

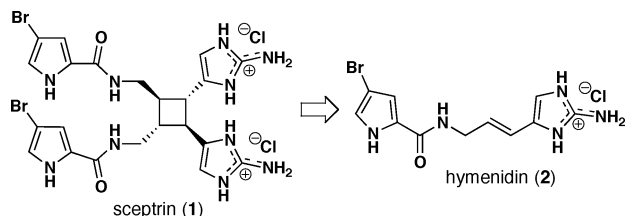
## Short Total Synthesis of (±)-Sceptrin

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Despite its potent activity as an antiviral, antimuscarinic, antibacterial, and antihistaminic agent, sceptrin (**1**) has remained a prominent unanswered synthetic challenge since its isolation from *Agelas sceptrum* and characterization in 1981 by Faulkner and Clardy.<sup>1,2</sup> Its recently identified potential as a treatment for cystic fibrosis and Alzheimer's disease adds a further sense of urgency for the invention of a pragmatic synthetic route.<sup>2</sup> Upon cursory inspection, sceptrin (**1**) appears to be a photodimer of hymenidin (**2**),<sup>3</sup> yet it is nonracemic ( $[\alpha]_D -7.4^\circ$ ) and was isolated at ocean depths with insufficient light to promote such a reaction photochemically, implying that an enzyme may be facilitating a formal head-to-head [2+2]-cycloaddition.<sup>1,4</sup> Indeed, attempted dimerization of hymenidin and various derivatives in the laboratory has been futile.<sup>5</sup> In this Communication, we describe a simple and practical synthesis of **1** and analogues thereof, overcoming a phalanx of problems due to unexpected reactivity, intermediate fragility, and forbidding elements of complexity.



The synthesis pathway is outlined in Scheme 1. Our strategy capitalizes on an observation made by Laing et al.<sup>6</sup> and further explored by Nelson et al.<sup>7</sup> for the rearrangement of 3-oxaquadri-cyclane **3**<sup>8</sup> to the *trans,trans,trans*-cyclobutane **4**.<sup>6</sup> By modifying reaction conditions,<sup>7</sup> we were able to obtain *trans,trans,trans*-cyclobutane **4** without chromatography (white needles, mp 73–75 °C) and in 50% yield by treating **3**<sup>8</sup> with concentrated H<sub>2</sub>SO<sub>4</sub> in methanol (0.084 M) for 24 h (23 °C) followed by an aqueous workup. The diester **4**<sup>6</sup> was then converted to the crude diazide **6** by the following sequence: (1) bis-protection as the dimethylketal [CH(OMe)<sub>2</sub>, MeOH, TsOH, 50 °C, 24 h]; (2) reduction to the diol **5** (DIBAL, CH<sub>2</sub>Cl<sub>2</sub>, –78 °C, 1.5 h, quantitative yield) and workup with AcOH to hydrolyze the resulting mixture of ketals (at least six compounds by TLC analysis prior to AcOH treatment); (3) mesylation (MsCl, py, 0 → 23 °C, 1 h); and (4) displacement with NaN<sub>3</sub>.

Reprotection of the crude diazide **6** [CH(OMe)<sub>2</sub>, MeOH, TsOH, reflux, 24 h] was necessary to avoid immediate scission of the sensitive cyclobutane in the ensuing steps. Reduction<sup>9</sup> (H<sub>2</sub>/Lindlar, MeOH, 23 °C, 12 h) of this crude bisdimethyl ketal gave an intermediate diamine which, when reacted with pyrrole **7**<sup>10</sup> in CH<sub>3</sub>CN, directly crystallized to form **8** (mp 177–179 °C) in 70% overall

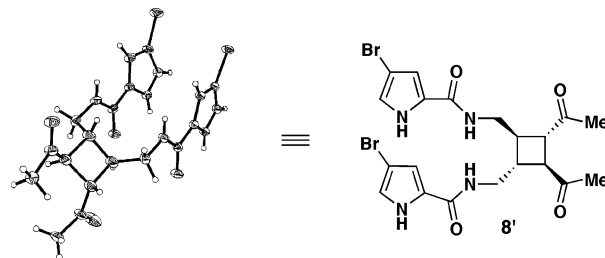


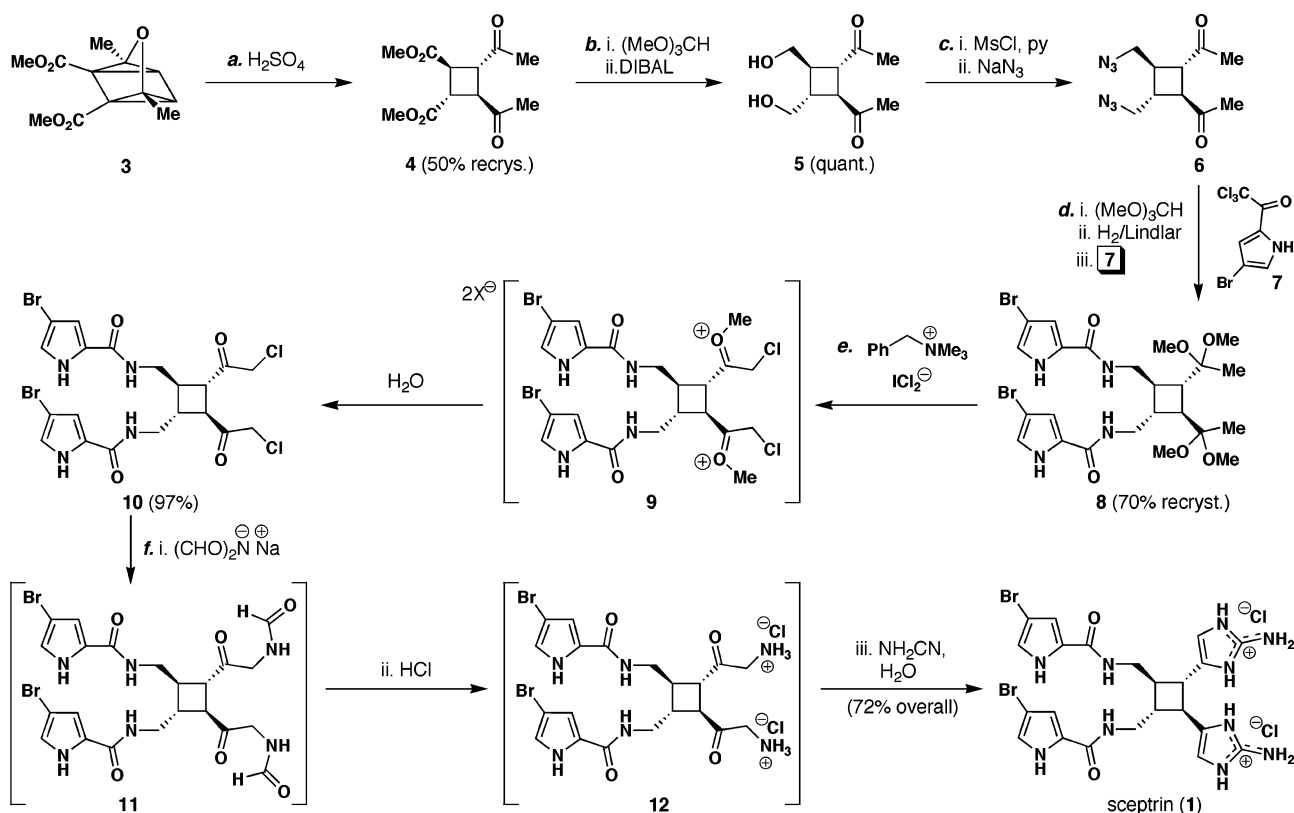
Figure 1. X-ray crystal structure of diketone **8**'.

yield from **5**. The stereochemistry of **8** was verified by X-ray crystallographic analysis of **8**' (colorless cubes, mp 225–227 °C, see ORTEP structure in Figure 1), derived by hydrolysis of the dimethylketal (AcOH, 5 min, 23 °C).

Chemo- and regioselective  $\alpha$ -halogenation of **8** or **8**' failed using a variety of known protocols due to interference of the pyrrole moieties, rapid polyhalogenation of the ketone, instability of products, and a tendency of the cyclobutane framework to fragment. Consequently, a new method was invented to convert **8** directly and in nearly quantitative yield into bis- $\alpha$ -chloroketone **10** (mp 174–176 °C dec) using benzyltrimethylammonium dichloroiodate (THF, 60 °C, 1.75 h, purified by aqueous workup). Surprisingly, treatment of **8**' under the same conditions did not provide **10**. We propose that this reaction proceeds through the intermediacy of an oxonium species such as **9** and have found it to be both general and programmable for access to either  $\alpha$ -chloroketones (THF solvent) or  $\alpha$ -chlorodimethylketals (2:1:0.1 THF–MeOH–CH(OMe)<sub>3</sub> solvent); these results will be reported in detail elsewhere.

The unexpected reactivity of these compounds surfaced yet again as known strategies to install the delicate 2-aminoimidazole subunits failed. A one-flask protocol emerged when **10** was treated with sodium diformylamide<sup>11</sup> (CH<sub>3</sub>CN, 35 °C, 40 h) to furnish bis-formylamide **11** (purified by trituration with water and CH<sub>2</sub>Cl<sub>2</sub>). The excess reagent (6.0 equiv) employed in this protocol is presumably responsible for deprotection of the initial bis-diformylamide adduct.<sup>11</sup> After hydrolysis (HCl, MeOH, 23 °C, 16 h) to reveal bis-aminoketone **12** and removal of solvent, reaction with cyanamide<sup>12</sup> in water (95 °C, 4 h, trituration to remove excess cyanamide) followed by a washing with cold *n*-BuOH completed the total synthesis of (±)-**1** [identical to a 1 mg sample purchased from A. G. Scientific, Inc. (>\$100) (<sup>1</sup>H and <sup>13</sup>C NMR, LC/MS, IR, TLC, HRMS and mp)].

In conclusion, noteworthy features of this concise synthesis include: (a) the first application of an oxaquadri-cyclane rearrangement in natural product synthesis; (b) a new chemo- and regio-

Scheme 1<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) H<sub>2</sub>SO<sub>4</sub>, MeOH, 24 h, 50%; (b) (i) MeOH, CH(OMe)<sub>3</sub> (14.0 equiv), TsOH (0.15 equiv), 50 °C, 24 h; (ii) DIBAL (6.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 1.5 h, then AcOH, H<sub>2</sub>O, 10 min; (c) (i) MsCl (4.4 equiv), py, 0 → 23 °C, 1 h; (ii) NaN<sub>3</sub> (6.0 equiv), DMF, 50 °C, 24 h; (d) (i) MeOH, CH(OMe)<sub>3</sub> (14.0 equiv), TsOH (0.15 equiv), 50 °C, 24 h; (ii) H<sub>2</sub>, Lindlar catalyst, MeOH, 12 h; (iii) **7** (2.2 equiv), CH<sub>3</sub>CN, 4 h, 70% overall from **5**; (e) (i) benzyltrimethylammonium dichloroiodate (3.3 equiv), THF, 60 °C, 1.75 h, 97%; (f) (i) (CHO)<sub>2</sub>NNa (5.5 equiv), 35 °C, 40 h; (ii) HCl, MeOH, 23 °C, 16 h; (iii) NH<sub>2</sub>CN, H<sub>2</sub>O, 95 °C, 4 h, 72% overall from **10**.

lective halogenation method; (c) mild 2-aminoimidazole forming events; (d) generally excellent yields; and (e) overall operational simplicity because it can be carried out on a preparative scale (over 350 mg of **1** has been synthesized so far) without HPLC or flash chromatography (24% overall yield from dimethyl acetylenedicarboxylate).<sup>13</sup>

The stage is now set for the synthesis of other members of the sceptrin family as well as the development of an asymmetric variant of the current synthesis. In addition, it should now be feasible to prepare analogues containing deeply rooted structural modifications for biological explorations.

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**Supporting Information Available:** Detailed experimental procedures, copies of all spectral data, full characterization and details of the stability profile of **1** (PDF and CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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