

## Concise Synthesis of $\nu$ -Coelenterazines

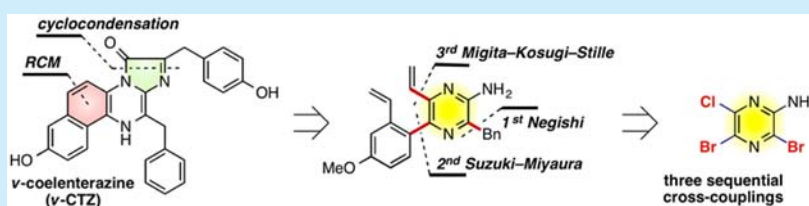
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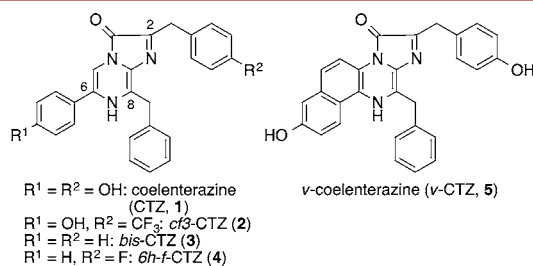
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### Supporting Information



**ABSTRACT:** A novel synthetic method for  $\nu$ -coelenterazine ( $\nu$ -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 of  $\nu$ -CTZ showed slightly more red-shifted luminescence than  $\nu$ -CTZ when it was used as a substrate for *Renilla* luciferases.

Coelenterazine (CTZ, **1**; Figure 1) is an imidazopyrazinone compound derived from marine organisms<sup>1</sup> and serves as



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

a light-emitting substrate for calcium-binding photoproteins, including aequorin, clytin, mitrocomin, and obelin.<sup>2</sup> 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*.<sup>3</sup> Since the pioneering works reported by Shimomura, Musicki, and Kishi in the late 1980s,<sup>4</sup> a number of CTZ analogs have been synthesized and their luminescence properties have been characterized.<sup>5,6</sup> In the course of our studies on CTZ chemistry and its uses for protein chemistry,<sup>7</sup> 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  $\text{Ca}^{2+}$ , which was useful for the cell-based G-protein-coupled receptor (GPCR) reporter assays.<sup>7b</sup> We also demonstrated that bisdeoxy analogs such as

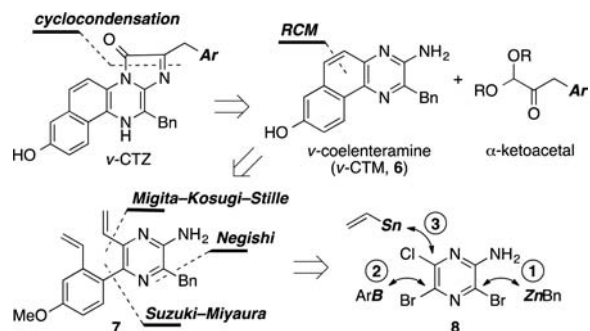
*bis*-CTZ (**3**) and *6h-f*-CTZ (**4**) serve as efficient substrates for the glow luminescence reaction of nanoKAZ, which is the mutated catalytic 19 kDa protein of *Oplophorus* luciferase.<sup>7d</sup>

$\nu$ -Coelenterazine ( $\nu$ -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,<sup>8</sup> although the details of the synthetic procedure were not disclosed.<sup>4a</sup> In 1997, Inouye and Shimomura observed a remarkable red-shifted emission spectrum using  $\nu$ -CTZ as a substrate for *Renilla* luciferase (RLase) ( $\lambda_{\text{max}} = 512$  nm) instead of native CTZ ( $\lambda_{\text{max}} = 475$  nm).<sup>5</sup> Moreover, Gambhir and co-workers prepared several RLase variants, such as RLase-547 (RLuc8.6-547), and achieved further red shifts using  $\nu$ -CTZ ( $\lambda_{\text{max}} = 588$  nm).<sup>9</sup> Although  $\nu$ -CTZ is a promising substrate for bioimaging systems using CTZ-utilizing luciferases, from the practical point of view,  $\nu$ -CTZ analogs with more improved characteristics, such as higher chemical stability and further red-shifted luminescence property, are sought after.<sup>10</sup> 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  $\nu$ -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  $\nu$ -CTZ that would enable easy access to various analogs with different substituents (Scheme 1). According to the conven-

Received: June 30, 2015

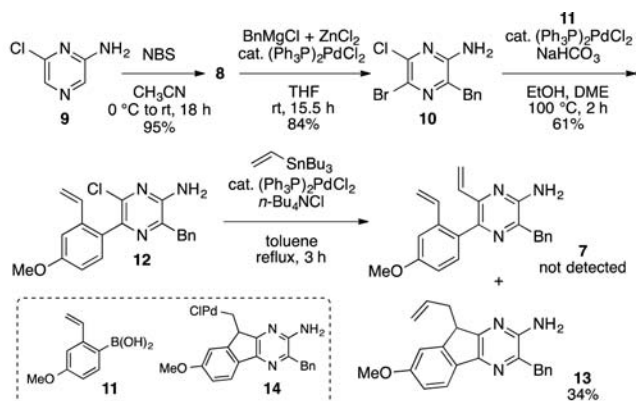
Published: July 21, 2015

Scheme 1. Retrosynthesis of *v*-Coelenterazine

tional method, we decided to perform cyclocondensation between *v*-coelenteramine (*v*-CTM, **6**) and an  $\alpha$ -ketoacetal<sup>11</sup> 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

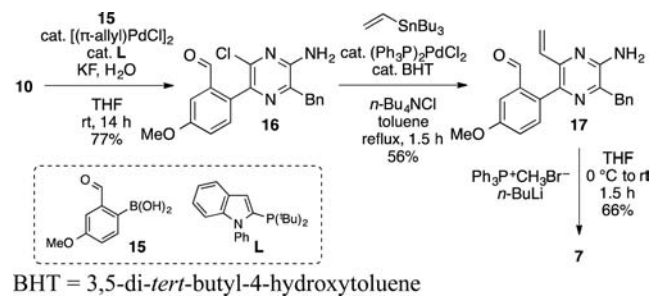


NBS = *N*-bromosuccinimide, DME = 1,2-dimethoxyethane

molecule 2-amino-3,5-dibromo-6-chloropyrazine (**8**) was prepared by dibromination of commercially available 2-amino-6-chloropyrazine (**9**).<sup>12</sup> Benzylation of **8** under the conditions of Negishi cross-coupling<sup>13</sup> proceeded in a regioselective manner under the direction of the unprotected amino group.<sup>14</sup> Subsequent Suzuki-Miyaura cross-coupling<sup>15</sup> 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<sup>16</sup> 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

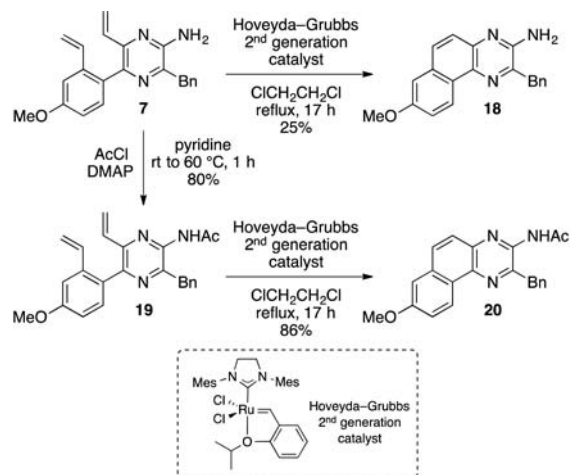


BHT = 3,5-di-*tert*-butyl-4-hydroxytoluene

potassium fluoride, with an equimolar amount of water and a catalytic amount of  $\pi$ -allylpalladium chloride dimer in combination with Beller's indolyl phosphine ligand **L**,<sup>17</sup> 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

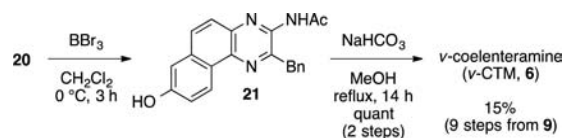
Scheme 4. Construction of Naphthopyrazine by RCM



DMAP = 4-(dimethylamino)pyridine, Mes = C<sub>6</sub>H<sub>2</sub>-2,4,6-(CH<sub>3</sub>)<sub>3</sub>

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<sup>18</sup> 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.

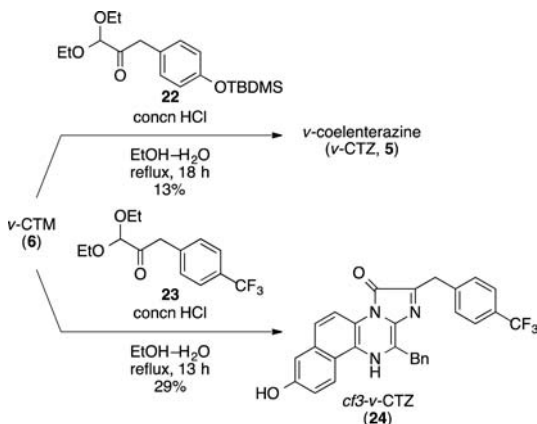
Deprotections of methoxy and acetamido moieties of naphthopyrazine **20** afforded *v*-CTM (**6**) (Scheme 5). Treatment of **20** with boron tribromide provided the

Scheme 5. Synthesis of *v*-Coelenteramine

demethylated product **21** quantitatively. Unexpectedly, transformation of amide **21** into  $\nu$ -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  $\pi$ -conjugation. Together, the synthesis of  $\nu$ -CTM (**6**) was achieved in 9 steps from commercially available pyrazine **9** with a 15% overall yield.

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

Scheme 6. Synthesis of  $\nu$ -Coelenterazines



susceptible to oxidation and unstable in solutions, heating a mixture of  $\nu$ -CTM (**6**) with  $\alpha$ -ketoacetal **22** in acidic aqueous ethanol provided  $\nu$ -CTZ (**2**) in 13% yield. The spectral data for chromatographically purified  $\nu$ -CTZ (**5**) were identical to those reported in the literature.<sup>4a</sup> We previously reported that some C2-modified CTZ analogs, such as  $cf3$ -CTZ (**2**), gained significantly improved stability in a buffer solution.<sup>7c</sup> Based on this observation, we also prepared a trifluoromethyl analog of  $\nu$ -CTZ, where cyclocondensation of  $\nu$ -CTM (**6**) with  $\alpha$ -ketoacetal **23**<sup>7b</sup> afforded the desired  $cf3$ - $\nu$ -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  $cf3$ - $\nu$ -CTZ (**24**) compared to  $\nu$ -CTZ (**5**) was improved, exhibiting a similar trend with our previous report for C2-modified CTZ analogs.<sup>7b,c</sup>

The newly synthesized  $cf3$ - $\nu$ -CTZ (**24**) was a good substrate for RLase (Table 1). The luminescence properties of the synthesized  $\nu$ -CTZ (**5**) were in good agreement with the results of previous reports,<sup>5,9</sup> 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  $cf3$ - $\nu$ -CTZ (**24**). The decreased luminescence intensities were observed for  $cf3$ - $\nu$ -CTZ (**24**) compared with  $\nu$ -CTZ (**5**). We previously observed a similar trend between  $cf3$ -CTZ (**2**) and CTZ (**1**),<sup>7c</sup> 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  $\nu$ -CTZ using three sequential cross-couplings and RCM as key reactions. The convergent approach should enable the preparation of an array of  $\nu$ -CTZs through the simple exchange

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

CTZ analog	RLase		RLase-547	
	$I_{\max}$ [Int.] <sup>a</sup> (%)	$\lambda_{\max}^b$ [FWHM] <sup>c</sup> (nm)	$I_{\max}$ [Int.] <sup>a</sup> (%)	$\lambda_{\max}^b$ [FWHM] <sup>c</sup> (nm)
CTZ ( <b>1</b> )	100 <sup>d</sup> [100] <sup>f</sup>	485 [95]	100 <sup>e</sup> [100] <sup>g</sup>	547 [124]
$\nu$ -CTZ ( <b>5</b> )	71.8 [47.3]	519 [105]	213 [73.4]	593 [130]
$cf3$ - $\nu$ -CTZ ( <b>24</b> )	18.9 [12.3]	526 [121]	16.9 [11.9]	599 [132]

<sup>a</sup>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 ( $n = 4$ ). <sup>b</sup>All bioluminescence spectra are corrected according to the manufacturer's protocol. <sup>c</sup>FWHM = full width at half-maximum. <sup>d</sup> $9.4 \times 10^7$  rlu/ $\mu$ g. <sup>e</sup> $6.9 \times 10^6$  rlu/ $\mu$ g. <sup>f</sup> $2.9 \times 10^{10}$  rlu/ $\mu$ g. <sup>g</sup> $3.7 \times 10^9$  rlu/ $\mu$ g (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.

## ■ ACKNOWLEDGMENTS

The authors thank Ms. Ayako Hosoya at Tokyo Medical and Dental University for HRMS analyses. This work was supported by Platform for Drug Discovery, Informatics, and Structural Life Science from MEXT and AMED, Japan, JSPS KAKENHI Grant Numbers 26560443 (T.H.) and 26350971 (S.Y.), and grants from The Noguchi Institute, Takeda Science Foundation, The Uehara Memorial Foundation (S.Y.), The Kurata Memorial Hitachi Science and Technology Foundation, and The Naito Foundation (T.H.).

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