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Dragmacidin E Synthesis Studies. Preparation of a Model Heptacyclic Core Structure

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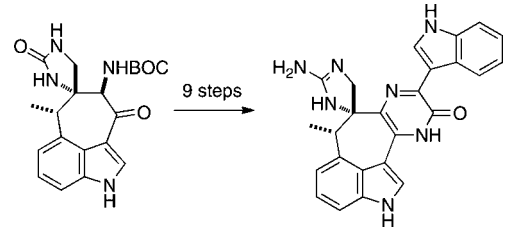
ABSTRACT



The conversion of a cycloheptannelated indole platform into the heptacyclic core structure of dragmacidin E proceeded over nine steps. Key sequences include a cyclocondensation to form an intermediate dihydropyrazinone ring and the conversion of a cyclic urea into the cyclic guanidine of the target.

The *Spongosorites* sp. metabolite dragmacidin E (**1**)[1] (Figure 1) along with congeners dragmacidins D and F are among the most structurally complex members of the dragmacidin family of bisindole-piperazine marine natural products. The unique structures and promising biological activity of members of this class have spawned numerous synthesis studies,[2] and Stoltz et al.'s total syntheses of dragmacidins D and F represent the frontier of the field.[3] Dragmacidin E has not yet been prepared by total synthesis, although model studies have been reported.[4]

Several structural features of **1** conspire to make it a challenging target, including (1) steric congestion along the upper periphery of the cycloheptane ring, (2) strain resulting from five contiguous sp^2 carbons in the seven-membered ring, and (3) a sensitive guanidine unit. Preliminary efforts from our laboratory on a des-C(7″) hydroxy model system established a route for the preparation of dragmacidin E's tetracyclic core **3** in racemic form from the simple tryptophan amide derivative **2** (Scheme 1).[4a] This chemistry featured a Wipkop photocyclization to forge the key C(4″)/C(6‴) bond and an indolic oxidation to introduce the C(6) carbonyl.

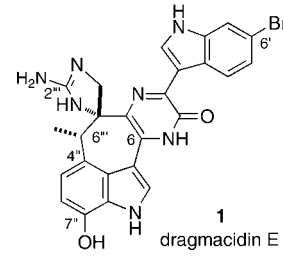


Figure 1. Dragmacidin E.

In this follow-up report, we describe the further development of this chemistry to arrive at a fully articulated heptacyclic dragmacidin E model that lacks only the C(7″) hydroxyl and the C(6′) bromide of the real system.

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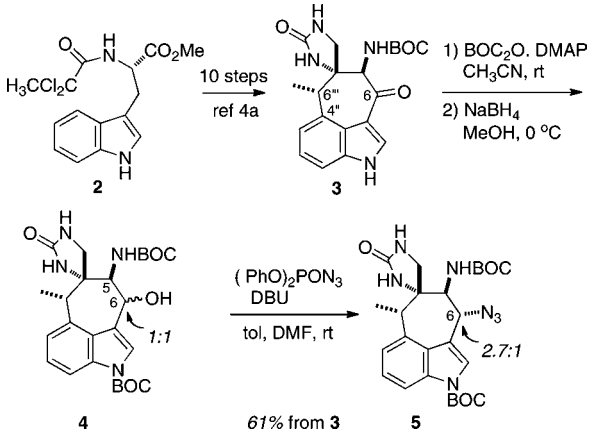
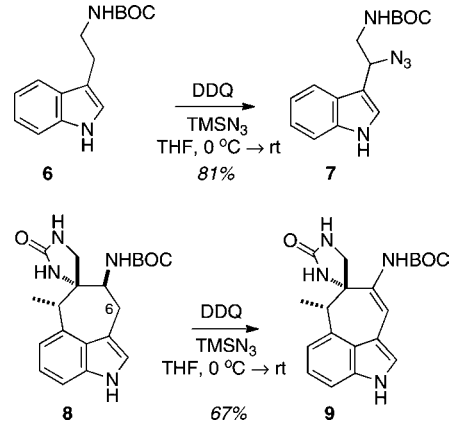
Starting from ketone **3**, which was in hand from the prior studies, several approaches for C(6) nitrogen introduction were explored. Attempts at direct nitrogen incorporation via imine formation or reductive amination failed, as only *N*-BOC-deprotected ketone **3** was returned in every case. Eventually, resorting to a three-step sequence that featured first BOC introduction and then ketone reduction to furnish the sensitive alcohol **4** proved successful (Scheme 1). The alcohol was isolated as an unbiased mixture of stereoisomers, but Mitsunobu-type introduction[5] of an azide moiety at C(6) of this alcohol mixture delivered the desired azide as a pair of diastereomers now favoring the α-isomer **5**. In addition, about 15% of a single diastereomer of the starting alcohol, which was tentatively assigned the *β*-stereochemistry based upon the H(6)−H(5) coupling constant ($J \sim 0$ Hz), was recovered. Speculation about the mechanism of this transformation might extend to either of two extremes: (a) an S_N2 process, as per the orthodox Mitsunobu reaction, that differentially favors reaction through the *β*-phosphonate intermediate, or (b) an S_N1-like reaction in which the phosphonate ester leaving group is expelled to give an intermediate acyl iminium ion that is quenched by azide preferentially from the face of the cycloheptane ring opposite of the NHBOC unit. Since C(6) is destined to become an sp^2 carbon in any event, both azide diastereomers were used in subsequent chemistry.

Scheme 1. Azide Introduction at C(6)



Some effort was expended in examining alternative and potentially briefer azide introduction procedures. A report describing the introduction of azide into the benzylic position of simple aromatics under oxidative conditions[6] raised the hope that a similar process at the indolic position of **8** (a precursor to **3**, see ref 4a) would shave several steps off of the synthesis route (Scheme 2). Scouting experiments with the simple tryptamine derivative **6** were encouraging; the azide function indeed could be introduced at the indolic position in good yield under DDQ mediation. Unfortunately, this chemistry did not translate to the dragmacidin skeleton, as exposure of **8** to these conditions did no more than produce the alkene-containing product **9**. Apparently, an intermediate indolic electrophile generated by DDQ-promoted oxidation suffered proton loss in preference to bimolecular attack by azide.

Scheme 2. Alternative C(6) Azide Introduction Attempt, Part 1



A second attempt at short-circuiting the chemistry of Scheme 1 is detailed in Scheme 3. This approach again was based upon direct oxidative azide introduction at the C(6) position, but in this case the hope was that by opening the spiroimidazolone ring more flexibility would be introduced into the cycloheptane ring, perhaps facilitating azide addition instead of proton elimination. To test this premise, the cycloheptannelated indole **10**, which is a precursor to **8** (see ref 4a), was converted to the triply N-protected substrate **11**. Treatment of this species with DDQ/azide did not preform as desired, as no azide incorporation was seen. Rather, the now flexible methylene carbamate unit at C(5‴) was able to trap the nascent indolic electrophile to give the caged

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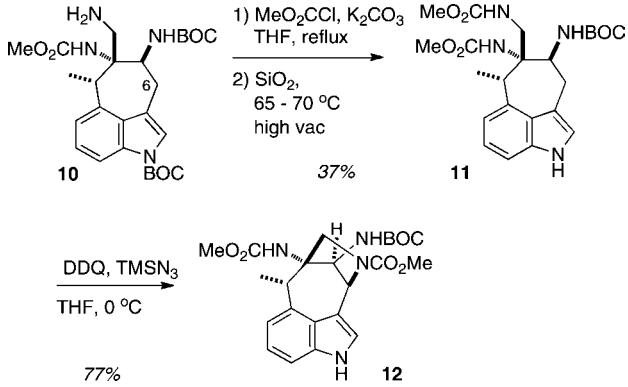
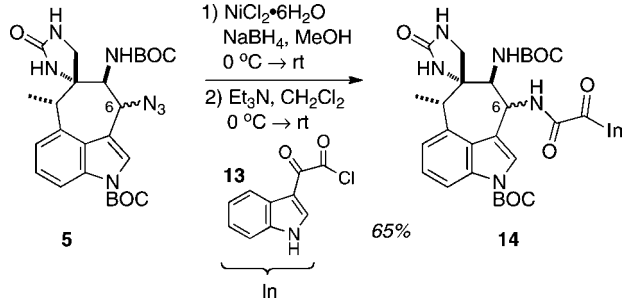
structure **12**.[7] Thus, we could not identify an alternative to the indirect azide introduction sequence **8** → **3** → C(6) alcohol → **5**.

Scheme 3. Alternative C(6) Azide Introduction Attempt, Part 2



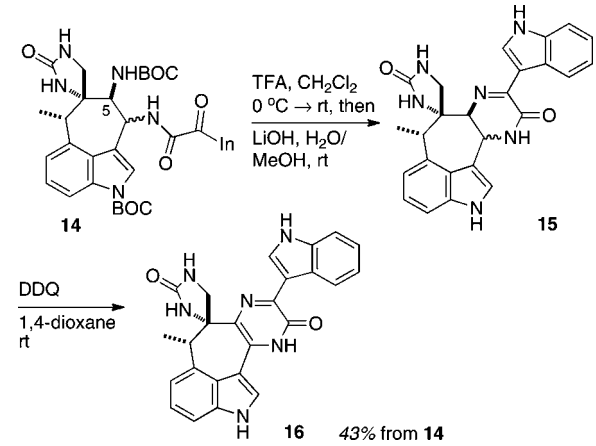
The azides **5** did prove to be useful intermediates in pyrazinone formation. Reduction of the mixture of stereoisomers **5** with $NaBH_4/NiCl_2$[8] generated an unisolated mixture of amines, which immediately was acylated with the indole oxalyl chloride **13** (Scheme 4). The product amide **14** was formed as a ~2:1 mixture of diastereomers. Attempted reduction of the azides **5** under simple hydrogenolysis conditions (Pd/H_2) led to a complex mixture of uncharacterized products.

Scheme 4. Attachment of the Second Indole Fragment



The acquisition of amide **14** sets the stage for attempts at pyrazinone formation (Scheme 5). Success in this cyclocondensation will depend upon the confluence of several reaction features: (a) acid-mediated BOC removal without concomitant acid promoted loss of the entire indole oxalyl amide unit, (b) access to the *s-cis* amide configuration, and (c) strict anti alignment of the carbonyls of the oxalyl unit. Whereas (c) should not present a problem, it was much less clear

Scheme 5. Cyclocondensation to Form the Central Pyrazinone Ring



whether conditions (a) and (b) would be met. In the event, several acids were screened, but only with TFA was cyclocondensation observed. Other acids (e.g., formic acid in refluxing dichloroethane) led to decomposition of substrate **14**. After presumed initial formation of the C(5) primary amine/TFA salt, treatment of the reaction mixture with base liberated the free amine and initiated the cyclization. The dihydropyrazinone **15** was formed along with varying amounts of the fully (air) oxidized pyrazinone-containing product **16**. Dihydropyrazinone **15** was too unstable to permit isolation, but its presence was suggested by the observation of a 439 (M + 1) amu peak in the mass spectrum of the crude worked-up reaction mixture. Unfortunately, further exposure of the crude **15**(major)/**16**(minor) mixture to air led to the decomposition of **15**. A better and more reproducible protocol that evolved from these observations relied on DDQ oxidation of the crude **15**/**16** mixture to give mostly **16** along with some decomposition products. The bright yellow color of **16** proved to be a valuable marker for success in this reaction.

The final operation of note in the dragmacidin E model system synthesis involves the formation of the spirocyclic ring guanidine function from the urea in **16**. This problem has arisen before, and a procedure developed by Kishi et al. in their pursuit of saxitoxin proved serviceable here (Scheme 6).[9] Thus, methylating **16** with Meerwein's salt occurred with

Scheme 6. Introduction of the Guanidine Function

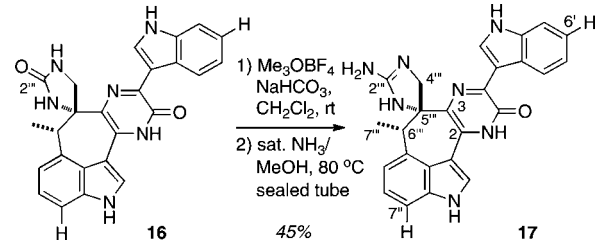


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Table 1. NMR Spectral Data Comparison between Heptacycle **17** and Authentic Dragmacidin E

	17		
solvent	d_6-DMSO[a]	CD_3OD	dragmacidin E[1] d_6-DMSO
H(4‴)	3.06, d (9.8 Hz)	3.26, d (10 Hz)	3.02, d (10.2 Hz)
H(4‴)	3.18, d (9.9 Hz)	3.38, d (10 Hz)	3.17, d (10.2 Hz)
H(6‴)	[b]	3.64, q (7.0 Hz)	3.46, q (7.2 Hz)
H(7‴)	1.12, d (6.9 Hz)	1.15, d (7.0 Hz)	1.06, d (7.2 Hz) in CD_3OD below
C(2‴)		161.0	160.6
C(4‴)		56.5	56.3
C(5‴)		72.0	72.1
C(6‴)		52.1	51.1
C(7)		19.7	19.7
C(2)		143.8	138.4[c]
C(3)		160.9	157.1

[a] **17** as TFA salt. [b] Obscured by H_2O peak. [c] In $CD_3OD/CDCl_3$.

complete regioselectivity for the desired urea carbonyl, leaving the pyrazinone carbonyl and the two indole nitrogens untouched. The derived methoxy amidine (65%) was separated from unreacted urea **16** (33%) by SiO_2 chromatography, and this pure compound was treated with ammonia in methanol at 80 °C (sealed tube) over 5 h. These conditions provided the desired guanidine-containing product **17** in overall moderate yield. The guanidine **17** was isolated after SiO_2 chromatography as a free base, and its spectral data were consistent with those reported for dragmacidin E for all of the salient absorbances (see Table 1). Thus, the conversion of tetracycle **3** into heptacycle **17** in nine steps provides a satisfying ending for these model system studies. Model compound **17** differs from the natural product only in the lack of functionality at C(7″) and C(6′). Efforts to translate the model system chemistry to the real system containing a C(7″) (protected) hydroxyl and the C(6′) bromide are underway.

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Supporting Information Available: Experimental procedures, full spectral data, and copies of ^1H and ^{13}C NMR spectra for **5**, **7**, **9**, **11**, **12**, **14**, **16**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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