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Enantioselective formal synthesis of *ent*-rhynchophylline and *ent*-isorhynchophylline†

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Starting from (*S*)-tryptophanol, a formal synthesis of *ent*-rhynchophylline and *ent*-isorhynchophylline, involving stereoselective cyclocondensation, spirocyclization, and alkylation reactions, and the final adjustment of the oxidation level at the oxindole and piperidine moieties, is reported.

Oxindole alkaloids are a diverse group of natural products[1] characterized by the presence of a spiro[pyrrolidine-3,3′-oxindole] ring system,[2] a privileged heterocyclic motif associated with a variety of bioactivity profiles.[3] Most of the oxindole alkaloids incorporate an unrearranged secologanin skeleton and are biogenetically formed by oxidative rearrangement of secoyohimbane- or heteroyohimbane-type indole alkaloids. Representative members of this group are rhynchophylline and isorhynchophylline (Fig. 1),[4] a pair of C-7 epimers that can be equilibrated through a ring-opened form *via* retro-Mannich/Mannich reactions. These alkaloids exhibit a number of pharmacological effects[5] and are the major tetracyclic oxindole components of *Uncaria* species, which have long been used in traditional Oriental medicine.[6]

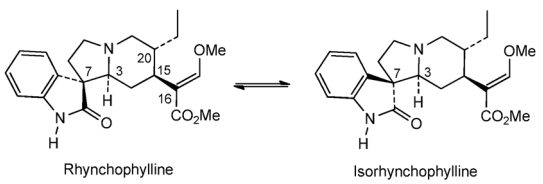
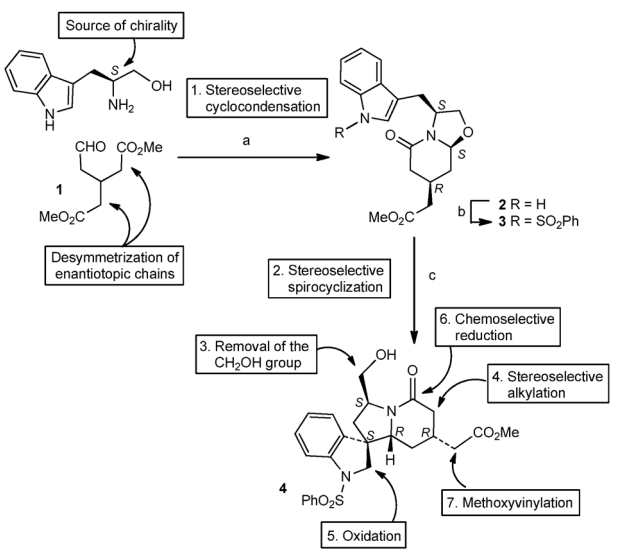


Fig. 1 Oxindole alkaloids.

Although the stereogenic quaternary spirocenter and the three stereogenic centers on the piperidine ring make rhynchophyllines attractively challenging synthetic targets, they have received limited attention from the synthetic standpoint.[7] In fact, only two different strategies have been used to assemble the spiro[pyrrolidine-3,3′-oxindole] moiety of these alkaloids: either a biomimetic oxidative rearrangement from an indolo[2,3-*a*]-quinolizidine derivative[4g,7c,d] or condensation of 2-hydroxytryptamine with an appropriate aldehyde.[7a,b]

We present here an enantioselective synthesis of *ent*-rhynchophylline and *ent*-isorhynchophylline using (*S*)-tryptophanol as the starting material, which not only incorporates the tryptamine moiety of the natural products but also acts as the source of chirality. Our approach takes advantage of the methodology we have reported for the enantioselective spirocyclization of tryptophanol-derived oxazolopiperidone lactams, involving a Lewis acid-promoted cyclization of the corresponding N_{ind}-tosyl



Scheme 1 Initial steps of the synthesis and synthetic strategy. *Reagents and conditions*: (a) toluene, Dean–Stark, reflux, 24 h, 65% (7,8a-*epi*-**2**, 10%); (b) 30% NaOH, Bu_4NCl, $PhSO_2Cl$, CH_2Cl_2, rt, 20 h, 90%; (c) Et_3SiH, $TiCl_4$, CH_2Cl_2, reflux, 20 h, 93%.

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, copies of ^1H and ^{13}C NMR spectra for all compounds. CCDC 912142 (**2**) and 912143 (**5**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc38540f

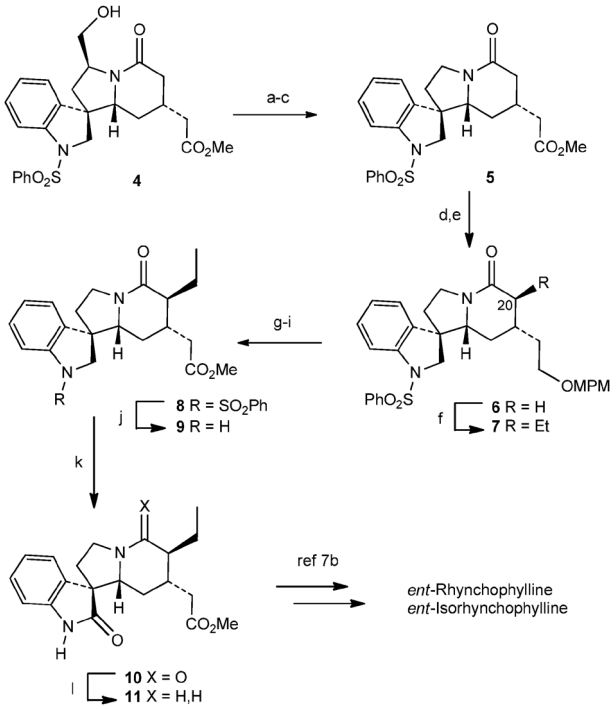
derivatives in the presence of Et_3SiH.[8] Scheme 1 outlines the initial steps of the synthesis and the overall synthetic strategy.

The required bicyclic lactam **2**, which already incorporates an acetate chain at the 4-position of the piperidone ring, was prepared[9] by cyclocondensation of (*S*)-tryptophanol with the prochiral aldehyde–diester **1**, in a process that involves the enantioselective desymmetrization[10] of two enantiotopic chains.[11] The *N*-indole deactivating group, needed to direct the key cyclization at the indole 3-position, was benzenesulfonyl,[12] which was introduced in excellent yield under conventional solid–liquid phase transfer conditions. Treatment of sulfonyl derivative **3** with $TiCl_4$ in the presence of Et_3SiH resulted in a regio- and stereocontrolled cyclization, with concomitant reduction of the initially formed spiroindoleninium intermediate, leading to the tetracyclic spiroindoline **4** as a single stereoisomer in 93% yield. Interestingly, **4** already embodies three of the four stereogenic centers of the target natural products, with the appropriate relative configuration.

As outlined in Scheme 1, the synthesis of rhynchophyllines from the spiroindoline **4** would involve the following transformations: (i) removal of the hydroxymethyl group, (ii) stereoselective introduction of the C-20 ethyl substituent to obtain the required *trans* C_{15}–C_{20} stereochemistry, (iii) oxidation of the indoline moiety to the oxindole functionality, (iv) chemoselective reduction of the lactam carbonyl, and finally, (v) introduction of the C-16 methoxyvinyl appendage.

The removal of the hydroxymethyl substituent, which has acted as an element of stereocontrol during the spirocyclization step, was accomplished by oxidation to a carboxylic acid, followed by a radical reductive decarbonylation *via* a selenoester[13] to give the tetracyclic lactam **5** (Scheme 2).

At this point, to complete the carbon skeleton of **11**, a known[7b] synthetic precursor of rhynchophyllines, only the introduction of the C-20 ethyl substituent remained to be done. However, to avoid the competitive alkylation at the α-position of the ester group, the alkylation was performed from the protected alcohol derivative **6**, which was obtained in good yield by $LiBH_4$ reduction of **5** followed by protection with *p*-methoxybenzyl chloride. The alkylation of **6** was performed with ethyl iodide, using KHMDS as the base and HMPA as the cosolvent, to stereoselectively give the expected *trans*-3,4-disubstituted 2-piperidone derivative **7**.[14] Then, the C-15 acetate chain was reinstalled (compound **8**) by oxidative removal of the *p*-methoxybenzyl protecting group of **7** with DDQ, followed by oxidation of the resulting alcohol to a carboxylic acid and a subsequent esterification. After a smooth and efficient deprotection of the indoline nitrogen with 5% Na/Hg, spiroindoline **9** was oxidized with PhIO, leading to oxindole **10** in 70% yield. Finally, chemoselective reduction of the six-membered lactam carbonyl, without affecting the oxindole moiety, was satisfactorily accomplished by sequential treatment of **10** with AlH_3 and $NaBH_3CN$.[15] The resulting oxindole **11** showed ^{1}H- and ^{13}C-NMR spectral data coincident with those reported[7c] for *rac*-**11**. Taking into account that *rac*-**11** has previously been converted[7b] to (±)-rhynchophylline and (±)-isorhynchophylline, the synthesis of oxindole **11** constitutes a formal enantioselective synthesis of the non-natural enantiomers of these alkaloids.



Scheme 2 Formal enantioselective synthesis of *ent*-rhynchophylline and *ent*-isorhynchophylline. *Reagents and conditions*: (a) IBX, DMSO, rt, 20 h, 79%; (b) $NaClO_2$, NaH_2PO_4, CH_3CN, *t*-BuOH, H_2O, 1-methylcyclohexene, rt, 1 h, then $(PhSe)_2$, *n*-PBu_3, CH_2Cl_2, reflux, 16 h, 64%; (c) AIBN, *n*-Bu_3SnH, benzene, reflux, 1 h, 65%; (d) $LiBH_4$, Et_2O, reflux, 48 h, 83%; (e) NaH, THF, rt, 2 h, then MPMCl, Bu_4NI, reflux, 16 h, 87%; (f) KHMDS, THF, rt, 2 h, then EtI, HMPA, rt, 16 h, 72% (20-*epi*-**7**, 19%); (g) DDQ, CH_2Cl_2/H_2O, rt, 1 h, 93%; (h) IBX, DMSO, rt, 20 h; (i) $NaClO_2$, NaH_2PO_4, CH_3CN, *t*-BuOH, H_2O, 1-Me-1-Chx, rt, 1.5 h, then Me_3SiCl, MeOH, rt, 24 h, 66% (three steps); (j) Na/Hg 5%, NaH_2PO_4, MeOH, 0 °C, 15 min, 88%; (k) PhIO, CH_2Cl_2, rt, 48 h, 70%; (l) AlH_3, THF, −78 °C (addition) to −50 °C, 30 min, then MeOH, rt, 20 min, then $NaBH_3CN$, AcOH, rt, 20 min, 47%.

The results reported herein further illustrate the potential of tryptophanol-derived oxazolopiperidone lactams for the enantioselective synthesis of indole alkaloids.[16] Two notable aspects of the synthesis are the efficient, highly convergent, and totally stereoselective assembling of the tetracyclic spiro[indoline-3,1′-indolizidine] ring system of rhynchophyllines and the generation of the required oxindole functionality by oxidation of an *N*-unsubstituted indoline.[17]

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