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Double Annulative Cascade of Tryptophan-Containing Peptides Triggered by Selectfluor

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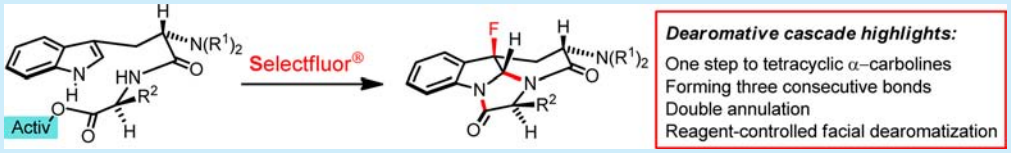
Supporting Information



ABSTRACT: A common dearomative strategy toward the kapakahines B/F and chaetominine natural products is reported. The proposed biomimetic strategy generates the tetracyclic α-carboline core in a single step, featuring a selectfluor-mediated dearomatization of preactivated *N*-*Phth*-Trp-Xaa-OR dipeptides at the *C*-terminus. The pivotal cascade includes a double annulation and the formation of three carbon−heteroatom bonds while gaining, for the first time, some insight on the diastereoselectivity outcome during the formation of the α-carboline fragment.

The kapakahine natural products are a family of six cyclic peptides isolated from the marine sponge *Cribrochalina olemda* by Scheuer, including the most active metabolite kapakahine B (**1**, Figure 1) having antileukemia activity (IC_{50} of 5.4 μM) against P388 murine leukemic cells.[1] A related alkaloidal metabolite, chaetominine (**3**) was isolated from the fungus *Chaetomium sp.* by Tan and presents even more important cytotoxic activity against the human leukemic K562 and colon cancer SW1116 cell lines with the corresponding IC_{50} values of 21.0 and 28.0 nM.[2] Chaetominine (**3**) and the kapakahine metabolites **1**−**2** have similar architectural features that drew us to propose a unified biomimetic design to access both tetracyclic α-carboline skeletons **6** (Figure 1). The substituents at the fused junction of the B and C rings present an *anti* stereorelationship to the tryptophan (Trp) α-nitrogen center, supposedly arising from a facial discrimination via an *anti*-approach of the electrophile (away from $^{\alpha}$*N*-Trp) during the dearomatization step.

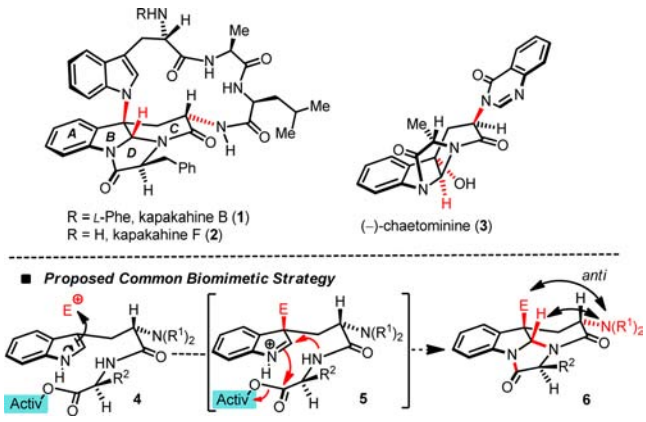


Figure 1. Hypothesis for a unified biomimetic construction of the tetracyclic α-carboline core of natural products (**1**−**3**).

A similar *anti*-relationship is observed in both natural products **1**/**2** and **3**, which could arise from analogous biosynthetic pathways in the *Cribrochalina olemda* and *Chaetomium sp.* organisms. Based on this hypothesis, we decided to examine a common dearomative strategy for both families of natural products (Figure 1). Our approach takes advantage of a peptidic activation at the *C*-terminus esters to enable an unprecedented cascade transformation, forming three carbon−heteroatom bonds consecutively in a single step. While dearomative cyclization of Trp building blocks to hexahydro-[2,3-*b*]pyrroloindole (HPI) fragments has been extensively studied, providing high *exo*-selectivity,[3] we are now reporting for the first time the stereochemical outcome for the synthesis of several hexahydro[2,3-*b*]pyridoindole (α-carboline) skeleton.

Previously, Papeo, Snider, Evano, Huang, Rainer, and Baran reported elegant constructions of the tricyclic skeleton (A, B, and C rings) during their total syntheses campaigns to the kapakahines B/F (**1**−**2**)[4] and chaetominine (**3**).[5] All previous synthetic strategies exploit the chiral pool as starting material (L- or D-tryptophans and corresponding dipeptides) for the key dearomatization step, but none of these syntheses achieved the assembly of the full tetracyclic core in a single operation.

Our biomimetic tactic to form the tetracyclic α-carboline in a single step requires mild oxidative conditions which will not only dearomatize the activated dipeptide **4**, but will also be amenable to the overall cascade of events (Figure 1). Dearomatized indolenium **5** should then undergo intramolecular cyclization at the C-2 position to unveil a

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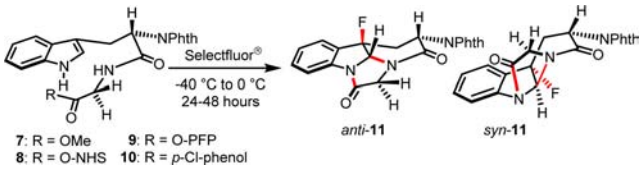
nucleophilic *sec*-aniline which would collapse onto the activated ester to form the last required peptidic bond of the tetracyclic α-carboline **6**. Such double annulative strategy[6] would complete the expedient entry to both families of natural products.

As anticipated, the dearomative cascade transformation of unprotected dipeptides **7**−**10** and **16** proved to be a difficult task. Most of the typical oxidative reagents known to achieve indole dearomatization were screened: *t*BuOCl, NBS, NCS, Selectfluor, Br_2, *N*-PSP, Oxone, *m*-CPBA, DMDO, Davis' oxaziridine, iodine(III) reagents (PIDA, PIFA), and others.[7] Reactions were followed by ^{1}H NMR, and after addition of two-thirds of the oxidant, no starting dipeptides remained in solution,[7] confirming that a destructive pathway through elimination and overoxidation of the indolic core may occur.[8] From this extensive study on dipeptide dearomatization, Selectfluor was found to be the only reagent to successfully initiate the dearomatization and achieve the cascade in valuable yields.[9]

The cascade triggered by Selectfluor was first examined on activated dipeptides *N*-*Phth*-Trp-Gly-OR **7**−**10** (Table 1).[7,9b] Dearomatization of a dipeptide methylester **7** did not enable the cascade to take place; instead, a sensitive indolenine product **12** was isolated.[10]

Table 1. Initial Discovery of a Dearomative Cascade of Unprotected Indole To Form the Tetracyclic α-Carboline 11



entry	dipeptide/solvent/additive[a]	% yield (*anti*-*syn* dr)[b]
1	**8**/acetone/−	0
2	**9**/acetone/−	35 (1.0:1.2)
3	**9**/acetone/−[c]	0
4	**9**/acetonitrile/−	0
5	**9**/acetone/$(DHQ)_2$PYR	0
6	**9**/acetone/$(DHQ)_2$AQN	28 (1.1:1.0)
7	**9**/acetone/$(DHQ)_2$PHAL[d]	31 (1.8:1.0)
8	**9**/acetonitrile/$(DHQ)_2$PHAL	20 (3.7:1.0)
9	**10**/acetone/−	27 (1.3:1.0)
10	**10**/acetone/$(DHQ)_2$PHAL	37 (2.9:1.0)
11	**10/acetonitrile/$(DHQ)_2$PHAL**	**34 (4.1:1.0)**

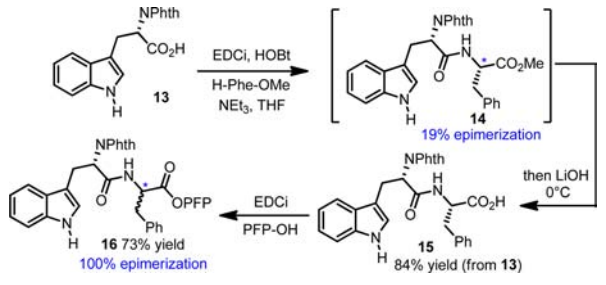
[a]Reagents: Selectfluor (1.2 equiv), $NaHCO_3$ (1.2−2.0 equiv), additive (1.2 equiv), solvent [0.01 M]. See the Supporting Information for detailed procedures. [b]*Anti*-*syn* diastereomeric ratios determined by ^{1}H NMR analysis of the crude reaction mixtures. [c]No base was used. [d]When $(DHQ)_2$PHAL was used in a catalytic amount (20 mol %), product **11** was isolated in 13% yield (1.0:1.8 dr).

This result endorses Evano's approach in which the α-carboline unit was obtained with unavoidable overoxidation.[5c] Thus, several known *C*-terminus activating groups for peptide assembly were tested on dipeptides **8**−**10** to facilitate the cascade. Dearomatization of the activated *N*-hydroxysuccinimide dipeptide ester **8**, proved unsuccessful, leading mostly to decomposition (entry 1). Then we turned our attention to phenolic activated ester (pentafluorophenol) **9** and (*p*-chlorophenol) **10** (entries 2−11). Both dipeptide **9** and **10** readily endure the dearomatization upon addition of Selectfluor and underwent the double annulative cascade to furnish the tetracyclic α-carboline **11** in 35% and 27% yield, respectively (entries 2 and 9). Surprisingly, both substrates **9** and **10** showed an opposite innate diastereofacial selectivity when reacting with Selectfluor, as much as 1.0:1.2 to 1.3:1.0 *anti*-*syn* ratios, respectively. These results diverge from the typical *syn*-selectivity (also called *exo*-selectivity) reported for most halocyclizations forming HPIs.[3] Reactions performed without base lead mostly to decomposition (entries 3 and 4). *To date, the standard conditions in acetone with $NaHCO_3$ proved to be the most reproducible and general in respect of all dipeptide substrates tested in the cascade reaction.*

We then screened chiral quinuclidine *Cinchona* alkaloidic dimers known to synergistically react with Selectfluor promoting enantioselective fluorination reactions (entries 5−8, 10, and 11).[11] As suggested in previous work, different orientation of the substrates inside of the dimeric alkaloid pocket can occur depending on the type of ligand used (PHAL, PYR or AQN) which will greatly affect the reaction stereochemical-outcome.[12] We observed such situation (entries 5−8) as shown by the inefficacy of $(DHQ)_2$PYR in promoting the cascade (entry 5), while both PHAL and AQN frameworks enable the cascade, leading to the desired tetracyclic compound **11** in 28% and 31% yield respectively (entries 6 and 7). Encouraged by the noticeable increase in facial-selectivity when using $(DHQ)_2$PHAL (entry 7; 1.8:1.0 dr), we tested the catalytic version of the reaction, for a catalyst-controlled cascade. This attempt yielded compound **11** in only 13% (no catalysis observed) with a surprising reversal of stereoselectivity leading to the *syn*-product **11** as major diastereomer (1.0:1.8 dr). Reaction in acetonitrile afforded the *anti*-product **11** with a much higher *anti*-stereoselectivity (3.7:1.0 dr) in 20% yield (entry 8). Finally, dipeptide **10** was subjected to the cascade upon fluorination with $(DHQ)_2$PHAL in acetone and acetonitrile (entry 10 and 11) to deliver the desired *anti*-product **11** respectively in 37% yield (2.9:1.0 dr) and 34% yield (4.1:1.0 dr). *The use of $(DHQ)_2$PHAL enabled a complete switch and an increase in antidiastereoselectivity for the cascade reaction affording the desired α-carboline anti-11*. *Anti* and *syn* products **11** relative stereochemistry were determined by NOE studies.[7]

Our first study completed, we prepared the suitable precursor for the dearomatization step in large scale (Scheme 1). Trp was first protected to the *N*-*Phth*-Trp-OH **13**. Compound **13** was engaged directly in a one pot coupling-hydrolysis sequence in tetrahydrofuran using first EDCi-HOBt as activators and lithium hydroxide for the *in situ* saponification to yield dipeptide *N*-*Phth*-Trp-Phe-OH **15** in 84%. Finally, decagram quantities of activated dipeptide *N*-*Phth*-Trp-Phe-OC_6F_5 **16**

Scheme 1. Synthesis of Activated Dipeptide *N*-*Phth*-Trp-Phe-OPFP 16[a]



[a]For a study on dipeptides **14** and **16** epimerization, see the Supporting Information.

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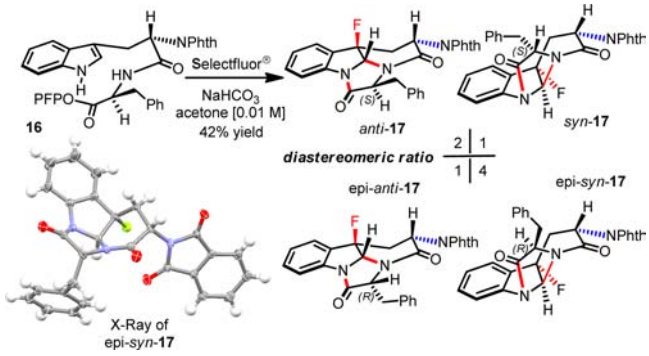
were prepared in 73% yield, requiring no chromatography purification through the overall three-step sequence. To our surprise, the activated dipeptide **16** is extremely sensitive to decomposition (silica or alumina flush), it required careful handling and was found to be fully epimerized.[7] We also observe that high level of epimerization (19%) occurred during the preparation of dipeptide **14**.[7,13] Results of an intensive effort to synthesize the rather simple dipeptide **14**, HATU/2,6-lutidine was found to be the best activating protocol to deliver **14** in 98% yield with less epimerization (10%).[7] Unfortunately, these efforts appeared rather futile, because of the unavoidable racemization occurring ($^{\alpha}$H Phe or Ala residues) during the final activation step with pentafluorophenol, leading to dipeptide **16** as a 1:1 epimeric mixture.[7] ^{1}H NMR studies confirmed that the synthetic Trp-containing dipeptides are epimerized and not mixtures of rotamers.[14]

The 1:1 epimeric mixture of dipeptide **16** was used for the key dearomatization step to determine the level of selectivity during the dearomative cascade reaction (Scheme 2). Under

Scheme 2. Cascade Reaction to Produce the Tetracyclic Core 17 in a Single Step with Facial *Syn*-Stereoselectivity[a]

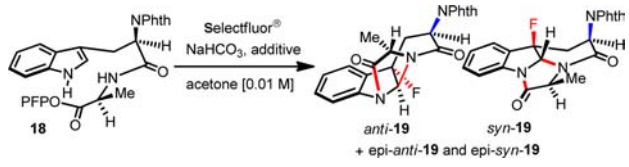


[a]Innate *anti-syn* diastereocontrol (3:5 dr).

the aforementioned optimized dearomative conditions, the tetracyclic α-carboline **17** was obtained in 42% yield as a mixture of four separable diastereomers (**2.0**:1.0:1.0:4.0; ***anti***:*syn*:epi-*anti*:epi-*syn* dr). Product **17** was not isolated in equimolar ratio of epimers, but in a 3:5 ratio overall (*syn*/*anti vs* epi-*syn*/epi-*anti*). This result shows that a kinetic resolution[15,7] is likely operating during the reaction, leading to the epi-*syn*-**17** diastereomer as major product. The diastereomers were separated and relative stereochemistry was confirmed by NOE studies and X-ray characterization of epi-*syn*-**11** (Scheme 2). Dearomative cascade using $(DHQ)_2$PHAL was then logically attempted on dipeptide **16** to counteract the kinetic resolution and promote the desired *anti*-diastereodiscrimination. Unfortunately, the reaction proceeded in extremely low yields (5−13%) without improving the desired *anti*-diastereoselectivity (**2.5**:5.0: 1.0:1.0; ***anti***:*syn*:epi-*anti*:epi-*syn* dr).[7]

Facing this unexpected diastereoselectivity issues, we then examined the reactivity of *N-Phth*-D-Trp-Ala-OPFP dipeptide **18** for an approach to chaetominine (**3**) (Table 2). Dipeptide **18** successfully underwent the cascade to afford tetracyclic α-carboline **19** in 29% yield (entry 1), while the innate substrate-induced diastereocontrol is quasi-non existent (**1.1**:1.6:1.0:1.2; ***anti***:*syn*:epi-*anti*:epi-*syn* dr).[7] To finalize our study, reaction was also attempted in presence of $(DHQ)_2$PHAL (entry 2). In this case, an impressive *syn*-selectivity was observed with an overall 15:2 *syn*/*anti*-diastereomeric ratio.[7]

Table 2. Cascade Reaction en Route to Chaetominine (3)



entry	additive	% yield (***anti***:*syn*:epi-*anti*: epi-*syn* dr)
1		29% (**1.1**:1.6:1.0:1.2)
2	$(DHQ)_2$PHAL	25% (**1**:10:1:5)

Figure 2 proposes an explanation for the observed diastereoselectivity during dearomatization of the Trp-contain-

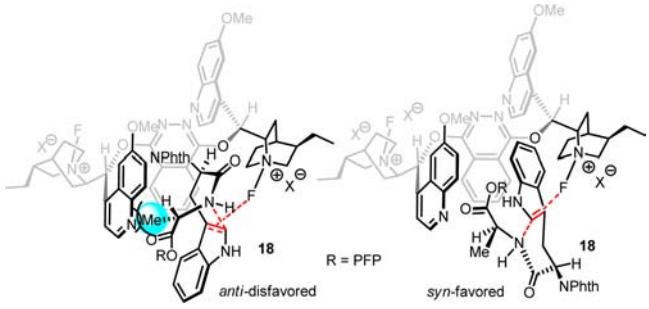


Figure 2. Proposed arrangements of dipeptide **18** for *syn* vs *anti* stereoselectivity mediated by $(DHQ)_2$PHAL.

ing dipeptides **18** with the *Cinchona* alkaloid $(DHQ)_2$PHAL.[16] Based on reported models by Corey, we envisioned that both side of the $(DHQ)_2$PHAL dimer play a role in the reaction; the methoxyquinoline moiety promoting π-interaction with the indolic aromatic core while the quinuclidine will promote the electrophilic fluorination reaction from the other side.[17] Stereochemical outcome of the cascade proved to depend on the bulkiness of the Xaa residue side chain (Gly vs Ala vs Phe) and the *C*-terminus peptidic activating group. While we were able to completely reverse the diastereoselectivity by using $(DHQ)_2$PHAL on the model glycine derivative **9** (Table 1, entry 11), both dipeptides **16** and **18**, having larger side chains, which may sterically clash with the quinuclidine moiety, afforded preferentially the more favorable *syn*-diastereomer arrangement.

In summary, we developed a novel double-annulative cascade reaction initiated by a fluorine-mediated dearomatization which demonstrates our ability to construct tetracyclic α-carboline architectures in a single step with reasonable diastereoselectivity. This strategy is the most efficient to date to build the stereochemically dense tetracyclic α-carbolines and the result of our design using a peptidic *C*-terminus activation mode to conclude the cascade.[6] Finally, C−F bond functionalizations[18] at the B−C ring junction to finalize both kapakahines B/F and chaetominine total syntheses are in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectral and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(7) See the Supporting Information for a complete list of screening conditions and experimental details.

(8) For an example of a cascade reaction highlighting the issue of substrate overoxidation, see the elegant work from Evano: refs 5b,c.

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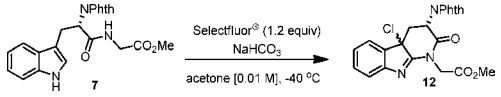
(10) Dearomatization of dipeptide **7** afforded the chlorinated α-carboline **12**, whose chlorination may result from fluoride−chloride exchange via a plausible carbocation intermediate.



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(15) A kinetic resolution could be occurring (see also Table 2 entry 2; 11:6 epimeric ratio of product **19**), but the low yields obtained for products **17** and **19** may also be the result of a severe decomposition of one of the epimers unable to undergo the cascade.

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References 5e−f were added on January 3, 2014.