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A Cycloaddition Protocol for the Assembly of the Hexacyclic Framework Associated with the Kopsifoline Alkaloids

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Abstract

An approach to the hexacyclic framework of the kopsifoline alkaloids has been developed and is based on a Rh(II)-catalyzed cyclization-cycloaddition cascade. The resulting [3+2]-cycloadduct was readily converted into the TBS enol ether 23. Oxidation of the primary alcohol present in 23 followed by reaction with CsF afforded compound 24 that contains the complete hexacyclic skeleton of the kopsifolines.

The Malaysian members of the genus *Kopsia* have yielded a prodigious harvest of new natural products possessing novel carbon skeletons as well as useful bioactivities.[1] In 2003, Kam and Choo reported the structures of several new hexacyclic monoterpenoid indoline alkaloids isolated from a Malayan *Kopsia* species known as *K. fruticosa*.[2] The major components of the alkaloidal extracts were identified as the kopsifolines.[3] The structures were secured by spectral analysis and are characterized by an unprecedented carbon skeleton, in which the C(18) carbon is linked to C(16). The kopsifolines are structurally intriguing compounds, related to and possibly derived from an aspidosperma-type alkaloid precursor **1**. A possible biogenetic pathway to the kopsifolines from **1** could involve an intramolecular epoxide-ring opening followed by loss of H_2O as shown in Scheme 1. The interesting biological activities of these compounds combined with their fascinating and synthetically challenging structure, make them attractive targets for synthesis.

Our own work on the synthesis of the kopsifolines represents one component of a broad program focused on the synthesis of various aspidosperma alkaloids using [3+2]-cycloaddition chemistry.[4] Our retrosynthetic analysis of **3** is shown in Scheme 2 and envisions the core skeleton to arise from a metal carbene-cyclization-cycloaddition cascade that our group has been studying for some time.[5,6] Using this metal-catalyzed domino reaction as a key step, the heterocyclic skeleton of the kopsifolines could eventually be built by a 1,3-dipolar cycloadddition of a carbonyl ylide dipole derived from diazo ketoester **4** across the indole π-bond.[7,8] Ring opening of the resulting cycloadduct **5** followed by a reductive dehydroxylation step[9] would lead to the critical silyl enol ether **6** necessary for the final F-ring closure. Although the very last step (*i.e.*, **6** → **7**) appears to be reasonable, no example of such a reaction had been previously reported in the literature. Accordingly, we decided to study the facility and stereoselectivity of this process with model substrates prior to commencing the total synthesis of the kopsifolines. In this communication we detail the successful implementation of this strategy.

To test what appeared to be a logical but not directly precedented ring F-closure, we first carried out a model study using cycloadduct **11** in order to test the viability of our design as well as the specific reactions to be used in a total synthesis effort. Diazoimide **10** was easily prepared

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by reacting acid chloride **8** with amide **9** in the presence of 4A° molecular sieves at room temperature followed by a diazo-transfer with MsN_3.[10] Heating a sample of **10** with catalytic $Rh_2(OAc)_4$ in benzene at 80 °C afforded cycloadduct **11** in 90% yield as a single diastereomer (Scheme 3). The isolation of **11** is the consequence of *endo* cycloaddition with regard to the dipole[7], and this is in full accord with the lowest energy transition state. The cycloaddition can also be considered doubly diastereoselective in that the indole moiety approaches the dipole exclusively from the side of the 2-(benzyloxy)ethyl group and away from the more sterically encumbered piperidone ring.

On the basis of our previous studies using related azaoxabicyclic systems,[11] we expected that treating cycloadduct **11** with Et_3SiH and BF_3**.**OEt_2 would result in a reductive ring opening reaction. We found, however, that the rearranged nine-membered lactone **14** was obtained as the only identifiable product in 60% yield. This unusual reorganization can be rationalized by the pathway proposed in Scheme 4. We assume that the first step involves a Lewis acid promoted debenzylation with Et_3SiH and the transient alcohol **12** so produced undergoes ready cyclization onto the adjacent carbonyl group to generate a hemiketal intermediate. A subsequent ring opening of the oxabicyclic ring affords N-acyliminium ion **13** which then undergoes cleavage of the C-C bond to dissipate the positive charge on the nitrogen atom thereby giving rise to the observed lactone **14**.

We next investigated the key F-ring closure step that is the foundation of our kopsifoline strategy by making use of hemiketal 15. For these feasibility studies (Scheme 5), we converted **15** into keto-ester **17** which possesses a side chain mesylate group that could undergo intramolecular displacement with the carbanion derived from ketoester **17.** Hemiketal **15** is easily available from cycloadduct **11** *via* lactam reduction followed by catalytic hydrogenation which causes reductive ring opening of the oxabicyclic ring, debenzylation and cyclization to give **15** in 43% yield for the three-step sequence. Treatment of **15** with tri-ethylamine/mesyl chloride furnished **16** (85%) which was then reduced with SmI_2 to give **17** in 60% yield. Unfortunately, all of our efforts to induce ring F-closure of **17** with various bases and under different experimental conditions were unsuccessful.

This outcome suggested that the mesylate group was not sufficiently reactive enough to undergo reaction with the anion resulting from deprotonation of the β-keto ester. Consequently, we turned our attention to replacing the mesylate group with a more reactive aldehyde functionality on the side chain. To access a suitable and useful substrate for the key aldol reaction, we first synthesized the related cycloadduct **18** which bears a 2-methyl acetate group at the ring juncture. This compound was readily available from the corresponding diazoimide in 98% yield as a single diastereomer by treating it with $Rh_2(OAc)_4$ in refluxing benzene. We then converted **18** into the ring-opened hydroxy ester **19** (68%) using the same 3-step protocol that was used in Scheme 5. At this point, the carbomethoxy and hydroxyl groups were sequentially removed using Cs_2CO_3 followed[9,12,13] by a samarium iodide reduction.[14] The remaining keto group was converted into the corresponding TBS enol ether and this was followed by a two-step reduction/oxidation of the ester functionality to give **20** in 59% yield for the five-step sequence (Scheme 6). Gratifyingly, when **20** was treated with CsF in CH_3CN at reflux, it was cleanly converted to the hexacyclic skeleton of the kopsifoline alkaloids (*i.e.*, **21**) in 78% yield and whose structure was confirmed by a single-crystal X-ray analysis.[15]

Since all members of the kopsifoline family of alkaloids contain a carbomethoxy group at the C(16)-position of the core skeleton, we decided to selectively remove the hydroxyl group from hydroxy ester **19**. To this end, the reduction of **19** was carried out with SmI_2 in HMPA and the expected ketoester **22** was isolated in 93% yield (Scheme 7). This compound was easily converted into the corresponding TBS silyl enol ether in 96% yield. Reaction of the enol ether

with LAH at 0 °C resulted in the selective reduction of the non-conjugated carbomethoxy group affording **23** in 91% yield. The primary alcohol so formed was then subjected to oxidation using TPAP/NMO at 0 °C and the crude reaction mixture was subsequently treated with CsF in refluxing CH_3CN to give the desired ring F-cyclized ester **24** in 34% yield for the two-step sequence. Despite the additional manipulations associated with the processing of intermediate **19** and the somewhat lower yield, only five steps are required to prepare a complex hexacyclic structure that contains the complete skeleton of the kopsifoline alkaloids.

In summary, the new cyclization chemistry described herein gives rapid access to the hexacyclic core skeleton of the kopsifoline alkaloids, and the products synthesized appear to be suitable for further manipulation toward the natural products and their close analogues. Further application of the metal carbene cyclization-cycloaddition cascade toward several other monoterpenoid indoline alkaloids is currently being investigated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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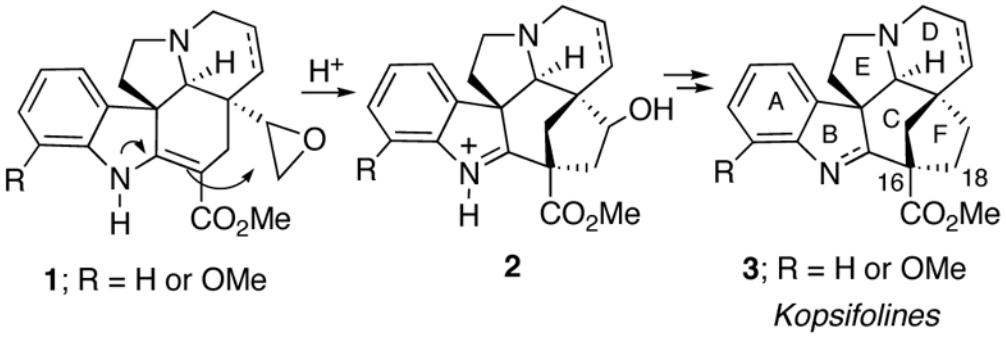
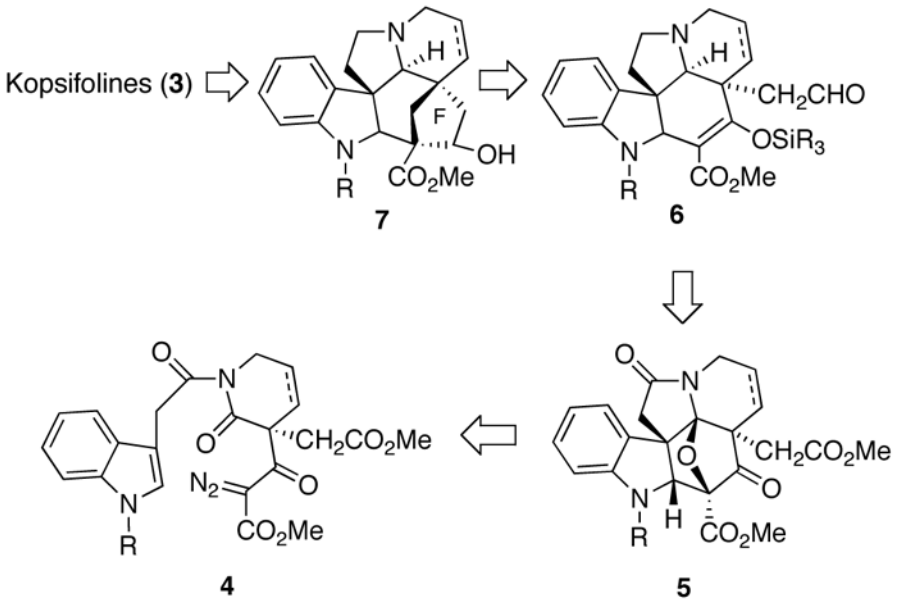
15. The authors have deposited coordinates for structure **21** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, B2 1EZ, UK.



Scheme 1.



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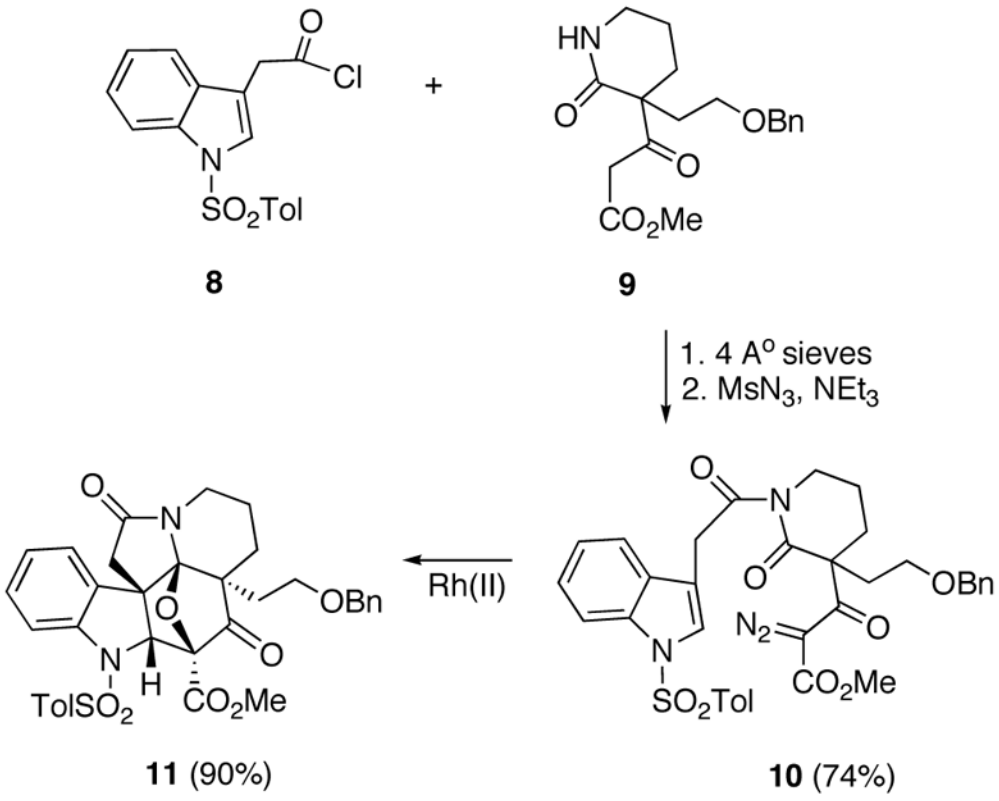

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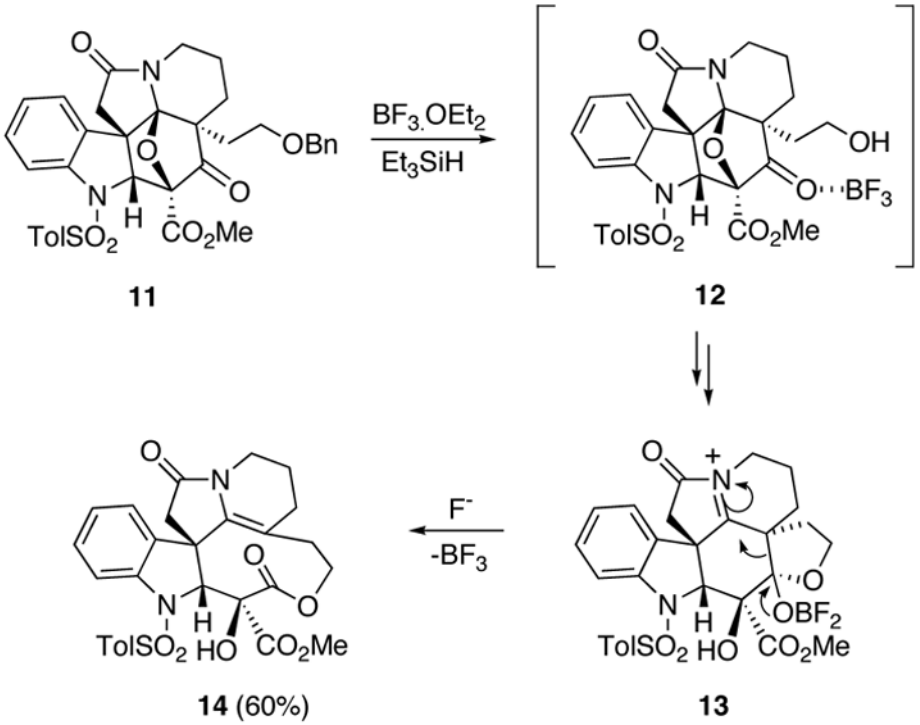

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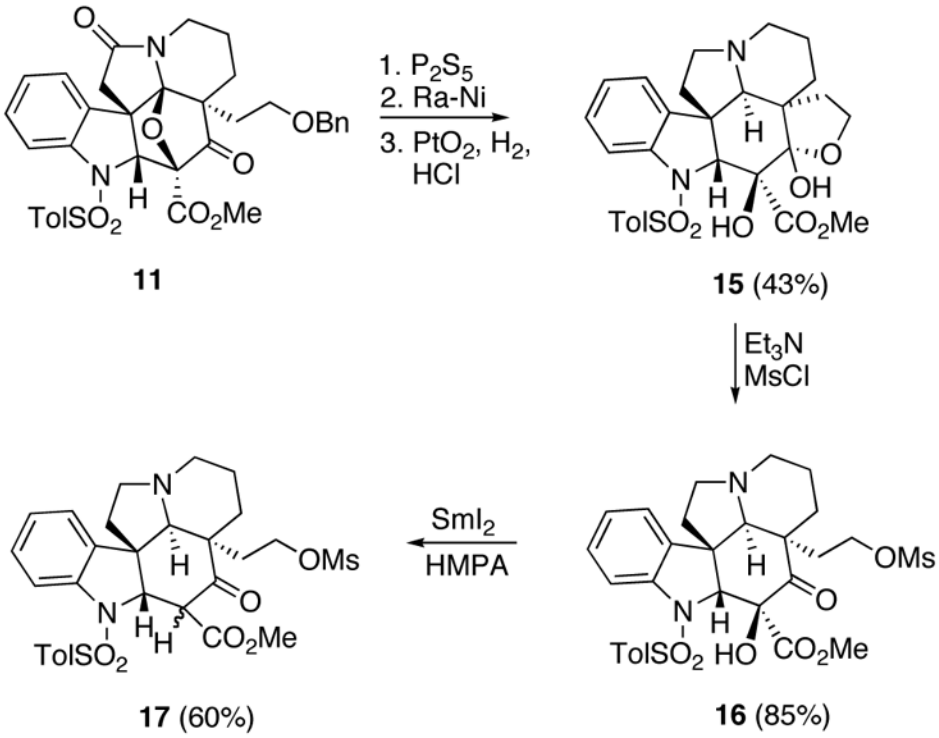


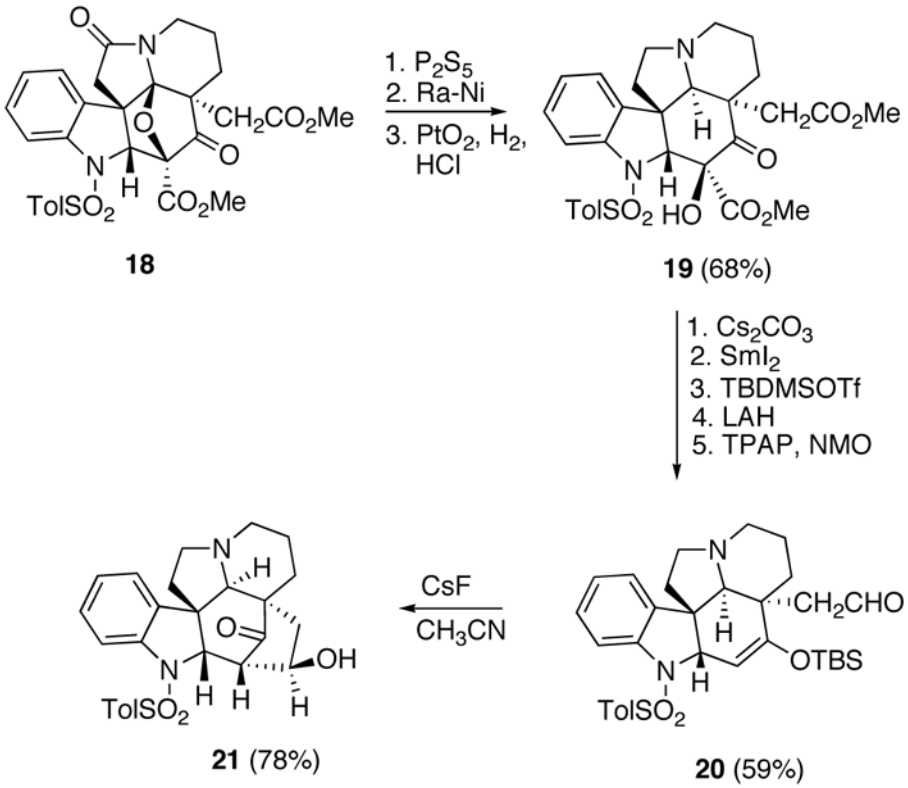
11

15 (43%)

16 (85%)

17 (60%)

Scheme 5.



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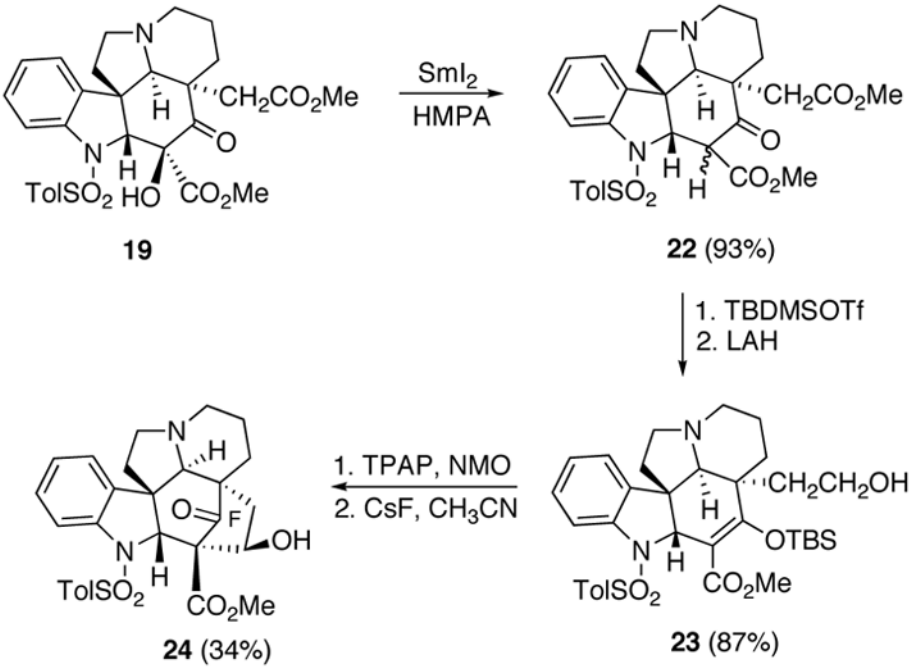

Scheme 7.