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Letter

Total Synthesis of (±)-Sceptrin

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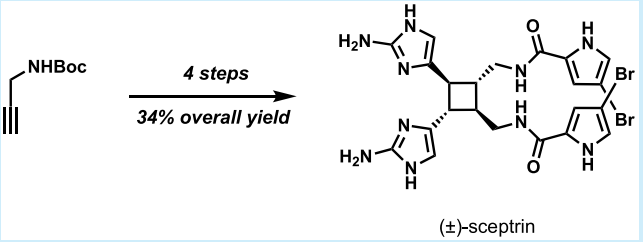
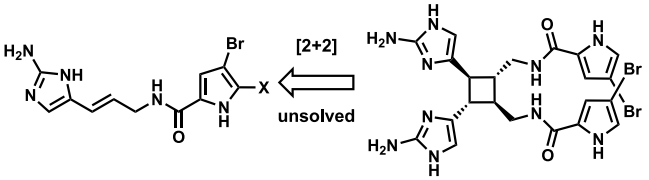
ABSTRACT: A four-step synthesis of the dimeric pyrrole–imidazole alkaloid sceptrin is reported. The brevity of the route is based on a simple solution developed for selective assembly of the cyclobutane core of the natural product. The photochemical intermolecular [2 + 2] dimerization of a useful hymenidin surrogate enables direct entry to this enigmatic class of biologically active marine secondary metabolites.



The dimeric pyrrole–imidazole alkaloid sceptrin (**3**) was first isolated from the Caribbean sponge *Agelas sceptrum* by Faulkner, Clardy, and co-workers in 1981.[1] They, and others since, surmised a biogenesis based on intermolecular head-to-head [2 + 2] dimerization of the marine metabolite hymenidin (**1**). However, despite the nearly 40 years following the seminal work and several elegant de novo approaches,[2] no such transformation has been demonstrated in any synthetic context (Figure 1).



Birman (2004):	11 steps	racemic
Baran (2004):	15 steps	racemic
Baran (2006):	20 steps	asymmetric
Chen (2014):	25 steps	asymmetric
This work (2020):	**4 steps**	**racemic**

Figure 1. Direct synthesis of **3** via dimerization of **1** is without precedent.

As a corollary to their finding that exposure of oroidin (**2**) to cell-free enzyme preparations from *A. sceptrum* led to the production of the cyclobutane congener benzosceptrin C (**5**), Romo and Molinski proposed that the biosynthesis of sceptrins proceeds via an oxidative single-electron transfer manifold.[3] Intriguingly, dibromosceptrin (**4**) was not coisolated during their studies, suggesting distinct mechanisms for the biogenesis of sceptrins and benzosceptrins (Figure 2).

Here we provide a solution to the long-standing riddle posed by **3** that enables its racemic assembly in four steps from commercially available starting materials. A new dimerization of a carefully designed imidazopyrimidine propeneamine using

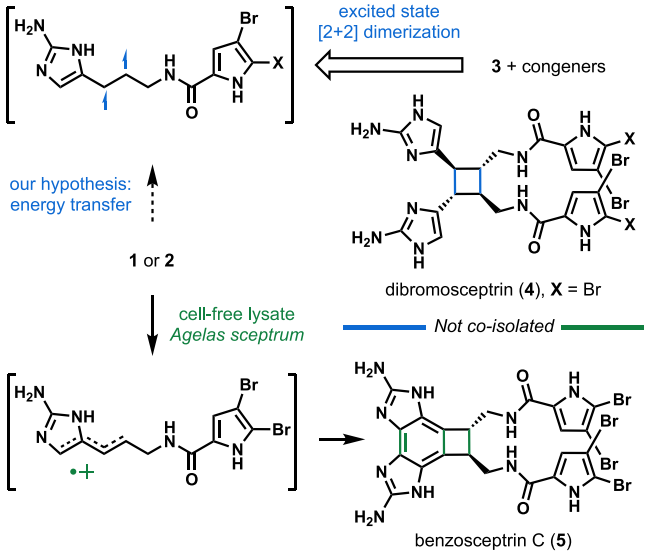


Figure 2. (top) Retrosynthesis of sceptrins via dimerization of an excited-state monomer. (bottom) Metabiosynthesis of congener **5** does not corroborate the origins of **4**.

catalytic energy transfer[4] delivers the complete carbon skeleton of the natural product in a single step with both regio- and diastereoselectivity. Final elaboration occurs readily in one pot and permits the shortest synthesis of **3** reported to date.

Our early analysis of **3** was, like those before us,[5] fixated on the viability of an intermolecular head-to-head dimerization of

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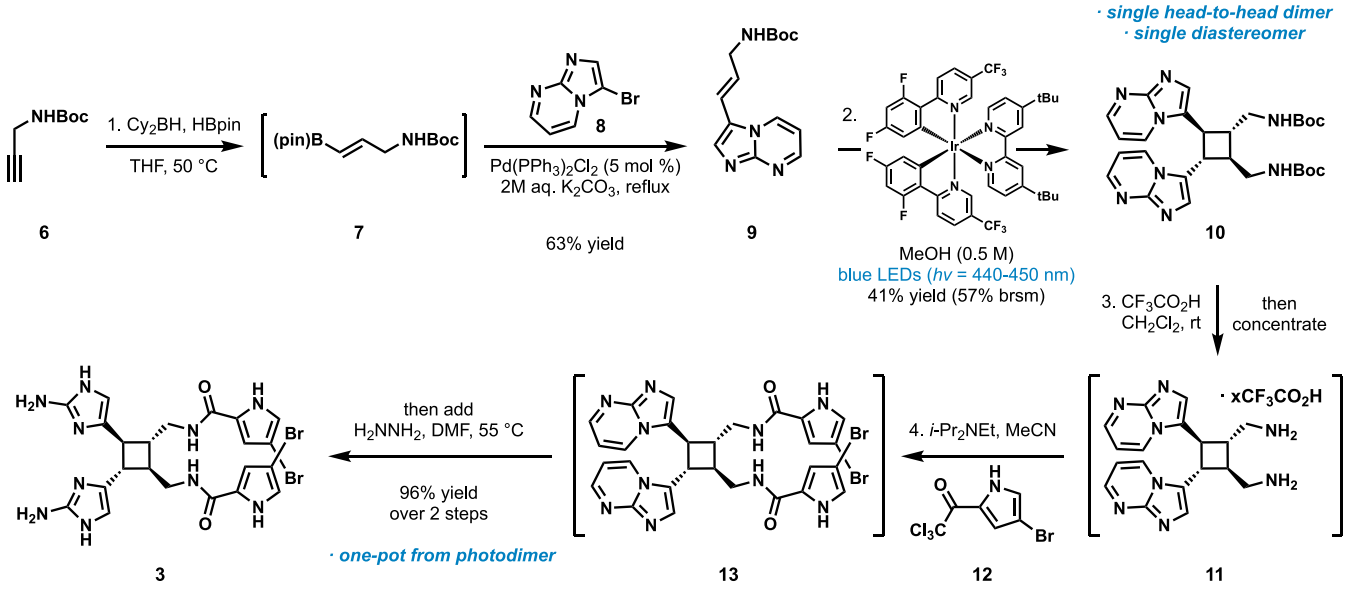
Scheme 1. Four-Step Total Synthesis of (±)-Sceptrin from *N*-Boc-propargylamine



a hymenidin derivative because it is intuitive and direct. We pondered the holistic value in re-evaluating a biomimetic synthesis of **3** through such a cycloaddition, although the operative mechanism by which the key transformation would proceed was uncertain.[6] Specifically, *photochemical* [2 + 2] dimerizations have been largely dismissed since *A. sceptrum* is isolated at oceanic depths with insufficient light (−20 to −30 m) and attempts involving irradiation of **2** in either solution or the solid state were reportedly fruitless.[1,2a]

We found inspiration in pioneering studies on "dark photochemistry" conducted by Cilento, White, Lamola, and co-workers in the late 1970s, in which strained endoperoxides[7] were shown to produce upon scission long-lived, high-energy triplet carbonyls capable of energy transfer.[8] Exemplary "photoproducts" accessed without light included lumisantonin, lumicolchicines, and cyclobutane pyrimidine and thymine dimers.[9] These data are conceptually interesting as they allude to nonobvious roles of electronically excited intermediates in secondary metabolite distributions where light is scarce.[9a,10] We reasoned that successful interpretation of this unusual biosynthetic hypothesis in the laboratory employing recent advancements in photochemical methods would yield concise entry to **3** and its congeners.

Carbon−carbon bond-forming reactions promoted by actinic sensitization of alkene substrates are not new. In the historical framework of the sceptrins, both the Baran[2d] and Al-Mourabit[11] groups have explored the utility of cyclobutane dimers derived from α,β-unsaturated carbonyl starting materials, a *notably privileged structural motif* within this class of photochemical transformations.[12] However, to the best of our knowledge, none of these cycloadducts have been successfully advanced to structures like **3**. Along these lines, our own experimentation reaffirmed the poor strategic efficiency of late-stage 2-aminoimidazole formation and the potential of the imidazopyrimidine heterocycle as a powerful 2-aminoimidazole mask.[13]

We designed the new hymenidin surrogate **9** (Scheme 1) possessing the same oxidation state as the native monomers and whereby the polar primary amine "head" and basic 2-aminoimidazole "tail" could be revealed with orthogonality. Although the intermolecular [2 + 2] dimerization of primary allylic amines possessed no precedent, we were motivated by the observation of photochemical alkene isomerization while scouting available aminoimidazolyl propeneamine derivatives[14] since it intimated the intermediacy of a critical diradical intermediate required for cycloaddition. Furthermore, we were enthused by an opportunity to solve a considerable synthetic challenge in the preparation of complex cyclobutanes.[15]

Building block **9** was prepared by initial hydroboration of commercially available *N*-Boc-propargylamine (**6**) with dicyclohexylborane (Cy_2BH) and pinacolborane (HBpin) to give the known vinylboronic pinacol ester **7**.[16] A tandem Suzuki−Miyaura cross-coupling[17] was executed by reaction with aqueous potassium carbonate (K_2CO_3), 3-bromoimidazopyrimidine (**8**), and bis(triphenylphosphine)palladium(II) dichloride (5 mol %) in refluxing tetrahydrofuran (THF) to deliver monomer **9** in 63% yield (one pot). The key dimerization was best accomplished by irradiating a methanolic solution of **9** with blue LEDs (440−450 nm) in the presence of catalytic $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (1.8 mol %).[18] The C_2-symmetric dimer **10** was isolated after flash column chromatography in 41% yield (57% based on recovered **9**, 3.36 g scale) as a single regioisomer and diastereomer. The relative stereochemical configuration of **10** was subsequently confirmed by the total synthesis of **3**.

Completion of the synthesis of **3** required exact choreography in order to install pendent acyl 3-bromopyrrole groups and unveil neighboring 2-aminoimidazoles. Optimally, this was conducted in a single flask by *tert*-butylcarbamate (Boc) cleavage followed by concentration to afford the diamine trifluoroacetic acid (TFA) salt **11**. This crude mixture was subsequently exposed to bromopyrrole **12**[19] and Hünig's base in acetonitrile (MeCN), after which "protected sceptrin" **13** precipitated from solution. The polar guanidine functionality of **3** was revealed last[13,14d] by direct addition of hydrazine (H_2NNH_2) in dimethylformamide (DMF) and warming of the resulting suspension until complete dissolution. Concentration and purification by flash column chromatography on amine-functionalized silica gel provided free-base **3** in 34% overall yield from **6**. Synthetic **3** prepared as described matched

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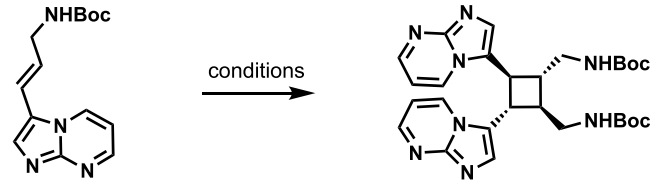
Table 1. Evaluation of Dimerization Reaction Parameters



9 10

entry[a]	photocatalyst	solvent[b]	E_T (kcal·mol $^{-1}$)	$E_{1/2}$(Pc*/Pc$^-$) (V vs SCE)	yield of **9** (%)[c]
1	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	MeOH	61	+0.89	31
2	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	CH_2Cl_2	61	+0.89	25
3	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	THF	61	+0.89	31
4	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	EtOAc	61	+0.89	24
5	Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6	MeCN	61	+0.89	32
6	Ru(bpz)$_3$(PF_6)$_2$	MeOH		+1.45	0
7	Ir(dtbbpy)(ppy)$_2PF_6$	MeOH	49.2	+0.66	0
8	Ir[dF(CF_3)ppy]$_2$(bpy)PF_6	MeOH			0
9	Ir[dF(CF_3)ppy]$_2$(4,4′-dCF_3bpy)PF_6	MeOH			0
10	Ru(bpy)$_3$(PF_6)$_2$	MeOH	46.5	+0.77	0
11	Mes-Acr-Ph(BF_4)	MeOH		> +2.0	0
12[d]	thioxanthone	MeOH	62		0
13[d]	2-bromothioxanone	MeOH	64		0
14[d]	Cu(dmp)(BINAP)BF_4	MeOH	64		0
15	none	MeOH			0
16[d]	none	MeOH			<5

[a]Reaction conditions: 0.1 mmol of **10**, 1 mol % photocatalyst, 0.5 M concentration, irradiation using blue LEDs (440−450 nm) with external cooling by a fan. [b]Reagent-grade solvents were degassed with Ar. [c]Determined by ^{1}H NMR analysis using mesitylene as an internal standard. [d]390 nm purple LEDs were used.

reported literature data (^{1}H and ^{13}C NMR)[2b] in addition to an authentic sample from *Agelas nakamurai* (HPLC, MS).[20]

Intermolecular [2 + 2] cycloadditions of the type demonstrated here are unprecedented and deserve some discussion. The efficiency of Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 as a promoter for the cycloaddition is noteworthy and in line with recent reports of its potency as a visible-light photosensitizer.[21] The selectivity of the transformation is equally impressive. Since 10 regio- and stereochemical permutations of the racemic dimer are statistically possible, we find the selective formation of a single isomer (**10**) in 57% yield (brsm) with a relative configuration matching the natural series remarkable given that its synthesis occurred in batch solvent and in the absence of any apparent templating phenomenon.[12,22]

An evaluation of reaction parameters as shown in Table 1 points to a working hypothesis based on catalytic energy transfer from an excited triplet state iridium complex to **9**, which subsequently combines with a ground-state monomer from its excited triplet state.[21a] Use of MeOH as the solvent gave the cleanest reaction mixtures, although the reaction yield was not critically dependent on the solvent identity (entries 1−5), which is consistent with an energy transfer mechanism. Furthermore, Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 is not sufficiently oxidizing in the excited state (+0.89 V)[18] to generate a radical cation from **9**, for which the peak oxidation potential was found to be +1.25 V vs SCE.[20] Evaluation of other catalysts, including photooxidants capable of oxidizing **10** from their respective excited states (Ru(bpz)$_3^{2+}$ and Mes-Acr-Ph$^+$, entries 6 and 11) in addition to other heteroleptic polypyridyl iridium complexes did not provide any **10**. Sensitizers with triplet energies greater than that of Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 but requiring irradiation with purple light (390 nm)[23] were not productive in this case. Finally, control experiments excluding any catalyst revealed that trace amounts of dimer **10** can be isolated following irradiation of **9** with purple light,[24] providing further support for a mechanism based on electronic excitation rather than a redox manifold.

In summary, a blend of biosynthetic logic and modern advances in catalytic photochemistry has enabled a four-step entry to the sceptrin alkaloids. Although the biogenesis of **3** is still a matter of conjecture and awaits experimental confirmation, the precision by which we arrived at the target structure demonstrates the utility of an energy transfer process in their de novo assembly. We have prepared multiple grams of the natural product to date and are currently studying its biological activity and potential interconversion to other dimeric pyrrole−imidazole alkaloids[2d,5] and exploring the utility of new hymenidin surrogates in biomimetic total synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01381.

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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