Tetrahedron: *Asymmetry* 28 (2017) 1803–1807

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

A convergent approach towards the synthesis of the 2-alkyl-substituted tetrahydroquinoline alkaloid (−)-cuspareine

M. V. Madhubabu [a], R. Shankar [a], T. Krishna [a], Y. Satish Kumar [a], Y. Chiranjeevi [a], Ch. Muralikrishna [a], H. Rama Mohan [a], Satish S. More [a], M. V. Basaveswara Rao [b,*], Raghunadh Akula [a,*]

[a] *Technology Development Centre, Custom Pharmaceutical Services, Dr. Reddy's Laboratories Ltd, Hyderabad 500049, India*
[b] *Department of Chemistry, Krishna University, Machilipatnam, Andhra Pradesh, India*

ARTICLE INFO

Article history:
Received 9 October 2017
Revised 23 October 2017
Accepted 25 October 2017
Available online 10 November 2017

ABSTRACT

A convergent approach towards the synthesis of the 2-alkyl-substituted tetrahydroquinoline alkaloid (−)-cuspareine via enantiospecific construction of the (*R*)-benzyl 2-formyl-3,4-dihydroquinoline-1(2*H*)-carboxylate. We have achieved an efficient enantiospecific synthesis of (−)-cuspareine starting from known key starting materials. The reactions employed for individual transformations are simple and high yielding, and the strategy could potentially be easily extended.

1. Introduction

Galipinine **1**, Galipeine **2**, Angustureine **3** and cuspareine **4** constitute a family of anti-malaria and tetrahydroquinoline alkaloids isolated by Jacquemond-Collet from the bark of *Galipea officinalis* Hancock (Fig. 1).[1] This shrub is indigenous to the mountains of Venezuela and belongs to the genus *Galipea* aublet. The biological activity of an ethanolic extract of *Galipea officinalis* bark against mycobacterium tuberculosis was initially tested by Houghton et al.,[2] which consists of approximately 20 species that are found in northern South America. Preparations from *Galipea officinalis* have been used in folk medicine for the treatment of various disorders such as dysentery and fever.[2] Over the years numerous synthetic routes have been developed for the preparation of this type of 2-substituted tetrahydroquinolines.[3]

The majority of the strategies towards the synthesis of (−)-cuspareine **4** are based on asymmetric hydrogenations of 2-alkyl quinolines, which also include transfer-hydrogenations.[4] Previous strategies used for the synthesis of tetrahydroquinoline alkaloids in general are enantioselective aza-michael reactions.[5]

Asymmetric hydroamination,[6] enantioselective petasis-type reaction,[7] asymmetric aza Diels–Alder reactions,[8] and conjugate addition of chiral lithium amides.[9]

2. Results and discussion

Herein, we describe the synthesis of (−)-cuspareine **4** from enantiomerically pure (*R*)-benzyl 2-formyl-3,4-dihydroquinoline-1(2*H*)-carboxylate **5**, obtained by the coupling of two key starting materials (2-nitrobenzyl)triphenylphosphonium bromide **7**[10] and (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **6**.[11] The retrosynthetic disconnection strategy for enantiospecific intermediate **5** is depicted in Scheme 1. Wittig and intramolecular Mitsunobu cyclization[12] reactions are the key steps for the synthesis (*R*)-benzyl 2-formyl-3,4-dihydroquinoline-1(2*H*)-carboxylate **5**.

Wittig reaction between the two key starting materials (2-nitrobenzyl)triphenylphosphonium bromide **7** and (*R*)-2, 2-dimethyl-1,3-dioxolane-4-carbaldehyde **6** yielded the intermediate **8**. Reduction of the nitro to an amine under Pd/C in methanol to obtain the amino dimethyl-1,3-dioxolane intermediate, which on further CBZ protection of amine group with CBZ chloride and diisopropylethylamine in dichloromethane followed by the selective cleavage of oxazolidine group with oxalic acid in acetonitrile and water yielded the intermediate **11**. The selective protection of primary alcohol with *tert*-butyldimethylsilyl chloride in THF to get the desired unprotected secondary alcohol **12** with 95% yield. The intramolecular Mitsunobu reaction of **12** between the amide and secondary alcohol was then attempted. Initially, the reaction was performed with **12** using diisopropyl azodicarboxylate (DIAD), triphenyl phosphine (Ph_3P) and the catalytic amount of pyridine provided 2-substituted tetrahydroquinoline **13** by the cyclization of amide with secondary alcohol under the Mitsunobu reaction conditions. Then the selective deprotection of the alcohol with tin(II) chloride in ethanol and water mixture followed by the

* Corresponding authors.
E-mail address: raghunadha@drreddys.com (R. Akula).

https://doi.org/10.1016/j.tetasy.2017.10.023
0957-4166/

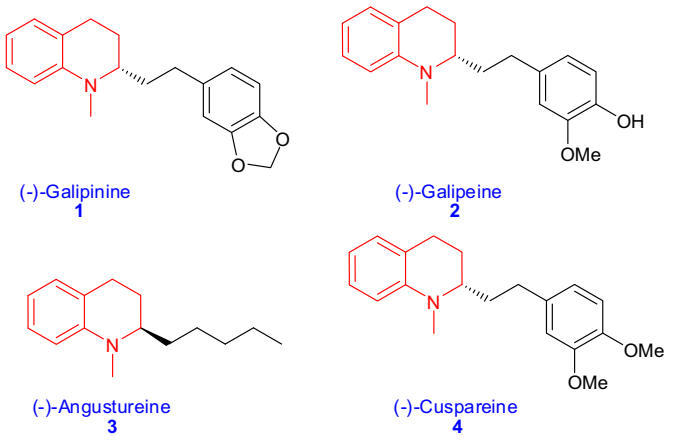


Figure 1. Examples of natural products which contain tetrahydroquinoline skeleton.

primary hydroxyl group in **14** was oxidized to the corresponding aldehyde by using Dess Martin periodinane in dichloromethane yielded the key intermediate (*R*)-benzyl 2-formyl-3,4-dihydroquinoline-1(2*H*)-carboxylate **5** with 30% yield in 8 linear steps as shown in Scheme 2.

Wittig reaction between (*R*)-benzyl 2-formyl-3,4-dihydroquinoline-1(2*H*)-carboxylate **5** and (3,4-dimethoxy benzyl)triphenylphosphonium bromide **15**[13] yielded the olefin **16** with 87% yield, which was further subjected to hydrogenation using Pd/C and ammonium formate in methanol to yield the CBZ deprotected and double bond reduced 2-alkyl tetrahydroquinoline intermediate **17** with 87% yield. Finally, N-alkylation of the secondary amine with methyl iodide and di-isopropyl ethylamine in DMF yielded (−)-cuspareine **4** from **17** in 90% yield (Scheme 3).

This enantiospecific strategy employed for the synthesis of (−)-Cuspareine **4** starting from (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **6** is efficient and is completed with an overall yield of 22% in eleven steps. The methodology can be extended to the synthesis of related natural products by choosing suitable Wittig reagents.

3. Conclusion

In conclusion, we have achieved enantiospecific synthesis of (−)-cuspareine starting from the known key starting materials. The strategy could be extended for the synthesis of other 2-alkyltetrahydroquinolines.

4. Experimental

4.1. Synthesis of (*S*,*E*)-2,2-dimethyl-4-(2-nitrostyryl)-1,3-dioxolane 8

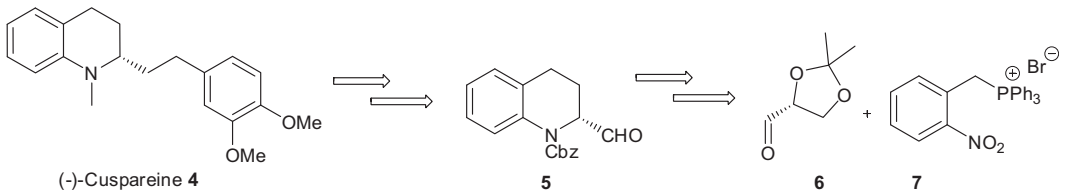
(*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde or (*R*)-glyceraldehyde acetonide **6** (2.6 g, 19.8 mmol) was added to the mixture of (2-nitrobenzyl)triphenylphosphonium bromide (**7**) (10.0 g, 20.9 mmol) and potassium carbonate (5.8 g, 41.8 mmol) in acetonitrile (100.0 mL) under nitrogen atmosphere. After completion of the reaction (by TLC), distilled acetonitrile under vacuum & diluted with water (100.0 mL). Extracted the product with ethyl acetate (2 × 50.0 mL) and washed with 10% aq sodium chloride solution. The organic layer was concentrated under vacuum and the crude product was purified column chromatography using ethyl acetate hexanes mixture (90:10) yielded the (*S*,*E*)-2,2-dimethyl-4-(2-nitrostyryl)-1,3-dioxolane **8** in 4.8 g (94%) as a pale yellow colour liquid. $[\alpha]_D^{25} = -79.4$ (*c* 1.37, EtOH); IR (neat, cm^{-1}): 3567, 2987, 2862, 2374, 1717, 1523, 1374, 860, 767; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.07 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H, ArH), 7.59–7.64 (m, 1H, ArH), 7.42–7.49 (m, 2H, ArH), 6.99 (d, *J* = 11.6 Hz, 1H, =CH—Ar), 5.84 (dd, *J* = 11.6 Hz, 9.2 Hz, 1H, =CH—CH), 4.52–4.58 (m, 1H, CH—O), 4.02 (dd, *J* = 8.2 Hz, 6.0 Hz, 1H, CH_2O), 3.67 (dd, *J* = 8.0 Hz, 7.2 Hz, 1H, CH_2—O), 1.33 (s, 3H, CH_3—C), 1.44 (s, 3H, CH_3—C); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 147.9 (ArC—NO_2), 133.1, 131.9, 131.6, 130.7, 130.2, 128.6 (=CH—Ar), 124.7 (=CH—CH), 109.5 (C—$(CH_3)_2$), 72.2 (CH—O), 69.5 (CH_2—O), 26.8 (CH_3—C), 25.8 (CH_3—C); GCMS (C.I): *m*/*z* (%) = 250.2 [M+H].

4.2. Synthesis of (*S*)-2-(2-(2,2-dimethyl-1,3-dioxolan-4-yl) ethyl) aniline 9

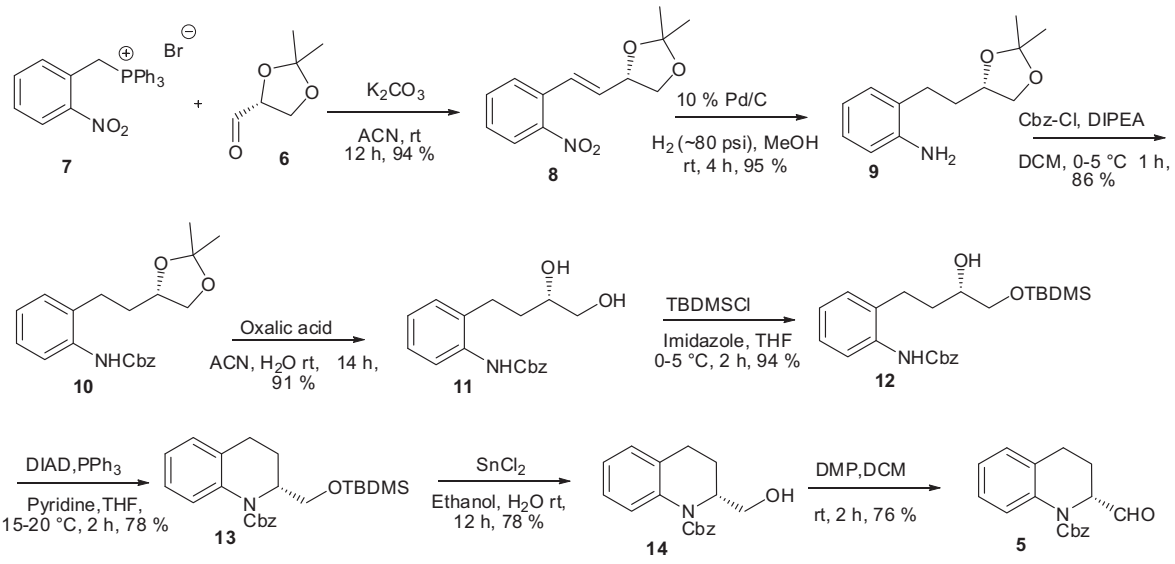
A mixture of 10% Pd/C catalyst (0.45 g) and (*S*,*E*)-2,2-dimethyl-4-(2-nitrostyryl)-1,3-dioxolane **8** (4.5 g, 18.0 mmol) were charged into a hydrogenator containing methanol (22.5 mL) and applied hydrogen gas (80 psi) at 25–35 °C After completion of the reaction (by TLC), catalyst was then filtered. Concentrated, the crude was further purified by column chromatography yielded **9** with 95% yield. $[\alpha]_D^{25} = -12.4$ (*c* 1.06, EtOH); IR (neat, cm^{-1}): 3464, 3373, 3008, 2936, 2873, 1894, 1624, 1380, 1056, 937, 753, 475; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.02–7.25 (m, 2H, ArH), 6.66–6.74 (m, 2H, ArH), 4.08–4.15 (m, 1H, CH—O), 4.03 (dd, *J* = 7.8 Hz, 5.6 Hz, 1H, CH_2—O), 3.77 (br, 2H, NH_2), 3.53 (t, *J* = 8.0 Hz, 1H, CH_2—O), 2.56–2.70 (m, 2H, CH_2—Ar), 1.77–1.94 (m, 2H, CH_2—C), 1.44 (s, 3H, CH_3—C), 1.37 (s, 3H, CH_3—C); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 144.4 (ArC—N), 129.5, 127.1, 125.6, 118.6, 115.5, 108.7 (C—$(CH_3)_2$), 75.1 (CH—O), 69.2 (CH_2—O), 33.0 (CH_2—C), 27.1 (CH_3—C), 26.9 (CH_3—C), 25.6 (CH_2—Ar); MS: *m*/*z* (%) = 222.20 [M+H]; HRMS: *m*/*z* [M+H] calcd for $C_{13}H_{20}NO_2$ [M+H]; 222.1494 [M+H]; found: 222.1493 [M+H].

4.3. Synthesis of benzyl (*S*)-(2-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)phenyl)carbamate 10

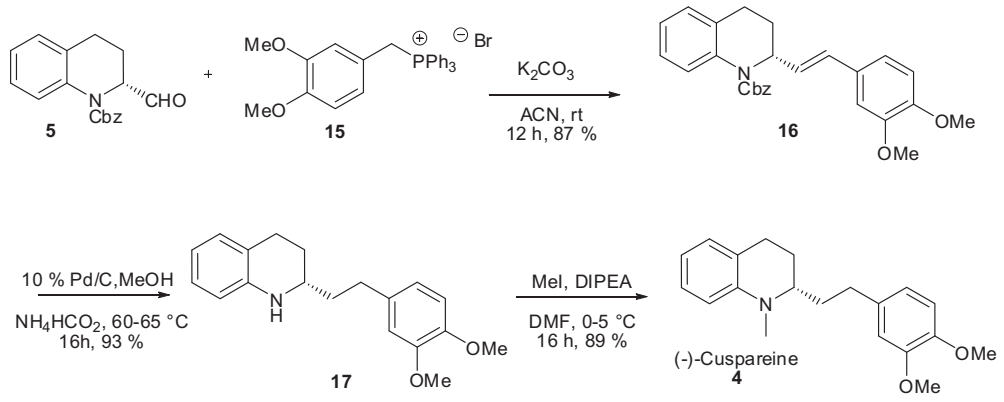
Benzyl chloroformate (Cbz-Cl) (2.83 g, 16.6 mmol) was added to the mixture of (*S*)-2-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)aniline **9** (3.5 g, 15.8 mmol) and di-isopropyl ethylamine (DIPEA, 3.06 g, 23.7 mmol) in DCM (35.0 mL) at 0–5 °C. Reaction was monitored by TLC and quenched with water (17.5 mL). Separated the layers and extracted the product with DCM (5.0 vol). Combined both the organic layers and washed with water twice (2 × 17.5 mL) concentrated the organic layer and crude product was purified by



Scheme 1. Retrosynthetic scheme for the synthesis of **5**.



Scheme 2. Synthesis of 2-formyl-3,4-dihydroquinoline-1(2*H*)-carboxylate **5**.



Scheme 3. Synthesis of Cuspareine **4**.

column chromatography yielded the **10** with 86% yield. $[\alpha]_D^{25}$ = +97.5 (*c* 1.7, EtOH); IR (Neat, cm^{-1}): 3309, 3032, 2985, 2878, 1952, 1732, 1538, 1371, 1048, 754, 698; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.82 (br, 2H, ArH and NH), 7.32–7.42 (m, 5H, ArH), 7.03–7.24 (m, 3H, ArH), 5.19 (s, 2H, O—CH_2—Ar), 3.97 (t, *J* = 7.6 Hz, 1H, CH_2—O), 3.89–3.94 (m, 1H, CH—O), 3.50 (t, *J* = 7.2 Hz, 1H, CH_2—O), 2.71–2.79 (m, 2H, CH_2—Ar), 1.75–1.84 (m, 2H, CH_2—C), 1.36 (s, 3H, CH_3—C), 1.27 (s, 3H, CH_3—C); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 154.2 (C=O), 136.3, 136.0, 131.1, 129.8, 128.5 (2C), 128.3 (2C), 128.2, 127.0, 124.2, 122.1, 109.2 (C—$(CH_3)_2$), 73.8 (CH—O), 69.2 (CH_2—O), 66.8 (O—CH_2—Ar), 34.1 (CH_2—C), 26.8 (CH_3—C), 26.7 (CH_3—C), 25.2 (CH_2—Ar); MS: *m*/*z* (%) = 356.30 [M+H]; HRMS: *m*/*z* [M+H] calcd for $C_{21}H_{26}NO_4$ [M+H]; 356.1862 [M+H]; found: 356.1866 [M+H].

4.4. Synthesis of benzyl (*S*)-(2-(3,4-dihydroxybutyl)phenyl) carbamate 11

A mixture of oxalic acid (2.4 g, 26.6 mmol) and water (4.5 mL) charged into the reaction mixture containing (*S*)-(2-(2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethyl)phenyl)carbamate **10** (4.5 g, 12.7 mmol) and acetonitrile (40.5 mL) under stirring at 25–35 °C. After completion of the reaction, add water (90.0 mL) and filter the product **11** with 91% yield. Melting point: 108–110 C; $[\alpha]_D^{25}$ = +13.5 (*c* 1.19, Chloroform); IR (KBr, cm^{-1}): 3686, 3310, 3019, 2400, 1731, 1591, 1453, 1216, 1052, 929, 770; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.82 (br, 2H, ArH and NH), 7.32–7.42 (m, 5H, ArH), 7.14–7.23 (m, 2H, ArH), 7.04–7.08 (m, 1H, ArH), 5.20 (s, 2H, O—CH_2—Ar), 3.53–3.61 (m, 2H, CH_2—O), 3.39–3.43 (m, 1H, CH—O), 2.69–2.81 (m, 2H, CH_2—Ar), 1.61–1.78 (m, 4H, CH_2—C and 2 × OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 154.5 (C=O), 136.4, 136.0, 131.9, 129.7 (2C), 128.5 (4C), 128.2 (2C), 127.0, 124.6, 70.3 (CH—O), 66.9 (O—CH_2—Ar), 66.7 (CH_2—O), 33.0 (CH_2—C), 26.3 (CH_2—Ar); MS: *m*/*z* (%) = 316.30 [M+H]; HRMS: *m*/*z* [M+H] calcd for $C_{18}H_{22}NO_4$ [M+H]; 316.1549 [M+H]; found: 316.1563 [M+H].

4.5. Synthesis of benzyl (*S*)-(2-(4-((*tert*-Butyldimethylsilyl)oxy)-3-hydroxybutyl)phenyl)carbamate 12

A solution of *tert*-butylchlorodimethylsilane (TBDMS-Cl, 1.5 g, 10.0 mmol) in THF (18.0 mL) was added drop wise to the reaction mixture containing (*S*)-(2-(3,4-dihydroxybutyl)phenyl)carbamate (**11**) (3.0 g, 9.5 mmol) and Imidazole (1.0 g, 14.2 mmol) in THF (18.0 mL) at 0–5 °C. After completion of the reaction, slowly quenched with water (30.0 mL) at 0–5 °C and extracted the

product with *n*-heptane (2 × 30.0 mL). The combined organic layer concentrated to give **12** with 94% yield. $[\alpha]_D^{25}$ = −4.2 (*c* 1.01, EtOH); IR (neat, cm^{-1}): 3686, 3304, 3019, 2400, 1729, 1591, 1452, 1215, 1124, 669, 467; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.08 (br, 1H, OH), 7.84 (br, 1H, NH), 7.31–7.44 (m, 5H, ArH), 7.15–7.26 (m, 3H, ArH), 7.04–7.07 (m, 1H, ArH), 5.72 (s, 2H, O—CH_2—Ar), 3.56–3.59 (m, 1H, CH_2—OSi), 3.47–3.52 (m, 1H, CH—O), 3.35–3.39 (m, 1H, CH_2—OSi), 2.80–2.88 (m, 1H, CH_2—Ar), 2.69–2.76 (m, 1H, CH_2—Ar), 1.70–1.78 (m, 1H, CH_2—C), 1.60–1.66 (m, 1H, CH_2—C), 0.89 (s, 9H, C$(CH_3)_3$), 0.06 (s, 3H, CH_3Si), 0.05 (s, 3H, CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 154.4 (C=O), 136.6, 136.4, 129.8, 128.5 (2C), 128.3 (2C), 128.1, 128.1, 126.9, 124.1, 122.1, 69.7 (CH—O), 67.1 (CH_2 OSi), 66.6 (O—CH_2Ar), 33.1 (CH_2CH), 26.2 (C—$(CH_3)_3$), 25.9 (3C, $(CH_3)_3$), 18.3 (CH_2Ar), −5.4 (CH_3Si), −5.4 (CH_3Si); HRMS: *m*/*z* [M+H] calcd for $C_{24}H_{36}NO_4Si$ [M+H]; 430.2414 [M+H]; found: 430.2416 [M+H].

4.6. Synthesis of benzyl (*R*)-2-(((*tert*-butyldimethylsilyl)oxy) methyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate 13

To a solution of benzyl (*S*)-(2-(4-((*tert*-butyldimethylsilyl)oxy)-3-hydroxybutyl)phenyl)carbamate **12** (3.5 g, 8.2 mmol) in THF (70.0 mL), under nitrogen atmosphere was added triphenyl phosphine (4.3 g, 16.3 mmol) and pyridine (0.35 mL), and cooled the reaction mixture to below 15–20 °C. A solution of Di isopropyl aza dicarboxylate (DIAD, 3.3 g, 16.3 mmol) in THF (35.0 mL) was added into the reaction mixture at 15–20 °C for 5–10 min, and stirred for 4 h. After reaction completion, RM was quenched with water (140.0 mL) and extracted the product with hexanes (2 × 35.0 mL). The organic layer concentrated and purified by column chromatography yielded the **13** with 78% yield. $[\alpha]_D^{25}$ = +86.0 (*c* 0.78, EtOH); IR (neat): 3685, 3019, 2956, 2400, 1695, 1472, 1215, 1025, 757, 669, 454; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.53 (d, *J* = 7.6 Hz, 1H, ArH), 7.27–7.39 (m, 4H, ArH), 7.13–7.19 (m, 2H, ArH), 7.08 (d, *J* = 6.0 Hz, 1H, ArH), 6.99–7.04 (m, 1H, ArH), 5.29 (d, *J* = 12.4 Hz, 1H, O—CH_2—Ar), 5.17 (d, *J* = 12.8 Hz, 1H, O—CH_2—Ar), 4.57–4.62 (m, 1H, CH—N), 3.65–3.69 (m, 1H, CH_2—OSi), 3.49–3.53 (m, 1H, CH_2—OSi), 2.61–2.68 (m, 2H, CH_2—Ar), 2.19–2.27 (m, 1H, CH_2—C), 1.74–1.80 (m, 1H, CH_2—C), 0.80 (s, 9H, C$(CH_3)_3$), −0.04 (s, 3H, CH_3Si), −0.06 (s, 3H, CH_3Si); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 154.9 (C=O), 137.3, 136.5, 128.5 (2C), 128.0, 127.9 (2C), 127.4, 126.0 (2C), 125.4, 124.1, 67.4 (CH—N), 63.8 (O—CH_2Ar), 55.0 (CH_2—OSi), 25.8 (C—$(CH_3)_3$), 25.7 (3C, $(CH_3)_3$), 25.4 (CH_2CH), 18.1 (CH_2Ar), −5.5 (2C, CH_3Si); HRMS: *m*/*z* [M+H] calcd for $C_{24}H_{34}NO_3Si$ [M+H]; 412.2308 [M+H]; found: 412.2292 [M+H].

4.7. Synthesis of benzyl (*R*)-2-(hydroxymethyl)-3,4-dihydro quinoline-1(2*H*)-carboxylate 14

A mixture of stannous chloride ($SnCl_2$, 0.46 g, 2.4 mmol) and water (2.0 mL) charged into the reaction mixture containing ((*R*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate **13** (2.0 g, 4.9 mmol) and ethanol (18.0 mL) under stirring at 25–35 °C. After completion of the reaction, diluted with water (40.0 mL) and extracted the product with Methyl *tertiary* butyl ether (MTBE, 2 × 10.0 mL). The combined organic Layer concentrated and crude product was purified by column chromatography yielded the **14** with 78% yield as a colorless liquid. $[\alpha]_D^{25}$ = 86.1 (*c* 0.99, $CHCl_3$); IR (neat, cm^{-1}): 3677, 3426, 3018, 2954, 2401, 1690, 1398, 1050, 758, 697, 468; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.43 (d, *J* = 8.0 Hz, 1H, ArH), 7.28–7.37 (m, 4H, ArH), 7.15–7.20 (m, 2H, ArH), 7.04–7.11 (m, 2H, ArH), 5.31 (d, *J* = 12.0 Hz, 1H, O—CH_2—Ar), 5.15 (d, *J* = 12.0 Hz, 1H, O—CH_2—Ar), 4.62–4.69 (m, 1H, CH-N), 3.59–3.63 (m, 1H, CH_2—O), 3.50–3.55 (m, 1H, CH_2—O), 2.59–2.69 (m, 3H, CH_2—Ar and CH_2—C), 2.26–2.34 (m, 1H, CH_2—C), 1.49–1.56 (m, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 156.3 (C=O), 136.5, 136.1, 133.3, 128.5, 128.4, 128.1, 127.9, 127.5, 127.4, 126.3, 125.9, 124.8, 67.8 (CH-N), 65.2 (O—CH_2-Ar), 56.1 (CH_2—O), 25.7 (CH_2—C), 22.0 (CH_2Ar); HRMS: *m*/*z* [M+H] calcd for $C_{18}H_{20}NO_3$ [M+H]; 298.1443 [M+H]; found: 298.1438 [M+H].

4.8. Synthesis of benzyl (*R*)-2-formyl-3,4-dihydroquinoline-1(2*H*)-carboxylate 5

Dess-Martin periodinane (2.78 g, 6.6 mmol) was charged lot wise into the reaction mixture containing (*R*)-2-(hydroxymethyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate **14** (0.75 g, 2.5 mmol) and DCM (15.0 mL) at 10–15 °C. Allowed the mass to 25–30 °C and stirred until reaction completion. After completion of the reaction, filtered the mass and concentrated and the crude product was further purified by column chromatography yielded **5** with76% yields as a pale yellow colour liquid. $[\alpha]_D^{25}$ = 69.3 (*c* 0.78, EtOH); IR (neat, cm^{-1}): 3683, 3020, 2958, 2852, 2400, 1700, 1585, 1215, 1141, 1027, 767, 463; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.55 (s, 1H, H—C=O), 7.72 (m, 1H, ArH), 7.31–7.37 (m, 5H, ArH), 7.20 (t, *J* = 7.6 Hz, 1H, ArH), 7.02–7.09 (m, 2H, ArH), 5.31 (d, *J* = 12.4 Hz, 1H, O—CH_2—Ar), 5.21 (d, *J* = 12.4 Hz, 1H, O—CH_2—Ar), 4.82 (t, *J* = 7.2 Hz, 1H, CH—N), 2.68–2.72 (m, 2H, CH_2-Ar), 2.26–2.30 (m, 1H, CH_2—C), 1.96–2.05 (m, 1H, CH_2—C); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 199.9 (H—C=O), 154.9 (N—C=O), 136.5, 135.7, 128.6, 128.6 (2C), 128.3, 128.2 (2C), 128.1, 127.5, 126.7, 124.4, 68.2 (CH—N), 62.8 (O—CH_2Ar), 25.4 (CH_2—C), 24.8 (CH_2Ar); HRMS: *m*/*z* [M+H] calcd for $C_{18}H_{18}NO_3$ [M+H]; 296.1287 [M+H]; found: 296.1294 [M+H].

4.9. Synthesis of (*R,E*)-benzyl 2-(3,4-dimethoxystyryl)-3,4-dihydroquinoline-1(2*H*)-carboxylate 16

(*R*)-Benzyl 2-formyl-3,4-dihydroquinoline-1(2*H*)-carboxylate **5** (1.0 g, 3.4 mmol) was added to the mixture of (3,4-dimethoxybenzyl)triphenylphosphonium bromide **15** (1.75 g, 3.5 mmol) and anhydrous potassium carbonate (0.9 g, 6.8 mmol) in anhydrous acetonitrile (10.0 mL) under nitrogen atmosphere. After completion of the reaction (by TLC), distilled acetonitrile under vacuum and diluted with water (100.0 mL). Extracted the product with ethyl acetate (2 × 10.0 mL) and washed with 10% aq. Sodium chloride solution. The organic layer was concentrated under vacuum and the crude product was purified by column chromatography yielded **16** with 87% yield as an off-white colour solid. Melting point: 125–127 °C; $[\alpha]_D^{25}$ = +67.5 (*c* 0.44, EtOH); IR (KBr, cm^{-1}): 3370, 3029, 2918, 1693, 1317, 1157, 755, 667, 458; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.67 (d, *J* = 8.4 Hz, 1H, ArH), 7.29–7.39 (m, 5H, ArH), 7.12–7.19 (m, 3H, ArH), 6.99–7.05 (m, 3H, ArH), 6.59 (dd, *J* = 14.4 Hz, 1.2 Hz, 1H, =CH—Ar), 6.23 (dd, *J* = 12.0 Hz, 5.2 Hz, 1H, =CH—C), 5.16–5.24 (m, 3H, CH-N and O—CH_2—Ar), 3.75 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 2.64–2.75 (m, 2H, CH_2—Ar), 2.22–2.29 (m, 1H, CH_2—C), 1.79–1.84 (m, 1H, CH_2—C); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 154.7 (C=O), 149.2 (ArC—OMe), 148.4 (ArC—OMe), 136.8, 136.3, 131.5 (=CH—Ar), 129.8 (=CH—C), 129.4, 128. 128.5 (2C), 128.0 (2C), 128.0 (2C), 126.2, 125.1, 124.1, 115.2, 114.3, 109.0, 67.6 (CH—N), 56.1 (CH_3—O), 56.0 (CH_3—O), 55.5 (O—CH_2—Ar), 30.0 (CH_2—C), 25.3 (CH_2—Ar); MS: *m*/*z* (%) = 430.30 [M+H].

4.10. Synthesis of (*S*)-2-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydroquinoline 17

A mixture of 10% Pd/C catalyst (0.2 g) and (*R,E*)-benzyl 2-(3,4-dimethoxystyryl)-3,4-dihydroquinoline-1(2*H*)-carboxylate **16** (1.0 g, 2.4 mmol) were charged into the round bottom flask containing methanol (22.5 mL) and ammonium formate (2.0 g).

Warmed the reaction mass to 60–65 °C and stirred. After completion of the reaction (by TLC), catalyst was then filtered off under vacuum. Filtrate was concentrated and the crude was purified by column chromatography yielded **17** with 93% yield as a pale yellow colour liquid. $[\alpha]_D^{25} = -65.9$ (*c* 0.96, Chloroform); IR (neat, cm^{-1}): 3389, 3018, 2954, 2400, 1697, 1489, 1215, 1042, 939, 755, 471; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.95–6.99 (m, 2H, ArH), 6.74–6.80 (m, 3H, ArH), 6.61 (td, J = 13.6 Hz, 1.6 Hz, 1H, ArH), 6.45 (d, J = 8.4 Hz, 1H, ArH), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.72 (br, 1H, NH), 3.30–3.34 (m, 1H, CH—N), 2.73–2.83 (m, 2H, CH_2—Ar), 2.68–2.72 (m, 2H, CH_2—Ar), 1.97–2.04 (m, 1H, CH_2—C), 1.80–1.86 (m, 2H, CH_2—C), 1.65–1.74 (m, 1H, CH_2—C); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 148.9 (ArC—O), 147.3 (ArC—O), 144.5 (ArC—N), 134.5, 129.2, 126.7, 121.3, 120.1, 117.1, 114.1, 111.7, 111.3, 56.0 (CH_3—O), 55.9 (CH_3—O), 51.2 (CH—N), 38.4 (CH_2—C), 31.8 (CH_2—Ar), 28.0 (CH_2—C), 26.2 (CH_2—Ar); MS: m/z (%) = 298.20 [M+H].

4.11. Synthesis of (−)-Cuspareine 4

Methyl iodide (MeI) (2.83 g, 16.6 mmol) was added to the mixture of (*S*)-2-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydroquinoline **17** (0.5 g, 1.7 mmol) and di-isopropyl ethylamine (DIPEA, 0.5 g, 3.7 mmol) in DMF (5.0 mL) at 0–5 °C. After completion of the reaction, RM was quenched with water (10.0 mL) and extracted with methyl *tertiary* butyl ether (MTBE, 5.0 vol) and organic layer washed with water (2 × 17.5 mL), organic layer was concentrated and crude product was purified by column chromatography yielded pure (−)-Cuspareine **4** with 89% yield. $[\alpha]_D^{25} = -20.6$[14] (*c* 1.24, Chloroform); IR (neat, cm^{-1}): 3685, 3390, 3020, 2937, 2400, 1601, 1500, 1260, 1028, 625, 479; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.08 (t, J = 8.0 Hz, 1H, ArH), 6.98 (d, J = 8.0 Hz, 1H, ArH), 6.78 (d, J = 8.4 Hz, 1H, ArH), 6.71–6.74 (m, 2H, ArH), 6.59 (t, J = 7.2 Hz, 1H, ArH), 6.53 (d, J = 8.4 Hz, 1H, ArH), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.27–3.30 (m, 1H, CH—N), 2.91 (s, 3H, NCH_3), 2.81–2.85 (m, 1H, CH_2—Ar), 2.63–2.72 (m, 2H, CH_2—Ar), 2.51–2.57 (m, 1H, CH_2—Ar), 1.88–1.96 (m, 3H, CH_2—C and CH_2—Ar), 1.73–1.76 (m, 1H, CH_2—C); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 148.9 (ArC—O), 147.2 (ArC—O), 145.3 (ArC—N), 134.6, 128.7, 127.1, 121.7, 120.0, 115.4, 111.6, 111.3, 110.6, 58.4 (CH—N), 55.9 (CH_3—O), 55.9 (CH_3—O), 38.1 (CH_3—N), 33.1 (CH_2—C), 31.9 (CH_2—Ar), 24.4 (CH_2—C), 23.5 (CH_2—Ar); MS: m/z (%) = 312.30 [M+H]; HRMS: m/z [M+H] calcd for $C_{20}H_{26}NO_2$ [M+H]; 312.1964 [M+H]; found: 312.1961 [M+H].

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetasy.2017.10.023.

References

1. (a) Jacquemond-Collet, I.; Benoit-Vical, F.; Valentin, M. A.; Stanislas, E.; Mallie, M.; Fouraste, I. *Planta Med.* **2002**, *68*, 68; (b) Jacquemond-Collet, I.; Hannedouche, S.; Fabre, N.; Fouraste, I.; Moulis, C. *Phytochemistry* **1999**, *51*, 1167; (c) Davies, S. G.; Fletcher, A. M.; Houlsby, I. T. T.; Roberts, P. M.; Thomson, J. E. *J. Org. Chem.* **2017**, *82*, 10673.
2. Houghton, P. J.; Woldemariam, T. Z.; Watanabe, T.; Yates, M. *Planta Med.* **1999**, *65*, 250.
3. (a) Avemaria, F.; Vanderheiden, S.; Brase, S. *Tetrahedron* **2003**, *59*, 6785–6796; (b) Li, H.; Wang, J.; Xie, H.; Zu, L.; Jiang, W.; Duesler, E. N.; Wang, W. *Org. Lett.* **2007**, *9*, 965–968; (c) Wang, D.-W.; Zeng, W.; Zhou, Y.-G. *Tetrahedron: Asymmetry* **2007**, *18*, 1103–1107; (d) Kouznetsoz, V. V.; Bohorquez, A. R. R.; Stashenko, E. E. *Tetrahedron Lett.* **2007**, *48*, 8855–8860; (e) Viera, T. O.; Alper, H. *Chem. Commun.* **2007**, 2710–2711; (f) Ishikura, M.; Oda, I.; Terashima, M. *Heterocycles* **1985**, *23*, 2375–2386; (g) Rueping, M.; Theissmann, T.; Antonchick, A. P. *Synlett* **2006**, 1071–1074; (h) Frank, K. E.; Aube, J. *J. Org. Chem.* **2000**, *65*, 655–666; (i) Ikeda, S.; Shibuya, M.; Iwabuchi, Y. *Chem. Commun.* **2007**, 504–506.
4. (a) Wang, W. B.; Lu, S. M.; Yang, P. Y.; Han, X. W.; Zhou, Y. G. *J. Am. Chem. Soc.* **2003**, *125*, 10536; (b) Lu, S. M.; Wang, Y. Q.; Han, X. W.; Zhou, Y. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2260; (c) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683; (d) Deport, C.; Buchotte, M.; Abecassis, K.; Tadaoka, H.; Ayad, T.; Ohshima, T.; Genet, J. P.; Mashima, K.; Ratovelomanana-Vidal, V. *Synlett* **2007**, 2743; (e) Wang, D. W.; Zeng, W.; Zhou, Y. G. *Tetrahedron: Asymmetry* **2007**, *18*, 1103; (f) Wang, X. B.; Zhou, Y. G. *J. Org. Chem.* **2008**, *73*, 5640; (g) Gou, F. R.; Li, W.; Zhang, X.; Liang, Y. M. *Adv. Synth. Catal.* **2010**, *352*, 2441; (h) Wang, T.; Zhuo, L. G.; Li, Z.; Chen, F.; Ding, Z.; He, Y.; Fan, Q. H.; Xiang, J.; Yu, Z. X.; Chan, A. S. C. *J. Am. Chem. Soc.* **2011**, *133*, 9878.
5. (a) Fustero, S.; Moscardo, J.; Jimenez, D.; Perez-Carrion, M. D.; Sánchez-Roselló, M.; del Pozo, C. *Chem. Eur. J.* **2008**, *14*, 9868; (b) Taylor, L. L.; Goldberg, F. W.; Hii, K. K. *Org. Biomol. Chem.* **2012**, *10*, 4424.
6. Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 6577.
7. Yamaoka, Y.; Miyabe, H.; Takemoto, Y. *J. Am. Chem. Soc.* **2007**, *129*, 6686.
8. a) Ishitani, H.; Kobayashi, S. *Tetrahedron* **2003**, *59*, 6785.
9. Bentley, S. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2011**, *13*, 2544.
10. Nguyen, V. H.; Vendier, L.; Etienne, M.; Despagnet-Ayoub, E.; Breuil, P. A. R.; Magna, L.; Proriol, D.; Olivier-Bourbigou, H.; Lorber, C.; Eur, J. *Org. Chem* **2011**, *34*, 6877.
11. Chavan, S. P.; Khairnar, L. B.; Pawar, K. P.; Chavan, P. N.; Kawale, S. A. *RSC Adv.* **2015**, *5*, 50580.
12. (a) Theeraladanon, C.; Arisawa, M.; Nakagawa, M. *Tetrahedron: Asymmetry* **2005**, *16*, 827; (b) Jae-Sang, R. *Bull. Korean Chem. Soc.* **2006**, *27*, 631; (c) Yuvraj, G.; Suraksha, G.; Satyendra Kumar, P. *RSC Adv.* **2015**, *5*, 38846; (d) Munoz, G. D.; Dudley, G. B. *Org. Prep. Proced. Int.* **2015**, *47*, 179.
13. (a) Alonso, F.; Riente, P.; Yus, M.; Eur, J. *Org. Chem* **2009**, *34*, 6034; (b) Zheng, Y.; Song, W. B.; Xuan, L. J. *Tetrahedron* **2016**, *72*, 5047.
14. (a) Satyanarayana, G.; Pflaesterer, D.; Helmchen, G.; Eur, J. *Org. Chem* **2011**, *34*, 6877; (b) Sirvent, J. A.; Foubelo, F.; Yus, M. *Heterocycles* **2014**, *88*, 1163; (c) Crisenza, G. E. M.; Dauncey, E. M.; Bower, J. F. *Org. Biol. Chem.* **2016**, *14*, 5820.