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Concise Total Synthesis of (±)-Marcfortine B

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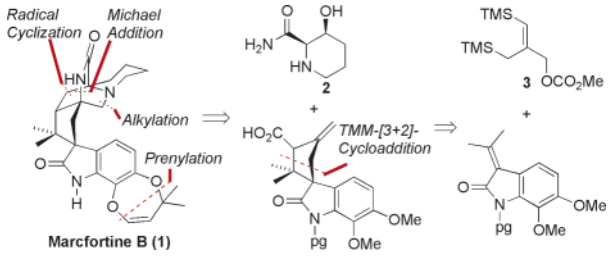
The marcfortine alkaloids and the closely related paraherquamide class are complex indolic secondary metabolites isolated from various *Penicillium* species.[1] Their potent anthelmintic activity[2] and intriguing molecular architecture have drawn the attention of organic chemists resulting in the syntheses of paraherquamide A and B.[3] We became interested in this class of compounds as their common central structural element, a heavily substituted spirocyclic cyclopentane ring, could be effectively accessed by our palladium-catalyzed trimethylenemethane (TMM) [3+2]-cycloaddition methodology.[4,5] We reasoned that a variation, the carboxylative TMM-cycloaddition,[6] could be employed to provide the cyclopentene core as well as the requisite carboxylic acid functionality (Scheme 1). Once constructed, we anticipated the use of the asymmetry of the spirocycle as a controlling element for establishing the remaining stereogenic centers of marcfortine B (**1**). In particular, the strained bicyclo[2.2.2]diazaoctane core would be assembled by an alkylation of 2-hydroxypipecolic amide (**2**), followed by an intramolecular Michael-addition and a radical ring closure. During the course of the campaign, this led to the discovery of a highly unusual eliminative radical cyclization establishing a viable pathway to **1**.

The TMM-acceptor **6** is accessible from the known oxindole **5**[7] in two steps (Scheme 2), whereas the synthesis of the TMM-donor **3** (Scheme 1) has been previously reported.[6] Pleasingly, the cycloaddition proceeded cleanly upon refluxing both substrates in toluene with a catalytic amount of palladium acetate and triisopropyl phosphite giving the spirocyclic acid **7** (Scheme 2). Methylester formation with dimethyl sulfate suppressed any double-bond migration that was observed with other methods and gave rise to ester **8** as a 1:1 diastereomeric mixture in excellent yield. Epoxidation and subsequent exposure to DBU yielded allylic alcohol **9** as a single diastereomer.

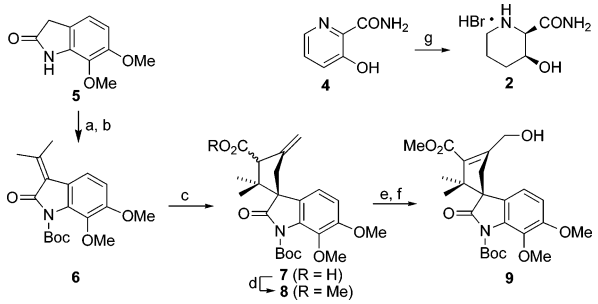
Activation of allylic alcohol **9** as the mesylate, followed by displacement with piperidine **2** (obtained from pyridine **4** in one step by catalytic hydrogenation, Scheme 2, upper right), and elimination of the secondary alcohol of the piperidine ring provided the corresponding α,*β*-unsaturated amide giving compound **10** (Scheme 3). Removal of the Boc-protecting group with tin tetrachloride[8] proved to be necessary to avoid decomposition during the following cyclization.

Upon treatment of the free oxindole **11** with potassium hexamethyldisilazide, smooth Michael-addition proceeded and gave the desired cyclized compound **13** as a single diastereomer in quantitative yield. The remarkable selectivity of this reaction is attributed to efficient shielding of the *re*-face of the Michael-acceptor by the aromatic portion of the molecule. Internal protonation of the resulting enolate **12** by the amide hydrogen then delivered the desired trans relationship of ester **13**. Regardless of the method of quenching the reaction, replacement of this hydrogen as its N-methylated congener inverted this selectively completely, giving exclusively the undesired epimeric ester. Because of the extremely poor solubility of cyclized compound **13**, a reprotection of it with

Scheme 1. Retrosynthesis of Marcfortine B



Scheme 2. Synthesis of Key Intermediates **2** and **9**[a]



[a] Conditions: (a) acetone, HCl, room temp, 70%; (b) Boc_2O, DMAP, NEt_3, CH_2Cl_2, 85%; (c) **3**, 5% PdOAc, 35% $P(Oi\text{-}Pr)_3$, toluene, reflux; (d); Me_2SO_4, K_2CO_3, acetone, reflux, 93% over two steps; (e) *m*CPBA, CH_2Cl_2, 0 °C, 89%; (f) DBU, THF, 0 °C to room temp, 72%; (g) 100 bar H_2, cat. Rh/Al_2O_3, aq HBr pH 3, 65 °C, quant.

p-methoxybenzylbromide was required. Chemoselective reduction of the ester with DIBAL gave the primary alcohol which was subsequently converted into xanthante ester **15** using standard procedures.

The stage was now set for the crucial radical cyclization. Although a wide range of conditions were investigated, the expected saturated product **20** was never obtained. Instead, alkene **19** was the sole isolable product. A possible explanation of this unusual result is an attack of the secondary alkyl radical **16** on the AIBN rather than reacting with tributylstannane.[9] In accord with this suggestion, we found that superstoichiometric amounts of AIBN and catalytic amounts of tributylstannane were necessary for optimum yields. The resulting nitrogen-centered radical **17** can then participate in a 1,4-hydrogen abstraction to generate alkyl radical **18**, which undergoes fragmentation to the observed unsaturated product **19**, an isobutyronitrile radical and a monoalkyl diazene which then fragments further (Scheme 3). Reduction of the alkene with Crabtree's catalyst gave the targeted saturated compound **20**. Although oxidative cleavage conditions for the removal of the *p*-methoxybenzyl group were found to be incompatible with the electron-rich oxindole core, smooth deprotection could be accomplished with refluxing TFA/anisole.[10]

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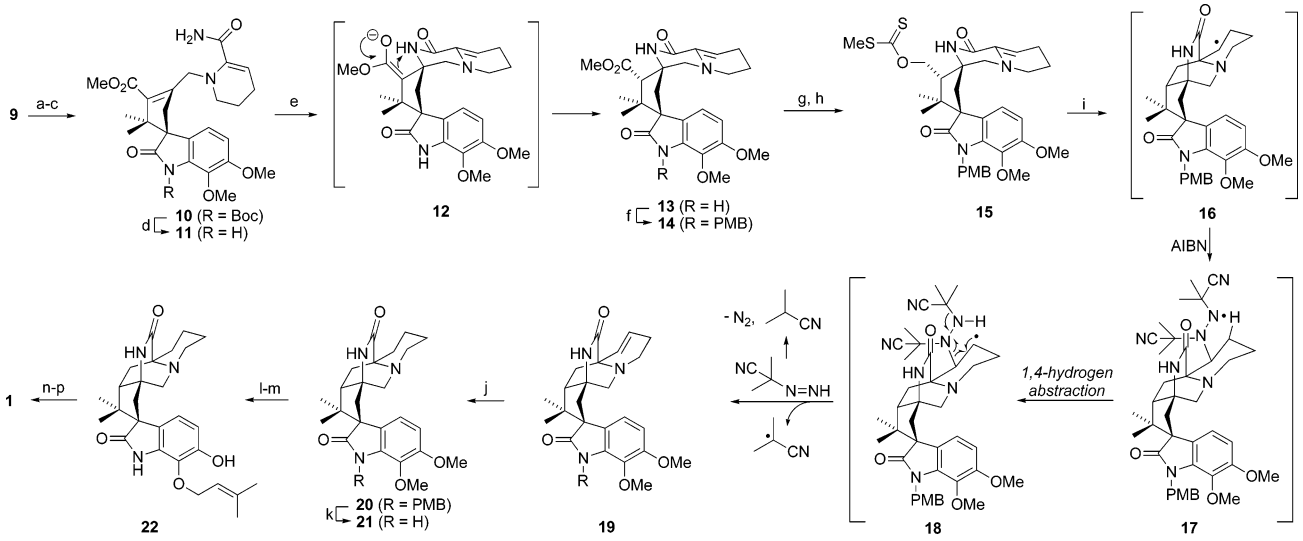
Scheme 3. Completion of the Synthesis[a]



[a] Conditions: (a) MsCl, NEt_3, CH_2Cl_2, 0 °C; (b) **2**, NEt_3, DMSO, room temp; (c) MsCl, NEt_3, CH_2Cl_2, 0 °C, then DBU, 84% over three steps; (d) $SnCl_4$, EtOAc, room temp, 89%; (e) KHMDS, THF, 0 °C to room temp, quant.; (f) PMBCl, Bu_4NI, K_2CO_3, acetone, reflux, 95%; (g) DIBAL, CH_2Cl_2, 0 °C, 86%; (h) KHMDS, THF, CS_2, −78 °C to room temp, then MeI, 75%; (i) 170% AIBN, 20% Bu_3SnH, C_6H_6, reflux, 61%; (j) 50 bar H_2, 15% Crabtree's catalyst, CH_2Cl_2, 89%; (k) TFA, anisole, reflux, 91%; (l) BBr_3, CH_2Cl_2, 0 °C; (m) prenylbromide, KI, Cs_2CO_3, acetone/H_2O 10:1, 62% over two steps; (n) *m*CPBA, $CHCl_3$, 0 °C to room temp, then aq $NaHSO_3$; (o) $SnCl_4$, dioxane, room temp; (p) $MeP(OPh)_3I$, DMPU, room temp, 42% over three steps.

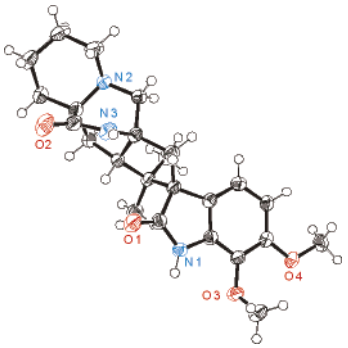


Figure 1. X-ray based ORTEP drawings of **21**. Spheres are drawn at the 60% probability level.

At this stage, an X-ray crystal structure of hexacycle **21** was obtained allowing the unambiguous determination of all stereochemical outcomes of the sequence (Figure 1). Having forged six of the seven rings of marcfortine B, the remaining dioxepine ring was constructed by a known four-step protocol.[11] The two methoxy ethers of **21** were cleaved with boron tribromide. The insolubility of the resulting catechol was somewhat problematic; however, it could be converted to the monoalkylated compound **22** with prenylbromide in an acetone/water mixture using cesium carbonate as base. Epoxidation of alkene **22** with *m*CPBA, followed by treatment of the diastereomeric epoxides with tin tetrachloride in dioxane promoted effectively endo cyclization forming the seven-membered ring. Elimination of the secondary alcohol gave marcfortine B. All spectroscopic data of the synthetic material proved to be in excellent agreement with an authentic sample (^1H and ^{13}C NMR, IR, mass).

In summary, we report the first total synthesis of marcfortine B, showcasing the palladium-catalyzed TMM cycloaddition as a powerful method for the rapid assembly of the complex cyclopentene structure from simple starting materials. The completed work highlights the utility of the intramolecular Michael-addition and free radical cyclization as synthetic tools in the construction of highly congested molecules. Investigations of an asymmetric variant of the carboxylative TMM-reaction and its application in the synthesis of related compounds are ongoing.

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Supporting Information Available: Complete ref 2a, X-ray diffraction data for **21**, experimental procedures, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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