Convergent total syntheses of fluvibactin and vibriobactin using molybdenum(VI) oxide-catalyzed dehydrative cyclization as a key step†

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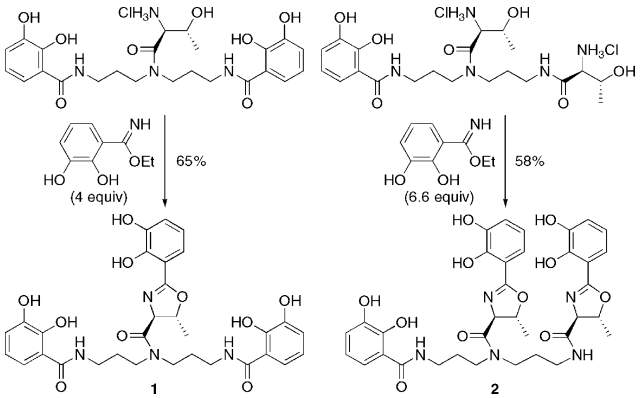
Efficient total syntheses of fluvibactin and vibriobactin have been achieved *via* molybdenum(VI) oxide-catalyzed dehydrative cyclization, $Sb(OEt)_3$-catalyzed ester–amide transformation, and WSCI and HOAt-promoted dehydrative amide formation.

Many oxazoline-containing natural products have been isolated from marine organisms.[1] The biosynthesis of these oxazolines appears to involve the dehydrative cyclization of serine and threonine residues.[1c] Fluvibactin (**1**)[2] and vibriobactin (**2**)[3] are representative catecholate siderophores that have been isolated from low-iron cultures of *Vibrio fluvialis* and *Vibrio cholerae*, respectively. These compounds consist of a norspermidine backbone with 2-(*o*,*m*-dihydroxyphenyl)oxazoline-4-carboxylate and 2,3-dihydroxybenzoate moieties. They serve as Fe(III) ion-specific chelators and facilitate Fe(III) ion uptake.[4] These siderophores have been attracting much attention from researchers, and several reports concerning their chemical syntheses, biosyntheses and biological activities have been published.[5]

The first total syntheses of **1**[6] and **2**[7] were reported by Bergeron *et al*.[8] According to their reports, synthesis of the 2-(*o*,*m*-dihydroxyphenyl)oxazoline structure is one of the most problematic steps. They synthesized the 2-(*o*,*m*-dihydroxyphenyl)oxazoline moieties by reacting L-threonine amides with 2,3-dihydroxybenzimidate at the last stage of the total synthesis (Scheme 1). However, the yields of the products were moderate (65 and 58%), despite the use of large amounts (4 and 6.6 equivalents) of 2,3-dihydroxybenzimidate. It is conceivable that steric hindrance of the L-threonine amides decreased the yields of **1** and **2**. Moreover, the synthesis of 2,3-dihydroxybenzimidate requires 6 steps (48% overall yield).[8b,9] For more efficient total syntheses of **1** and **2**, construction of the 2-(*o*,*m*-dihydroxyphenyl)oxazoline moiety at an early stage, if possible, would be more desirable.

Recently, we reported that molybdenum(VI) oxides were highly effective dehydrative cyclization catalysts for the synthesis of oxazolines and thiazolines.[10] As in biosynthesis, the molybdenum(VI) oxide-catalyzed dehydrative cyclization of L-threonine derivatives proceeds with retention of configuration at the β-position of the threonine residue. Therefore, this catalytic method is quite useful for the synthesis of naturally occurring oxazolines derived from an L-threonine residue. This Mo(VI)=O-catalyzed method was effective for the synthesis of

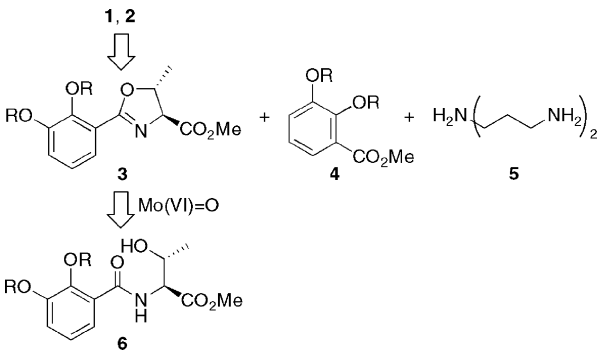


Scheme 1 Bergeron's first total syntheses of fluvibactin (**1**) and vibriobactin (**2**).

(*o*-hydroxyphenyl)oxazolines, and we achieved the first synthesis of BE-70016, an antitumor substance, using the Mo(VI)=O-catalyzed method as a key step.[11] Since the Mo(VI)=O-catalyzed method was expected to work for the synthesis of 2-(*o*,*m*-dihydroxyphenyl)oxazoline structures, we investigated the total syntheses of **1** and **2** using Mo(VI)=O-catalyzed dehydrative cyclization as a key step.

Our plan for the convergent synthesis of fluvibactin (**1**) and vibriobactin (**2**) is illustrated in Scheme 2. We planned to synthesize 2-(*o*,*m*-dialkoxyphenyl)oxazoline **3** at an early stage from *N*-(*o*,*m*-dialkoxybenzoyl)-L-threonine **6** *via* the Mo(VI)=O-catalyzed method. Compounds **1** and **2** would be synthesized by the assembly of **3**, 2,3-dialkoxybenzoate **4** and norspermidine (**5**).

First, we investigated the molybdenum(VI) oxide-catalyzed dehydrative cyclization of **6** (Table 1). Recently, we reported that the dehydrative cyclization of *N*-(*o*-hydroxybenzoyl)-L-threonine methyl ester could proceed using the combination of $(NH_4)_2MoO_4$ and pentafluorobenzoic acid ($C_6F_5CO_2H$), even without protection of the *o*-hydroxyl group, to give the



Scheme 2 Plan for the synthesis of **1** and **2**.

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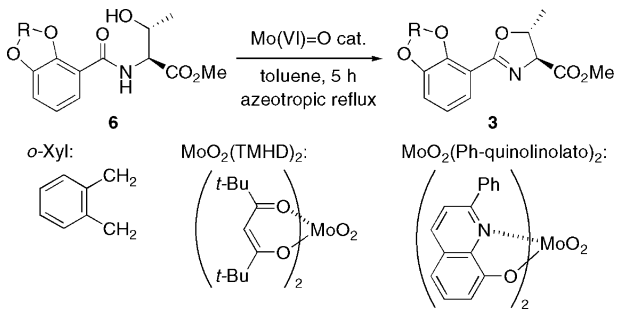
corresponding oxazoline in good yield.[11] However, the combination of $(NH_4)_2MoO_4$ and $C_6F_5CO_2H$ did not work for the dehydrative cyclization of *N*-(*o*,*m*-dihydroxybenzoyl)-L-threonine methyl ester (**6a**) (entries 1 and 2), probably due to rapid oxidation of the unprotected catechol moiety of **6a**. The present Mo(VI)=O-catalyzed reaction required protection of the catechol moiety. In fact, *N*-(*o*,*m*-dimethoxybenzoyl)threonine methyl ester (**6b**) showed good reactivity for $(NH_4)_2MoO_4$-catalyzed dehydrative cyclization under azeotropic reflux conditions in toluene, to give the corresponding oxazoline **3b** in 88% yield (entry 3). Methyl protection of the hydroxyl groups completely suppressed decomposition of the catechol moiety. Unfortunately, such methyl protection was difficult to remove at the last stage of our synthesis of **1** and **2**. Therefore, we investigated other protecting groups that could be more easily removed at the last step. Benzyl-protected substrate **6c** showed lower reactivity than **6b**, giving oxazoline **3c** in 46% yield (entry 4). The bulkiness of the benzyl group might decrease the reactivity of **6c**. In contrast to methyl protection, the benzyl groups in **3c** could be easily removed by conventional hydrogenolysis (H_2, Pd/C). Therefore, we examined other Mo(VI)=O catalysts for the dehydrative cyclization of **6c**. As a result, commercially available $MoO_2(acac)_2$ and $MoO_2(TMHD)_2$ were found to have good catalytic activities, and gave **3c** in respective yields of 77 and 91% (entries 5 and 6). Corey *et al*. reported the dehydrative cyclization of *p*-methoxybenzoyl-L-threonine methyl ester using TsOH as a catalyst.[12] However, the catalytic activity of TsOH was lower than that of $MoO_2(TMHD)_2$ for the reaction of **6c** (entry 7).

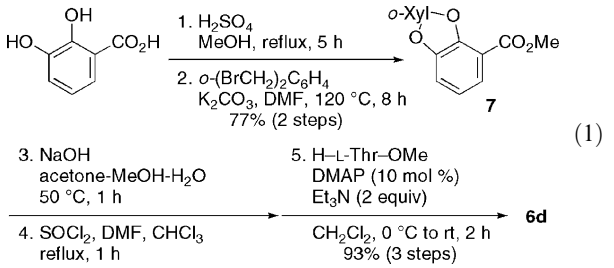
Table 1 Mo(VI)=O-catalyzed dehydrative cyclization of **6**[a]



Entry	R (**6**)	Mo(VI)=O cat. (mol%)[b]	Yield (%)[c]
1	H, H (**6a**)	$(NH_4)_2MoO_4$, 10	0
2[d]	H, H (**6a**)	$(NH_4)_2MoO_4$, 10	10
3	Me, Me (**6b**)	$(NH_4)_2MoO_4$, 10	88
4	Bn, Bn (**6c**)	$(NH_4)_2MoO_4$, 10	46
5	Bn, Bn (**6c**)	$MoO_2(acac)_2$, 10	77
6	Bn, Bn (**6c**)	$MoO_2(TMHD)_2$, 10	91
7[e]	Bn, Bn (**6c**)	TsOH, 10	44
8	*o*-Xyl (**6d**)	$(NH_4)_2MoO_4$, 10	96
9	*o*-Xyl (**6d**)	$MoO_2(TMHD)_2$, 0.5	94 [90][f]
10	*o*-Xyl (**6d**)	MoO_2(Ph-quinolinolato)$_2$, 1	83

[a] The reaction of **6** (1 mmol) was conducted with molybdenum(VI) oxide (10 mol%) in toluene (100 mL) under azeotropic reflux conditions for 5 h. [b] The amount of catalyst was calculated based on the metal. [c] Determined by ^1H NMR analysis. [d] The reaction was conducted in the presence of $C_6F_5CO_2H$ (10 mol%) in mesitylene–DMF (9 : 1 v/v) for 12 h. [e] The reaction was conducted in toluene (3 mL). [f] The reaction was conducted for 3 h.

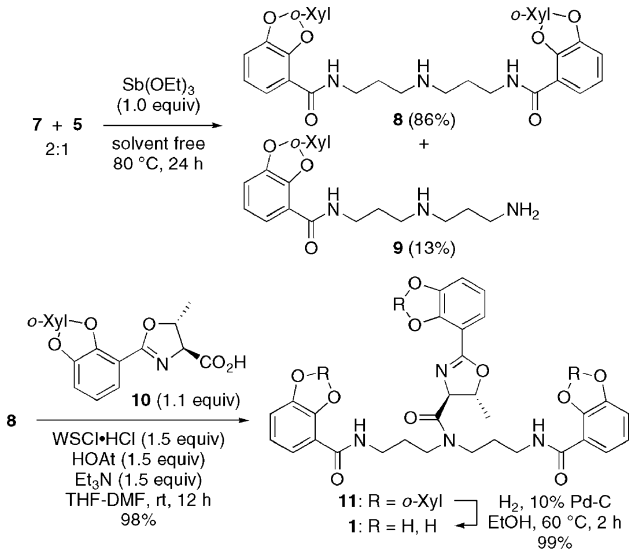
Further investigation of the protecting groups for the hydroxyl groups of the catechol moiety revealed that compound **6d** protected by a cyclic *o*-xylylene group (*o*-Xyl)[13] showed excellent reactivity. When the reaction of **6d** was conducted with 10 mol% of $(NH_4)_2MoO_4$, oxazoline **3d** was obtained in 96% yield (entry 8). Very interestingly, only 0.5 mol% of $MoO_2(TMHD)_2$ efficiently promoted the reaction of **6d** to give **3d** in 94% yield (entry 9). The high reactivity of **6d** might be attributed to the lower steric hindrance of the *o*-xylylene group. Furthermore, the *o*-xylylene group in **3d** could be easily removed by conventional hydrogenolysis (H_2, Pd/C). Recently, we reported that *cis*-bis(2-phenyl-8-quinolinolato-*N*,*O*)-dioxomolybdenum(VI) [MoO_2(Ph-quinolinolato)$_2$] showed good catalytic activity for the dehydrative cyclization of *N*-acyl-L-threonines to oxazolines.[10b] However, the activity of MoO_2(Ph-quinolinolato)$_2$ was lower than that of $MoO_2(TMHD)_2$ for the dehydrative cyclization of **6d** (entry 10). Compound **6d** could be easily prepared from commercially available 2,3-dihydroxybenzoic acid by a five-step transformation *via* compound **7** (72% overall yield) (eqn (1)).



(1)

Next, we investigated the synthesis of fluvibactin (**1**) using **3d** as a key building block (Scheme 3). Sb(III) alkoxide-catalyzed ester–amide transformation[14] worked well for the selective synthesis of diamide **8**, although the reaction required an equimolar amount of Sb(III) alkoxide. When the reaction of a 2 : 1 mixture of **7** and norspermidine (**5**) was conducted in the presence of $Sb(OEt)_3$ (1.0 equiv) under solvent-free conditions at 80 °C, the desired diamide **8** was obtained in 86% yield along with monoamide **9** (13%). Interestingly, the present ester–amide transformation gave the best results under solvent-free conditions, although Sb(III)-templated macrolactamization was conducted in benzene or toluene under azeotropic reflux conditions.[14] The ester–amide transformation between **7** and **5** in toluene under azeotropic reflux conditions resulted in 6% yield.‡

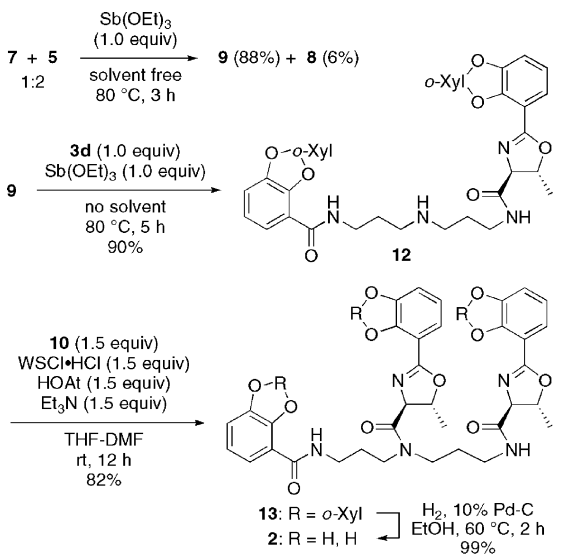
With the key synthetic intermediate **8** in hand, the stage was set for amide formation at the secondary amine in **8**. In contrast to the primary amines, the amide formation at the secondary amine in **8** was extremely difficult to promote. In fact, attempts with Sb(III)-catalyzed ester–amide transformation between **3d** and **8** failed under several reaction conditions, and resulted in decomposition of the oxazoline moiety of **3d** to give a mixture of byproducts.§ Therefore, we investigated the dehydrative condensation of **8** with carboxylic acid **10** which was prepared from **3d** in 97% yield [CsOH (2 equiv), acetone–MeOH–H_2O (2 : 1 : 1 v/v/v), 0 °C, 1 h]. Through the intensive examination of dehydrative condensation of **8** with **10**, we found that WSCI·HCl and HOAt (1.5 equiv) showed high activity for the condensation of **8** with **10** (1.1 equiv) and gave the desired triamide **11** in 98% yield. Finally, the three *o*-xylylene groups in **11** were



Scheme 3 Synthesis of fluvibactin (**1**). WSCI·HCl = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; HOAt = 1-hydroxy-7-azobenzotriazole.

easily removed by hydrogenolysis using 10% Pd/C to give **1** in 99% yield. Synthetic **1** showed ^{1}H and ^{13}C NMR spectra and HRMS data† that were identical to those reported for natural fluvibactin.[2] The longest linear sequence required 9 steps from 2,3-dihydroxybenzoic acid, with an overall yield of 65%.

Vibriobactin (**2**) could be synthesized from **9**, **3d** and **10** *via* a strategy similar to that for fluvibactin (**1**) (Scheme 4). Selective monoamide formation between **5** and **7** could also be performed using $Sb(OEt)_3$. When the reaction of a 1 : 2 mixture of **7** and **5** was conducted in the presence of $Sb(OEt)_3$ (1.0 equiv) under solvent-free conditions at 80 °C, monoamide **9** was obtained in 88% yield along with diamide **8** (6%). Monoamide **9** was then subjected to the second ester–amide transformation with an equimolar amount of **3d** using $Sb(OEt)_3$ (1.0 equiv), and gave diamide **12** in 90% yield. As in the case of fluvibactin, condensation of **12** with **10** (1.5 equiv) using WSCI·HCl and HOAt (1.5 equiv) successfully gave triamide **13** in 82% yield.¶ The final removal of the *o*-xylylene groups in **13** gave **2** in 99% yield.† The



Scheme 4 Synthesis of vibriobactin (**2**).

longest linear sequence required 9 steps from 2,3-dihydroxybenzoic acid, with an overall yield of 50%.

In conclusion, we have convergently synthesized fluvibactin (**1**) and vibriobactin (**2**) in respective overall yields of 65 and 50%. Our $MoO_2(TMHD)_2$-catalyzed dehydrative cyclization was found to be a powerful protocol for constructing the 2-(*o*,*m*-dihydroxyphenyl)oxazoline core at an early stage in the total synthesis. A cyclic *o*-xylylene group was very effective for protecting the catechol moieties. This compact protecting group helped the dehydrative cyclization of **6d** to proceed rapidly. $Sb(OEt)_3$-catalyzed ester–amide transformation of the primary amines was conducted under solvent-free conditions, and diamide **8** and monoamide **9** could be selectively synthesized just by appropriately setting the ratio of **5** and **7**. Furthermore, WSCI·HCl and HOAt successfully promoted amide formation at the secondary amines in **8** and **12** with carboxylic acid **10**. These successes significantly increased the overall yields of **1** and **2**.

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Notes and references

‡ Compound **7** was recovered in 50% yield. Monoamide **9** was obtained in 14% yield.
§ The structures of the byproducts were not determined.
¶ Attempts at triamide formation between **12** and **3d** using $Sb(OEt)_3$ failed, and led to decomposition of the oxazoline moiety of **3d**.

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