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Dragmacidin E Synthesis Studies. Preparation of a Model Cycloheptannelated Indole Fragment

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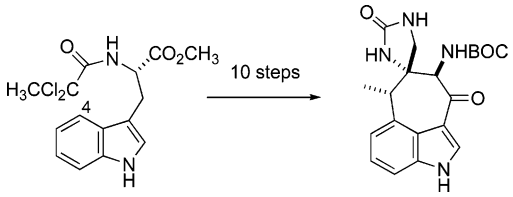
ABSTRACT



The conversion of *N*-2,2-dichloropropionyl indole methyl ester into a tetracyclic cycloheptannelated indole model compound for the synthesis of dragmacidin E was accomplished in 10 steps. Key reactions include a Witkop cyclization to fashion a C–C bond at C(4) of the indole nucleus and a subsequent Dieckmann cyclization to deliver the desired cycloheptanoid ring.

Dragmacidin E (**1**) and related structures dragmacidins D and F represent a small class of bis-indole-derived sponge metabolites isolated from a *Spongosorites* sp. found in Australian waters.[1] Their novel architecture and promising selective phosphatase inhibitory activity has fueled many synthesis studies on these species,[2] with recent preparations of dragmacidin D[3a] and F[3b,c] representing the apotheosis of this field at the moment. However, the synthesis challenges posed by dragmacidin E, including (1) the timing of guanidine introduction, (2) establishing the C(6‴) quaternary center with correct relative stereochemistry, and (3) forging the pyrazinone unit in a sterically demanding environment, have yet to be addressed. Furthermore, an asymmetric synthesis of **1** would secure the absolute stereochemistry, suggested as shown in Scheme 1 by Stoltz,[3c] and if correlated with the known absolute stereochemistry of dragmacidins D and F, would lend credence to the prevailing biosynthetic hypothesis[1,3a] connecting these dragmacidins.

These considerations presented both an opportunity and a challenge; using a tryptophan derivative as a starting point might permit ready entry into the chiral series, but forming the necessary C−C bond to C(4) of the indole moiety could prove problematic. One tryptophan C(4) functionalization reaction that merited consideration is the Witkop photocyclization of *N*-haloacetyl derivatives,[4] a transform that was used with great success by Moody's group[5] but has seen only sporadic use since.[6] However, whereas this reaction affords cyclooctannelated indole products with facility,

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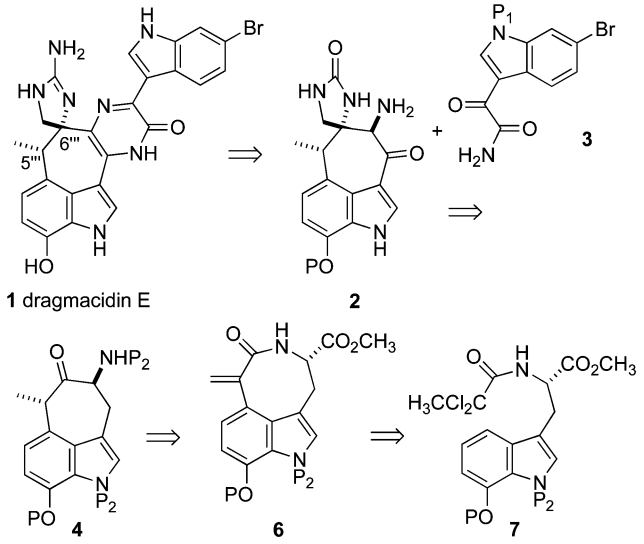
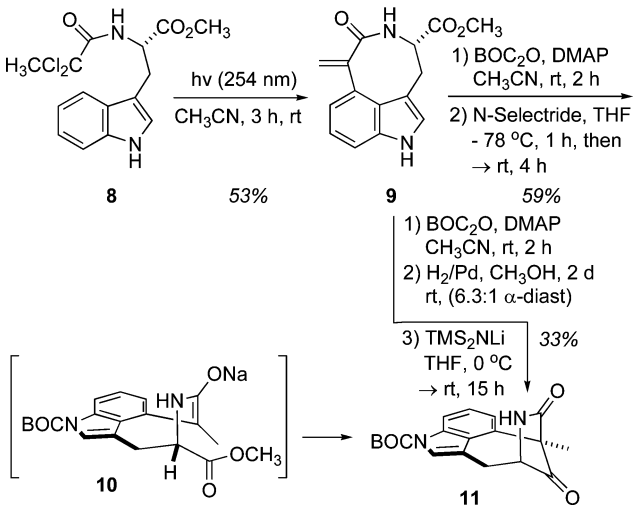
Scheme 1. Retrosynthesis Analysis for Dragmacidin E



Scheme 2. Key Witkop/Dieckmann Sequence To Fashion the Cycloheptannelated Indole Core



attempts to prepare lower homologues largely met with failure.[5b] Thus, application of this useful C(4) functionalization reaction to the dragmacidin E problem would require some modification or extension of the basic transform in order to secure the desired cycloheptannelated structure of **1**.

This line of reasoning led to the retrosynthesis shown in Scheme 1, wherein dragmadicin E (**1**) was envisioned to derive from a cyclocondensation between aminoketone **2** and the ketoamide **3**. The aminoketone **2** embodies appropriate functionality and stereochemistry along its periphery to deliver the requisite guanidine unit of the natural product. The C(6‴) quaternary center of **2** might be introduced by formal Strecker chemistry on the ketone within **4**, the pivotal cycloheptannelated indole intermediate. In the key sequence of a projected synthesis of **2**, this cycloheptane ring might originate from an unusual Dieckmann cyclization within the cyclooctanoid construct **6**, an obvious target for Witkop photocyclization chemistry.

Synthesis of the model dragmacidin E tetracycle **18** commenced with the dichloroamide derivative **8** of tryptophan methyl ester, available by simple acylation of the parent amine (97%) (Scheme 2). This Witkop reaction substrate contains both the *N*-unprotected indole electron donor unit and chlorocarbonyl electron acceptor in close proximity, and so, not surprisingly, irradiation of a 5.0 mM solution of **8** in CH_3CN led to reasonably efficient conversion into the C(4)-cyclized species **9**. Yields in the Wipkop procedure rarely exceed 50%, and it is possible that the added benefit of a second radical stabilizing chloride within **8** contributed to the relatively higher yield with this substrate. Presumably, an unobserved intermediate C(5‴)-methyl, -chloride-bearing species is formed en route to **9**, but a second photochemically mediated dehydrochlorination intervenes to deliver the alkene of the product. Similar chemistry has been reported in related systems.[5c] Conversion of the cyclooctanoid skeleton of **9** into the carbocyclic cycloheptanoid bridge of the target occupied a second pivotal role in the synthesis strategy. Although several routes could be envisioned, after much experimentation, an efficient and scalable sequence, which featured treatment of an *N*-BOC derivative of the enone **9** with a hydride source, was identified. Presumably, the unobserved enolate **10**, derived from conjugate addition of [H^-], played a central role in this transformation. Dieckmann closure into the proximal ester moiety then completes the preparation of **11**. This Dieckmann cyclization lacks the usually cited driving force associated with high-yielding conversion (deprotonation of an acidic product), but it likely benefits from relief of steric compression as the endo-disposed ester unit is incorporated into the molecular framework. The imide BOC group is cleaved during this transformation, but it can be readily reinstalled in the next step. An alternative route to **11**, which involved initial hydrogenation of the alkene within the *N*-BOC derivative of **9** to afford an α-methyl ketone and then treatment with base, was explored briefly but offered no advantage.

Two more operations of note were required to process **11** into **18**: (1) installation of the spiroimidazolone ring at C(6‴) and (2) scission of the imide bridge. A priori, it was not clear if any benefit attended sequencing step (1) before step (2) or vice versa, and so the former course was selected for study first (Scheme 3). The bridging amide **11** could be

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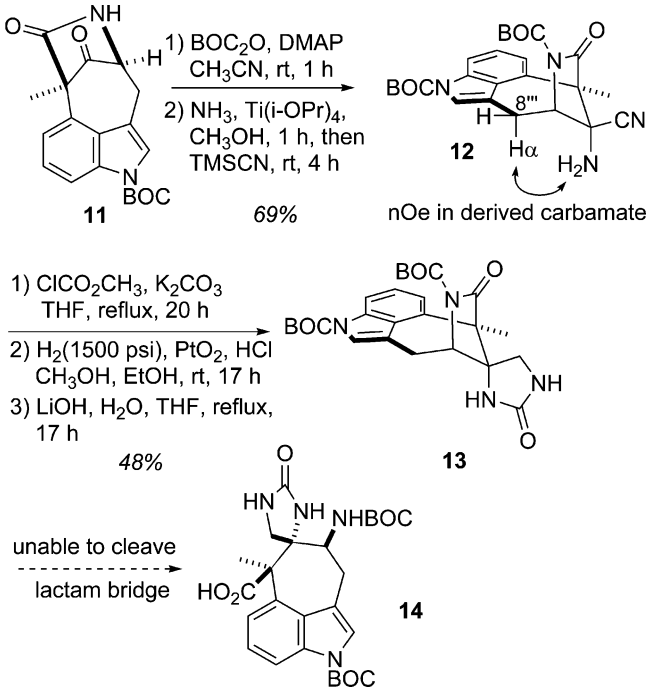
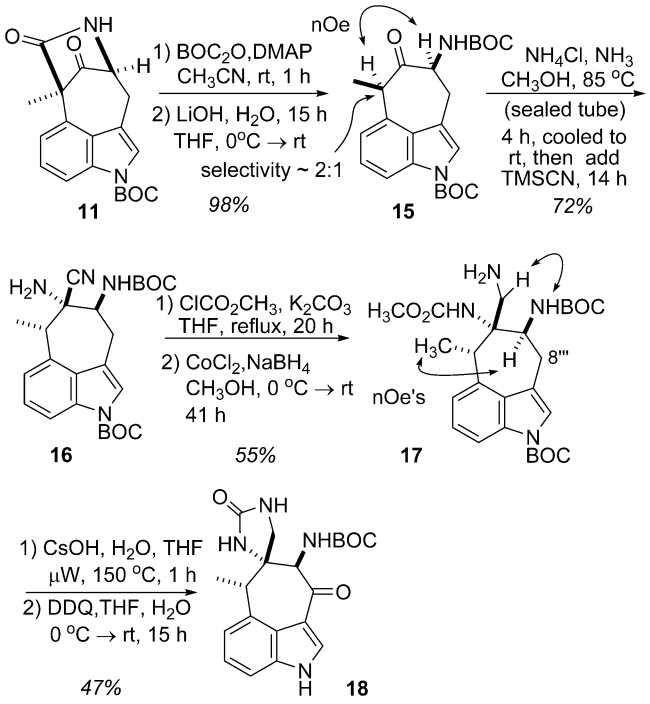
Scheme 3. Synthesis of a Pentacyclic Dead End



Scheme 4. Synthesis of the Tetracyclic Dragmacidin E Model System



converted into a single Strecker product **12** cleanly and in good yield and then into the imidazolone-containing species **13**. The relative stereochemistry indicated in **13** is tentative and based upon the observation of an NOE signal between the α-positioned proton on C(8‴) and the N*H* of the carbamate derived by acylation of **12**. Unfortunately, all attempts to cleave the imide bridge failed, either returning starting material **13** or a deprotected version of same missing one or both BOC groups. It appears that the functionality surrounding the imide unit effectively encapsulates the bridge's carbonyl and deflects all nucleophiles examined ($LiOH/H_2O$/THF, KOH/DMSO, Cs_2CO_3/THF/H_2O, H_2SO_4/H_2O, $LiAlH_4$, $LiEt_3BH$, $NaBH_4$, $NaBH_3NMe_2$, $LiBH_3NH_2$, NH_2NH_2, inter alia).

Examination of the alternative functionalization sequence proved more fruitful (Scheme 4). The apparently less hindered lactam bridge of the imide derived by BOC protection of **11** underwent facile hydrolysis under unexceptional conditions to provide the cycloheptanone product **15** in excellent yield. Thus, the imidazolone ring in **13** appeared to provide the decisive steric obstacle to nucleophile addition for that bridged system. Decarboxylation attended this hydrolysis, and enolate protonation led to a relatively unbiased mixture of diastereomeric secondary methyl groups at C(5‴) slightly favoring the *β*-isomer as shown. Treatment of partially purified samples of **15** with LiOH led to the same ~ 2:1 mixture of isomers, suggesting that thermodymanic equilibration prevails upon formation of the cycloheptanone product. Epimerization at C(5‴) might not be problematic, however, provided that there was some exploitable preference in the next species to be formed, the cyanoamine **16**. Exposure of the diastereomeric mixture **15** to forcing Strecker conditions generated an intermediate imine, and then condensation of that imine with TMSCN furnished a single diastereomer of the cyanoamine product **16**. Molecular mechanics calculations (Macromodel 9.0) on the intermediate imine bearing either diastereomeric methyl appendage suggested that the α-methyl species would be preferred by as much as 3.0 kcal/mol, plausibly as a consequence of unavoidable $A^{1,3}$ interactions in the alternative *β*-methyl isomer (see the Supporting Information). Furthermore, inspection of the α-methyl isomer generated by this modeling process held forth the promise that the kinetically preferred trajectory of cyanide addition would follow a pathway opposite to the pseudoaxial methyl unit (Supporting Information). That one isomer was formed in this Strecker sequence was intriguing, but unambiguous stereochemical assignment had to await preparation of a derivative with more diagnostic NMR signals. Toward this end, conversion of aminonitrile **16** into the aminocarbamate **17** afforded a species whose relative stereochemistry could be ascertained by initial application of HMBC/HMQC NMR techniques to identify proton resonances and then by NOE measurements (cf. **17**) to assign the stereochemistry. Interestingly, attempts at hydrogenation (various Pd or Pt sources/H_2 at various pressures) of the carbamate nitrile derived from **16** ($ClCO_2CH_3$, K_2CO_3) led only to recovered starting material or to a secondary amine presumably resulting from reduction of the *N*-carbomethoxyimine derived from HCN ejection. The difference in succeptibility to hydrogenation between the carbamate nitrile prepared from **12** and that from **16** is striking but defies ready explanation. Fortunately, the cobalt-

mediated reduction methodology of Battersby,[7] which failed with the carbamate nitrile derived from **12**, worked superbly in this case.

The possibility exists that under the harsh conditions of the Strecker reaction, epimerization of the NHBOC-bearing C(7‴) center could occur, much as it does at C(5‴). Examination of **16** and **17** by polarimetry led to the disappointing but incontrovertable conclusion that this concern was borne out in practice, as largely racemic material was isolated. In fact, unreacted ketone **15** recovered from incomplete conversion displayed only minimal optical activity, indicating that epimerization at C(7‴) was unavoidable under these imine-forming reaction conditions. However, even without preservation of the starting chirality of tryptophan, further exploration of amine **17**'s downstream functionalization chemistry seemed warranted.

The final two operations of this model system synthesis involved base-promoted imidazolone closure (with concomitant BOC removal from the indole ring) and DDQ-mediated oxidation at C(8‴). Both transformations occurred smoothly and without complications. No evidence for oxidation products at the alternative benzylic position C(5‴) was detected, and the desired C(8‴) ketone-containing product **18** was delivered in good yield.

In summary, the development of a Witkop/Dieckmann cyclization strategy permitted the synthesis of an advanced but essentially racemic dragmacidin E model system from tryptophan methyl ester in 11 steps. Efforts to apply this chemistry to dragmacidin E itself are underway, and results will be reported in due course.

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Supporting Information Available: Experimental procedures and full characterization data for **8**, **9**, **11**−**13**, and **15**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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