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An enantioselective approach to 2-alkyl substituted tetrahydroquinolines: total synthesis of (+)-angustureine

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A simple and highly efficient synthetic approach to enantiopure 2-alkyl substituted tetrahydroquinolines **1** skeleton from aldehydes as starting material and its application to the total synthesis of (+)-angustureine **2** is described. Key transformations include, proline catalyzed aminoxylation, Corey-Fuchs protocol, Sonogashira coupling and intramolecular Mitsunobu reactions.

Keywords: tetrahydroquinolines, aminoxylation, Corey-Fuchs protocol, Sonogashira coupling, Mitsunobu reaction, organocatalyst.

Introduction

Quinoline and tetrahydroquinoline alkaloids are found abundantly in nature and most of them exhibits interesting biological activity.[1] Enantiomerically pure 2-alkyl substituted tetrahydroquinolines alkaloids **1** from which angustureine **2**, galipeine **3**, cuspareine **4**, and galipinine **5** were first extracted from the bark of *Galipea officinalis* Hancock shrub tree found in the mountains of Venezuela (Figure 1).[2]

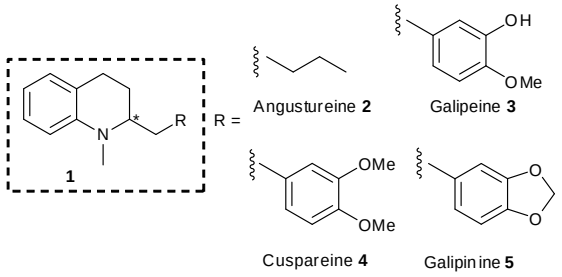

Figure 1. Some naturally occurring 2-alkyl substituted tetrahydroquinoline alkaloids.

These alkaloids exhibits anti-malarial, anti-tuberculous, cytotoxic, and antiplasmodial activities.[3] *Galipea* species have also been used in folk medicine for the treatment of dysentery, dyspepsia, chronic diarrhea, spinal motor nerve problems and fevers.[4] Enantiomerically pure 2-alkyl substituted tetrahydroquinoline alkaloids have synthetic target of considerable interest due to their wide range of important biological activities and with an array of functionalities. Various methods for the synthesis of (+)-angustureine **2** and others **3**-**5** have been documented in the literature.[5] Very recently, M. Yus and co-workers reported the synthesis of the (+)-angustureine **2** using diastereoselective addition of an allylic indium intermediate to chiral *O*-bromophenyl *N*-tert-butylsulfinyl aldimines.[5v] Herein, we wish to report a new, general and highly efficient synthetic approach for enantiopure 2-alkyl substituted tetrahydroquinolines **1** and its application to the total synthesis of (+)-angustureine **2** employing proline catalyzed asymmetric aminoxylation, Corey-Fuchs protocol, palladium catalyzed Sonogashira coupling, and Mitsunobu reaction as key steps.

Results and discussion

Our retrosynthetic approach for the synthesis of 2-alkyl substituted tetrahydroquinolines **1** including (+)-angustureine **2** is outlined in Scheme 1. We envisioned that the aryl nitro-alkyne derivative **6** from which 2-alkyl substituted tetrahydro-quinolines **1** and (+)-angustureine **2** could be synthesized *via* hydrogenation, Mitsunobu intramolecular ring closer in S_N2 fashion followed by alkylation. The aryl nitro-alkyne derivative **6** could be obtained from the monoprotected alkyne derivative **7** through palladium catalyzed Sonogashira coupling reaction with suitable aromatic nitro-halides**.** The alkyne derivative **7** in turn could be obtained by means of Corey-Fuchs protocol from the aldehyde synthesized from oxidation of monoprotected alcohol **8**. Enantiomerically pure monoprotected alcohol **8** could be obtained from the commercially available aldehydes

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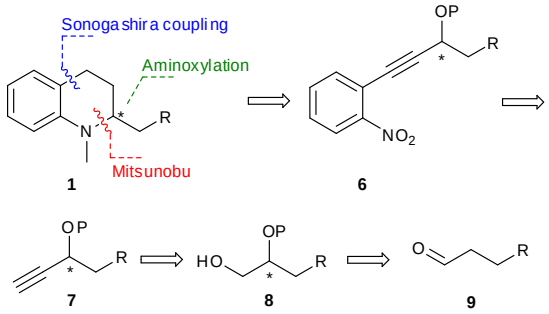
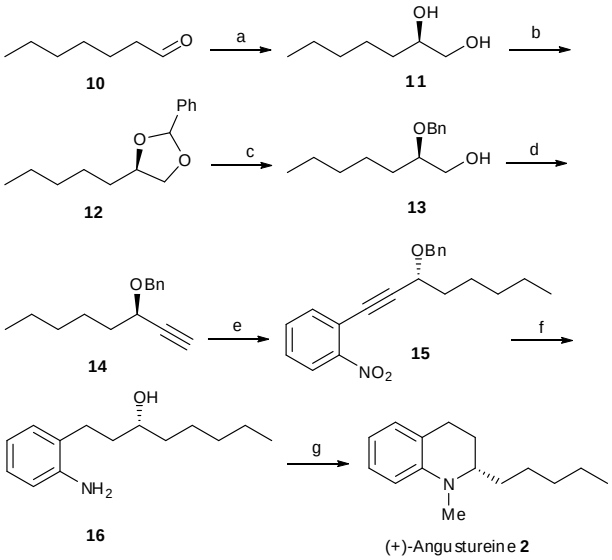
† Electronic Supplementary Information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of compounds 2 and 11-16. See DOI: 10.1039/x0xx00000x



Scheme 1. Retrosynthetic approach to 2-alkyl substituted tetrahydroquinolines **1** and (+)-angustureine **2**.

9 *via* proline catalyzed aminoxylation followed by standard organic transformation. The (*S*)- and (*R*)- configuration of the 2-alkyl substituted tetrahydroquinolines **1** and (+)-angustureine **2** could be manipulated by simply changing the D-proline and L-proline, respectively, during organocatalytic step.



Scheme 2. Reagents and conditions: (a) i) Nitrosobenzene, L-proline, DMSO, rt, 12 h, ii) $NaBH_4$, CH_3OH, 0 ^oC, 15 min, iii) $CuSO_4.5H_2O$, CH_3OH, 0 ^oC to rt, 12 h, 71% (one pot, three steps) (b) $PhCH(OMe)_2$, C_6H_6, PPTS, reflux, 1 h, 89% (c) DIBAL-H, CH_2Cl_2, -40 ^oC to rt, 2 h, 93% (d) i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 ^oC to -60 ^oC, 2 h, ii) CBr_4, PPh_3, CH_2Cl_2, 0 ^oC, 30 min, iii) *n*-BuLi, THF, -78 ^oC to rt, 3 h, 86% (over three steps) (e) 1-iodo-2-nitrobenzene, 2 mol % $Pd(PPh_3)_2Cl_2$, 1 mol % CuI, Et_3N, DMF, reflux, 3 h, 95% (f) H_2, Pd/C (10%), EtOAc, rt, 24 h, 96% (g) i) PPh_3, DEAD, CH_2Cl_2, rt, 12 h, ii) HCHO, $Na(CN)BH_3$, AcOH, CH_3CN, rt, 10 h, 88% (over two steps).

The synthesis of (+)-angustureine **2** started from the commercially available *n*-heptanal **10**, which on treatment with nitrosobenzene in the presence of catalytic amount of L-proline (10 mol %) in DMSO at room temperature afforded α-aminoxylated aldehyde which on subsequent reduction with $NaBH_4/CH_3OH$ followed by benzylamine cleavage with $CuSO_4.5H_2O$ afforded the required diol **11** in 71% yield over three steps with >99% ee.[6] $\{[\alpha]_D^{25}$ -14.4 (*c* 1, CH_3OH). The physical and spectroscopic data were in full agreement with those reported in literature (Scheme 2).

With enantiomerically pure diol **11** in hand, we then subjected it to protection with benzaldehyde dimethyl acetal in presence of catalytic amount of PPTS, which furnished 1,2-benzylidene acetal **12** in 89% yield.[7] Regioselective reductive opening of 1,2-benzylidene acetal **12** with DIBAL-H afforded monobenzyl protected alcohol **13** in 93% yield. Oxidation of alcohol **13** under Swern conditions[8] and subsequent treatment with CBr_4/TPP followed by treatment with *n*-BuLi under Corey-Fuchs protocol[9] afforded the terminal alkyne **14** in 86% yield. The terminal alkyne **14** under Sonogashira coupling conditions[10] with commercially available 1-iodo-2-nitro benzene in the presence of Et_3N as a base afforded the 2-nitrobenzene-alkyne derivative **15** in excellent yield (95%). Concomitant reduction of the triple bond, nitro group to amine and deprotection of benzyl group of 2-nitrobenzene-alkyne derivative **15** was achieved in one pot *via* hydrogenation under 1 atm. pressure in presence of catalytic amount of Pd/C (10%) which furnished the key intermediate amino alcohol **16** in 96% yield. Cyclization of amino alcohol **16** under Mitsunobu conditions[11] (DEAD, PPh_3, CH_2Cl_2, rt) afforded the tetrahydroquinoline (norangustureine), and subsequent methylation using reductive amination with formaldehyde in presence of $Na(CN)BH_3$ afforded the target compound (+)-angustureine **2** in 88% yield $\{[\alpha]_D^{25}$ +7.6 (*c* 0.4, $CHCl_3$) [Lit.[5t] +7.5 (*c* 0.4, $CHCl_3$,)}. The physical and spectroscopic data were in full agreement with those documented in literature.

Conclusions

In conclusion, a simple, flexible and highly efficient synthetic approach for 2-alkyl substituted tetrahydroquinolines **1** and its application to the total synthesis of (+)-angustureine **2** has been developed. The overall yield for alkaloid (+)-angustureine **2** was 41% in ten steps. The merits of this synthesis are high enantioselectivity with high yielding reaction steps. The synthetic strategy described has significant potential for stereochemical variation and further extension to 2-alkyl substituted tetrahydroquinolines derived natural products with interesting pharmacological activities.

Experimental

The solvents and chemicals were purchased from Merck and Sigma Aldrich chemical company. Progress of the reactions was monitored by TLC using precoated aluminium plates of Merck kieselgel 60 F254. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise mentioned) on JEOL ECS operating at 400 and 100 MHz, respectively. Chemical shifts are reported in δ (ppm), referenced to TMS. IR spectra were recorded on Agilent resolution Pro 600 FT-IR spectrometer, fitted with a beam-condensing ATR accessory. HRMS were recorded using Electron Spray Ionization. Optical rotations were measured on Automatic polarimeter AA-65. Column chromatography was performed on silica gel (60-120 and 100-

200 mesh) using a mixture of hexane and ethyl acetate. All reactions were carried out under argon or nitrogen in oven-dried glassware using standard glass syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use.

(*R*)-Heptane-1,2-diol, 11

To a DMSO solution (60 mL) of L-proline (168 mg, 1.46 mmol) was added *n*-heptanal **10** (5.0 g, 43.86 mmol) and nitrosobenzene (1.56 g, 14.6 mmol) successively at room temperature. After stirring the reaction mixture for 12 h, MeOH (20 mL) and $NaBH_4$ (835 mg, 22 mmol) were added and the reaction mixture was stirred for 15 min at 0 ^oC. The reaction was quenched with aqueous saturated NH_4Cl solution, extracted with ethyl acetate (3 x 10 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*.

The residue thus obtained above was dissolved in MeOH (15 mL) and subjected to treatment with $CuSO_4.5H_2O$ (913 mg, 3.65 mmol) at 0 ^oC and warm to room temperature over 12 h. After completion of reaction as monitored by TLC, it was quenched with aqueous saturated NH_4Cl solution. The organic layer was separated and the aqueous phase extracted with EtOAc (3 x 20 mL). The combined organic phase was dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography (EtOAc/hexanes 1:1 v/v) to afford the desired diol **11** (1.35 g, 71%). {$[\alpha]_D^{25}$ -14.4 (*c* 1, CH_3OH) [Lit.[12] -14.1 (*c* 1, CH_3OH)]}; IR (CH_2Cl_2) *v*: 3359, 2941, 2853, 1462, 1312, 1062, 927 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.6 (m, 2H), 3.4 (m, 1H), 2.67 (bs, 2H), 1.29-1.43 (m, 8H), 0.9 (t, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 72.3, 66.8, 33.1, 31.8, 25.2, 22.5, 14.0; HRMS (ESI) m/z calcd for $C_7H_{16}O_2Na$ [M + Na^+] 155.1043; found 155.1041.

(4*R*)-4-Pentyl-2-phenyl-1,3-dioxolane, 12

To a benzene solution (50 mL) of diol **11** (1.35 g, 10.4 mmol) was added benzaldehyde dimethylacetal (1.58 g, 10.4 mmol) and catalytic amount of PPTS (260 mg, 1.04 mmol). The mixture was then heated to reflux with a Dean-Stark apparatus. After 1 h, triethylamine (1 mL) was added to the mixture, and the solvent was removed under reduced pressure. The resulting residue was purified by silica gel chromatography (EtOAc/hexanes 1:99 v/v) to afford the 1,2-benzylidene acetal **12** (2.0 g, 89%). $[\alpha]_D^{25}$ -11.5 (*c* 1, $CHCl_3$); IR (CH_2Cl_2) *v*: 1478, 1366, 1260, 1120, 1015 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.35-7.48 (m, 5H), 5.92 (s, 1H), 4.2 (m, 2H), 3.59-3.67 (m, 1H), 1.31-1.75 (m, 8H), 0.9 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 138.4, 129.0, 128.3, 126.4, 103.0, 70.8, 33.3, 31.8, 25.4, 22.5, 14.0; HRMS (ESI) m/z calcd for $C_{14}H_{21}O_2$ [M + 1] 221.1536; found 221.1537.

(*R*)-2-(Benzyloxy)heptan-1-ol, 13

To a solution of 1,2-benzylidene acetal **12** (2.0 g, 9.2 mmol) in dry CH_2Cl_2 (30 mL) at -40 °C was added dropwise DIBAL-H (6.3 mL, 11.1 mmol, 1.75 M in toluene) through a syringe. The reaction mixture was allowed to warm at room temperature over a period of 2 h, then re-cooled to 0 ^oC and treated with saturated aqueous solution of potassium sodium tartrate. The solid material was filtered through a pad of Celite and concentrated *in vacuo*. Silica gel column chromatography of the crude product using EtOAc/hexane (3:7 v/v) as eluent furnished monobenzyl protected alcohol **13** (1.9 g, 93%) as a pale yellow oil. $[\alpha]_D^{25}$ -44.7 (*c* 1, $CHCl_3$); IR (CH_2Cl_2) *v*: 2957, 2902, 2820, 1609, 1505, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.33-7.36 (m, 5H), 4.56 (s, 2H), 3.8 (m, 1H), 3.5 (m, 1H), 3.3 (m, 1H), 2.4 (s, 1H), 1.28-1.43 (m, 8H), 0.9 (t, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 137.9, 128.4, 127.8, 127.7, 74.6, 73.3, 70.4, 33.0, 31.8, 25.2, 22.5, 14.0. HRMS (ESI) m/z calcd for $C_{14}H_{22}O_2Na$ [M + Na^+] 245.1512; found 245.1510.

(*R*)-((Oct-1-yn-3-yloxyl)methyl)benzene, 14

To a solution of oxalyl chloride (1.63 g, 1.1 mL, 12.84 mmol) in dry CH_2Cl_2 (30 mL) at -78 °C was added dropwise DMSO (2.07 g, 1.9 mL, 26.53 mmol) in CH_2Cl_2 (10 mL) over 15 min. The reaction mixture was stirred for 30 min and a solution of monobenzyl protected alcohol **13** (1.9 g, 8.56 mmol) in CH_2Cl_2 (20 mL) was added dropwise over 15 min. The reaction mixture was stirred for 30 min at -60 °C and then Et_3N (3.80 g, 5.20 mL, 37.7 mmol) was added dropwise and stirred for 1 h. The reaction mixture was poured into saturated solution of $NaHCO_3$ (50 mL) and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude aldehyde, which was used as such for the next step without further purification.

To a solution of CBr_4 (5.68 g, 17.12 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C was added PPh_3 (8.97 g, 34.24 mmol) and stirred for 15 min at 0 °C. To this reaction mixture, a solution of crude aldehyde obtained above in dry CH_2Cl_2 (20 mL) was added dropwise and stirred for 15 min at 0 °C. The reaction mixture was quenched with water and aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude dibromoolefin, which was used as such for the next step without further purification. To a solution of above crude dibromoolefin in dry THF (30 mL) at -78 °C was added *n*-BuLi (6.85 mL, 17.12 mmol, 2.5 M in hexane). The reaction mixture was stirred for 1 h at -78 °C and 2 h at 0 °C. The reaction mixture was quenched with saturated aqueous solution of NH_4Cl and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel column chromatography of the crude product using EtOAc/hexane (1:19 v/v) as eluent furnished the corresponding terminal alkynes **14** (1.59 g, 86% over three steps) as a pale yellow oil. $[\alpha]_D^{25}$ +34.2 (*c* 1, $CHCl_3$); IR (CH_2Cl_2) *v*: 3302, 2952, 2851, 2125, 1610, 1512, 1102 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ: 7.26-7.36 (m, 5H), 4.8 (m, 1H), 4.5 (m, 1H), 4.0 (m, 1H), 2.46 (d, 1H, *J* = 1.84 Hz), 1.28-1.78 (m, 8H), 0.9 (t, 3H, *J* = 6.88 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 137.9, 128.4, 128.0, 127.7, 83.0, 73.7, 70.5, 68.5, 35.6, 31.4, 24.9, 22.5, 14.0; HRMS (ESI) m/z calcd for $C_{15}H_{21}O$ [M + 1] 217.1587; found 217.1587.

(*R*)-1-(3-(Benzyloxy)oct-1-ynyl)-2-nitrobenzene, 15

A mixture of 1-iodo-2-nitrobenzene (1.67 g, 6.7 mmol), $Pd(PPh_3)_2Cl_2$ (94 mg, 0.134 mmol, 2 mol %), CuI (13 mg, 0.067 mmol, 1 mol %), Et_3N (60 mL) and **14** (1.45 g, 6.7 mmol) in 20 mL DMF was purged with nitrogen for 10 min. The resulting mixture was then stirred at 100 ^oC for 3 h. It was then concentrated, diluted with water, extracted with ether, dried over sodium sulfate and concentrated *in vacuo*. Silica gel column chromatography of the crude product using EtOAc/hexane (1:19 v/v) as eluent gave the coupled product **15** (2.15 g, 95%) as a yellow oil. $[\alpha]_D^{25}$ -121.3 (*c* 1, $CHCl_3$); IR (CH_2Cl_2) *v*: 3275, 1540, 1341, 2205, 870 cm^{-1}; ^1H NMR ($CDCl_3$,

400 MHz) δ: 8.0 (m, 1H), 7.6 (m, 2H), 7.26-7.42 (m, 6H), 4.9 (d, 1H, J = 11.5 Hz), 4.6 (d, 1H, J = 11.9 Hz), 4.3 (t, 1H, J = 6.8 Hz), 1.84-1.88 (m, 2H), 1.5 (m, 2H), 1.3 (m, 4H), 0.9 (t, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 149.8, 137.9, 134.9, 132.8, 128.7, 128.4, 128.2, 127.7, 124.6, 118.3, 97.0, 81.1, 70.8, 69.1, 35.5, 31.5, 25.0, 22.5, 14.0; HRMS (ESI) m/z calcd for $C_{21}H_{24}NO_3$ [M + 1] 338.1779; found 338.1780.

(*R*)-1-(2-Aminophenyl)octan-3-ol, 16

To a solution of **15** (1.0 g, 2.96 mmol) in EtOAc (12 mL) was added catalytic amount of HCl followed by addition of 10% Pd/C (150 mg, 5 mol %). The reaction mixture was subjected to hydrogenation under 1 atmosphere pressure for 24 h. After this time, a solution of saturated Na_2CO_3 was added to the reaction mixture, filtered through a pad of Celite and washed with additional EtOAc (30 mL) and organic layer separated. The resulting organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel column chromatography purification (EtOAc/hexanes 1:1 v/v) of the crude product furnished amino alcohol **16** (630 mg, 96 %) as a yellow oil. $[\alpha]_D^{25}$ -94.5 (*c* 1, $CHCl_3$); IR (CH_2Cl_2) v: 3472, 3302, 937, 632 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.0 (m, 2H), 6.7 (m, 2H), 3.5 (m, 1H), 3.2 (bs, 2H), 2.6 (m, 2H), 2.1 (bs, 1H), 1.7 (m, 2H), 1.25-1.28 (m, 8H), 0.87 (t, 3H, J = 6.88 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 144.0, 129.6, 127.0, 119.2, 116.1, 70.9, 37.7, 37.0, 31.9, 27.0, 25.4, 22.6, 14.0; HRMS (ESI) m/z calcd for $C_{14}H_{23}NONa$ [M + Na$^+$] 244.1710; found 244.1711.

(+)-Angustureine, 2

To a solution of amino alcohol **16** (400 mg, 1.8 mmol) in dry CH_2Cl_2 (6.0 mL) was slowly added triphenylphosphine (520 mg, 1.98 mmol) in portion wise at room temperature. To the resulting solution, diethylazodicarboxylate (345 mg, 1.98 mmol) in CH_2Cl_2 (5.0 mL) was added dropwise and stirred at room temperature for 12 h. After this time, the solution was quenched with water, diluted with CH_2Cl_2 and organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford the crude tetrahydroquinolone (norangustureine), which was used as such for next step without further purification.

To a acetonitrile solution (6 mL) of above crude tetrahydro quinolone (norangustureine) was added formaldehyde (37% w/w in H_2O, 1.5 mL, 18 mmol), sodium cyanoborohydride (1.13 g, 18 mmol) and acetic acid (1 mL, 18 mmol) and stirred for 10 h at room temperature. TLC monitoring showed complete conversion {hexane/ethyl acetate 19:1 v/v, R_f = 0.60}. The mixture was diluted with diethyl ether and the aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. Silica gel column chromatography of the crude product using EtOAc/hexane (1:99 v/v) as eluent furnished the target compound (+)-angustureine **2** (345 mg, 88% over two steps) as pale yellow oil. {$[\alpha]_D^{25}$ +7.6 (*c* 0.4, $CHCl_3$) [Lit.[5t] +7.5 (*c* 0.4, $CHCl_3$); IR (CH_2Cl_2) *v*: 2930, 2860, 950, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.1 (t, 1H, J = 7.2 Hz), 6.9 (d, 1H, J = 7.2 Hz), 6.57 (t, 1H, J = 7.2 Hz), 6.52 (d, 1H, J = 7.2 Hz), 3.2 (m, 1H), 2.92 (s, 3H), 2.66 (m, 1H), 2.62 (m, 1H), 1.8 (m, 2H), 1.56 (m, 1H), 1.25-1.3 (m, 7H), 0.9 (t, 3H, J = 6.84 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 145.3, 128.6, 127.0, 121.8, 115.1, 110.3, 58.9, 37.9, 32.0, 31.1, 25.7, 24.3, 23.5, 22.7, 14.0; HRMS (ESI) m/z calcd for $C_{15}H_{24}N$ [M + 1] 218.1902; found 218.1902.

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