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Total syntheses of mitragynine, paynantheine and speciogynine *via* an enantioselective thiourea-catalysed Pictet–Spengler reaction†

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The pharmacologically interesting indole alkaloids (–)-mitragynine, (+)-paynantheine and (+)-speciogynine were synthesised in nine steps from 4-methoxytryptamine by a route featuring (i) an enantioselective thiourea-catalysed Pictet–Spengler reaction, providing the tetrahydro-β-carboline ring and (ii) a Pd-catalysed Tsuji–Trost allylic alkylation, closing the D-ring.

Mitragynine (**1**) is the principal alkaloid in the leaves of the tropical tree *Mitragyna speciosa* (Rubiaceae) native to Thailand and Malaysia (Fig. 1).[1] The leaves and extracts of this plant are well-known as "kratom", which traditionally has a reputation as an opium substitute and is consumed either by smoking, chewing, or drinking a broth form.[2] More recently mitragynine was shown to have potent analgesic activity.[3] Although the alkaloid was first isolated more than a century ago,[4] it was not until 1965 that its structure was confirmed by X-ray analysis of its hydroiodide salt.[5] Minor alkaloids, accompanying mitragynine in the plant, are paynantheine (**2**) and speciogynine (**3**),[6] all of them are Corynanthe alkaloids with a characteristic 9-methoxy group (Fig. 1). Alkaloids **1** and **3** are isomeric at C20, while **2** is the C20 vinyl analogue of **3**. The C9 methoxy group is essential for the biological activity of mitragynine as a central nervous system stimulant. The alkaloid corynantheidine lacking the methoxy group is an antagonist.[3] Clearly, mitragynine and its congeners have relevant biological activities and as such are important targets for total synthesis.

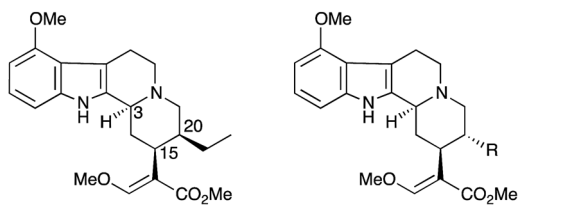

Fig. 1 Structures of the target alkaloids.

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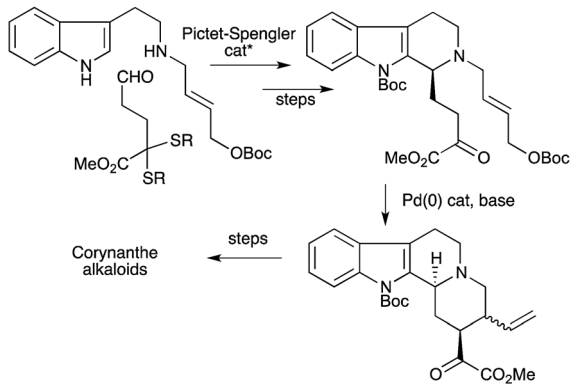
Synthetic work toward (−)-mitragynine is rather scarce in the literature. The first total synthesis was reported by Takayama *et al.* in 1995 using an enzymatic resolution to obtain the correct absolute stereochemistry.[7] A few years ago, Cook and co-workers published a total synthesis using 4-methoxytryptophan which was made *via* auxiliary-controlled asymmetric synthesis.[8] Recently, Sun and Ma synthesised a key intermediate in the Cook total synthesis by using asymmetric organocatalysis.[9] Total syntheses of alkaloids **2** and **3** are not known in the literature as far as we know.

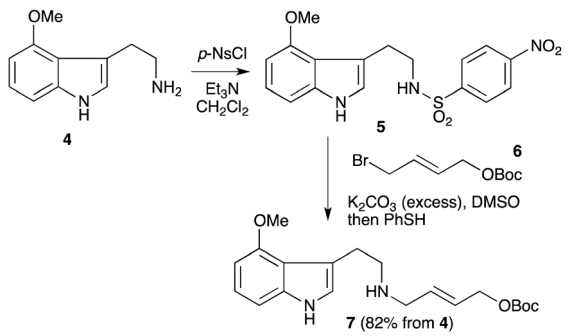
We recently reported an enantioselective total synthesis of Corynanthe alkaloids lacking the methoxy group by using an enantioselective Pictet–Spengler cyclisation as the key step with the chirality arising from a binaphthylphosphoric acid catalyst (Scheme 1).[10] In another key step the D-ring was closed *via* a Tsuji–Trost allylic alkylation with the use of an α-ketoester enolate as the nucleophile.[10] In this communication we wish to report efficient total syntheses of the three title alkaloids by a similar approach. However, the presence of the methoxy group considerably influenced the Pictet–Spengler reaction and it appeared necessary to apply a different chiral organocatalyst than the binaphthyl-phosphoric acid used in our previous study.[10]

Our synthetic endeavour started from 4-methoxytryptamine (**4**),[11] which was allylated on nitrogen according to the Fukuyama procedure.[12] Thus, reaction of **4** with nosyl chloride in the presence of triethylamine gave the sulfonamide **5**. Allylation with bromide **6**[10] in DMSO with excess potassium carbonate, directly followed by removal of the sulfonyl group with thiophenol in a one-pot process, provided secondary amine **7** in 82% yield from **4** (Scheme 2).

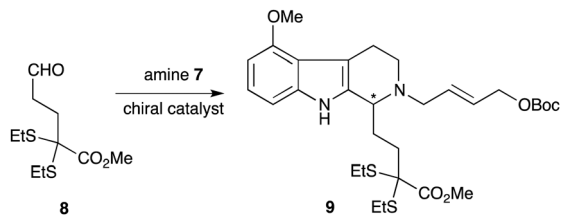
With the key amine in hand we set out to investigate the enantioselective Pictet–Spengler reaction with thioacetal **8**[13] as the aldehyde component (1.2 equiv.), as in our earlier work, to prepare the desired tetrahydro-β-carboline **9** (Scheme 3). We screened the well-known enantiopure phosphoric acids **10–12** (2 mol%, Fig. 2) as catalysts in toluene at 0 °C in the presence of 4 Å molecular sieves (MS). The desired product was formed in good yields, but the ee's were very low. Upon further investigation the Pictet–Spengler reactions appeared to proceed also without phosphoric acid. However, when MS were left out or replaced by sodium or magnesium sulphate yields dropped considerably. Apparently, the methoxy group renders the aromatic system so nucleophilic that MS suffice to bring about the cyclisation.



Scheme 1 Total synthesis of Corynanthe alkaloids according to ref. 10.



Scheme 2 Synthesis of the amine for the Pictet–Spengler reaction.



Scheme 3 The enantioselective Pictet–Spengler reaction.

Inspired by the impressive results by Jacobsen and co-workers[14] on the use of enantiopure thiourea catalysts for Pictet–Spengler reactions of tryptamines, we then investigated such catalysts for our key Pictet–Spengler process. It was reported that the thioureas work particularly well with more nucleophilic indole systems.[14] In the event of treatment of amine **7** with aldehyde **8** (1.2 equiv.) in toluene at room temperature with the chiral thiourea-containing catalysts **13–16** indeed gave the desired product **9** in yields and ee's as indicated in Table 1. The commercially available Jacobsen's catalyst **13**[15] gave an ee of 53%, while a comparable catalyst **14**, developed by Takemoto,[16] furnished the opposite enantiomer in an improved ee of 81%. The best catalyst was the quinine-derived thiourea **16** providing a synthetically useful ee of 89%.[17] Remarkably, the quinine-derived catalyst **15** with the thiourea connected to the quinoline ring gave poor results.[18]

For the synthesis of the title alkaloids in the natural configuration, **16** obviously was our catalyst of choice. Further optimisation studies indicated that with freshly purified aldehyde **8** (acid-free) reproducible yields and ee's could be best obtained if 20 mol% of benzoic acid was added to the reaction

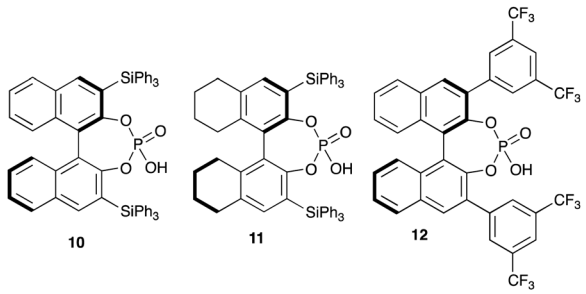
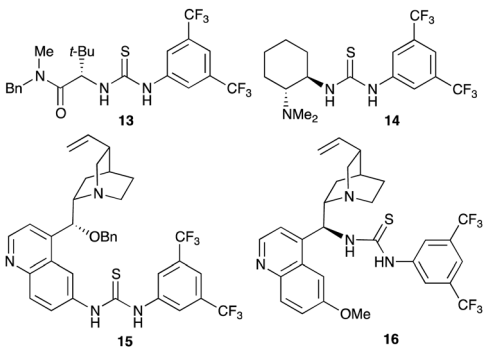


Fig. 2 Structures of the chiral phosphoric acid catalysts used.

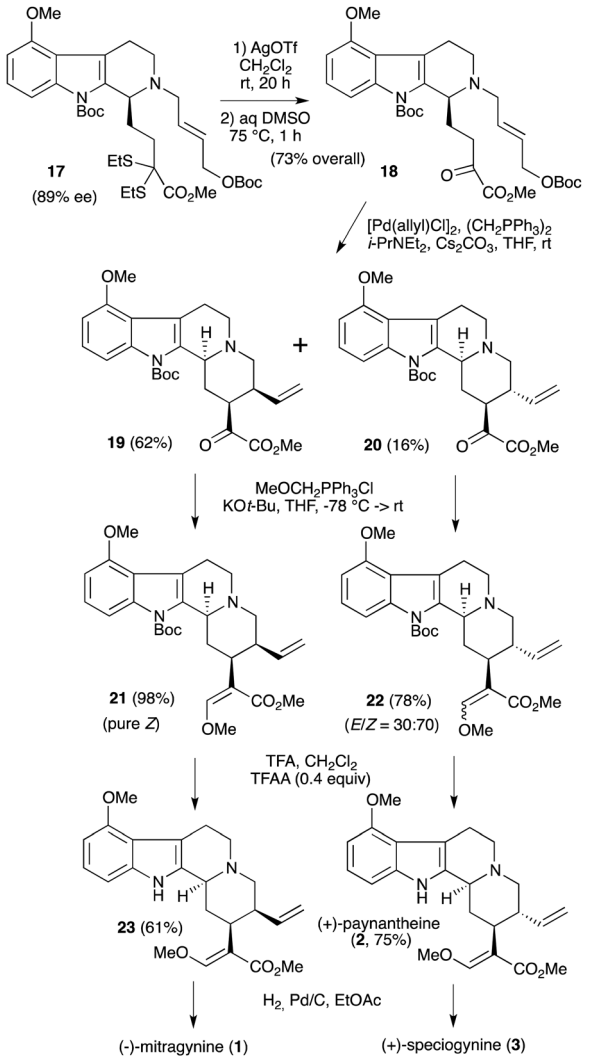
Table 1 Results of the thiourea-catalysed reaction of Scheme 3 (20 mol% of catalyst, room temperature, toluene)



Catalyst	Time (h)	Yield (%)	ee (%)	Major
13	48	68	53	*S*
14	96	57	81	*R*
15	72	29	7	*R*
16	72	90	89	*S*

mixture. The favourable effect of the added carboxylic acid was observed earlier by Klausen and Jacobsen.[14] Toluene was the best solvent and the highest ee's were obtained at room temperature.

To continue the total synthesis of mitragynine we followed the procedure described earlier for corynantheidine (Scheme 4).[10] Before liberation of the ketone the indole nitrogen in (*S*)-**9** (89% ee) was protected with a Boc group (Boc_2O, DMAP, toluene, 40 °C) to give **17** in 90% yield. Apart from stabilising the electron rich indole moiety, this Boc protection was also required to prevent an irreversible reaction between the indole nitrogen and the liberated ketone. Hydrolysis of the dithioacetal occurred upon treatment of **17** with silver triflate followed by aqueous DMSO at 75 °C. As reported before, the amine nitrogen plays a crucial role here by facilitating the hydrolysis *via* a cyclic intermediary ammonium triflate.[10] The α-ketoester **18** was the substrate for the palladium-catalysed Tsuji–Trost cyclisation. The best result was obtained by using bis-1,2-diphenylphosphinoethane as the ligand and a mixture of diethylisopropylamine and cesium carbonate as the base. This procedure led to a mixture of the C15–C20 *cis*-product **19** and *trans*-product **20** in a 4 : 1 ratio (total yield 78%). The compounds were easily separated in useful quantities for completion of the total synthesis. The use of the stronger base DBU in dichloromethane gave a 1 : 1 mixture of **19** and **20**, but the formation of a third and inseparable isomer,



Scheme 4 Total syntheses of the title alkaloids.

namely the C15 epimer of **19**, caused this method to be unattractive.[19]

Both **19** and **20** were then separately treated with the ylide from methoxymethylene triphenylphosphonium chloride to yield the expected enol ethers **21** and **22**. The first was obtained as a pure (*Z*)-isomer in high yield. Upon attempted crystallisation a small amount of the racemate crystallised leaving the desired enantiomer in the filtrate in 98% ee. From here the total synthesis of mitragynine was carried on *via* TFA-mediated removal of the Boc-group and concomitant isomerisation of the enol ether to provide **23** in 61% yield.[20] Finally, hydrogenation of **23** gave synthetic (−)-mitragynine showing an optical rotation ($[\alpha]_D = -128$, $c = 0.66$, $CHCl_3$) close to that of the natural product ($[\alpha]_D = -126$, $c = 1.2$, $CHCl_3$).[4] In addition, the NMR spectra of synthetic and natural material were virtually identical. Enol ether **22** was obtained as a mixture of geometric isomers. The minor *E*-isomer could be separated and crystallised to enantiopurity. Removal of the Boc group led to synthetic (+)-paynantheine ($[\alpha]_D = +20.2$, $c = 0.91$, $CHCl_3$, lit.[21] $[\alpha]_D = +29.4$, $c = 1.2$, $CHCl_3$). Hydrogenation gave synthetic (+)-speciogynine ($[\alpha]_D = +22.8$, $c = 0.89$, $CHCl_3$, lit.[19] $[\alpha]_D = +26.8$, $c = 0.85$, $CHCl_3$).

In summary, a total synthesis of (−)-mitragynine was realised starting from 4-methoxytryptamine in nine steps by using as the key step an enantioselective Pictet–Spengler reaction catalysed by a chiral thiourea. This route also provided the first total syntheses of the related natural products paynantheine and speciogynine. Our work once again emphasises the power of asymmetric organocatalysis in an appropriate combination with transition-metal catalysis for the total synthesis of natural products.[22]

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