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Enantioselective Syntheses of Corynanthe Alkaloids by Chiral Brønsted Acid and Palladium Catalysis

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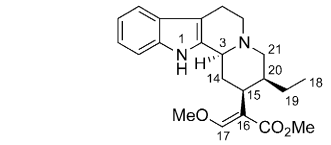
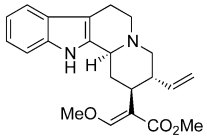
Dedicated to Professor Barry M. Trost on the occasion of his 70th birthday

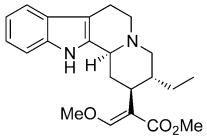
Over the last decade, enantioselective organocatalysis has become an integral part of the catalysis field. Meanwhile, several enantioselective organocatalysis-based total syntheses have been reported.[1] Recently, we have published an enantioselective organocatalytic approach to tetrahydro-β-carbolines using an asymmetric binol phosphoric acid-catalyzed Pictet–Spengler reaction as the key step,[2] culminating in a short total synthesis of (−)-arboricine.[2c] Herein, we report total syntheses of the corynanthe indole alkaloids (−)-corynantheidine **1**, (+)-corynantheine, **2** and (+)-dihydrocorynantheine **3** by a combination of enantioselective organocatalysis and a novel variant of the palladium-catalyzed allylic alkylation reaction.



(−)-corynantheidine (**1**)



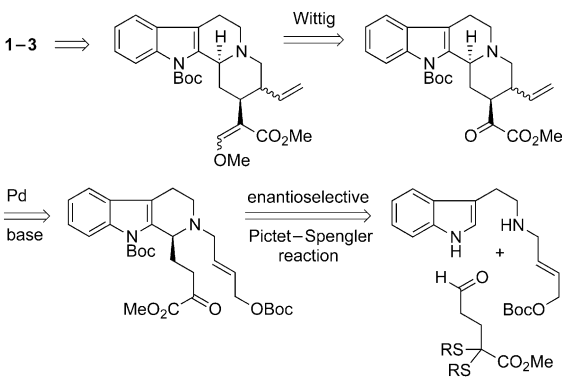
(+)-corynantheine (**2**)



(+)-dihydro-corynantheine (**3**)

The alkaloids **1**–**3** were all isolated from the stem bark of the African tree *Pseudocinchona africana*.[3,4] Pharmacological evaluation showed that corynantheidine **1** antagonizes μ-opioid receptors,[5] whereas **2** and **3** serve as inhibitors of Leishmania major promastigotes.[4] Over the years several racemic and partial enantioselective syntheses of corynantheidine **1** and its C20-epimer (+)-dihydrocorynantheine **3** have been published, but only a few enantioselective total syntheses have appeared.[6] (+)-Corynantheine **2** contains a C20-vinyl substituent, and although it is the most frequently described member of the corynanthe family, no enantioselective total synthesis of **2** has been reported yet. Most of the existing corynanthe syntheses share tryptophan as the chiral source in a Pictet–Spengler reaction thus requiring additional steps to remove the carboxyl group. It would be advantageous to use tryptamine as the starting material in combinaton with a catalytic asymmetric Pictet–Spengler reaction.[7] Recently, Jacobsen's and our group developed catalytic asymmetric versions differing in the tryptamine precursor and catalyst type. Jacobsen's approach requires unsubstituted tryptamine in an acyl Pictet–Spengler reaction, in combination with a peptidic thiourea catalyst.[8] Our approach involves the direct use of N_b-alkyl-substituted tryptamines in combination with binol phosphoric acid-type catalysts.[2]

In Scheme 1 we present the synthetic strategy toward the corynanthe alkaloids **1**–**3**, based on this binol phosphoric acid-promoted enantioselective Pictet–Spengler reaction between the *tert*-butyl carbonate of 2-butenyl-functionalized tryptamine and methyl 5-oxo-2,2-(dialkylthio)pentanoate as the aldehyde. The D-ring of the indolo[2,3-*a*]quinolizidine ring system was envisaged to be formed by an unprecedented Pd-catalyzed allylic alkylation with an α-ketoester anion



Scheme 1. Retrosynthetic analysis of the corynanthe alkaloids.

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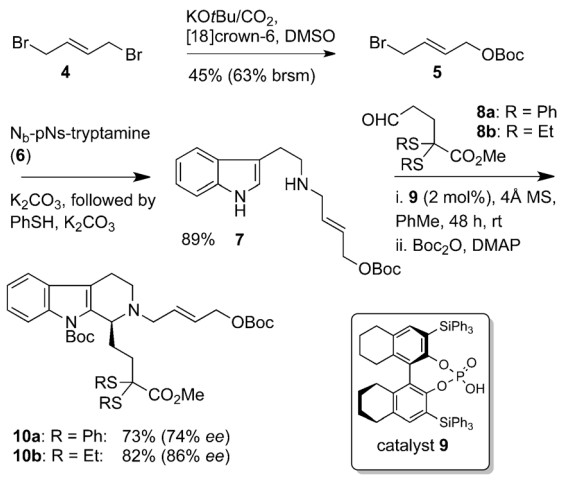
as the nucleophile, immediately followed by a Wittig reaction to construct the β-methoxyacrylate unit. In contrast to the previously published approaches, this novel method would give direct access to the vinyl-substituted indolo[2,3-*a*]quinolizidine ring system as present in **2**.

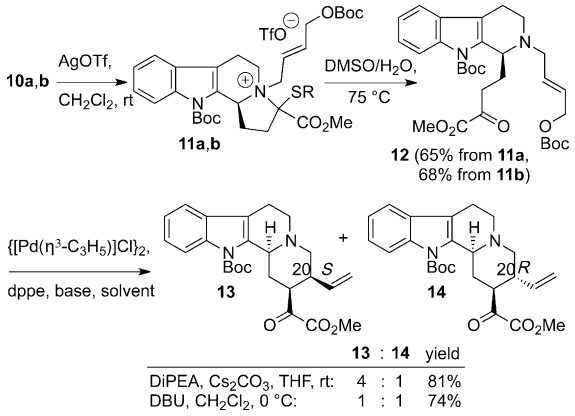
The synthesis commenced with the N_b-functionalization of tryptamine with a *tert*-butyl carbonate-protected butenyl side chain by alkylation of *p*-nosyl-tryptamine (**6**) with bromide **5**, in a Fukuyama protocol, to give **7** in 89% yield (Scheme 2).[9] Bromide **5**, free from its *Z* isomer, was prepared in a single step from commercially available (*E*)-1,4-dibromobut-2-ene (**4**). The subsequent Pictet–Spengler reaction was initially carried out with the previously described aldehyde **8a**,[10] in which the ketone carbonyl was protected as a diphenylthioacetal. Protection of the ketone was required to avoid rearrangement of the intermediate iminium species to the enamine forming a stable and isolatable conjugated system with the enolized ketone (not shown). After screening several binol phosphoric acid-type catalysts[11] it was found that (*R*)-3,3′-bis(triphenylsilyl)-octahydrobinol-phosphoric acid (**9**) gave the best results providing, after a one-pot indole-*N* protection with a *tert*-butoxycarbonyl (Boc) group, tetrahydro-β-carboline **10a** isolated in 73% yield but with an unsatisfactory 74% enantiomeric excess (*ee*). Fortunately, both the yield and *ee* value could be improved by replacing the diphenyl thioacetal for a diethyl thioacetal giving **10b** in a yield of 82% and with 86% *ee*. It is worth mentioning that only 2% of catalyst was required to give complete conversion in a reaction time of 48 h at room temperature. Previous work has shown that (*R*)-binol phosphoric acid catalysts are required for obtaining the (*S*)-configured tetrahydro-β-carboline, which corresponds with the (*S*)-configuration at C3 in the corynanthe alkaloid series.[2]



Scheme 2. Enantioselective synthesis of the tetrahydro-β-carboline skeleton through the enantioselective Brønsted-acid catalyzed Pictet–Spengler reaction. DMAP = 4-dimethylaminopyridine; brsm = based on recovered starting material.

Next, the crucial α-ester carbonyl had to be liberated by thioacetal hydrolysis. The Boc group was first introduced to prevent irreversible ring closure of the indole nitrogen onto the α-ketoester once formed, and to protect the indole ring against oxidation during dithioacetal hydrolysis. Still, one-pot hydrolysis of the electron-poor thioacetal under several standard conditions was not possible. After extensive experimentation a reliable two-step procedure was found in which at first, after AgOTf treatment in dry dichloromethane at room temperature, the stable pyrrolidinium salts **11a** and **11b** were formed from **10a** and **10b** as a mixture of diastereomers. Treatment of **11a** and **11b** with aqueous DMSO at elevated temperature gave the desired hydrolysis of the *N,S*-acetal providing ketone **12** in overall yields of 65% from **10a**, and 68% from **10b**.

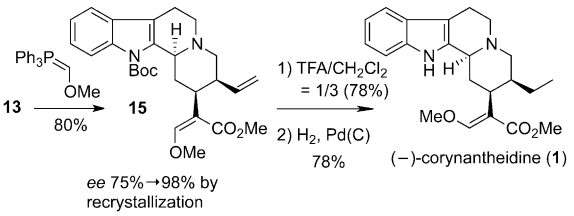
Now the scene was set for the closure of the final ring by trapping of a π-allyl complex with the ketoester-derived enolate. Treatment of **12** with 5 mol% $\{[Pd(\eta^3\text{-}C_3H_5)]Cl\}_2$ in the presence of base gave **13**, showing the correct C14–C20 *cis* stereochemistry for the corynantheidine skeleton, and **14** with the *trans* configuration required for the corynantheine series. By using a mixture of diisopropylethylamine (DiPEA)/Cs_2CO_3 as a base, a maximum *cis/trans* ratio of 4:1 was obtained. However, using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base, the *cis* and *trans* diastereomers were obtained in equal amounts. The α-ketoester protons are less acidic than for example, β-ketoesters or malonates, but more acidic then the corresponding methyl ketone, which was not reactive in this allylic alkylation (Scheme 3).[12]



Scheme 3. Closure of the final ring by trapping of a Pd-π-allyl complex with an α-ketoester-derived enolate. dppe = 1,2-bis(diphenylphosphino)-ethane.

A second asset of the α-ketoester moiety in **13** became clear in the construction of the β-methoxyacrylate unit, adding a valuable method to the commonly used ester anion formylation/methylation sequence.[6b] Wittig reaction of **13** with (methoxymethylene)triphenylphosphorane selectively gave the *Z* enol ester **15** isolated in 80% yield as a solid of

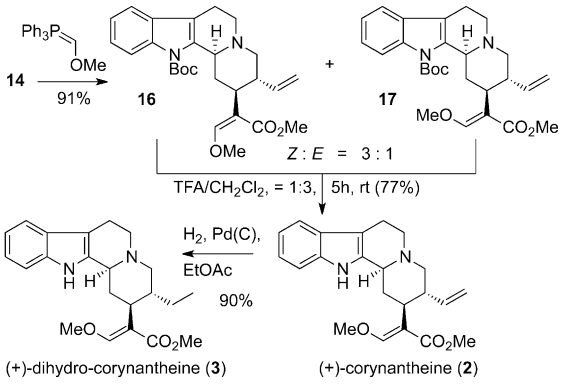
which the optical purity could be increased to 98% *ee* by recrystallization. We were pleasantly surprised that the subsequent acidic removal of the Boc protecting group was accompanied by complete isomerization of the *Z* enol ether to the desired *E* isomer. Final Pd(C)-catalyzed hydrogenation of the vinylic double bound gave (−)-corynantheidine **1** in 83% yield. Starting from tryptamine we thus accomplished the enantioselective synthesis of corynantheidine in 10 steps in 9% overall yield (Scheme 4).



Scheme 4. The final steps towards (−)-corynantheidine (**1**).

With **14** in hand, the syntheses of (+)-corynantheine (**2**) and (+)-dihydrocorynantheine (**3**) were also completed in a similar fashion. Reaction of **14** with (methoxymethylene)triphenylphosphorane now gave a mixture of the *Z*/*E* isomers **16** and **17** in a ratio of 3:1 and a combined yield of 91%. Subjection of this mixture to trifluoroacetic acid (TFA) to remove the Boc protecting group was again accompanied by complete isomerization of the enol ether to the desired *Z*-configuration to give (+)-corynantheine (**2**) in 80% yield. Selective Pd(C)-catalyzed hydrogenolysis of **2** furnished (+)-dihydrocorynantheine (**3**) in 90% yield (Scheme 5).

In summary, we have completed efficient total syntheses of three corynanthe alkaloids, with an α-ketoester playing a major role as nucleophile in an intramolecular Tsuji–Trost-type allylic alkylation and as Wittig precursor in the construction of β-methoxyacrylates. In particular, the Pd-catalyzed ring closure proceeded easily compared with, for example, Heck-type or Ni-catalyzed processes and directly produced the vinyl substituent as it is present in corynantheine. The binol phosphoric acid-catalyzed Pictet–Spengler condensation between an *N*-substituted tryptamine and a masked α-ketoester efficiently introduced the required enantioselectivity.



Scheme 5. The final steps towards (+)-dihydro-corynantheine (**2**) and (+)-corynantheine (**3**).

Acknowledgements

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