m), 1.50 (3H, s), 1.53-1.65 (5H, m), 1.75-1.89 (4H, m), 2.08-2.14 (2H, m), 2.24 (1H, dt, *J* = 17.5, 2.5 Hz), 2.90 (1H, d, *J* = 14.5 Hz), 4.82 (1H, s), 4.98 (1H, t, *J* = 2.0 Hz), 5.93 (1H, s), 7.70 (2H, d, *J* = 8.5 Hz), 7.86 (2H, d, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.4, 155.5, 139.9, 132.5, 132.5, 127.1, 127.1, 118.0, 114.7, 103.3, 80.1, 56.9, 56.1, 54.2, 47.3, 47.3, 41.4, 40.7, 39.7, 39.3, 38.9, 35.5, 26.9, 20.0, 19.6, 17.9, 17.9; HRESIMS *m/z* 419.2688 $[M + H]^+$ (calcd for $C_{27}H_{35}N_2O_2$,

419.2699).

*N-(Thiophene-2-carbonyl)-4α-amino-19-nor-ent-13-hydroxykaur-16-ene (**36**).* Following the general procedure, compound **36** was prepared from **20** (60 mg, 0.19 mmol), using thiophene-2-carbonyl chloride (85.5 μL, 0.8 mmol); white powder (15.8 mg, 19.0%); $[\alpha]^{28}_{D}$ –84.5 (*c* 1.0, $CHCl_3$); R_f 0.50 [*n*-hexane-EtOAc (2:1)]; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (1H, m, H-1), 1.00-1.04 (2H, m), 1.12 (1H, td, *J* = 11.5, 3.5 Hz), 1.24 (3H, s), 1.32 (1H, dd, *J* =9.0, 1.5 Hz), 1.39-1.47 (2H, m), 1.49 (3H, s,), 1.52-1.63 (5H, m), 1.74-1.87 (4H, m), 2.08-2.16 (2H, m), 2.23 (1H, dt, *J* = 14.5, 2.0 Hz), 2.88 (1H, d, *J* = 12.0 Hz), 4.82 (1H, s), 4.98 (1H, t, *J* = 2.5 Hz), 5.80 (1H, s), 7.04 (1H, dd, *J* = 4.0, 3.0 Hz), 7.36 (1H, dd, *J* = 4.0, 1.0 Hz), 7.40 (1H, dd, *J* = 3.0, 1.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 160.8, 155.6, 140.7, 129.3, 127.6, 127.3, 103.2, 80.2, 56.6, 56.1, 5 4.3, 47.4, 47.3, 41.4, 40.8, 39.8, 39.3, 38.9, 35.7, 27.1, 20.0, 19.5, 17.9, 17.7; HRESIMS *m/z* 400.2318 $[M + H]^+$ (calcd for $C_{24}H_{34}NO_2S$, 400.2310).

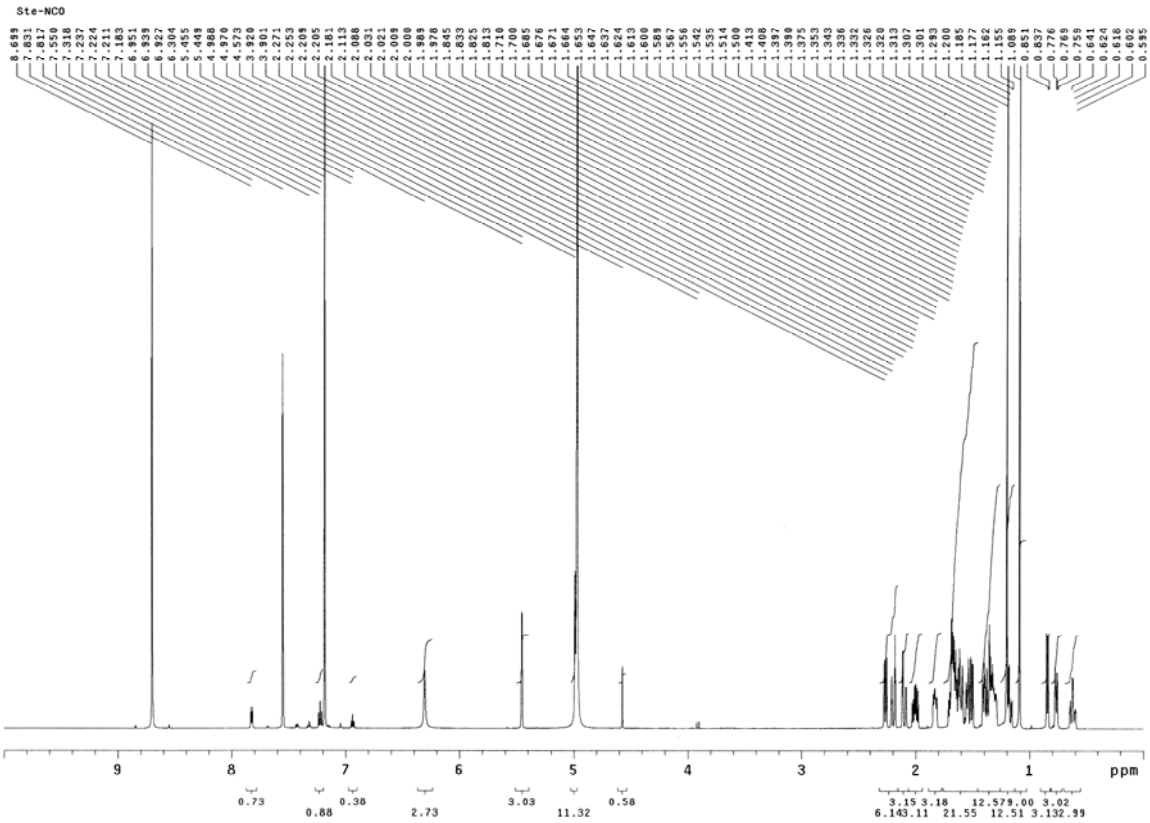

Figure S1. ^{1}H NMR spectrum of **2** (C_5D_5N, 500 MHz)

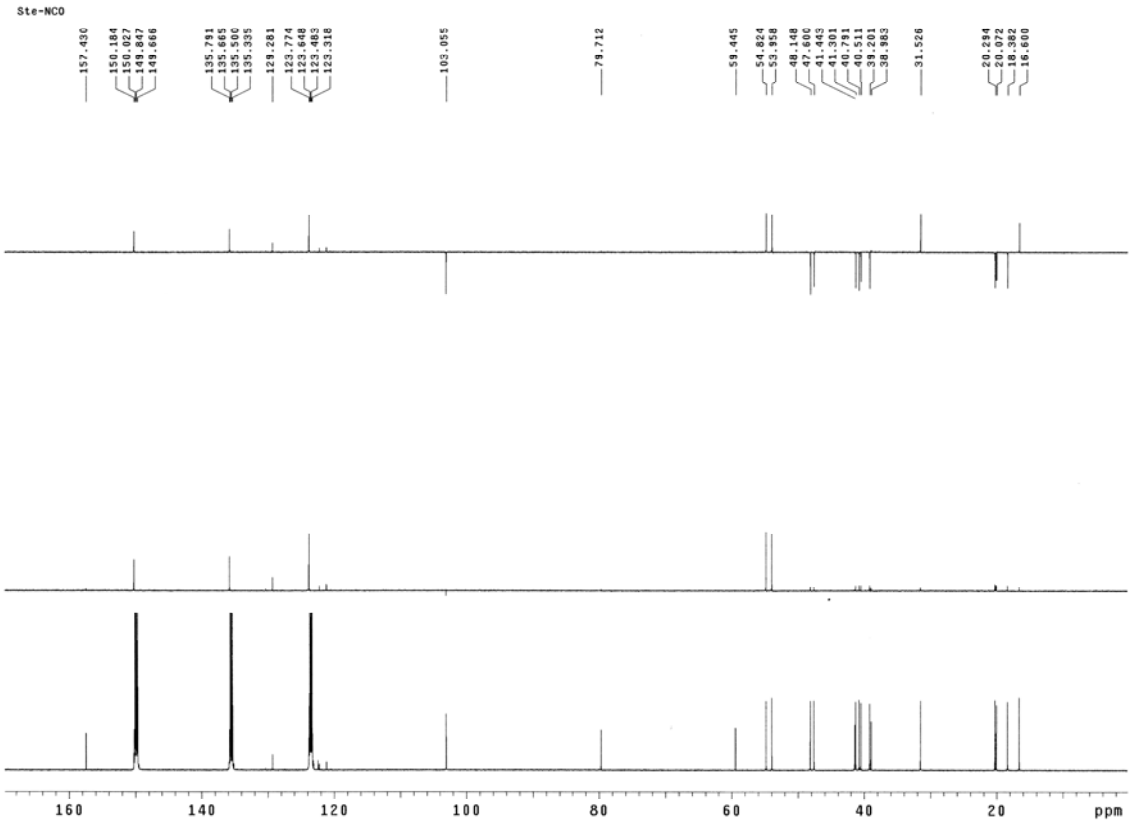

Figure S2. ^{13}C NMR and DEPT spectra of **2** (C_5D_5N, 125 MHz)

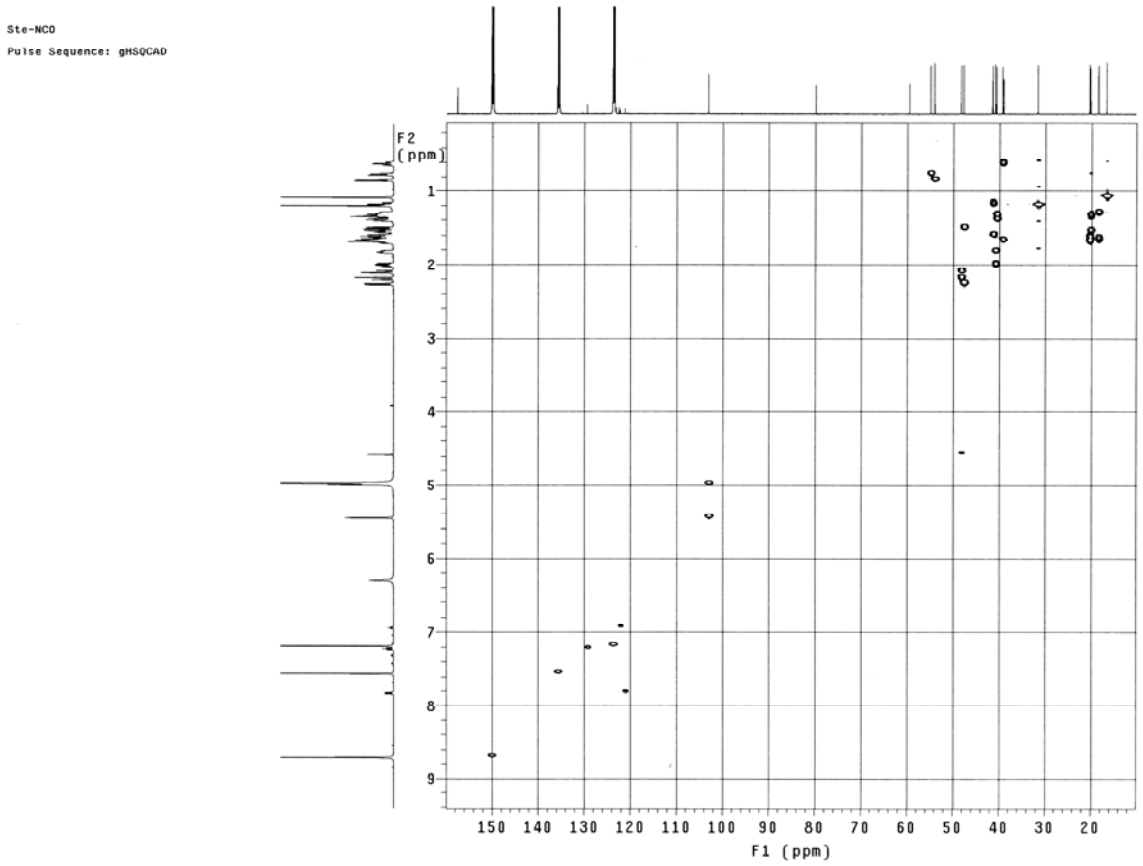

Figure S3. HSQC spectrum of **2** (C_5D_5N)

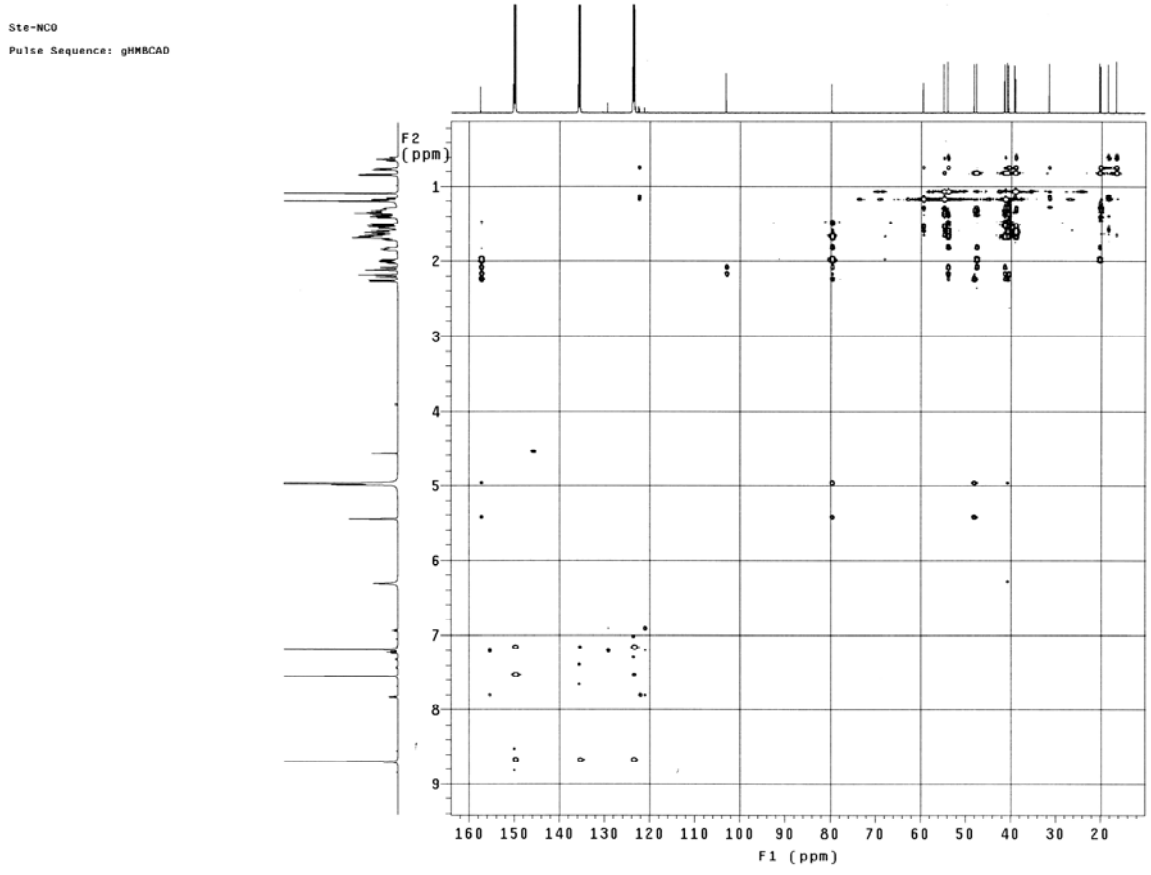

Figure S4. HMBC spectrum of **2** (C_5D_5N)

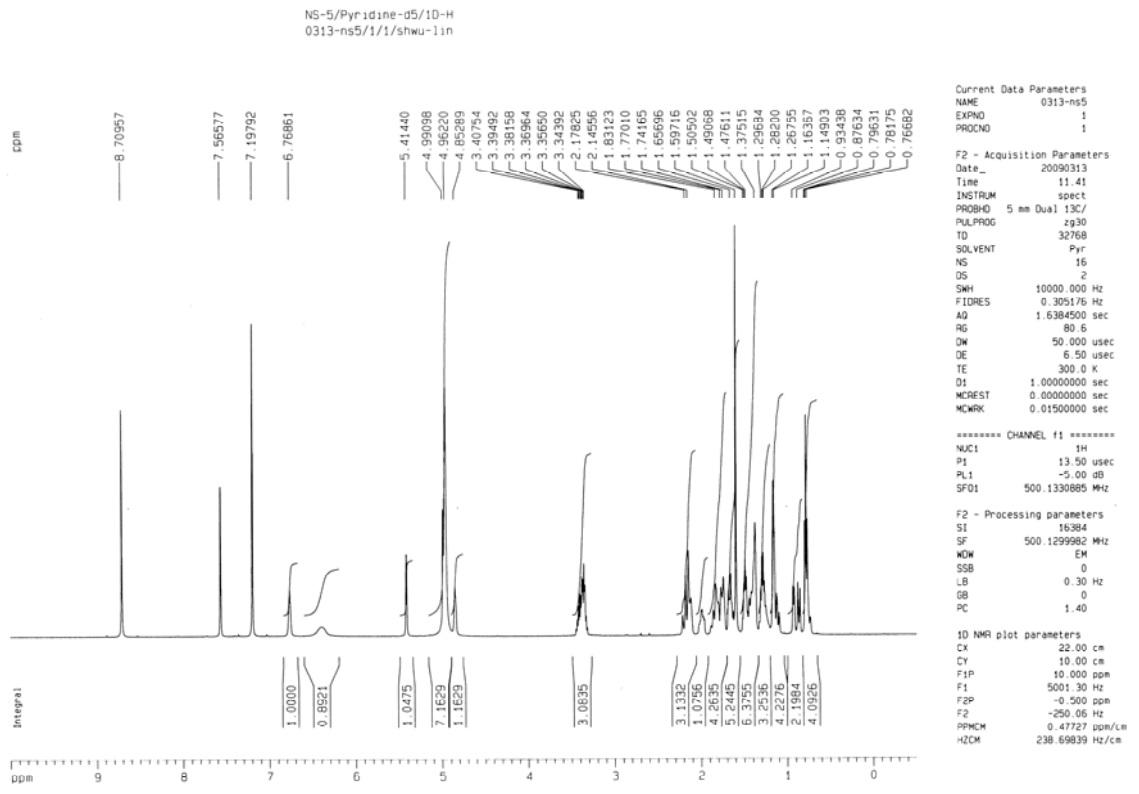

Figure S5. ^{1}H NMR spectrum of **6** (C_5D_5N, 500 MHz)

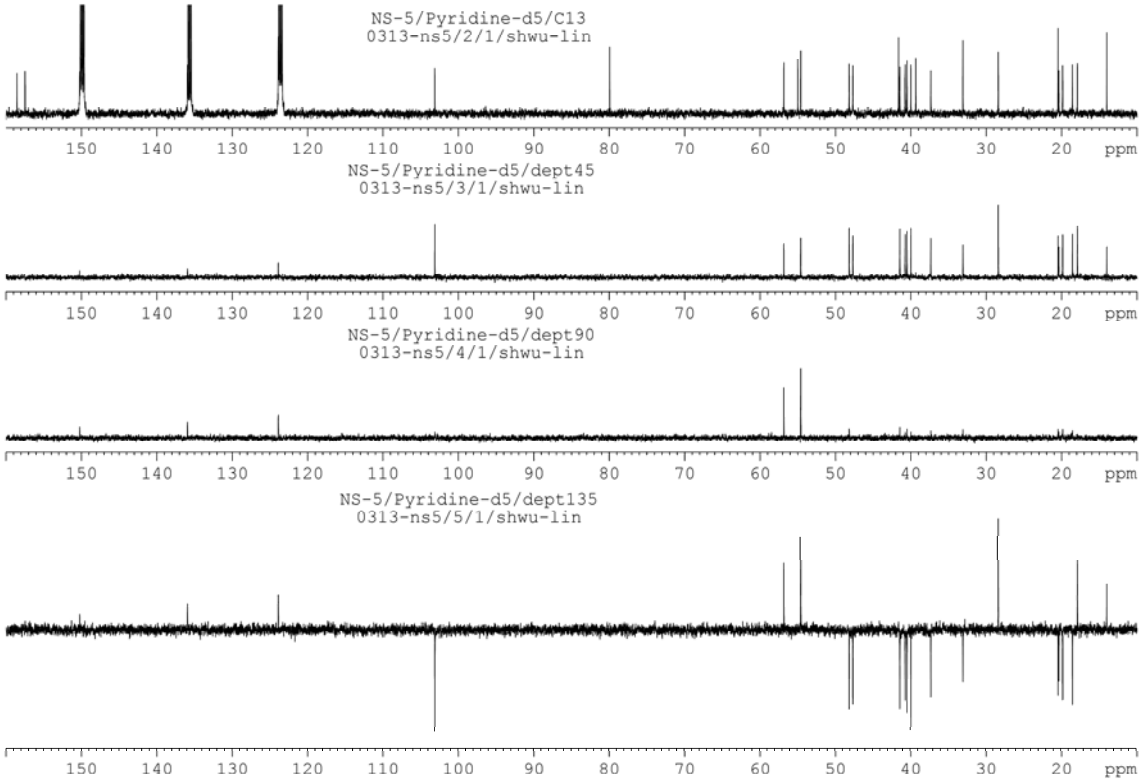

Figure S6. ^{13}C NMR and DEPT spectra of **6** (C_5D_5N, 125 MHz)

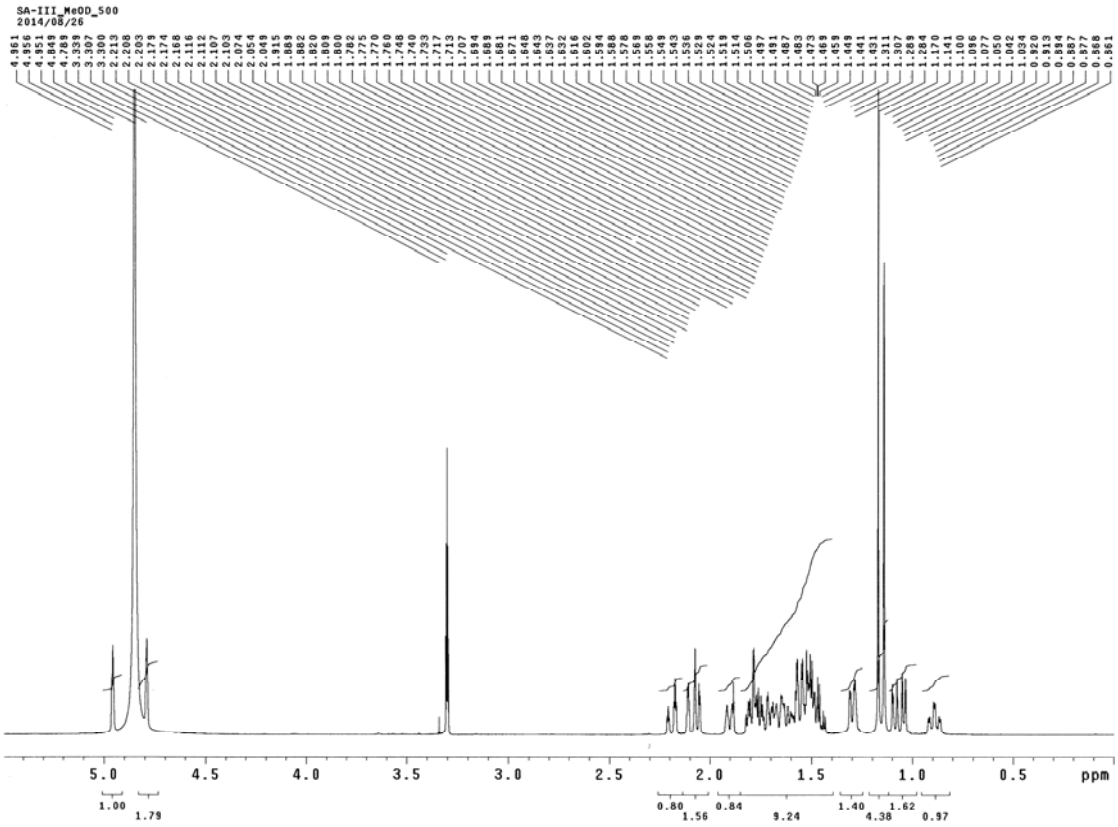

Figure S7. ^{1}H NMR spectrum of **20** (CD_3OD, 500 MHz)

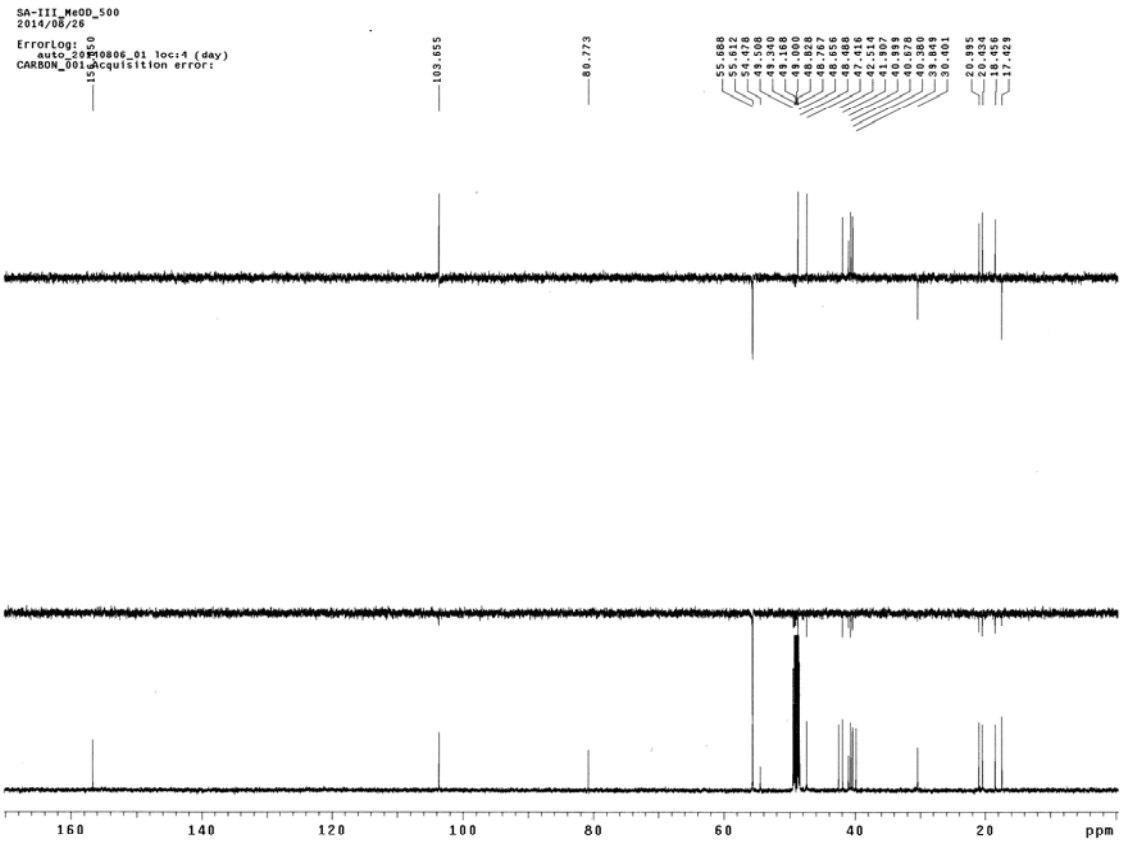

Figure S8. ^{13}C NMR and DEPT spectra of **20** (CD_3OD, 125 MHz)

Table S1. Anti-Hepatitis B Virus (HBV) Activities of Steviol Derivatives

compound	TC_{50}[a]	HBsAg[b]		HBeAg[c]		DNA replication	
	(μM)	IC_{50}[d] (μM)	SI[e]	IC_{50}[d] (μM)	SI[e]	IC_{50}[d] (μM)	SI[e]
3	213.2	61.8	3.5	100.8	2.1	87.4	2.4
4	246.7	77.2	3.2	116.9	2.1	121.8	2.0
5	482.1	72.9	6.6	74.8	6.4	60.6	8.0
7	147.5	22.6	6.5	38.8	3.8	52.2	2.8
8	354.5	70.3	5.0	30.5	11.6	53.3	6.7
9	778.1	59.6	13.1	64.4	12.1	58.2	13.4
10	24.8	33.5	0.7	16.5	1.5	20.7	1.2
11	20.3	13.1	1.6	14.3	1.4	2.8	1.0
12	23.8	18.6	1.3	14.4	1.7	12.5	1.9
13	29.7	8.0	3.7	5.0	5.9	4.5	6.6
14	14.9	56.1	0.3	10.7	1.4	14.2	1.1
15	309.3	59.6	5.2	15.9	19.5	22.8	13.6
16	49.1	13.2	3.7	13.6	3.6	14.7	3.3
17	30.2	14.0	2.2	12.5	2.4	14.3	2.1
18	37.3	11.7	3.2	7.7	4.8	6.3	5.9
19	44.8	14.8	3.0	17.7	2.5	21.9	2.0
21	681.1	34.8	19.6	49.6	13.7	46.6	14.6
22	677.5	63.7	10.6	150.1	4.5	117.5	5.8
23	1504.0	132.0	11.4	311.3	4.8	237.5	6.3
24	60.0	13.9	4.3	19.6	3.1	23.1	2.6
25	25.3	9.6	2.6	29.5	0.9	24.9	1.0
26	52.5	23.3	2.3	20.5	2.6	26.2	2.0
27	33.4	17.5	1.9	25.0	1.3	20.6	1.6
28	375.1	37.1	10.1	99.8	3.8	47.6	7.9
29	134.1	17.9	7.5	97.9	1.4	89.9	1.5
31	24.7	16.0	1.5	12.4	2.0	16.6	1.5
32	43.7	10.7	4.1	7.0	6.2	4.6	9.5
33	47.3	25.1	1.9	28.7	1.7	26.3	1.8
36	48.4	29.3	1.7	31.0	1.6	25.9	1.9
5-Fu[f]	227.9	–	–	–	–	–	–
lamivudine[g]	2360.9	–	–	–	–	107.5	22.0

[a]TC_{50}, 50% cytotoxic concentration in HepG2.2.15 cells. [b]HBsAg, HBV surface antigen. [c]HBeAg, HBV e antigen. [d]IC_{50}, 50% inhibitory concentration. [e]SI (selectivity index) = TC_{50}/IC_{50}. [f]5-FU (fluorouracil), positive control of cytotoxicity. [g]Lamivudine (3TC) as the antiviral positive control.