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# Concise Synthesis of *v*-Coelenterazines

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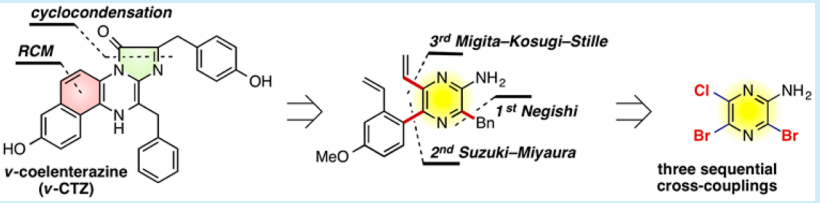
Supporting Information




**ABSTRACT:** A novel synthetic method for *v*-coelenterazine (*v*-CTZ), which is a vinylene-bridged analog of native CTZ with a large red-shifted luminescence property, is described. The synthesis was achieved in a concise way through the use of three sequential cross-coupling reactions and ring-closing metathesis (RCM). A newly synthesized C2-modified trifluoromethyl analog *cf3-v*-CTZ showed slightly more red-shifted luminescence than *v*-CTZ when it was used as a substrate for *Renilla* luciferases.

Coelenterazine (CTZ, **1**; Figure 1) is an imidazopyrazinone compound derived from marine organisms[1] and serves as a light-emitting substrate for calcium-binding photoproteins, including aequorin, clytin, mitrocomin, and obelin.[2] CTZ is also commonly used as a luciferin in the luminescence reaction catalyzed by marine-derived luciferases from *Renilla*, *Oplophorus*, *Periphylla*, *Gaussia*, *Metridia*, and *Conchoecia*.[3] Since the pioneering works reported by Shimomura, Musicki, and Kishi in the late 1980s,[4] a number of CTZ analogs have been synthesized and their luminescence properties have been characterized.[5,6] In the course of our studies on CTZ chemistry and its uses for protein chemistry,[7] we previously synthesized eight new analogs modified at the C2-position and found that semisynthetic aequorin with trifluoromethyl analog *cf3*-CTZ (**2**) as the substrate showed a slow decay of the luminescence pattern with less sensitivity to $Ca^{2+}$, which was useful for the cell-based G-protein-coupled receptor (GPCR) reporter assays.[7b] We also demonstrated that bisdeoxy analogs such as *bis*-CTZ (**3**) and *6h-f*-CTZ (**4**) serve as efficient substrates for the glow luminescence reaction of nanoKAZ, which is the mutated catalytic 19 kDa protein of *Oplophorus* luciferase.[7d]

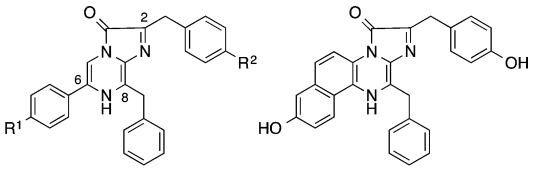



**Figure 1.** Coelenterazine (CTZ, **1**) and CTZ analogs.

*v*-Coelenterazine (*v*-CTZ, **5**) is a vinylene-bridged $\pi$-extended analog of CTZ that was prepared by Shimomura, Musicki, and Kishi in 1988 using the conventional synthetic method for CTZ,[8] although the details of the synthetic procedure were not disclosed.[4a] In 1997, Inouye and Shimomura observed a remarkable red-shifted emission spectrum using *v*-CTZ as a substrate for *Renilla* luciferase (RLase) ($\lambda_{max}$ = 512 nm) instead of native CTZ ($\lambda_{max}$ = 475 nm).[5] Moreover, Gambhir and co-workers prepared several RLase variants, such as RLase-547 (RLuc8.6-547), and achieved further red shifts using *v*-CTZ ($\lambda_{max}$ = 588 nm).[9] Although *v*-CTZ is a promising substrate for bioimaging systems using CTZ-utilizing luciferases, from the practical point of view, *v*-CTZ analogs with more improved characteristics, such as higher chemical stability and further red-shifted luminescence property, are sought after.[10] To address this issue, a more flexible synthetic method that makes an array of analogs more available was desired. Herein, we demonstrate a new approach to synthesizing *v*-CTZ according to a convergent strategy.

Considering that substituents at the C2-, C6-, or C8-position of CTZ considerably affect the bioluminescent properties and chemical stability, we designed a convergent synthetic route to *v*-CTZ that would enable easy access to various analogs with different substituents (Scheme 1). According to the conven-

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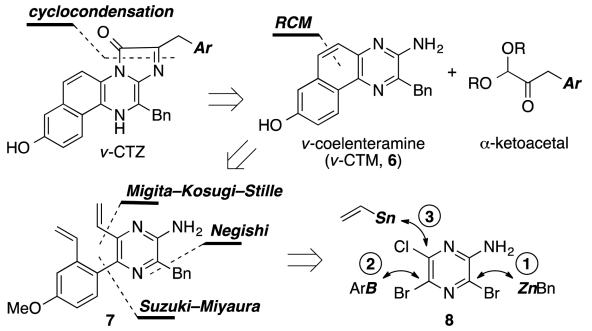
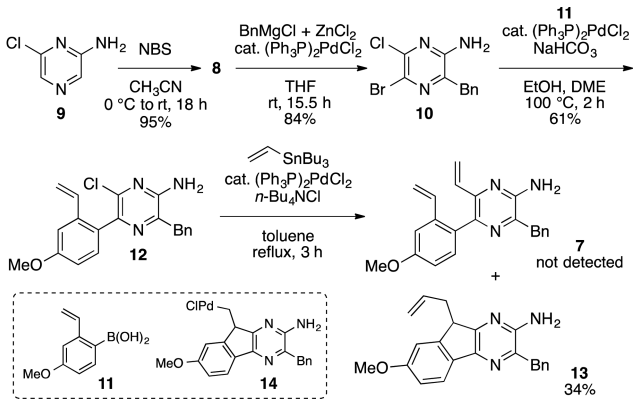
**Scheme 1. Retrosynthesis of *v*-Coelenterazine**




tional method, we decided to perform cyclocondensation between *v*-coelenteramine (*v*-CTM, **6**) and an *α*-ketoacetal[11] at the final step. Construction of a naphthopyrazine skeleton to obtain the key intermediate **6** was intended to be achieved via ring-closing metathesis (RCM) of a tetrasubstituted pyrazine **7** with two vinyl groups. This idea enabled disconnection of three carbon−carbon bonds on the pyrazine ring of **7**, which were planned to be formed through three sequential regioselective palladium-catalyzed cross-coupling reactions of trihalogenated aminopyrazine **8**.

Our initial attempt to synthesize divinyl intermediate **7** was unsuccessful (Scheme 2). The trihalogenated platform

**Scheme 2. An Attempt to Prepare the Divinyl Intermediate**

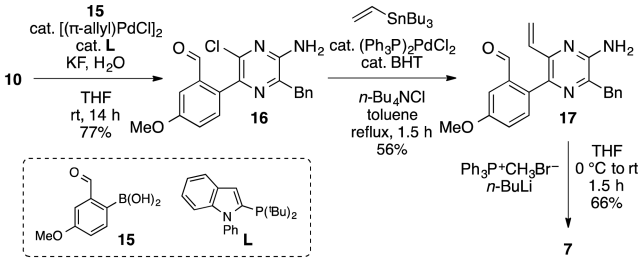



NBS = *N*-bromosuccinimide, DME = 1,2-dimethoxyethane

molecule 2-amino-3,5-dibromo-6-chloropyrazine (**8**) was prepared by dibromination of commercially available 2-amino-6-chloropyrazine (**9**).[12] Benzylation of **8** under the conditions of Negishi cross-coupling[13] proceeded in a regioselective manner under the direction of the unprotected amino group.[14] Subsequent Suzuki−Miyaura cross-coupling[15] of the resulting bromochloropyrazine **10** with arylboronic acid **11** bearing a vinyl group also proceeded selectively leaving the chloride group untouched. However, all attempts for vinylation of chloride **12** using cross-coupling reactions failed. For example, Migita−Kosugi−Stille coupling[16] between **12** and vinylstannane did not produce the desired divinyl product **7**. Instead, allylindenopyrazine **13** was obtained in moderate yield, which was possibly formed via the intramolecularly carbopalladated intermediate **14**.

We could avoid the undesired intramolecular reaction by performing vinylation using a formyl substrate instead of a vinyl one (Scheme 3). Thus, Suzuki−Miyaura cross-coupling of bromide **10** with formylarylboronic acid **15** in the presence of

**Scheme 3. Synthesis of the Divinyl Intermediate**

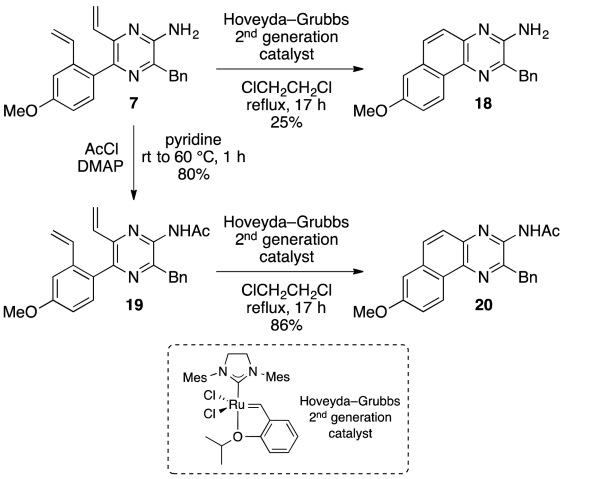



BHT = 3,5-di-*tert*-butyl-4-hydroxytoluene

potassium fluoride, with an equimolar amount of water and a catalytic amount of *π*-allylpalladium chloride dimer in combination with Beller's indolyl phosphine ligand **L**,[17] afforded the desired product **16** in high yield. Interestingly, the coupling product **16** was not obtained without addition of water. In the case of chloride **16**, Migita−Kosugi−Stille cross-coupling proceeded to yield the vinylated product **17**. The following Wittig methylenation of aldehyde **17** could be performed smoothly despite the presence of an unprotected pyrazylamino group, affording the desired divinyl compound **7** in good yield.

RCM of the divinyl intermediate was effective in constructing the naphthopyrazine skeleton (Scheme 4). However, our initial

**Scheme 4. Construction of Naphthopyrazine by RCM**

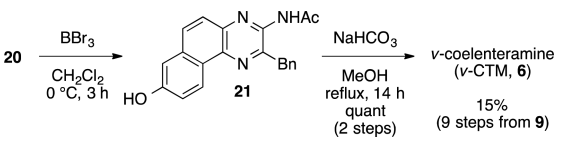



DMAP = 4-(dimethylamino)pyridine, Mes = $C_6H_2$-2,4,6-$(CH_3)_3$

attempts to obtain the RCM product directly from diene **7** led to poor results. For example, RCM of **7** using the Hoveyda−Grubbs second generation catalyst[18] afforded the desired product **18** in low yield. The efficiency of the reaction was largely improved by conducting the RCM using *N*-acetylated diene **19**, which provided naphthopyrazine **20** in high yield.

Deprotections of methoxy and acetamido moieties of naphthopyrazine **20** afforded *v*-CTM (**6**) (Scheme 5). Treatment of **20** with boron tribromide provided the

**Scheme 5. Synthesis of *v*-Coelenteramine**



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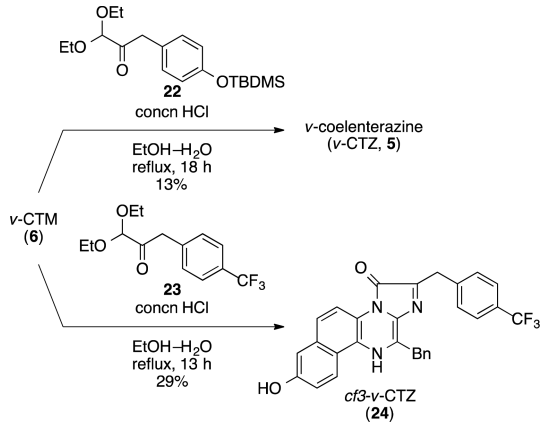
demethylated product **21** quantitatively. Unexpectedly, transformation of amide **21** into *v*-CTM (**6**) by deacetylation was efficiently accomplished under mild conditions, such as treatment with sodium bicarbonate in refluxing methanol, which could be due to assistance from the phenolic hydroxy group through extended π-conjugation. Together, the synthesis of *v*-CTM (**6**) was achieved in 9 steps from commercially available pyrazine **9** with a 15% overall yield.

*v*-CTZ (**5**) and a C2-modified analog were successfully synthesized by the cyclocondensation reaction of *v*-CTM (**6**) with α-ketoacetals (Scheme 6). Although *v*-CTZ (**5**) is highly

**Scheme 6. Synthesis of *v*-Coelenterazines**




susceptible to oxidation and unstable in solutions, heating a mixture of *v*-CTM (**6**) with α-ketoacetal **22** in acidic aqueous ethanol provided *v*-CTZ (**2**) in 13% yield. The spectral data for chromatographically purified *v*-CTZ (**5**) were identical to those reported in the literature.[4a] We previously reported that some C2-modified CTZ analogs, such as *cf*3-CTZ (**2**), gained significantly improved stability in a buffer solution.[7c] Based on this observation, we also prepared a trifluoromethyl analog of *v*-CTZ, where cyclocondensation of *v*-CTM (**6**) with α-ketoacetal **23**[7b] afforded the desired *cf*3-*v*-CTZ (**24**) in 29% yield. Although further studies to improve the efficiency of the cyclocondensation step are needed, the isolated yields indicated that the stability of *cf*3-*v*-CTZ (**24**) compared to *v*-CTZ (**5**) was improved, exhibiting a similar trend with our previous report for C2-modified CTZ analogs.[7b,c]

The newly synthesized *cf*3-*v*-CTZ (**24**) was a good substrate for RLase (Table 1). The luminescence properties of the synthesized *v*-CTZ (**5**) were in good agreement with the results of previous reports,[5,9] where remarkable red-shifted emission spectra were obtained when it was used as a substrate for RLase ($\lambda_{max}$ = 485 nm shifted to 519 nm) or RLase-547 ($\lambda_{max}$ = 547 nm shifted to 593 nm) compared with native CTZ (**1**). Slightly increased red shifts, $\lambda_{max}$ = 526 and 599 nm for RLase and RLase-547, respectively, were observed for *cf*3-*v*-CTZ (**24**). The decreased luminescence intensities were observed for *cf*3-*v*-CTZ (**24**) compared with *v*-CTZ (**5**). We previously observed a similar trend between *cf*3-CTZ (**2**) and CTZ (**1**),[7c] suggesting that the modification of the 4-hydroxybenzyl group at the C2 position of CTZs to 4-(trifluoromethyl)benzyl group affects the luminescence properties.

In summary, we have developed a concise synthetic method for *v*-CTZ using three sequential cross-couplings and RCM as key reactions. The convergent approach should enable the preparation of an array of *v*-CTZs through the simple exchange

**Table 1. Luminescence Properties of CTZ Analogs as a Substrate of RLase and RLase-547**

| | RLase | | RLase-547 | |
|---|---|---|---|---|
| CTZ analog | $I_{max}$ [Int.][a] (%) | $\lambda_{max}$[b] [FWHM][c] (nm) | $I_{max}$ [Int.][a] (%) | $\lambda_{max}$[b] [FWHM][c] (nm) |
| CTZ (**1**) | 100[d] | 485 | 100[e] | 547 |
| | [100][f] | [95] | [100][g] | [124] |
| *v*-CTZ (**5**) | 71.8 | 519 | 213 | 593 |
| | [47.3] | [105] | [73.4] | [130] |
| *cf*3-*v*-CTZ (**24**) | 18.9 | 526 | 16.9 | 599 |
| | [12.3] | [121] | [11.9] | [132] |

[a]The maximum intensity of luminescence ($I_{max}$) and the integrated value of luminescence (Int.) are obtained in 0.1 s intervals for 60 s, and the relative activity is expressed as a percentage of the mean value with respect to coelenterazine ($n$ = 4). [b]All bioluminescence spectra are corrected according to the manufacture's protocol. [c]FWHM = full width at half-maximum. [d]$9.4 \times 10^7$ rlu/μg. [e]$6.9 \times 10^6$ rlu/μg. [f]$2.9 \times 10^{10}$ rlu/μg. [g]$3.7 \times 10^9$ rlu/μg (rlu = relative light units).

of the coupling partners. Further studies on CTZ analogs and CTZ-utilizing luciferases will allow the development of efficient bioimaging systems, including in vivo imaging of living animals.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures and characterization data including copies of NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01872.

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### Notes

The authors declare no competing financial interest.

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