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

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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

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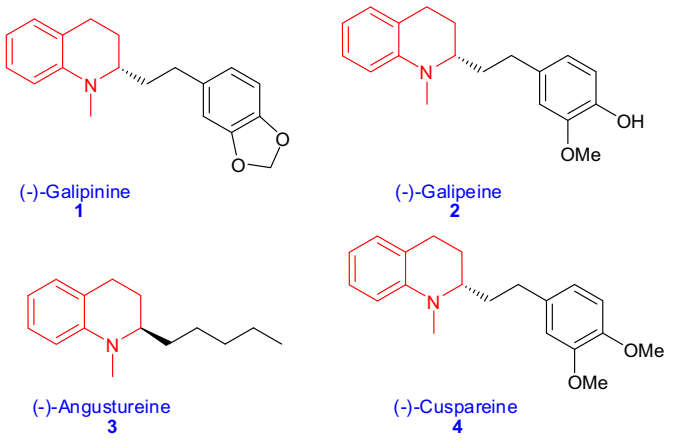


Figure 1. Examples of natural products which contain tetrahydroquinoline skeleton.

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

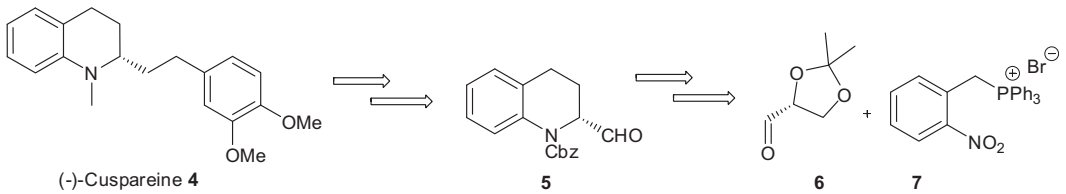
(*R*)-2,2-Dimethyl-1,3-dioxolane-4-carbaldehyde or (*R*)-glyceraldehyde acetonide **6** (2.6 g, 19.8 mmol) was added to the mixture of (2-nitrobenzyl)triphenylphosphonium bromide (**7**) (10.0 g, 20.9 mmol) and potassium carbonate (5.8 g, 41.8 mmol) in acetonitrile (100.0 mL) under nitrogen atmosphere. 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**.