

Research Article

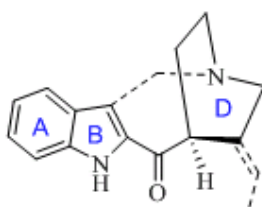
Synthetic Studies Towards the Stereoselective Construction of Tri-cyclic Core of (+) Conolidine

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ABSTRACT

The synthesis of tricyclic core (A B D ring) **2** of (+) conolidine is described. The synthetic strategy involved stereocontrol allylation of lactone, Sonagashira coupling, formation of lactam and indole ring as key steps.



Keywords: Alkaloid, Indole, Sonagashira coupling, Lactam.

1. INTRODUCTION

Plants of the genus *Tabernaemontana* (Apocynaceae) have a widespread distribution and are rich in alkaloids. These plants are found in Malaysia, India and also in other tropical countries. There are two distinct varieties in this family of plant, the single-flower and double-flower variety¹ and both occur widely in Malaysia. The ethanol extract of the leaves (double flower variety) collected in Petaling Jaya, Malaysia gave minor amounts of voaharine² and conophylline³ in addition to the major alkaloids voaphylline and *N*-methylvoaphylline.⁴ Voaharine represents the first example of a *Tabernaemontana* alkaloid derived biogenetically from tryptamine and secologanine but containing a 3-quinolone instead of indole chromophore. A total of 42 alkaloids were obtained from the stem-bark extract of the Malayan *Tabernaemontana divaricata* (double-flower variety), of which six are new alkaloid: (3*S*)-3-cyanocoronaridine,⁵ (3*S*)-3-cyanoisovoacangine,⁶ conolobine A,⁷ conolobine B, conolidine,⁸ and (3*R*/3*S*)-ethoxyvoacangine.⁹ Of these, three are ibogan compounds, while the other three are new vallesamineapparicine derivatives. Conolidine **1** is a potent nonopioid analgesic that is effective at alleviating chemically induced, acute and persistent tonic pain. Further studies in neuropathic pain models will be

undertaken to determine more widespread therapeutic promise for the treatment of chronic pain. Pharmacological mechanism of action associated with the potent analgesic properties of this alkaloid remains an area of intense current investigation, the results of these studies mark the establishment of a chemical foundation suitable for investigating the therapeutic potential of this unique alkaloid as a potent non-opioid analgesic.

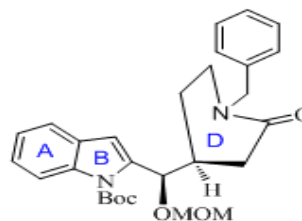


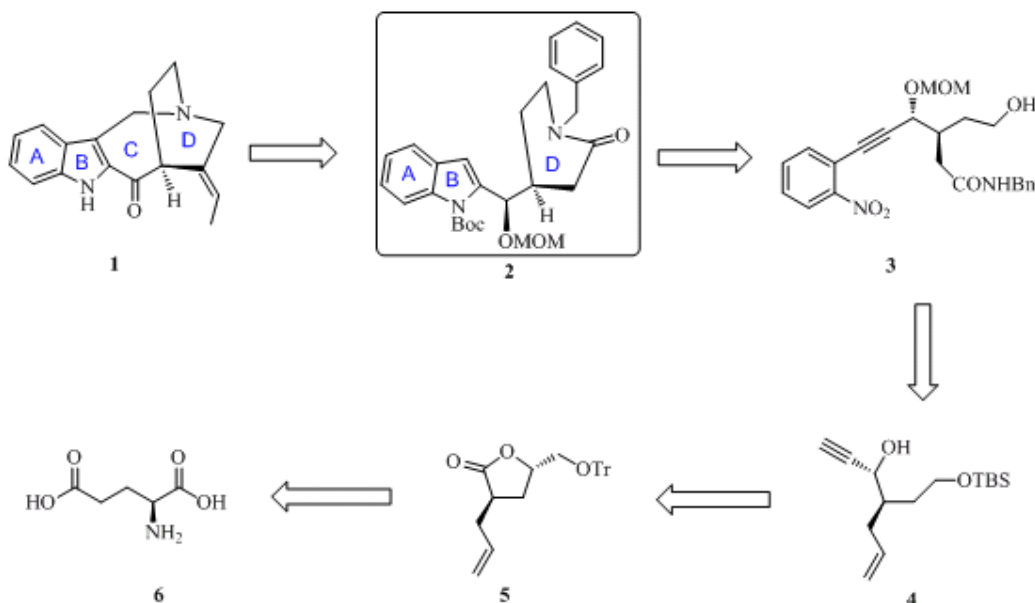
Fig. 1: Structure of tricyclic core conolidine 2

2. RESULTS AND DISCUSSION

A retro synthetic strategy of the present work towards the synthesis of conolidine is summarized in scheme 1. Because of the exceptional bioactivity and complex structural features, conolidine became attractive and challenging task to synthesize. The structure of lactam core **2** can be derived from amide alcohol **3**. The amide alcohol **3** can be

obtained from Sonagashira coupling of 1-iodo-2-nitrobenzene with mono protected diol **4**. The mono protected diol **4** can be further

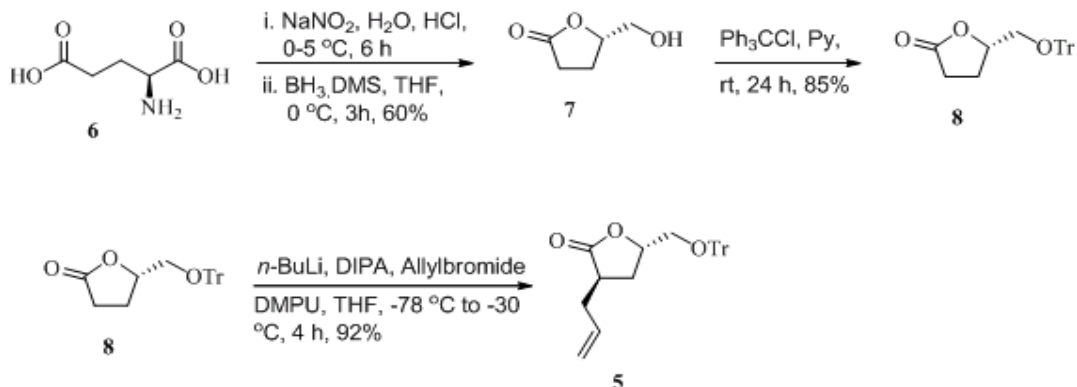
obtained from stereo controlled allylation of lactone **5**. This can be easily prepared from commercially available L-glutamic acid **6**.



Scheme. 1: Retrosynthetic analysis of tricyclic core conolidine 1

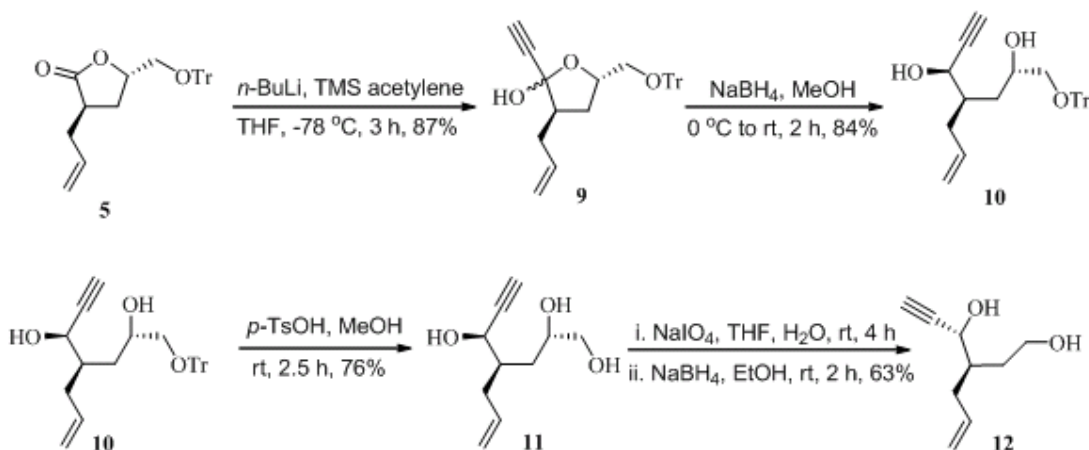
The synthetic plan was executed by choosing commercially available (*S*)-2-aminopentandioic acid (L-glutamic acid) **6** which on treatment with diazotization reaction in presence of NaNO_2 and HCl got converted to the lactone compound. The acid was reduced with $\text{BH}_3\cdot\text{DMS}$ in THF to give the alcohol compound **7** in 60% yield (over two steps).¹⁰ The hydroxyl group of **7** was protected as its triphenyl methyl ether using trityl chloride in pyridine as solvent. The reaction was monitored at room

temperature, and found to complete in 24 hours of vigorous stirring. The next objective was stereo controlled allylation adjacent to the carbonyl functional of lactone **8**.¹¹ Accordingly, **8** was treated with lithiumdiisopropylamide (LDA) as a base in THF as a solvent. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) was used as an anion stabilizer thus increasing the yield and allyl bromide was used as a source of allyl moiety.



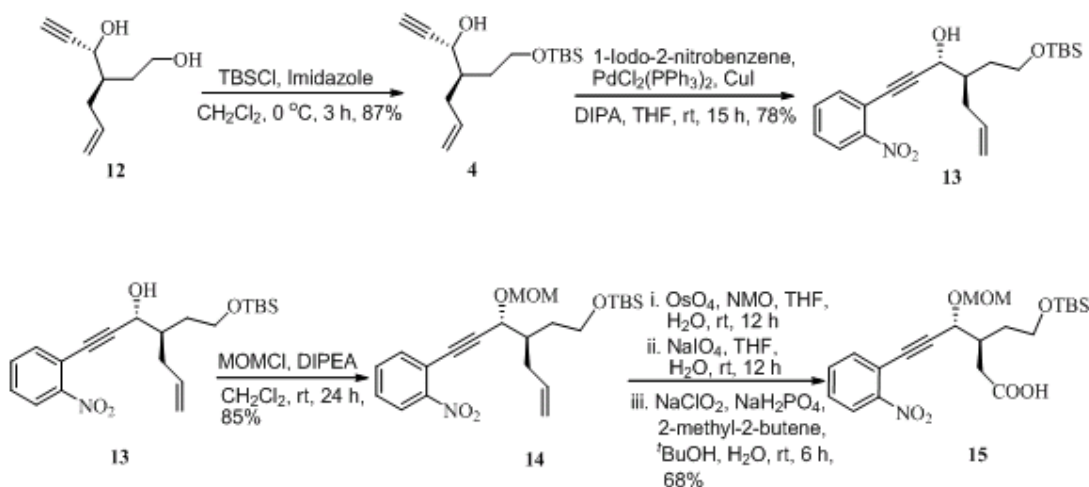
Nucleophilic addition of **5** was achieved by using TMS-acetylene and *n*-BuLi to afford the hemiketal **9** in 87% yield. Hemiketal **9** was reduced with NaBH₄ in MeOH to diol **10** in 84% yield. Deprotection of triphenylmethyl (trityl) group was carried out using *p*-TsOH in

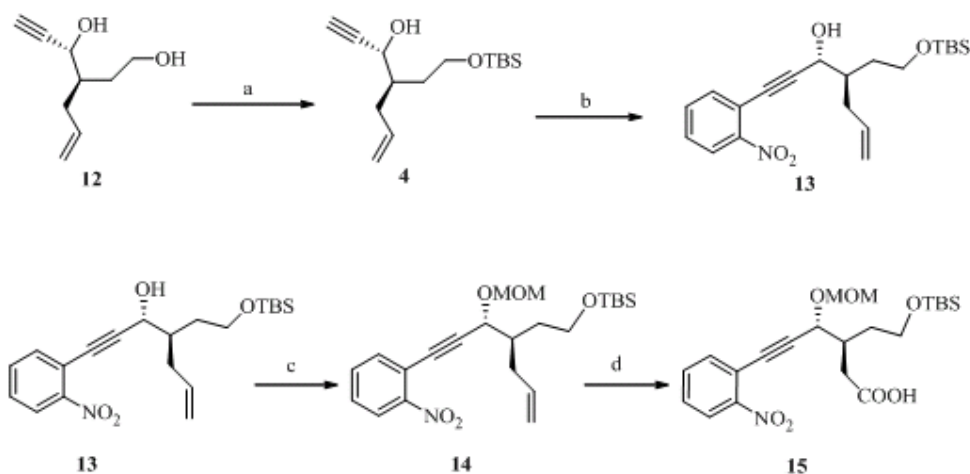
MeOH to produce vicinal diol **11**. The resultant vicinal diol functionality in **11** was oxidatively cleaved with NaIO₄ which resulted in lactol. The lactol was subjected to reduction using NaBH₄ to produce alcohol **12**.



The primary alcohol **12** was selectively protected as its TBS ether using TBSCl, imidazole in CH₂Cl₂ at 0 °C (87% yield). Sonagashira coupling of resultant alkyne derivative **4** with 1-iodo-2-nitrobenzene¹³ in THF/diisopropylamine (1:1) using Pd(PPh₃)₂Cl₂, CuI provided nitro compound **13** in 86% yield. Compound **13** was protected as its MOM ether **14** using MOMCl and DIPEA in CH₂Cl₂ for 12 h. The dihydroxylation

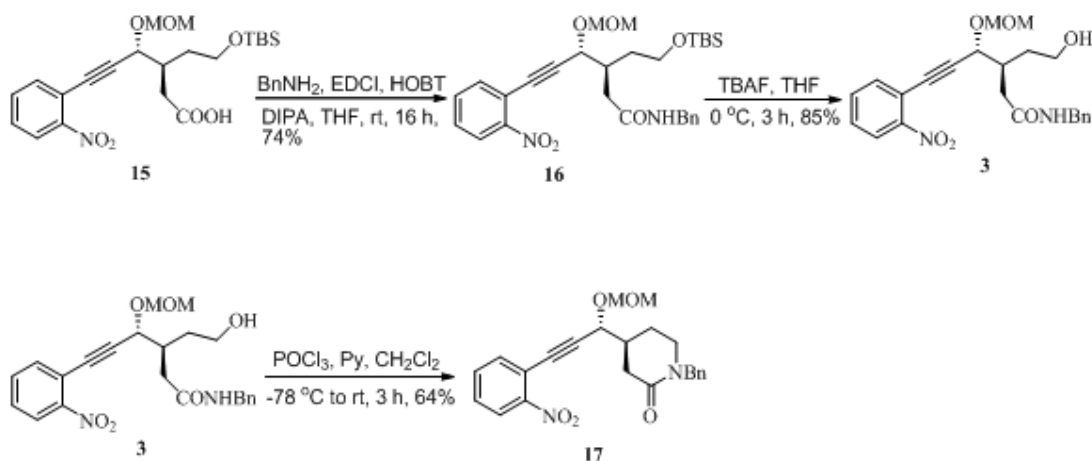
followed by cleavage of olefin **14** led to aldehyde. However, the aldehyde was observed to be unstable in silica gel chromatography. Hence, the aldehyde was not purified and the crude product was taken to next step. The aldehyde was then transformed to the acid **15** using NaH₂PO₄, NaClO₂ in ^tBuOH:H₂O (1:1) solvent. The acid **15** was isolated as thick gummy oil.





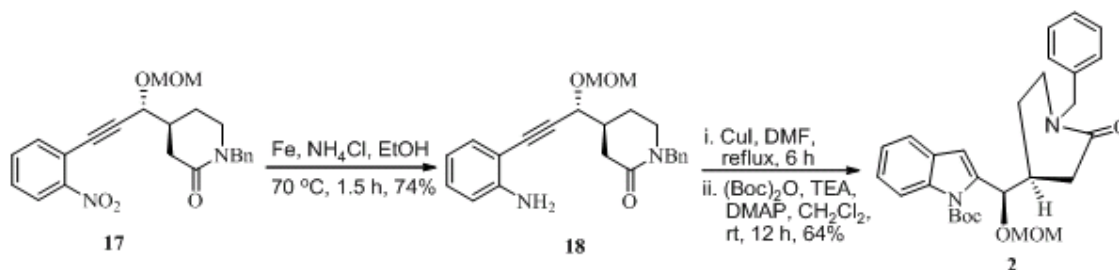
Benzylamine was coupled with acid **15** under classical conditions using EDCI, HOBT and DIPEA in THF as solvent for 12 h to afford amide **16** in 74% yield. Desilylation of **16** in

THF with TBAF in 2 h afforded alcohol **3** in 85% yield. Alcohol **3** was cyclized¹⁴ to **17** (lactam formation) using POCl₃, pyridine in CH₂Cl₂ at -78 °C.



The nitro functionality in **17** was reduced with Fe, NH₄Cl in ethanol as a solvent to produce amine **18**.¹⁵ The next objective was construction of indole ring. Accordingly, the

compound **18** was heated at 140 °C for 6 h in DMF solvent by using CuI. The indole was isolated as a Boc protected compound **2** on treatment with Boc anhydride in CH₂Cl₂.



3. CONCLUSION

In summary, we successfully synthesized the core compound **2** of (+) conolidine through

stereocontrol allylation of lactone, Sonogashira coupling and formation of lactam and indole ring as key reactions.

4. ACKNOWLEDGMENTS

M.S. thanks the UGC, New Delhi for research fellowship and S.C. is thankful to the DST, New Delhi for the research grant.

5. Experimental Section

Spectral data for selected compounds.

(S)-5-(Hydroxymethyl) dihydrofuran-2(3H)-one(7)

A solution of NaNO₂ (42 g, 612.24 mmol) in H₂O (85 mL) was added to a mixture of L-glutamic acid **6** (60 g, 408.16 mmol) in water (150 mL) and con HCl (84 mL) at 0-5 °C under vigorous stirring for 6 h. The clear solution was stirred at room temperature over night. Evaporation to dryness gave pale yellow suspension oil together with colourless crystals. Ethyl acetate (200 mL) was added, and the soluble material was filtered off and organic solvent was dried over Na₂SO₄. The organic solution was evaporated to get viscous oil, which was taken next step without purification.

To a solution of acid in THF (300 mL) at 0 °C, was slowly added BH₃·SMe₂ (28.73 mL, 343.99 mmol, 10 M solution in THF) over a period of 30 min. The reaction mixture was stirred at 0 °C for 3 h under nitrogen, followed by the slow addition of anhydrous MeOH (40 mL). After removal of the solvent on rotary evaporator, the residue was purified by flash chromatography on silica gel, eluting with CH₂Cl₂/MeOH (95:5) to give the alcohol compound **7** as a colourless oil (18.41 g, 60 %).

IR (KBr): ν_{max} 3185, 3048, 2109, 1747, 1695, 1470, 1274, 1100, 761 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.57-4.69 (m, 1H), 3.90 (dd, *J* = 2.3, 12.5 Hz, 1H), 3.64 (dd, *J* = 4.5, 12.5 Hz, 1H), 2.46-2.69 (m, 2H), 2.03-2.33 (m, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ 178.3, 80.9, 63.4, 28.3, 22.8; ESIMS *m/z* 153 [M+Na]⁺.

(S)-5-(Trityloxymethyl)dihydrofuran-2(3H)-one(8)

To a solution of alcohol **7** (18.0 g, 155.17 mmol) in pyridine (200 mL) was added trityl chloride (51.91 g, 278.78 mmol) and the whole mixture was stirred for 24 h at room temperature. After the completion of reaction, solvent was removed on rotary evaporator. The residue was dissolved in ethyl acetate and water (100 mL) was added. The organic layer was separated and aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with water (1 x 50 mL), brine (1 x 50 mL) and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the

crude product was purified by silica gel column chromatography (30% EtOAc in petroleum ether) to afford the compound **8** (47.2 g, 85 %) as colourless needles.

IR (KBr): ν_{max} 3020, 2926, 1770, 1447, 1216, 1180, 1033, 743 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 7.43 (d, *J* = 7.2 Hz, 6H), 7.20-7.34 (m, 9H), 4.57-4.68 (m, 1H), 3.41 (dd, *J* = 3.4, 10.4 Hz, 1H), 3.14 (dd, *J* = 4.2, 10.4 Hz, 1H), 2.59-2.74 (m, 1H), 2.41-2.56 (m, 1H), 2.13-2.28 (m, 1H), 1.94-2.07 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 177.4, 143.3, 128.5, 127.8, 127.1, 86.8, 79.0, 65.1, 28.3, 24.0; ESIMS *m/z* 381 [M+Na]⁺.

(3R,5S)-3-Allyl-5-(trityloxymethyl) dihydrofuran-2(3H)-one(5)

Lithium diisopropylamide (LDA) was generated *in situ* in the reaction flask with diisopropylamine (27.75 mL, 196.92 mmol) and *n*-BuLi (78.77 mL, 196.92 mmol, 2.5 M in hexane) in anhydrous THF (80 mL) at -15 °C over the period of 30 min. Complete inert atmosphere was maintained throughout the reaction. Then the reaction flask was cooled to -78 °C and to that the compound **8** (47 g, 131.28 mmol) in THF (250 mL) was added slowly over the period of 30 min. Then 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) (70 mL) was added and the reaction mixture was stirred for another 45 min at -78 °C. Then allyl bromide (15.1 mL, 183.79 mmol) was added dropwise and the reaction was further allowed to stir for 1 h at -78 °C then warm to -30 °C and stir for 3 h. Upon completion of the reaction, as monitored by TLC, the reaction mixture was brought to room temperature and quenched with saturated solution of NH₄Cl (50 mL) and stirred for a period of 10 min. The organic layer was separated and aqueous layers were extracted with EtOAc (3 x 150 mL). The combined organic layer was washed with water (1 x 150 mL), brine (1 x 50 mL) and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (15% EtOAc in petroleum ether) to afford the compound **5** (48 g, 92 %) as a liquid.

IR (KBr): ν_{max} 3021, 2872, 1765, 1447, 1218, 1173, 744 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 7.40-7.44 (m, 6H), 7.28-7.33 (m, 6H), 7.22-7.26 (m, 3H), 5.71-5.81 (m, 1H), 5.07-5.15 (m, 2H), 4.55-4.60 (m, 1H), 3.42 (dd, *J* = 3.5, 10.4 Hz, 1H), 3.12 (dd, *J* = 4.1, 10.4 Hz, 1H), 2.91 (dq, *J* = 4.6, 9.0 Hz, 1H), 2.55-2.62 (m, 1H), 2.23-2.31 (m, 1H), 2.12-2.18 (m, 1H), 1.96-2.04 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 178.9, 143.4, 134.4, 128.5, 127.9, 127.1,

117.7, 87.0, 76.9, 65.2, 38.9, 35.1, 29.5; ESIMS m/z 421 $[M+Na]^+$; $[\alpha]_D^{20}$: +24.8 ($c = 2.0$, $CHCl_3$).

(3R,5S)-3-Allyl-2-ethynyl-5-(trityloxy – methyl)tetrahydrofuran-2-ol(9)

TMS-acetylene (21.23 mL, 153.51 mmol) was dissolved in dry THF (100 mL) and cooled to -78 °C. To this solution was added n -BuLi (61.4 mL, 153.51 mmol, 2.5 M in THF) dropwise into the resulting solution for 30 min while maintaining the temperature at -78 °C. To this homogeneous solution was added lactone **5** (47 g, 118.09 mmol) as a solution in THF (200 mL) dropwise and stirred at -78 °C for 3 h. Progress of the reaction was monitored by TLC. Upon complete disappearance of the lactone, the mixture was diluted with additional 25 mL of THF and quenched with addition of saturated NH_4Cl (50 mL). The organic layer was extracted in to EtOAc (2 x 150 mL) and washed with water (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 , and the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (20% EtOAc in petroleum ether) to afford the compound **9** (43 g, 87 %) as a colourless liquid.

IR (KBr): ν_{max} 3297, 3019, 2924, 2092, 1766, 1677, 1446, 1074, 744 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$): δ 7.44-7.49 (m, 2H), 7.39-7.43 (m, 4H), 7.27-7.33 (m, 6H), 7.20-7.26 (m, 3H), 5.74-5.91 (m, 0.4H), 5.62-5.72 (m, 0.6H), 4.99-5.13 (m, 2H), 4.34-4.42 (m, 0.3H), 3.75-3.82 (m, 0.7H), 3.22 (s, 1H), 3.09-3.17 (m, 1H), 3.0-3.06 (m, 0.5H), 2.91-2.98 (m, 0.5H), 2.47-2.57 (m, 1H), 2.25-2.38 (m, 1H), 2.10-2.21 (m, 0.4H), 1.97-2.07 (m, 0.5H), 1.86-1.94 (m, 0.4H), 1.78-1.85 (m, 0.6H), 1.54-1.62 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.8, 143.6, 134.3, 128.7, 128.5, 127.8, 127.6, 127.0, 126.8, 117.6, 98.0, 86.7, 86.4, 79.4, 77.5, 71.4, 68.4, 67.6, 49.7, 49.1, 48.8, 35.2, 35.6, 34.3, 33.5; HRMS: Calculated for $C_{29}H_{28}NaO_3$ $[M+Na]^+$ 447.1930; found 447.1959.

(2S,4R,5R)-4-Allyl-1-(trityloxy)hept-6-yne-2,5-diol(10)

Hemiketal **9** (43 g, 101.41 mmol) was taken in absolute EtOH (300 mL) and cooled to 0 °C in ice bath. $NaBH_4$ (5.78 g, 152.12 mmol) was then added to the solution. The solution was allowed to warm to rt and stirred for 2 h. The reaction mixture was then quenched with dropwise addition of AcOH and pH was adjusted to 7.0. The solution was then diluted with EtOAc (75 mL) and the organic layer was washed with water (200 mL) and dried over Na_2SO_4 . The crude residue was purified by

column chromatography using 7:3 Hex/EtOAc as eluent, which gave diol **10** (36.29 g, 84 %) as a 9:1 mixture of diastereomers.

IR (KBr): ν_{max} 2922, 2853, 2102, 1726, 1447, 1215, 1073 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$): δ 7.43-7.47 (m, 6H), 7.38 (s, 1H), 7.30-7.35 (m, 5H), 7.24-7.29 (m, 3H), 5.66-5.77 (m, 1H), 4.98-5.09 (m, 2H), 4.45 (t, $J = 2.7, 5.3$ Hz, 1H), 4.07-4.14 (m, 1H), 3.08-3.19 (m, 2H), 2.45 (d, $J = 2.3$ Hz, 1H), 2.21-2.28 (m, 1H), 2.05-2.14 (m, 1H), 1.90-1.98 (m, 1H), 1.72-1.80 (m, 1H), 1.48-1.56 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.7, 136.3, 128.5, 127.8, 127.1, 116.8, 86.7, 83.1, 73.9, 68.4, 67.3, 64.9, 39.8, 35.6, 33.3; HRMS: Calculated for $C_{25}H_{30}O_3Na$ $[M+Na]^+$ 449.2087; found 449.2118; $[\alpha]_D^{20}$: -2.4 ($c = 2.0$, $CHCl_3$).

(2S,4R,5R)-4-Allylhept-6-yne-1,2,5-triol(11)

To a round-bottom flask were added diol **10** (29.2 g, 84.5 mmol) in MeOH (250 mL) and p -toluenesulfonic acid (1.6 g, 8.45 mmol). The solution was stirred at room temperature for 2.5 h then saturated aqueous $NaHCO_3$ (50 mL) was added and the mixture was extracted with EtOAc (4 x 100 mL). The combined organic layers were washed with water (1 x 50 mL), brine (1 x 50 mL) and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (70% EtOAc in petroleum ether) to afford the compound **11** (11.81 g, 76 %) as a liquid.

IR (KBr): ν_{max} 3303, 3015, 2929, 2090, 1640, 1215, 1031, 747 cm^{-1} ; 1H NMR (500 MHz, $CDCl_3$): δ 5.71-5.81 (m, 1H), 5.03-5.11 (m, 2H), 4.52 (t, $J = 2.7, 5.3$ Hz, 1H), 4.0-4.07 (m, 1H), 3.59-3.68 (m, 1H), 3.46-3.53 (m, 1H), 2.51 (d, $J = 2.1$ Hz, 1H), 2.18-2.25 (m, 1H), 2.07-2.14 (m, 1H), 2.0-2.07 (m, 1H), 1.74-1.80 (m, 1H), 1.49-1.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 136.2, 117.1, 82.6, 74.6, 69.9, 66.3, 64.9, 39.5, 36.2, 33.3; HRMS: Calculated for $C_{10}H_{17}O_3$ $[M+H]^+$ 185.1172; found 185.1183; $[\alpha]_D^{20}$: -34.17 ($c = 2.0$, $CHCl_3$).

(3R,4R)-3-Allylhex-5-yne-1,4-diol(12)

Triol compound **11** (11.5 g, 62.5 mmol) was dissolved in THF: H_2O (4:1) and cooled to 0 °C. To this solution was added $NaIO_4$ (26.75 g, 125 mmol) portion wise. The reaction mixture was stirred for 4 h at room temperature. After reaction was completed the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 50 mL). The organic layer was washed with sodium thiosulphate (2 x 35 mL), brine (35 mL), and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure, and the crude product was

taken in absolute EtOH (100 mL) and cooled to 0 °C in ice bath. NaBH₄ (3.56 g, 93.75 mmol) was then added to the reaction mixture. The reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction mixture was then diluted with EtOAc (50 mL) and the organic layer was washed with water (50 mL) and dried over Na₂SO₄. The crude residue was purified by column chromatography using 7:3 Hex/EtOAc as eluent, which gave diol **12** (6.06 g, 63 %) as a liquid.

IR (KBr): ν_{max} 3302, 2923, 2853, 2170, 1717, 1037, 771 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 5.72-5.83 (m, 1H), 5.03-5.11 (m, 2H), 4.45 (t, *J* = 2.4, 5.0 Hz, 1H), 3.84-3.90 (m, 1H), 2.49 (d, *J* = 2.1 Hz, 1H), 2.16-2.23 (m, 1H), 2.06-2.14 (m, 1H), 1.86-1.95 (m, 2H), 1.61-1.69 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 136.1, 117.0, 82.9, 74.3, 64.9, 61.5, 42.8, 36.6, 32.7; ESIMS *m/z* 155 [M+H]⁺; [α]_D²⁰: -0.62 (*c* = 0.16, CHCl₃).

(3R,4R)-4-(2-(tert-Butyl dimethyl silyloxy)ethyl)hept-6-en-1-yn-3-ol(4)

To an ice cooled solution of diol **12** (5.9 g, 38.31 mmol) in dichloromethane (80 mL), were added imidazole (3.38 g, 49.8 mmol) and TBDMSCI (6.89 g, 45.97 mmol). The reaction mixture was stirred at 0 °C for 3 h and quenched with NH₄Cl solution and extracted with CH₂Cl₂ (2 x 40 mL). The combined organic layer was washed with water (1 x 50 mL), brine (1 x 20 mL) and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford the compound **4** (8.93 g, 87 %) as a liquid.

IR (KBr): ν_{max} 2953, 2872, 2150, 1457, 1280, 1217, 1038, 771 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 5.72-5.84 (m, 1H), 5.02-5.12 (m, 2H), 4.32-4.37 (m, 1H), 3.94 (d, *J* = 7.2 Hz, 1H), 3.71-3.77 (m, 1H), 3.62-3.69 (m, 1H), 2.44 (d, *J* = 2.1 Hz, 1H), 2.36-2.43 (m, 1H), 2.05-2.24 (m, 1H), 1.86-1.95 (m, 2H), 1.63-1.71 (m, 1H), 0.91 (s, 9H), 0.09 (d, *J* = 2.4 Hz, 6H); ¹³C NMR (CDCl₃, 125 MHz): δ 136.4, 116.6, 84.3, 72.8, 64.3, 60.2, 42.1, 34.3, 32.0, 25.6, 18.0, -5.7; HRMS: Calculated for C₁₅H₂₉O₂Si [M+H]⁺ 269.1931; found 269.1947; [α]_D²⁰: -14.3 (*c* = 0.5, CHCl₃).

(3R,4R)-4-(2-(tert-Butyl dimethyl silyloxy)ethyl)-1-(2-nitrophenyl)hept-6-en-1-yn-3-ol (13)

To a solution containing an alkyne **4** (8.5 g, 31.71 mmol) and 1-iodo-2-nitrobenzene (8.68 g, 34.88 mmol) in diisopropylamine (60 mL) and THF (60 mL) at room temperature were added

dichlorobis(triphenylphosphine)palladium(II) (1.11 g, 1.58 mmol) and CuI (0.6 g, 3.17 mmol). The resulting mixture was stirred at room temperature for 15 h and was then filtered through a celite pad eluting with EtOAc. The filtrate was concentrated under reduced pressure and the residue was purified by flash silica gel column chromatography (15 % EtOAc in petroleum ether) to afford the compound **13** (9.62 g, 78 %) as a liquid.

IR (KBr): ν_{max} 3330, 2925, 2885, 1523, 1342, 1039, 997, 744 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 8.00 (d, *J* = 8.4 Hz, 1H), 7.60-7.64 (m, 1H), 7.54 (t, *J* = 7.6, 15.2 Hz, 1H), 7.43 (t, *J* = 7.5, 16.0 Hz, 1H), 5.70-5.87 (m, 1H), 5.01-5.19 (m, 2H), 4.59-4.68 (m, 1H), 3.83-3.91 (m, 1H), 3.59-3.78 (m, 1H), 2.27-2.36 (m, 1H), 2.12-2.23 (m, 1H), 1.95-2.09 (m, 2H), 1.57-1.92 (m, 1H), 0.89 (s, 9H), 0.08 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz): δ 149.6, 136.6, 134.8, 132.6, 128.5, 127.8, 124.5, 117.0, 98.4, 80.4, 65.3, 60.4, 42.6, 34.6, 32.3, 29.6, 25.8, -5.4; HRMS: Calculated for C₂₁H₃₂NO₄Si [M+H]⁺ 390.2095; found 390.2121; [α]_D²⁰: -31.4 (*c* = 2.4, CHCl₃).

(5R,6R)-6-Allyl-10,10,11,11-tetramethyl-5-((2-nitrophenyl)ethynyl)-2,4,9-trioxa-10-siladodecane (14)

To a solution of alcohol **13** (9 g, 23.13 mmol) and diisopropylethylamine (DIPEA) (8 mL, 46.27 mmol) in CH₂Cl₂ (100 mL) was added MOMCl (2.46 mL, 32.39 mmol) at room temperature. After stirring for 24 h, the reaction was quenched with saturated NH₄Cl (50 mL) and extracted with CHCl₃ (3 x 35 mL). The combined organic layer was washed with water (50 mL), brine (1 x 20 mL) and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (10% EtOAc in petroleum ether) to afford the compound **14** (8.5 g, 85 %) as a liquid.

IR (KBr): ν_{max} 2929, 2856, 1527, 1343, 1253, 1093, 1031, 833, 774 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 8.04 (d, *J* = 8.5 Hz, 1H), 7.60-7.63 (m, 1H), 7.56 (t, *J* = 7.5, 15.1 Hz, 1H), 7.46 (t, *J* = 7.3, 15.6 Hz, 1H), 5.78-5.90 (m, 1H), 5.08-5.16 (m, 1H), 5.01-5.08 (m, 1H), 4.65-4.75 (m, 1H), 3.75 (t, *J* = 6.6, 13.3 Hz, 2H), 3.42 (d, *J* = 5.0 Hz, 3H), 2.20-2.52 (m, 2H), 2.02-2.12 (m, 1H), 1.80-1.98 (m, 1H), 1.54-1.75 (m, 1H), 0.89 (d, *J* = 3.2 Hz, 9H), 0.05 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz): δ 149.6, 136.7, 136.4, 134.9, 132.7, 128.6, 124.5, 117.0, 98.4, 79.9, 65.9, 65.3, 64.9, 60.4, 42.6, 37.1, 34.6, 32.3, 25.8, -5.5; HRMS: Calculated for C₂₃H₃₆NO₅Si [M+H]⁺ 434.2357; found 434.2369; [α]_D²⁰: -15.9 (*c* = 1.0, CHCl₃).

(3S,4R)-3-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-4-(methoxymethoxy)-6-(2-nitrophenyl)hex-5-ynoic acid(15)

To a stirred solution of alkene **14** (8.0 g, 18.47 mmol) in THF:H₂O (3:2), 4-methylmorpholine *N*-oxide (2.99 g, 22.17 mmol) and osmium tetroxide (46 mg, 0.184 mmol) were added and stirred at room temperature overnight. After completion of reaction, water (50 mL) and ethyl acetate (50 mL) were added to the reaction mixture. The aqueous phase was extracted with more ethyl acetate (4 x 40 mL) and the organic phases were collected together, washed with water (25 mL) and brine (25 mL), dried over anhydrous Na₂SO₄, concentrated in *vacuo*. The residue obtained was dissolved in THF (24 mL) and water (60 mL). To this solution sodium periodate (7.98 g, 36.95 mmol) was added and it was stirred at room temperature overnight. The reaction mixture was diluted with water (50 mL) and extracted with EtOAc (3 x 35 mL). The organic layer was washed with sodium thiosulphate (2 x 25 mL), brine (25 mL) and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the crude product was taken to next step without further purification.

The crude product was dissolved in *t*BuOH (40 mL) and water (40 mL) then cooled to 0 °C. Then sodium perchlorate (3.54 g, 36.95 mmol), sodium dihydrogen phosphate (5.76 g, 36.95 mmol) and 2-methyl-2-butene (18.4 mL, 36.95 mmol, 2 M solution in THF) were added. The reaction mixture was stirred vigorously for 6 h. Upon completion of the reaction, monitored by TLC, the reaction mixture was partitioned between EtOAc (30 mL) and water (30 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in *vacuo* purified by silica gel column chromatography (70% EtOAc in petroleum ether) to afford the compound **15** (6.0 g, 68 %) as a liquid.

IR (KBr): ν_{max} 3305, 2928, 2855, 2106, 1647, 1525, 1343, 1093, 1026, 834, 744 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 8.04-8.08 (m, 1H), 7.61-7.64 (m, 1H), 7.55-7.60 (m, 1H), 7.45-7.50 (m, 1H), 5.04 (dd, *J* = 6.9, 12.5 Hz, 1H), 4.75 (d, *J* = 5.2 Hz, 1H), 4.67 (dd, *J* = 2.6, 5.2 Hz, 1H), 3.74-3.80 (m, 2H), 3.42 (d, *J* = 5.2 Hz, 3H), 2.50-2.86 (m, 3H), 1.85-2.04 (m, 1H), 1.65-1.79 (m, 1H), 0.89 (s, 9H), 0.06 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz): δ 178.7, 149.5, 134.9, 132.8, 128.8, 124.6, 117.8, 94.6, 94.4, 94.1, 68.3, 61.1, 55.9, 37.3, 35.1, 33.4, 32.8, 25.8, -5.4; HRMS: Calculated for C₂₂H₃₃NO₇SiNa [M+Na]⁺ 474.1912; found 474.1908; [α]_D²⁰: -2.4 (*c* = 2.0, CHCl₃).

(3S,4R)-*N*-Benzyl-3-(2-(*tert*-butyldimethylsilyloxy)ethyl)-4-(methoxymethoxy)-6-(2-nitrophenyl) hex-5-ynamide(16)

1-Ethyl-3-(3-dimethyl aminopropyl) carbodimide (EDCI) (4.65 g, 24.39 mmol) was added to a mixture of acid **15** (5.5 g, 12.19 mmol), benzyl amine (1.46 mL, 13.41 mmol), 1-hydroxybenzotriazole (1.81 g, 13.41 mmol) and diisopropylamine (3.4 mL, 24.39 mmol) in tetrahydrofuran (65 mL) and the mixture was stirred at room temperature for 16 h. The reaction mixture was diluted with saturated sodium bicarbonate (35 mL) and extracted with ethyl acetate (2 x 35 mL). The combined extract was washed with brine (25 mL), dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (30% EtOAc in petroleum ether) to afford the compound **16** (4.88 g, 74 %) as a liquid.

IR (KBr): ν_{max} 3308, 2929, 2855, 2150, 1647, 1525, 1343, 1216, 1027, 772, 745 cm⁻¹; ¹H NMR (500 MHz, CDCl₃): δ 8.04 (d, *J* = 8.2 Hz, 1H), 7.60-7.64 (m, 1H), 7.55-7.59 (m, 1H), 7.44-7.49 (m, 1H), 7.21-7.33 (m, 1H), 6.30 (t, *J* = 5.5, 11.0 Hz, 1H), 4.98 (d, *J* = 7.0 Hz, 1H), 4.74 (d, *J* = 3.8 Hz, 1H), 4.65 (d, *J* = 7.0 Hz, 1H), 4.40-4.51 (m, 2H), 3.72-3.81 (m, 2H), 3.40 (s, 4H), 2.47-2.61 (m, 3H), 1.96-2.04 (m, 1H), 1.65-1.77 (m, 1H), 0.88 (s, 9H), 0.05 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz): δ 171.6, 149.4, 138.4, 134.9, 132.9, 128.8, 128.5, 127.7, 127.2, 124.6, 117.9, 94.9, 94.5, 68.5, 61.4, 55.8, 43.5, 37.7, 32.7, 29.6, 25.9, -5.4; HRMS: Calculated for C₂₉H₄₁N₂O₆Si [M+H]⁺ 541.272; found 541.271; [α]_D²⁰: + 9.4 (*c* = 2.0, CHCl₃).

(3S,4R)-*N*-Benzyl-3-(2-hydroxyethyl)-4-(methoxymethoxy)6-(2-nitrophenyl)hex-5-ynamide(3)

A solution of the TBS ether **16** (4.5 g, 8.33 mmol) in THF (50 mL) was treated with TBAF (12.49 mL, 1 M in THF, 12.49 mmol) at 0 °C and stirred for 3 h at room temperature. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layer was washed with brine (25 mL), dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (60% EtOAc in petroleum ether) to afford the compound **3** (3 g, 85 %) as a liquid.

IR (KBr): ν_{max} 3414, 2928, 2892, 1671, 1626, 1522, 1343, 1026, 753 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 8.04 (d, *J* = 8.1 Hz, 1H), 7.55-7.65 (m, 2H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.22-7.37 (m, 5H), 6.15-6.30 (m, 1H), 4.99 (t, *J* =

5.3 Hz, 1H), 4.60-4.71 (m, 2H), 4.42-4.51 (m, 2H), 3.65-3.81 (m, 2H), 3.40 (d, $J = 4.5$ Hz, 3H), 2.58-2.83 (m, 2H), 2.33-2.51 (m, 1H), 1.87-2.09 (m, 1H), 1.58-1.79 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 169.7, 148.7, 139.4, 136.9, 132.5, 130.8, 128.6, 127.1, 126.7, 124.6, 109.9, 94.3, 93.7, 93.3, 67.8, 59.6, 55.7, 47.4, 33.9, 32.7, 29.6; HRMS: Calculated for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_8\text{Na}$ $[\text{M}+\text{Na}]^+$ 449.1682; found 449.1668; $[\alpha]_{\text{D}}^{20}$: + 37.7 ($c = 0.5$, CHCl_3).

***tert*-Butyl-2-((*R*)-((*S*)-1-benzyl-2-oxopiperidin-4-yl) (methoxymethoxy) methyl-1*H*-indole-1-carboxylate (17)**

To a stirred mixture of alcohol **3** (2.8 g, 6.57 mmol) and pyridine (2.65 mL, 32.86 mmol) in CH_2Cl_2 (35 mL) was added dropwise a solution of phosphoryl chloride (0.67 mL, 7.23 mmol) at -78 °C and then the reaction mixture was allowed to warm to room temperature. After 3 h, the reaction mixture was treated with 10% aqueous NH_4Cl solution at 0 °C and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (40% EtOAc in petroleum ether) to afford the compound **17** (1.71 g, 64 %) as a liquid.

IR (KBr): ν_{max} 2925, 2854, 1629, 1524, 1342, 1022, 771, 745 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 8.07 (d, $J = 8.1$ Hz, 1H), 7.55-7.66 (m, 1H), 7.48 (t, $J = 8.5$, 15.1 Hz, 1H), 7.22-7.38 (m, 6H), 5.07 (dd, $J = 2.5$, 6.8 Hz, 1H), 4.62-4.77 (m, 2H), 4.41-4.57 (m, 2H), 3.41 (d, $J = 3.6$ Hz, 3H), 3.22-3.36 (m, 2H), 2.70-2.85 (m, 1H), 2.42-2.61 (m, 1H), 2.25-2.41 (m, 1H), 1.57-1.87 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 169.1, 149.6, 136.9, 134.9, 133.0, 129.2, 128.6, 128.0, 127.4, 124.7, 117.6, 94.3, 93.5, 82.3, 68.5, 55.9, 50.0, 46.1, 37.9, 34.6, 24.8; HRMS: Calculated for $\text{C}_{23}\text{H}_{25}\text{N}_2\text{O}_5$ $[\text{M}+\text{H}]^+$ 409.1758; found 409.1775; $[\alpha]_{\text{D}}^{20}$: + 58.8 ($c = 0.5$, CHCl_3).

(*S*)-4-((*R*)-3-(2-Aminophenyl)-1-(methoxy methoxy)prop-2-ynyl)-1 benzylpiperidin-2-one(18)

To a solution of nitro compound **17** (1.5 g, 3.67 mmol) in EtOH (15 mL) and water (5 mL) were added iron powder (1.02 g, 18.38 mmol) and NH_4Cl (0.97 g, 18.38 mmol). The reaction mixture was heated at 70 °C for 1.5 h and then cooled to room temperature. The residue was diluted with EtOAc (25 mL) and water (20 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine (15 mL), dried over

anhydrous Na_2SO_4 . The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel (50% EtOAc in petroleum ether) to afford the amine compound **18** (1.02 g, 74 %) as a liquid.

IR (KBr): ν_{max} 3460, 3349, 2925, 2212, 1622, 1493, 1452, 1027, 772 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 7.36 (s, 1H), 7.23-7.35 (m, 7H), 7.12 (t, $J = 8.7$, 15.6 Hz, 1H), 6.64-6.70 (m, 2H), 5.01-5.04 (m, 1H), 4.68-4.74 (m, 1H), 4.62-4.66 (m, 1H), 4.49-4.56 (m, 2H), 3.40 (d, $J = 4.7$ Hz, 3H), 3.21-3.32 (m, 2H), 2.72-2.82 (m, 1H), 2.43-2.57 (m, 1H), 2.25-2.34 (m, 1H), 2.02-2.13 (m, 1H), 1.66-1.81 (m, 1H); ^{13}C NMR (CDCl_3 , 75 MHz): δ 169.3, 148.2, 136.9, 132.4, 130.1, 128.6, 128.3, 128.1, 127.4, 94.3, 93.5, 90.5, 69.0, 55.9, 50.0, 46.1, 38.2, 34.5, 25.1; HRMS: Calculated for $\text{C}_{23}\text{H}_{27}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 379.20162; found 379.20405; $[\alpha]_{\text{D}}^{20}$: + 67.7 ($c = 0.35$, CHCl_3).

***tert*-Butyl-2-((*R*)-((*S*)-1-benzyl-2-oxopiperidin-4-yl) (methoxymethoxy) methyl)-1*H*-indole-1-carboxylate (2)**

A suspension of 0.9 g (2.38 mmol) of compound **18** and 0.9 g (4.76 mmol) of CuI in 20 mL of DMF was refluxed for 6 h. After completion of the reaction solvent was removed in vacuo. The dark residue was used as such without further purification. The compound was dissolved in dichloromethane (15 mL), $(\text{Boc})_2\text{O}$ (0.34 mL, 3.57 mmol) and 4-dimethylaminopyridine (DMAP) (290 mg, 2.38 mmol) were added and stirred for overnight at room temperature. Water (10 mL) was added to the reaction mixture and the organic layer was separated, then the aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with water (1 x 10 mL), brine (1 x 10 mL) and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (40% EtOAc in petroleum ether) to afford the compound **2** (0.64 g, 64 %) as liquid.

IR (KBr): ν_{max} 2923, 2853, 1730, 1453, 1326, 1153, 1082, 1029, 750 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3): δ 8.04 (d, $J = 8.4$ Hz, 1H), 7.49 (d, $J = 7.3$ Hz, 1H), 7.19-7.33 (m, 7H), 6.63 (s, 1H), 5.49 (d, $J = 3.4$ Hz, 1H), 4.81 (d, $J = 14.6$ Hz, 1H), 4.70 (d, $J = 7.0$ Hz, 1H), 4.60 (d, $J = 7.0$ Hz, 1H), 4.35 (d, $J = 14.6$ Hz, 1H), 3.43 (s, 3H), 3.19-3.26 (m, 1H), 3.05 (dt, $J = 5.0$, 12.1 Hz, 1H), 2.65 (d, $J = 9.0$ Hz, 1H), 2.26-2.40 (m, 1H), 1.79-1.86 (m, 1H), 1.64-1.72 (m, 10H); ^{13}C NMR (CDCl_3 , 125 MHz): δ 169.8, 150.2, 137.1, 136.6, 128.5, 127.9, 127.2, 123.9, 122.9, 120.3, 115.7, 108.5, 99.7, 95.2,

84.6, 73.8, 56.3, 49.8, 46.4, 37.9, 29.6, 28.2, 22.8; HRMS: Calculated for $C_{28}H_{35}N_2O_5$ $[M+H]^+$ 479.2540; found 479.2543; $[\alpha]_D^{20}$: +22.3 ($c = 1.0$, $CHCl_3$).

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