

Research Article

Synthetic Studies Towards (-)-(15R)-Hydroxycryptopleurine

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ABSTRACT

Asymmetric synthesis of core structure of (-)-(15R)-Hydroxycryptopleurine is described. The key steps involved in this synthesis are Wittig reaction, Sharpless asymmetric dihydroxylation, lactum ring formation.

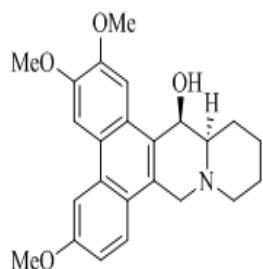
Keywords: Hydroxycryptopleurine, antitumor activity, phenanthrene ring formation.

1. INTRODUCTION

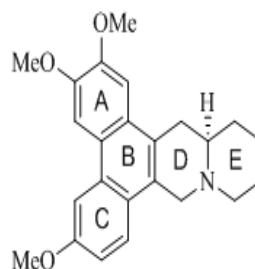
Hypoxia is a pathological condition, where the body or a region of the body is deprived of an adequate oxygen supply. In tumor cells, development of hypoxic regions enables tumors to develop their own blood supply. Hypoxia inducible factors (HIF-1) are transcription factors which control the cellular response to hypoxia. HIF-1 consists of an oxygen regulated α -subunit and a constitutively expressed β -subunit. In human cancer cell, HIF-1 α is over expressed, which causes the treatment failure. So in cancer chemotherapy, HIF-1 α could be an important target. (-)-(15R)-Hydroxycryptopleurine inhibits the accumulation of HIF-1 α protein in AGS human gastric cancer cells and also the expression of vascular endothelial growth factor.¹ It potently inhibits the hypoxia induced

expression of the HRE-reporter gene with IC_{50} values of 48.1 nM.¹

(-)-(15R)-Hydroxycryptopleurine (**1**, **Figure 1**) belongs to Phenanthroquinolizidine alkaloids. Despite of small groups, Phenanthroquinolizidine alkaloids have their own importance due to their unique biological properties including vesicant,² antimicrobial,³ antiviral⁴ and anticancer activities.⁵ Cryptopleurine (**2**, **Figure 1**) is a representative member of these alkaloids.^{2,6} (-)-(15R)-Hydroxycryptopleurine is a hydroxylated cryptopleurine. It has been isolated from the roots of *Boehmeria pinnosa* by Lee and co-workers in the year 2006¹. They elucidated its structure including the absolute configuration using spectroscopic method. Till date, two racemic syntheses of this molecule have been reported.^{7,8}



(-)-(15R)-Hydroxycryptopleurine (1)



Cryptopleurine (2)

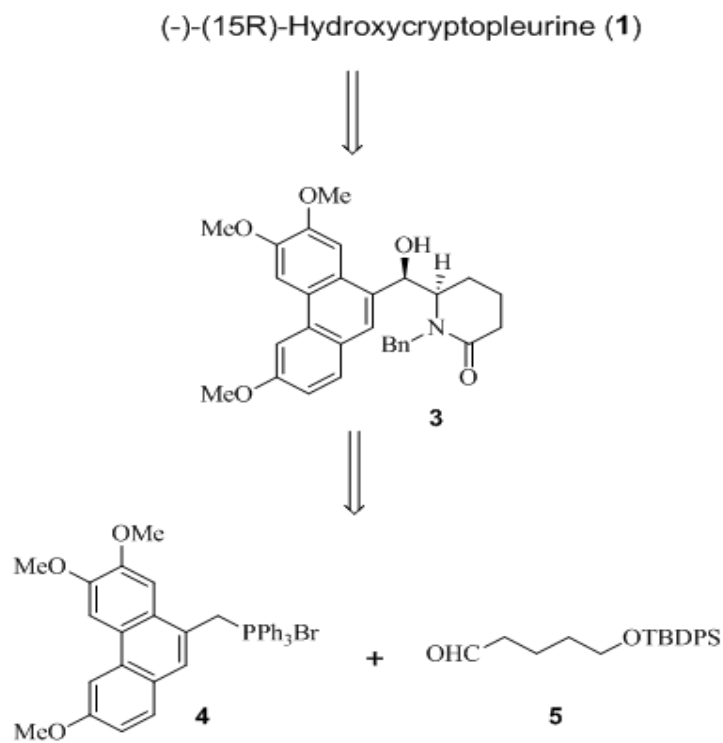
Fig. 1: Structures of (-)-(15R)-Hydroxycryptopleurine and Cryptopleurine

Herein, we report the first asymmetric synthesis towards core structure of (-)-(15R)-Hydroxycryptoleurine.

2. RESULTS AND DISCUSSION

Retrosynthetic analysis reveals the construction of key intermediate **3** synthesized

from phenanthrene Wittig salt **4** and aldehyde **5** by Wittig olefination reaction (**Scheme 1**). Key reactions used in build this compound were phenanthrene ring formation, Wittig reaction, Sharpless asymmetric dihydroxylation, selective protection of benzylic alcohol, lactum ring formation.

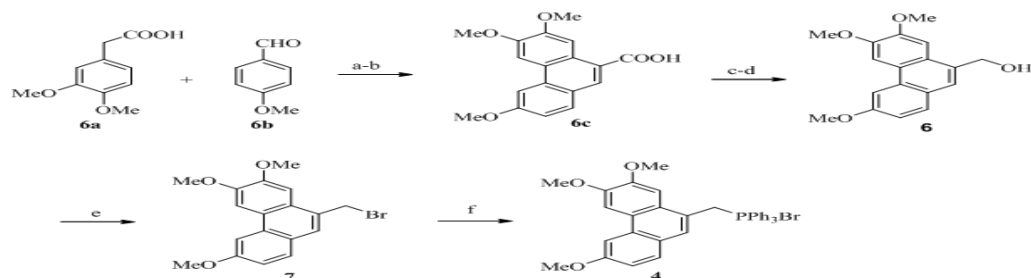


Scheme 1: Retrosynthesis of (-)-(15R)-Hydroxycryptoleurine

The synthesis of phenanthrene (A, B and C ring of Cryptoleurine **2** in figure 1) and quinolizidine rings (E) are the important concern of phenanthro-quinolizidine alkaloids. Construction of phenanthrene ring and D ring have already been reported.^{9,10} So our initial study focused on the synthesis of quinolizidine ring E.

We started our synthesis by using (3,6,7-trimethoxyphenanthrene-9-yl)methanol **6** as a starting material, which has been synthesized

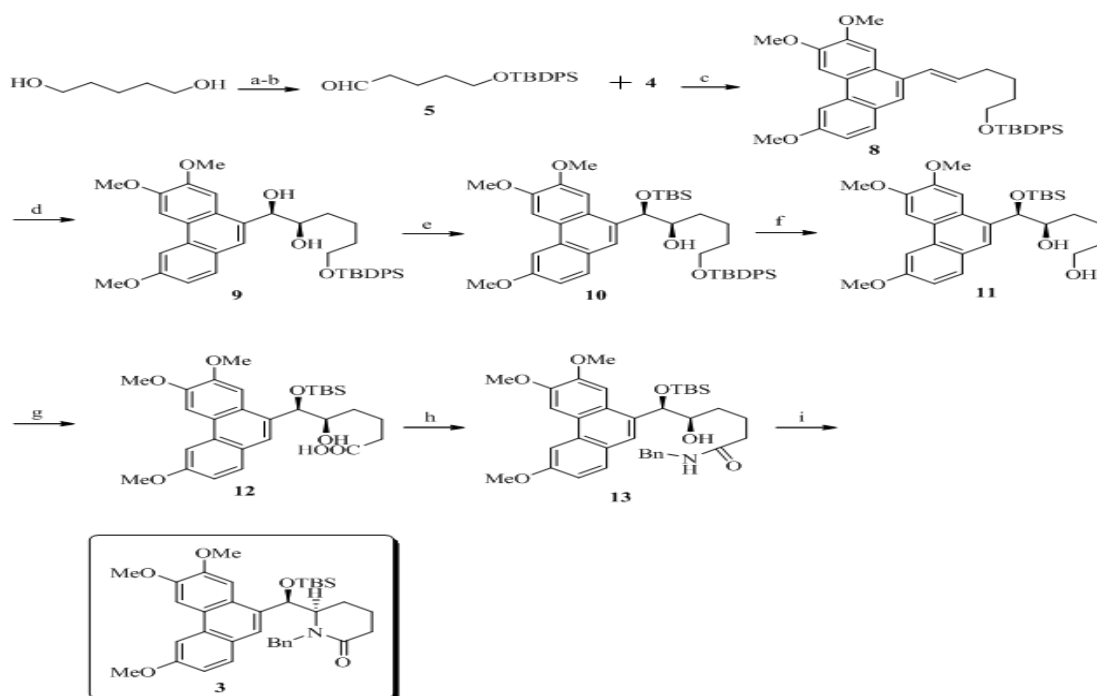
from 3,4-dimethoxyphenyl acetic acid **6a** and 4-methoxybenzaldehyde **6b** following a known procedure.^{9,11} Bromination of compound **6** with tetrabromomethane and triphenylphosphine gave 10-(bromomethyl)-2,3,6-trimethoxyphenanthrene **7** in 82% yield,¹² which on treatment with triphenyl phosphine afforded Wittig salt **4** in quantitative yield (**Scheme 2**).¹³



Scheme. 2: Preparation of Wittig salt 4 Reagents and conditions: (a) Ac_2O , Et_3N , rt to 115°C , 20 h, 73%; (b) FeCl_3 , CH_2Cl_2 , rt, 8 h, 78%; (c) MeOH , H_2SO_4 , rt to 70°C , 6 h, 76%; (d) LiAlH_4 , THF, 0°C to rt, 3 h, 67%; (e) CBr_4 , Ph_3P , CH_3CN , rt, 3 h, 82% (f) Ph_3P , toluene, 110°C .

Aldehyde 5 has been synthesized from commercially available 1,5-pentanediol in two steps from a known procedure.¹⁴ Wittig olefination reaction of salt 4 and aldehyde 5 using LHMDS afforded olefin 8 in 76% yield with 3:1 ratio of diastereomers, which has been shown from HPLC report.¹⁵ Sharpless asymmetric dihydroxylation of olefin 8 using $(\text{DHQD})_2\text{PHAL}$ gave the diol compound 9 in 52% yield with $> 99\%$ ee (HPLC analysis).¹⁶ Selective protection of benzylic alcohol in compound 9 with TBSOTf at -78°C gave the compound 10 with 76% yield.¹⁷ Desilylation of compound 10 by

using ammonium fluoride afforded primary alcohol 11 in 77% yield.¹⁸ Oxidation of primary alcohol in compound 11 with BAIB and TEMPO gave the acid 12 in 56% yield.¹⁹ The coupling of acid 12 with benzyl amine furnished amide 13 in 75% yield.²⁰ The cyclization of amide 13 was carried out with POCl_3 to afford lactum 3 in 53% yield²¹ (Scheme 3). This cyclized product 3 consists of phenanthrene ring as well as nitrogen containing ring as present in (-)-(15R)-Hydroxycryptoleurine with the required stereochemistry.



Scheme. 3: Synthesis of compound 3: Reagents and conditions: (a) TBDPS-Cl, Imidazole, CH_2Cl_2 , -15°C , 0.25 h, 75%; (b) BAIB, TEMPO, CH_2Cl_2 , 0°C to rt, 1 h, 78%; (c) LHMDS, THF, 0°C to rt, 3 h, 76%; (d) $\text{K}_3\text{Fe}(\text{CN})_6$, K_2CO_3 , $(\text{DHQD})_2\text{PHAL}$, OsO_4 , $\text{CH}_3\text{SO}_2\text{NH}_2$, $\text{Bu}^t\text{OH}:\text{H}_2\text{O}$ (1:1), 4°C , 60 h, 52%; (e) TBSOTf, 2,6-Lutidine, CH_2Cl_2 , -78°C , 0.5 h, 76%; (f) NH_4F , MeOH, 60°C , 3 h, 77%; (g) BAIB, TEMPO, $\text{CH}_3\text{CN}:\text{H}_2\text{O}$ (1:1), 0°C to rt, overnight, 56%; (h) BnNH_2 , EDCI, HOBT, Et_3N , THF, rt, overnight, 75%; (i) POCl_3 , Py, CH_2Cl_2 , -78°C to rt, 3 h, 53%.

3. Experimental Section

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography over silica gel of 60-120 mesh. IR spectra were recorded on Perkin-Elmer spectrometer. Optical rotations were obtained on digital polarimeter. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 solution on a Bruker Advance 300 and Bruker Advance 500 spectrometers. Chemical shifts were reported in parts per million with respect to internal TMS. Coupling constants (J) are quoted in Hz. Mass spectra were obtained on an Agilent Technologies LC/MSD trap SL.

(*E*)-*tert*-butyldiphenyl(6-(3,6,7-trimethoxyphenanthren-9-yl)hex-5-enyloxy)silane, 8

To a stirred solution of alcohol **6** (0.845 g, 2.83 mmol) in 40 mL of dry acetonitrile, TPP (1.19 g, 4.53 mmol), and CBr_4 (1.41 g, 4.25 mmol), were added at 0 °C and stirred for 3 h. Then acetonitrile was removed under reduced pressure and crude obtained was put over silicagel filter column and first eluting with hexane and then with chloroform. The column fractions were collected together, concentrated under reduced pressure and the compound **7** (0.84 g, 82% yield) was used for next reaction with some impurity, which was collected from column along with the compound.

The bromo compound **7** (0.813 g, 2.25 mmol) was dissolved in 20 mL of dry toluene and TPP (0.768 g, 2.92 mmol) was added to it at room temperature. The reaction mixture was kept for reflux at 110 °C for overnight. Next day, it was cooled to room temperature and toluene was removed under reduced pressure and dried completely. The solid obtained was washed properly with distilled hexane by scratching with spatula and then with ethyl acetate. Then it was dried completely to give the Wittig salt **4** (1.4 g), of compound **6** in quantitative yield.

Wittig salt **4** (1.28 g, 2.06 mmol), was dissolved in 30 mL of dry THF, cooled to 0 °C and to it, LHMDS (0.313 g, 1.87 mmol) was added dropwise and stirred for 0.5 h. Aldehyde **5** (0.637 g, 1.87 mmol) dissolved in 10 mL of THF was added to the reaction mixture at 0 °C and then stirred at room temperature for 3 h. The reaction mixture was quenched with 5 mL of ice-water, diluted with ethyl acetate (30 mL) and the organic layer was extracted, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure in rotavapour and crude obtained was purified over silica gel column eluting with hexane/EtOAc (19:1) to give compound **8** (0.86 g, 76 % yield). The de ratio

formed is 3:1; IR (neat): 2927, 2855, 2075, 1630, 1522, 1469, 1268, 1207, 1161, 1110, 704 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 7.95-7.90 (m, 2H), 7.88-7.82 (m, 1H), 7.79-7.74 (m, 1H), 7.71-7.60 (m, 5H), 7.41-7.33 (m, 6H), 7.19 (dd, $J = 2.4, 8.6$ Hz, 1H), 6.97 (d, $J = 15.4$ Hz, 1H), 6.30-6.19 (m, 1H), 4.12 (s, 3H), 4.03-3.99 (m, 6H), 3.74 (t, $J = 5.9$ Hz, 2H), 2.35 (q, $J = 6.6, 13.5$ Hz, 2H), 1.75-1.62 (m, 4H), 1.06 (s, 6H), 1.00 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 157.9, 149.1, 148.7, 135.5, 134.0, 133.9, 131.5, 130.0, 129.5, 127.7, 127.5, 126.2, 124.3, 122.6, 115.4, 105.0, 103.8, 103.7, 63.7, 56.0, 55.8, 55.5, 33.0, 32.1, 29.6, 26.8, 25.6; HRMS (ESI) Calcd for $\text{C}_{39}\text{H}_{44}\text{NaO}_4$: 627.2901 $[\text{M}+\text{Na}]^+$. Found: 627.2892 $[\text{M}+\text{Na}]^+$.

(1*R*,2*R*)-6-(*tert*-butyldiphenylsilyloxy)-1-(3,6,7-trimethoxyphenanthren-9-yl)hexane-1,2-diol, 9

$\text{K}_3\text{Fe}(\text{CN})_6$ (1.39 g, 4.23 mmol) and K_2CO_3 (0.585 g, 4.23 mmol) powder were taken in a round bottom flask and was dissolved in 40 mL of *tert*-BuOH:H₂O (1:1) at 0 °C. To it, ligand (DHQD)₂PHAL (0.011 g, 0.014 mmol) was added followed by olefin **8** (0.855 g, 1.41 mmol) dissolved in 2 mL of CHCl_3 and 5 mL of *tert*-BuOH at the same temperature and stirred for 0.5 h. Then OsO_4 (0.0014 g, 0.0056 mmol), was added to the reaction mixture followed by methanesulfonamide (0.201 g, 2.12 mmol) at 0 °C and stirred for 60 h at 4 °C. After completion of reaction, it was quenched with solid Na_2SO_3 , filtered and washed with chloroform, dried over anhyd. Na_2SO_4 and concentrated under reduced pressure in rotavapour and crude obtained was purified over silica gel column eluting with hexane/EtOAc (9:1) to give compound **9** (0.47 g, 52 % yield) with 100% ee ratio; $[\alpha]_D^{25}$ -4.7° (c 0.7, CHCl_3); IR (neat): 2924, 2854, 1612, 1524, 1465, 1220, 1110, 772, 704 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz): δ 7.88 (s, 1H), 7.82-7.76 (m, 3H), 7.69 (s, 1H), 7.64-7.58 (m, 5H), 7.44 (s, 1H), 7.39-7.30 (m, 4H), 7.20 (dd, $J = 2.2, 8.3$ Hz, 1H), 5.16 (d, $J = 5.2$ Hz, 1H), 4.10 (s, 3H), 4.01 (s, 3H), 3.96 (s, 3H), 3.63-3.53 (m, 3H), 1.57-1.35 (m, 6H), 0.99 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 158.3, 149.0, 148.6, 135.4, 133.9, 130.3, 129.5, 127.5, 125.4, 124.9, 123.5, 115.5, 104.5, 103.8, 74.8, 74.5, 63.7, 55.9, 55.8, 55.5, 33.1, 32.3, 26.8, 22.2; HRMS (ESI) Calcd for $\text{C}_{39}\text{H}_{46}\text{NaO}_6$: 661.2956 $[\text{M}+\text{Na}]^+$. Found: 661.2992 $[\text{M}+\text{Na}]^+$.

(5*R*,6*R*)-2,2,3,3,13,13-hexamethyl-12,12-diphenyl-5-(3,6,7-trimethoxyphenanthren-9-yl)-4,11-dioxo-3,12-disilatetradecan-6-ol, 10

Diol **9** (0.457 g, 0.71 mmol) was dissolved in 30 mL of dry CH_2Cl_2 and cooled to -78 °C. To

it, 2,6- lutidine (0.153 g, 1.42 mmol) was added followed by TBSOTf (0.189 g, 0.71 mmol) and stirred for 0.5 h at the same temperature. Then it was diluted with water (5 mL) and chloroform (30 mL). The organic layer was extracted, dried over anhyd. Na₂SO₄ and concentrated under reduced pressure in rotavapour and crude obtained was purified over silica gel column eluting with hexane/EtOAc (24:1) to give compound **10** (0.41g, 76 % yield); $[\alpha]_D^{25}$ -3.47° (c 0.75, CHCl₃); IR (neat): 2999, 2931, 2857, 1612, 1524, 1470, 1427, 1268, 1235, 1207, 1109, 878, 835, 777, 704, 613, 505 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.95 (s, 1H), 7.85 (d, *J* = 2.1 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 1H), 7.68-7.65 (m, 5H), 7.44-7.35 (m, 6H), 7.33-7.30 (m, 1H), 7.20 (dd, *J* = 2.4, 8.7 Hz, 1H), 5.26 (d, *J* = 4.1 Hz, 1H), 4.12 (s, 3H), 4.08-4.05 (m, 1H), 4.02 (s, 3H), 3.95 (s, 3H), 3.67 (t, *J* = 5.6 Hz, 2H), 1.67-1.55 (m, 6H), 1.05 (s, 9H), 0.83 (s, 9H), -0.21 (s, 3H), -0.60 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 158.2, 148.9, 148.3, 135.5, 133.8, 132.3, 130.5, 130.2, 129.5, 127.6, 127.5, 125.5, 124.9, 123.5, 115.4, 104.0, 103.9, 103.7, 74.6, 72.3, 63.6, 55.8, 55.4, 34.8, 32.9, 26.8, 25.8, 22.0, -4.7, -5.4; HRMS (ESI) Calcd for C₄₅H₆₀NaO₆Si₂: 775.3821 [M+Na]⁺. Found: 775.3844 [M+Na]⁺.

(5R,6R)-6-(tert-butylidimethylsilyloxy)-6-(3,6,7-trimethoxyphenanthren-9-yl)hexane-1,5-diol, 11

To a stirred solution of compound **10** (0.266 g, 0.35 mmol) in 10 mL of methanol, NH₄F (0.182 g, 4.94 mmol) was added at room temperature and then heated at 60 °C for 3 h. Then methanol was removed under reduced pressure in rotavapour, the solid obtained was diluted with 10 mL of ethyl acetate, cooled to 0 °C and quenched with saturated NH₄Cl solution (2 mL). The organic layer was collected, dried over anhyd. Na₂SO₄ and concentrated under reduced pressure in rotavapour and crude obtained was purified over silica gel column eluting with hexane/EtOAc (19:1) to give compound **11** (0.14 g, 77 % yield); $[\alpha]_D^{25}$ -4.0° (c 0.5, CHCl₃); IR (neat): 2929, 2856, 1612, 1524, 1470, 1267, 1220, 1159, 1071, 1037, 836, 772 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.94 (s, 1H), 7.84 (d, *J* = 2.3 Hz, 1H), 7.79-7.76 (m, 1H), 7.67 (s, 1H), 7.34 (s, 1H), 7.21-7.18 (m, 1H), 5.27 (d, *J* = 2.6 Hz, 1H), 4.12 (s, 3H), 4.08-4.04 (m, 1H), 4.03 (s, 3H), 4.02 (s, 3H), 3.64 (t, *J* = 5.8 Hz, 2H), 1.90-1.81 (m, 1H), 1.46-1.37 (m, 1H), 1.36-1.28 (m, 2H), 1.27-1.22 (m, 2H), 0.83 (s, 9H), -0.20 (s, 3H), -0.59 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 158.1, 149.1, 149.0, 132.2, 130.5, 130.4, 125.7, 125.5,

124.9, 124.7, 115.4, 104.1, 103.9, 103.8, 74.6, 74.5, 62.6, 55.9, 55.5, 55.4, 34.6, 32.8, 32.7, 25.8, 21.8, -4.7, -5.3; HRMS (ESI) Calcd for C₂₉H₄₂NaO₆Si: 537.2643 [M+Na]⁺. Found: 537.2639 [M+Na]⁺.

(5R,6R)-6-(tert-butylidimethylsilyloxy)-5-hydroxy-6-(3,6,7-trimethoxyphenanthren-9-yl)hexanoic acid, 12

Compound **11** (0.134 g, 0.26 mmol) was dissolved in 10 mL of 1:1 CH₃CN:H₂O and cooled to 0 °C. To it, BAIB (0.335 g, 1.04 mmol) and TEMPO (0.022 g, 0.13 mmol), were added at the same temperature and then stirred at room temperature for overnight. Acetonitrile was removed under reduced pressure in rotavapour. The reaction mass was diluted with 10 mL of ethyl acetate and solid Na₂S₂O₃ was added to it and stirred for 0.25 h and then organic layer was separated. The aqueous layer was extracted 3 times with ethyl acetate (10 mL), dried over anhyd. Na₂SO₄ and concentrated under reduced pressure in rotavapour and crude obtained was purified over silica gel column eluting with hexane/EtOAc (7:3) to give compound **12** (0.077 g, 56 % yield); $[\alpha]_D^{25}$ -4.36° (c 0.1, CHCl₃); IR (neat): 3447, 2957, 2925, 2855, 1741, 1621, 1460, 1379, 1260, 1094, 1020, 800 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.95-7.93 (m, 1H), 7.85-7.83 (m, 1H), 7.77 (d, *J* = 8.7 Hz, 1H), 7.68-7.65 (m, 1H), 7.34-7.31 (m, 1H), 7.22-7.18 (m, 1H), 5.27 (d, *J* = 2.4 Hz, 1H), 4.26-4.21 (m, 1H), 4.03 (s, 2H), 4.03 (s, 3H), 4.02 (s, 4H), 2.42-2.29 (m, 2H), 1.92-1.83 (m, 3H), 1.62-1.57 (m, 1H), 0.83 (s, 9H), -0.19 (s, 3H), -0.60 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 177.0, 158.1, 148.5, 148.4, 133.6, 130.5, 128.5, 125.7, 125.5, 123.5, 123.3, 115.5, 104.1, 104.1, 103.9, 73.7, 72.4, 55.9, 55.5, 55.4, 34.3, 31.9, 30.3, 25.8, 20.8, -4.7, -5.3; MASS : MA(APCI) m/z 527.0 [M-H]⁺.

(5R,6R)-N-benzyl-6-(tert-butylidimethylsilyloxy)-5-hydroxy-6-(3,6,7-trimethoxyphenanthren-9-yl)hexanamide, 13

To a stirred solution of acid **12** (0.074 g, 0.14 mmol) in 5 mL of dry THF, HOBt (0.021 g, 0.15 mmol) and Et₃N (0.016 g, 0.156 mmol) were added at room temperature. After that benzyl amine (0.017 g, 0.15 mmol) followed by EDCI (0.053 g, 0.28 mmol) were added to the reaction mixture at the same temperature and stirred for overnight. Then the reaction mixture was diluted with water (0.5 mL) and ethyl acetate (5 mL). The organic layer was extracted, dried over anhyd. Na₂SO₄ and concentrated under reduced pressure in rotavapour and crude obtained was purified

over silica gel column eluting with hexane/EtOAc (3:2) to give compound **13** (0.065 g, 75 % yield); $[\alpha]_D^{25}$ -8.46° (c 0.26, CHCl₃); IR (neat): 3791, 2927, 2856, 2360, 1727, 1601, 1445, 1362, 1217, 890, 760 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.90 (s, 2H), 7.83 (d, *J* = 2.3 Hz, 1H), 7.77 (d, *J* = 8.7 Hz, 1H), 7.66 (s, 1H), 7.35-7.29 (m, 3H), 7.21-7.18 (m, 2H), 7.15-7.12 (m, 2H), 5.26 (d, *J* = 2.4 Hz, 1H), 4.39 (s, 1H), 4.38 (s, 1H), 4.24-4.20 (m, 1H), 4.03 (s, 4H), 4.01 (s, 3H), 4.0 (s, 2H), 2.02-1.97 (m, 2H), 1.92-1.82 (m, 2H), 1.39-1.31 (m, 2H), 0.83 (s, 9H), -0.19 (s, 3H), -0.58 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 172.4, 158.2, 148.5, 148.4, 138.2, 132.1, 130.4, 130.2, 128.7, 128.6, 127.7, 127.6, 127.5, 125.2, 125.0, 124.9, 124.7, 115.5, 104.1, 104.0, 74.4, 74.3, 56.1, 56.0, 55.9, 43.5, 36.6, 34.5, 30.6, 25.8, 21.7, -4.7, -5.3; HRMS (ESI) Calcd for C₃₆H₄₇NNaO₆Si: 640.3065 [M+Na]⁺. Found: 640.3069 [M+Na]⁺.

(R)-1-benzyl-6-((R)-(tert-butylidimethylsilyloxy)(3,6,7-trimethoxyphenanthren-9-yl)methyl)piperidin-2-one, 3

Compound **13** (0.062 g, 0.10 mmol) was dissolved in 2 mL of dry CH₂Cl₂ and cooled to -78 °C. Then pyridine (0.04 g, 0.5 mmol) was added followed by POC₃ (0.017 g, 0.11 mmol) and the temperature was raised to room temperature and stirred for overnight. The reaction mixture was quenched with 1 mL of 10 % NH₄Cl solution at 0 °C and stirred for 5 h. Then it was diluted with 5 mL of chloroform. The organic layer was washed with saturated 1 mL of CuSO₄ solution, dried over anhyd. Na₂SO₄ and concentrated under reduced pressure in rotavapour and crude obtained was purified over silica gel column eluting with hexane/EtOAc (4:1) to give compound **3** (0.032 g, 53 % yield); $[\alpha]_D^{25}$ +4.5° (c 0.2, CHCl₃); IR (neat): 3383, 2957, 2924, 2854, 1741, 1616, 1518, 1461, 1378, 1261, 1094, 1023, 801, 701 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 8.17 (s, 1H), 8.13 (s, 1H), 7.89 (d, *J* = 1.8 Hz, 2H), 7.83 (d, *J* = 2.1 Hz, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 7.25-7.22 (m, 3H), 7.19 (d, *J* = 1.8 Hz, 1H), 7.19-7.17 (m, 1H), 5.34 (d, *J* = 4.2 Hz, 1H), 4.37 (s, 1H), 4.36 (s, 1H), 4.12 (s, 3H), 4.11-4.07 (m, 1H), 4.05 (s, 3H), 4.01 (s, 3H), 2.33-2.29 (m, 2H), 2.26-2.20 (m, 2H), 1.88-1.83 (m, 2H), 0.90 (s, 9H), 0.12 (s, 3H), 0.05 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ 170.4, 157.8, 149.2, 148.7, 135.5, 129.6, 128.8, 127.6, 126.8, 126.1, 125.5, 115.5, 107.4, 105.3, 103.5, 77.5, 71.7, 56.0, 55.7, 55.6, 46.7, 33.4, 31.9, 29.7, 26.8, 22.7, -4.2, -5.6; HRMS (ESI) Calcd for C₃₆H₄₆NO₅Si: 600.314 [M+H]⁺. Found: 600.3185 [M+Na]⁺.

4. CONCLUSION

In summary, we have accomplished a simple and straightforward asymmetric synthesis of core skeleton of (-)-(15R)-Hydroxycryptopleurine with excellent stereoselectivity.

5. ACKNOWLEDGEMENT

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