Natural Products

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Total Synthesis of Phalarine**

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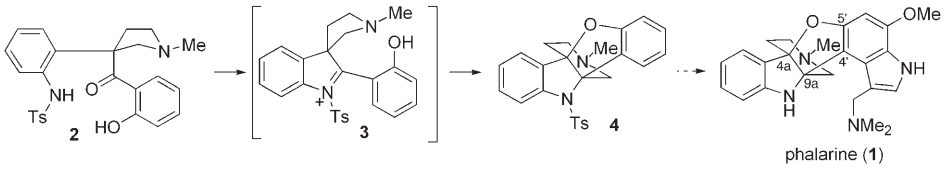
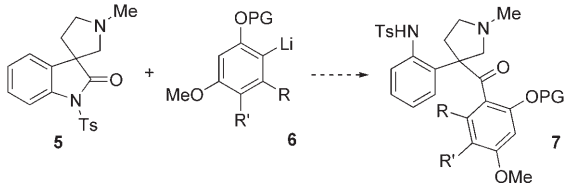
Our research group has been addressing the total synthesis of an alkaloid, phalarine (**1**), with an unusual structure. Pursuant to this goal, in the previous Communication we described a novel rearrangement of an azaspiroindolenine **3** (derived from **2**) to a prototype precursor **4** to phalarine (Scheme 1).[1] Some interesting mechanistic issues associated with this rearrangement were elucidated and we assumed that a total synthesis of **1** would be a straightforward matter. As described below, we were indeed able to accomplish the inaugural total synthesis of phalarine using the rearrangement strategy, although significant obstacles had to be overcome.



Scheme 1. Original strategy toward phalarine. Ts = toluene-4-sulfonyl.

For a total synthesis of phalarine, it would be best if the rearrangement could be conducted on an advanced-stage arylated ketone. This would reduce the complexity in going from the rearrangement product to the desired phalarine. However, as we were to learn, the key C–C bond-forming step, which would join for example, an aryl species **6** to an oxindole **5**, became highly problematic if conducted with complex C4 lithiated indoles (Scheme 2). As we conceded ground in the complexity of the aryllithium species **6** in the joining step, the pathway to phalarine from the post-rearrangement product became increasingly challenging. Harmonization of these competing vectors (the feasibility of coupling the aryl nucleophile to the azaspiroindolenine species versus access to the final target system from the rearrangement step) became the hallmark of the expedition.

Under our first approach, we envisioned coupling the lithio species **9** (prepared from **8**[2]) with the oxindole **5** (Scheme 3). Unfortunately, yields from this coupling were very low. Given these and the other failures encountered in the coupling reactions of carbonyl electrophiles with complicated, hindered aryl lithium reagents, we decided to attempt the coupling of lithio derivative **12** (generated from bromo compound **11**) with oxindole **5**. Indeed, carbon–carbon coupling was realized to afford ketone **13**. Fortunately, the anticipated rearrangement of azaspiroindolenine to the phalarine precursor took place under the conditions shown in Scheme 3, to provide **14** in 72% yield.



Scheme 2. Generalized strategy toward the rearrangement precursor. PG = protecting group.

A two-step sequence accomplished the *ortho* amination of **14** (Scheme 4). Thus, reaction of **14** with azodicarboxylate derivative **15** provided adduct **16**[3] which, under strongly reducing conditions, afforded amine derivative **17**.[4] Following our plan, this compound was nitrosated. The resulting diazonium chloride **18** was subjected to a Japp–Klingemann condensation with the β-ketoester **19**.[5] The reaction worked remarkably well and the elaborated phenylhydrazone **20** was produced. Unfortunately, all attempts to accomplish Fischer indolization to afford **21** were at best low yielding. While the reaction pathways were not fully characterized, at least three competitive lines could be discerned. One involved complete loss of the carbazate side chain with apparent formation of **14**. Another involved the cleavage of the N–N bond with the reappearance of the starting amine **17**. Still another involved *ipso* indolization at the methoxy-bearing carbon atom and reductive demethoxylation to afford the undesired indole **22**.[6] The failure to accomplish Fischer indolization of substrate **20** is shown in Scheme 4.

Given the setbacks described above, we sought a method from which we could construct a usable indole from **17**,

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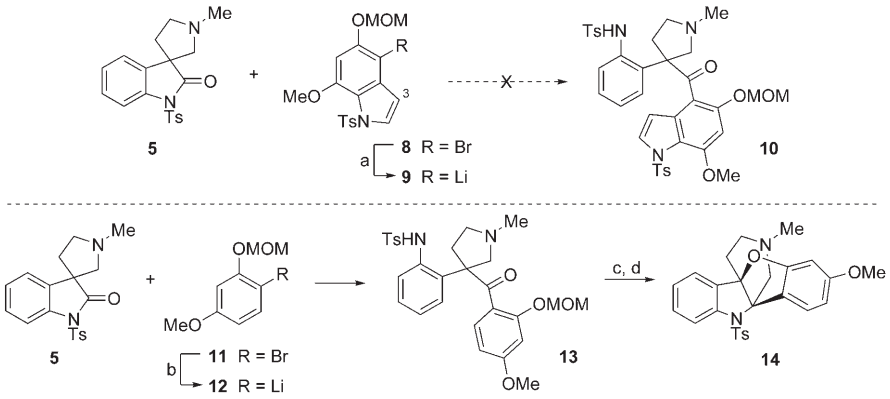
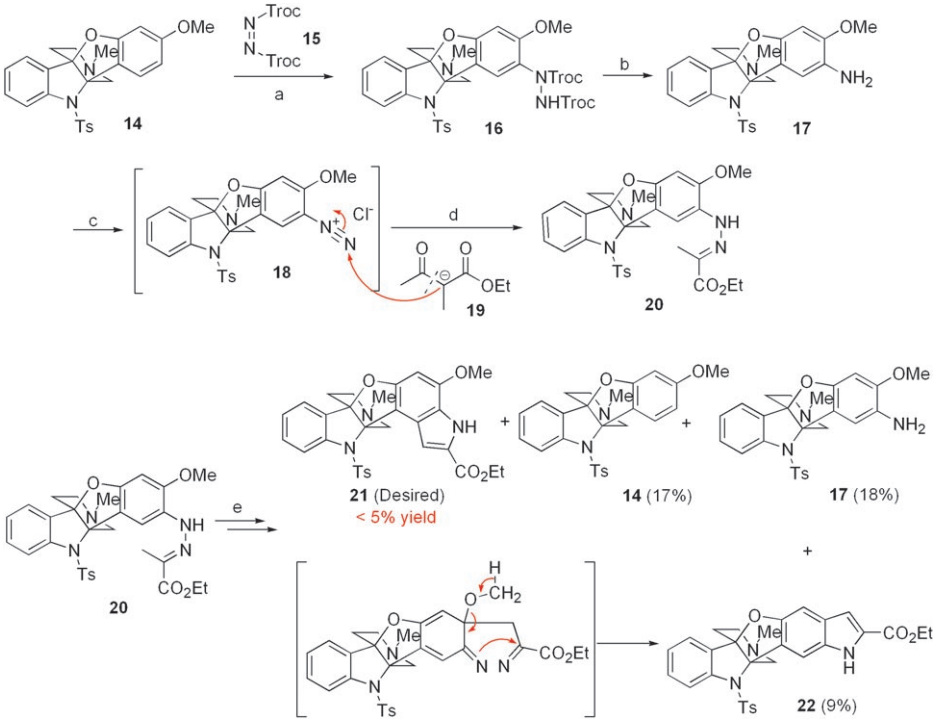
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



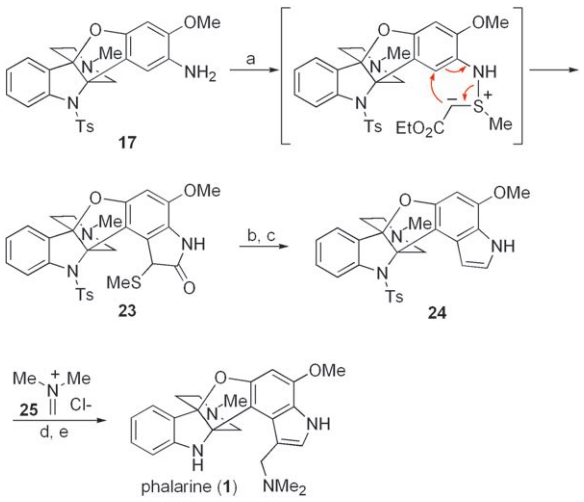
Scheme 3. Reagents and conditions: a) *t*BuLi or *n*BuLi; b) *t*BuLi, THF, −78 °C, 96%; c) TFA, CH_2Cl_2, 0 °C, 98%; d) CSA, toluene, 130 °C, 72%. CSA = camphorsulfonic acid, MOM = methoxymethyl, TFA = trifluoroacetic acid.



Scheme 4. Reagents and conditions: a) **15**, TFA, 95%; b) Zn dust, AcOH, 88%; c) $NaNO_2$, aqueous HCl, −5 °C; d) **19**, aq KOH, EtOH, −5 °C, 81%; e) TsOH, toluene, 80 °C, < 5%. Troc = 2,2,2-trichloroethoxycarbonyl.

without interference from the adjacent *ortho*-methoxy group. Fortunately, the Gassman oxindole synthesis proved to be very useful in this regard.[7] Thus, treatment of compound **17** with the ethyl ester of thiomethylacetic acid followed by reaction with sulfuryl chloride afforded oxindole **23** (Scheme 5). Following the mechanistic proposals of Gassman et al., this cyclization is interpretable in terms of a [2,3] sigmatropic rearrangement of the intermediate azasulfonium ylide.[7] Fortunately, this process, unlike the attempted Fischer indolization, was not undermined by the presence of the *ortho*-methoxy group. The oxindole **23** was converted into **24** as shown.[8] In another critical step, the indole reacted with *N*,*N*-dimethylmethylene ammonium chloride (**25**)[9] to produce a gramine intermediate, which upon cleavage of the sulfonamide function, afforded (±)-phalarine (**1**). The ^1H and ^{13}C NMR spectra of the racemic compound produced by the total synthesis corresponded to those reported for natural phalarine.[10]

In summary, the total synthesis of racemic phalarine has been achieved, though not without the need to deal with several serious, but manageable complications. Given what we have learned about the fundamentals of the rearrangement of azaspiroindolenine to the precursor to phalarine (**3**→**4**),[1] the application of this rearrangement (which provides



Scheme 5. Reagents and conditions: a) 1. $MeSCH_2CO_2Et$, SO_2Cl_2, CH_2Cl_2, −78 °C; 2. **17**, proton sponge, CH_2Cl_2, −78 °C; 3. Et_3N, CH_2Cl_2, −78 °C to RT; 4. AcOH, 2 h, 66% (78% based on recovered starting material); b) BH_3, THF, 0 °C; c) Raney Ni, EtOH, 90% for 2 steps; d) **25**, AcOH, 74%; e) Na(Hg), Na_2HPO_4, MeOH, 0 °C to RT, 90%.

the racemate) to reach substantially enantiomerically pure phalarine (without resolution) will require that one deals with some additional challenging issues. Such research is underway.

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