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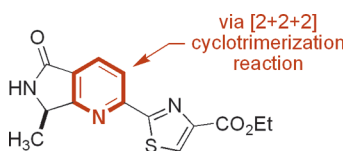
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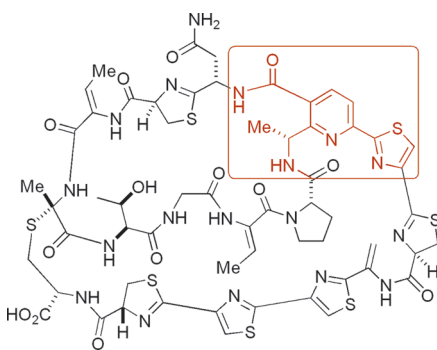
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## ABSTRACT



A highly convergent synthesis of the pyridine core of the thiopeptide antibiotic cyclothiazomycin has been developed based on a [2 + 2 + 2] cyclotrimerization key step. The regioselective assembly of the heterocyclic center of this important class of antibiotics takes advantage of a temporary silicon tether and the ruthenium-catalyzed cyclotrimerization reaction of a diyne and an electron-poor thiazole nitrile.

Thiopeptide antibiotics have attracted considerable attention due to their intriguing architecture and their inhibition of bacterial protein synthesis, preventing the growth of gram-positive bacteria, including methicillin-resistant *S. aureus*.<sup>1</sup> Cyclothiazomycin (**1**) is 1 of 76 structurally distinct actinomycete thiopeptide antibiotics (Figure 1).<sup>1</sup>



**Figure 1.** Structure of cyclothiazomycin (**1**), a representative thiopeptide antibiotic.

The peptide **1** bears a central 2,3,6-trisubstituted pyridine motif, which is also found in a number of other

thiopeptide antibiotics, including berninamycins, genthiocin, promothiocins, radamycin, and thioxamycin. However, previous syntheses of thiopeptide antibiotics have often struggled with the assembly of the pyridine core. Several groups have developed sophisticated and specially designed approaches, including aza-Diels–Alder reactions<sup>2,3</sup> and heteroannulations.<sup>4,5</sup> To date, three syntheses of the pyridine motif present in cyclothiazomycin (**1**) have been reported.<sup>6–8</sup> However, only one of the three approaches is a stereospecific synthesis<sup>8</sup> and utilizes a Bohlmann–Rahtz reaction to assemble the trisubstituted pyridine ring from an enantiomerically pure  $\beta$ -ketoester and ethyl 2-(propynoyl)thiazole-4-carboxylate. No total synthesis of cyclothiazomycin is known.

[2 + 2 + 2] Cyclotrimerization reactions have been applied as efficient tools in the construction of highly

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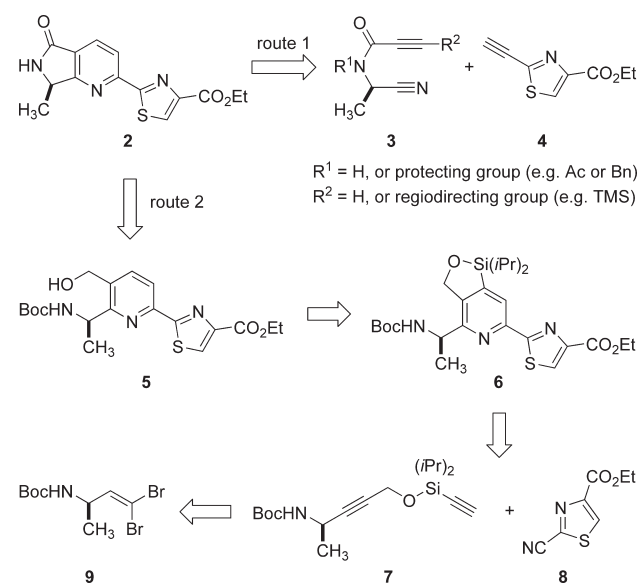
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functionalized benzene and pyridine rings.<sup>9–14</sup> The [2 + 2] cyclotrimerization reaction tolerates a variety of functional groups, which allows for its application in the facile synthesis of multisubstituted carbo- and heteroaromatic ring systems in a single step.<sup>15–30</sup> Based on our previous successes in applying cyclotrimerization reactions in the synthesis of important, naturally occurring structural motifs,<sup>31–36</sup> we are reporting a regioselective approach to the formation of the pyridine domain of thiopeptide antibiotics via a transition-metal-catalyzed [2 + 2 + 2] cyclotrimerization reaction as the key step. Two different retrosynthetic analyses of **2** are shown in Scheme 1. We first envisioned that **2** could be assembled from the cyclotrimerization of the enantiopure alkynynitrile **3** and the thiazole alkyne **4** (route 1). Although this route is highly convergent, this approach potentially entails several pitfalls: (1) Alkynynitriles are traditionally poor substrates in cyclotrimerization reactions due to the possibility of several undesired side reactions.<sup>17,37,38</sup> (2) The cyclotrimerization precursor **3** can exist as two different amide isomers, of which only the one shown can undergo the desired reaction. (3) The cyclotrimerization reaction can yield mixtures of regioisomers,<sup>17</sup> a problem that could possibly be solved through the installation of a temporary regiodirecting group R<sup>2</sup>.

**Scheme 1.** Retrosynthetic Analysis of **2**



However, the cyclotrimerization reaction of the alkynynitrile **3** (R<sup>1</sup> = Ac, R<sup>2</sup> = TMS) and the thiazole alkyne **4** did not proceed as expected (data not shown). Even though a wide range of conditions were explored, a number of catalysts were investigated at different temperatures, with and without microwave irradiation, the product yields were generally below 15%.

Based on our<sup>39</sup> and others<sup>40–43</sup> recent successes in constructing highly substituted benzenes and pyridines via a silyl-tethered [2 + 2 + 2] cyclotrimerization reaction, we applied a similar approach to the synthesis of the pyridine core **2** of cyclothiazomycin (**1**) (Scheme 1, route 2). The silyl tether transforms an otherwise intermolecular cyclotrimerization reaction into an intramolecular one, providing enhanced regio- and chemoselectivity. Here, the application of a silyl tether enabled switching of the synthetic approach from a notoriously difficult<sup>17,38</sup> to cyclotrimerize alkynynitrile to a regular diyne cyclotrimerization precursor. The linker can be easily and selectively removed in a traceless fashion, delivering the desired product.

We envisioned that **2** could be obtained from the oxidation of the alcohol **5**, which in turn could be synthesized through removal of the silyl group from **6**. The pyridine ring **6** could be assembled by a [2 + 2 + 2] cyclotrimerization reaction of the enantiopure diyne **7** and the

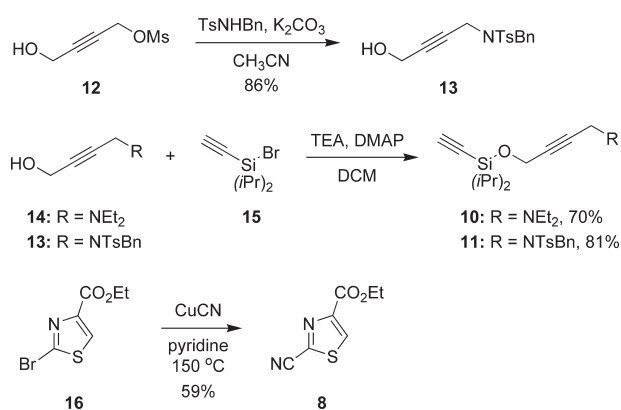
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thiazolecarbonitrile **8**. The diyne **7** could be synthesized from the known dibromoalkene **9**.

We first investigated the ability to react various silyl ether diynes in [2 + 2 + 2] cyclotrimerization reactions. Two model substrates, silyl ether diynes **10** and **11**, were synthesized (Scheme 2). The diyne **10** was prepared in one step from the commercially available alcohol **14** and freshly prepared alkynylsilyl bromide **15**.<sup>40</sup> The synthesis of the diyne **11** was accomplished in two steps via an S<sub>N</sub>2 reaction of *N*-benzyl-*p*-toluenesulfonamide with 4-hydroxybut-2-ynyl methanesulfonate, followed by reacting **13** with alkynylsilyl bromide to form **11** in good yields. The known thiazolecarbonitrile **8** was prepared in one step from commercially available ethyl 2-bromothiazole-4-carboxylate (**16**) in 59% yield.<sup>44</sup>

**Scheme 2.** Synthesis of Model Cyclotrimerization Substrates



With the model diynes and nitriles in hand, we investigated the cyclotrimerization reactions under different reaction conditions (Table 1). The CpCo(CO)<sub>2</sub> catalyst was the first used due to its wide application in the formation of pyridines.<sup>9,13,45,46</sup> However, no product was obtained from the diynes **10**–**11** and benzonitrile or thiazolecarbonitrile **8** under microwave irradiation (entries 1, 2, and 4). When the cyclotrimerization reaction between **10** and benzonitrile was thermally heated to 150 °C in the presence of CpCo(CO)<sub>2</sub>, only 39% of the desired product **18** was obtained (entry 3). Yamamoto et al.<sup>47</sup> successfully used Cp\*RuCl(COD) as the catalyst for cyclotrimerization reactions of electron-deficient nitriles. Gratifyingly, the diyne **17** underwent a smooth cyclotrimerization reaction with the electron-poor thiazolecarbonitrile **8** in the presence of Cp\*RuCl(COD) at either room temperature or 60 °C (entries 6 and 7), furnishing the desired pyridine **21** in excellent yields. The cyclotrimerization reaction between diyne **11** and thiazolecarbonitrile **8** was successful and the

product **22** was obtained in good yield and with excellent regioselectivity. This was the first time a thiazole nitrile was employed in a [2 + 2 + 2] cyclotrimerization reaction. The successful reaction between the silyl-tethered diyne solved potential regioselectivity problems and previously encountered reactivity problems of alkynyl nitriles. These discovered results were subsequently applied to the synthesis of the pyridine core of cyclothiazomycin (**1**).

**Table 1.** Cyclotrimerization Reactions of Model Substrates

		<b>10, 11, 17</b>		<b>18–22</b>		(not observed)	
entry	subs.	R <sup>1</sup>	X	Y	R <sup>2</sup>	cat.	prod. yield
1	<b>10</b>	CH <sub>2</sub> NEt <sub>2</sub>	O	Si( <i>i</i> Pr) <sub>2</sub>	Ph	a	<b>18</b> -
2	<b>10</b>	CH <sub>2</sub> NEt <sub>2</sub>	O	Si( <i>i</i> Pr) <sub>2</sub>		a	<b>19</b> -
3	<b>10</b>	CH <sub>2</sub> NEt <sub>2</sub>	O	Si( <i>i</i> Pr) <sub>2</sub>	Ph	b	<b>18</b> 39%
4	<b>11</b>	CH <sub>2</sub> NBnTs	O	Si( <i>i</i> Pr) <sub>2</sub>	Ph	a	<b>20</b> -
5	<b>11</b>	CH <sub>2</sub> NBnTs	O	Si( <i>i</i> Pr) <sub>2</sub>	Ph	c	<b>20</b> -
6	<b>17</b>	H	C(CO <sub>2</sub> Et) <sub>2</sub>	CH <sub>2</sub>		d	<b>21</b> 93%
7	<b>17</b>	H	C(CO <sub>2</sub> Et) <sub>2</sub>	CH <sub>2</sub>		e	<b>21</b> 95%
8	<b>11</b>	CH <sub>2</sub> NBnTs	O	Si( <i>i</i> Pr) <sub>2</sub>		d	<b>22</b> 78%

<sup>a</sup> CpCo(CO)<sub>2</sub>, toluene, MW 300 W. <sup>b</sup> CpCo(CO)<sub>2</sub>, xylene, 150 °C, 16 h. <sup>c</sup> CpCo(COD), 150 °C, 16 h. <sup>d</sup> Cp\*RuCl(COD), DCM, rt, 20 h. <sup>e</sup> Cp\*RuCl(COD), DCE, 60 °C, 20 h.

The synthesis of **2** commences with the known dibromoalkene **9** which was synthesized in three steps from (*R*)-2-aminopropan-1-ol following a literature procedure.<sup>48</sup> The dibromoalkene **9** was deprotonated with *n*-BuLi and reacted with DMF to the corresponding aldehyde which was directly reduced to the propargyl alcohol **23** (Scheme 3).<sup>49</sup> The alcohol **23** was alkylated with freshly prepared alkynylsilyl bromide,<sup>40</sup> producing the silyl ether-tethered cyclotrimerization precursor **7** in 84% yield. As expected from the model studies, the diyne **7** underwent an efficient [2 + 2 + 2] cyclotrimerization reaction with the thiazolecarbonitrile **8** in the presence of Cp\*RuCl(COD), delivering the tetrasubstituted pyridine **6** in 82% yield. Importantly, the reaction proceeded with complete regio- and chemoselectivity, as no other cyclotrimerization

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CC(C)C(Br)C(Br)C(=O)OC(C)(C)C (**9**)  $\xrightarrow[50\%]{\begin{array}{l} 1. n\text{-BuLi, THF} \\ \text{then DMF} \\ 2. \text{citric acid} \\ 3. \text{NaBH}_4 \\ \text{EtOH} \end{array}}$  CC(C)C(O)C#CC(=O)OC(C)(C)C (**23**) + CC(C)(C)Si(Br)C#C (**15**)

CC(C)C(O)C#CC(=O)OC(C)(C)C (**23**)  $\xrightarrow[84\%]{\begin{array}{l} \text{TEA, DMAP} \\ \text{DCM} \end{array}}$  CC(C)C(OC(C)(C)C#C)C#CC(=O)OC(C)(C)C (**7**) + CCOC(=O)c1cnc(s1)C#N (**8**)

CC(C)C(OC(C)(C)C#C)C#CC(=O)OC(C)(C)C (**7**)  $\xrightarrow[82\%]{\begin{array}{l} \text{Cp}^*\text{RuCl(COD)} \\ \text{DCE} \\ 60^\circ\text{C} \end{array}}$  CC(C)C(OC(C)(C)C#C)C1=CC=C(C2=CC(=C(C=C2)OC(C)(C)C#C)N1C3=CC(=C(C=C3)C#N)C(=O)OCC)N (**6**)

CC(C)C(OC(C)(C)C#C)C1=CC=C(C2=CC(=C(C=C2)OC(C)(C)C#C)N1C3=CC(=C(C=C3)C#N)C(=O)OCC)N (**6**)  $\xrightarrow[97\%]{\begin{array}{l} \text{TBAF} \\ \text{THF} \end{array}}$  CC(C)C(O)C#CC(=O)OC(C)(C)C (**23**)

CC(C)C(O)C#CC(=O)OC(C)(C)C (**23**)  $\xrightarrow[80\%]{\begin{array}{l} 1. \text{Jones' reagent} \\ \text{acetone} \\ 0^\circ\text{C} - \text{rt} \\ 2. \text{TFA, DCM} \end{array}}$  CC(C)C(=O)C1=CC=C(C2=CC(=C(C=C2)OC(C)(C)C#C)N1C3=CC(=C(C=C3)C#N)C(=O)OCC)N (**5**)

CC(C)C(=O)C1=CC=C(C2=CC(=C(C=C2)OC(C)(C)C#C)N1C3=CC(=C(C=C3)C#N)C(=O)OCC)N (**5**)  $\xrightarrow{\text{reagents}}$  CC(C)C(=O)C1=CC=C(C2=CC(=C(C=C2)OC(C)(C)C#C)N1C3=CC(=C(C=C3)C#N)C(=O)OCC)N (**2**)

CC(C)C(=O)C1=CC=C(C2=CC(=C(C=C2)OC(C)(C)C#C)N1C3=CC(=C(C=C3)C#N)C(=O)OCC)N (**2**)  $\xrightarrow{\text{reagents}}$  CC(C)C(=O)C1=CC=C(C2=CC(=C(C=C2)OC(C)(C)C#C)N1C3=CC(=C(C=C3)C#N)C(=O)OCC)N (**24**)

pyridine core of cyclothiazomycin was efficiently assembled in regio- and enantiomerically pure form. The stereochemical information was retained throughout the entire synthesis, as the optical rotation of **2** ( $[\alpha]_{\text{D}}^{20} + 51.9$  ( $c$  0.54,  $\text{CHCl}_3$ )) is in excellent agreement with the literature reported value ( $[\alpha]_{\text{D}}^{24} + 48.1$  ( $c$  0.54,  $\text{CHCl}_3$ )).<sup>8</sup> The lactam **2** has previously been converted to the hydrolysate **24** of cyclothiazomycin.<sup>8</sup> Even though our synthetic approach is slightly longer than Bagley's published route,<sup>8</sup> the overall efficiency of both synthesis is comparable, with our approach being more easily adaptable to the synthesis of structural analogs.

In summary, we have described an effective and regioselective approach to the pyridine core of cyclothiazomycin (**1**). The key step of the synthesis is a transition-metal-catalyzed [2 + 2 + 2] cyclotrimerization reaction of a diyne and a nitrile. The electron-deficient nature of the thiazole-bearing nitrile enables ruthenium catalysis under mild reaction conditions with excellent yields. Complete chemo- and regioselectivity in the construction of the trisubstituted pyridine core were achieved by applying a temporary silyl tether. We believe that this approach, of tethering functionalized alkynes and cyclotrimerizing them with heterocyclic nitriles, will be applicable to a wide range of pyridine motifs found in natural products and pharmacologically relevant molecules.

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**Supporting Information Available.** Experimental protocols and analytical data, as well as  $^1\text{H}$  NMR spectra for compounds **2**, **5–8**, **10**, **11**, **13**, **18**, and **21–23**. This information is available free of charge via the Internet at <http://pubs.acs.org>.