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## A CATALYTIC C–C BOND-FORMATION WITH MINIMAL USE OF PROTECTING GROUPS: CONSTRUCTION OF FUNCTIONALIZED ISOTETRONIC ACID DERIVATIVES

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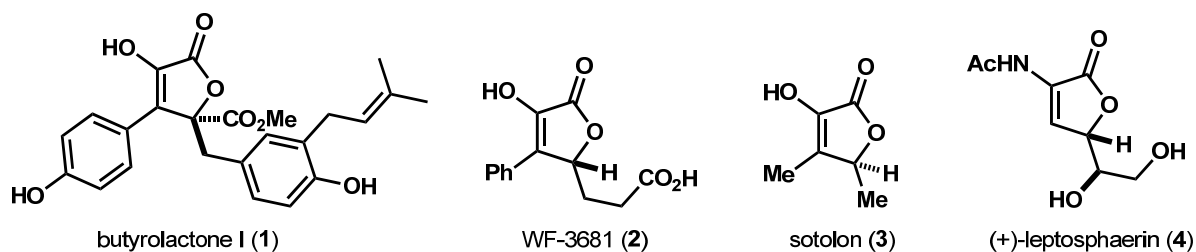
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*This paper is dedicated to Professor Victor Snieckus on the occasion of his 77th birthday.*

**Abstract** – A catalytic method to construct multi-functionalized isotetronic acids was developed using cyclic hemiacetals and pyruvic acid derivatives as substrates. The key to success was the combination of catalytic amounts of iron(III) trifluoroacetate and 2-mercaptopyridine. A catalytic asymmetric variant was also developed using 6,6'-dimethoxy-binaphthyl phosphate instead of 2-mercaptopyridine.

Isotetronic acids are an important class of natural compounds (Figure 1.) that exhibit various biological activities.<sup>1</sup> For example, butyrolactone I is a cyclin-dependent kinase inhibitor,<sup>1a</sup> and WF-3681 exhibits aldose reductase-inhibiting activity.<sup>1b</sup> This structural motif is also widely used as a versatile intermediate in the synthesis of complex natural products,<sup>2</sup> and there are several approaches to constructing the isotetronic acid skeleton.<sup>3-5</sup> The cross aldol reaction of aldehydes and pyruvic acid derivatives<sup>6</sup> is straightforward, and a highly efficient method of accessing various isotetronic acids. Organocatalysts are especially effective for the cross aldol reaction, affording high enantioselectivity even when only water is used as the solvent.<sup>5b-d</sup> To our knowledge, however, all reported examples used simple aldehydes as the substrate, giving products with non-functionalized alkyl or aromatic side chains. Here we report the first catalytic addition of pyruvic acid derivatives to cyclic hemiacetals,<sup>7</sup> affording isotetronic acids containing functionalized side chains. This method will be effective for synthesizing biologically active isotetronic

acids, because natural products and biologically active compounds usually have polar functional groups on their side chains.



**Figure 1.** Representative natural products containing isotetronic acid structure

We chose the reaction between phenylpyruvic acid (**5a**) and 6-membered lactol **6a** for optimization of the conditions. Considering the effectiveness of organocatalysts for isotetronic acid synthesis, we first examined L-proline and diphenylboric acid as catalysts (Table 1, entries 1 and 2). Diphenylboric acid gave only a trace amount of product **7aa**, however, and L-proline afforded no product at all. We then turned our attention to metal-based Brønsted base catalysts. Although lithium acetate and zinc acetate did not give promising results (entries 3 and 5), copper acetate and iron acetate afforded the desired product in 5% yield (entries 4 and 6). We then studied the counterion effects of the iron catalyst and found that an iron trifluoroacetate complex<sup>8</sup> gave superior reactivity (entry 7). To realize higher reactivity, several

**Table 1.** Catalyst screening

entry	catalyst	additive	yield (%) <sup>a</sup>
1	L-proline	—	0
2	Ph <sub>2</sub> B(OH)	—	3
3	LiOAc	—	0
4	Cu(OAc) <sub>2</sub> ·H <sub>2</sub> O	—	5
5	Zn(OAc) <sub>2</sub>	—	0
6	Fe(OAc) <sub>2</sub> (OH)	—	5
7 <sup>b</sup>	Fe <sub>3</sub> O(CF <sub>3</sub> COO) <sub>6</sub> (H <sub>2</sub> O) <sub>3</sub>	—	23
8 <sup>b</sup>	Fe <sub>3</sub> O(CF <sub>3</sub> COO) <sub>6</sub> (H <sub>2</sub> O) <sub>3</sub>	2,6-di- <i>tert</i> -butylpyridine	41
9 <sup>b</sup>	Fe <sub>3</sub> O(CF <sub>3</sub> COO) <sub>6</sub> (H <sub>2</sub> O) <sub>3</sub>	2-hydroxypyridine	78
10 <sup>b</sup>	Fe <sub>3</sub> O(CF <sub>3</sub> COO) <sub>6</sub> (H <sub>2</sub> O) <sub>3</sub>	2-mercaptopyridine	99
11 <sup>c</sup>	Fe <sub>3</sub> O(CF <sub>3</sub> COO) <sub>6</sub> (H <sub>2</sub> O) <sub>3</sub>	2-mercaptopyridine	24

<sup>a</sup>Determined by <sup>1</sup>H NMR using *t*BuOMe as an internal standard. <sup>b</sup>3.3 mol% of iron complex was used. <sup>c</sup>Water was used as solvent instead of DCE.

**Table 2.** Substrate scope of catalyzed isotetronic acid synthesis

$\text{R-CH}_2\text{-C(=O)-CH(OH)-COOH} + \text{electrophile} \xrightarrow[\text{DCE, 60 }^\circ\text{C}]{\text{Fe}_3\text{O}(\text{CF}_3\text{COO})_6(\text{H}_2\text{O})_3 (3.3 \text{ mol}\%), \text{2-mercaptopyridine (10 mol}\%)}$

entry	R	electrophile	product	yield (%) <sup>a</sup>	entry	R	electrophile	product	yield (%)
1	Ph 5a			78	8	Ph 5a	$(\text{HCHO})_n$ 6h		50
2	Ph 5a			99	9	Ph 5a			36
3	Ph 5a			58	10	Ph 5a			59
4	Ph 5a			48 (1.4:1) <sup>b</sup>	11 <sup>f</sup>	<i>p</i> -OH-C <sub>6</sub> H <sub>4</sub> 5b	6b		71
5 <sup>c</sup>	Ph 5a			64 (1:1) <sup>b</sup>	12	<i>o</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> 5c	6b		64
6 <sup>c</sup>	Ph 5a			21 (3.4:1) <sup>b</sup>	13 <sup>g</sup>	Me 5d	6b		12
7 <sup>d,e</sup>	Ph 5a			24 (11:1) <sup>b</sup>					

<sup>a</sup>Isolated yield. <sup>b</sup>Diastereomeric ratio was determined by crude <sup>1</sup>H NMR analysis. <sup>c</sup>DCE-MeCN (2:1) solvent was used. <sup>d</sup>DCE-dioxane-H<sub>2</sub>O (4:2:1) solvent was used. <sup>e</sup>Imidazole (10 mol%) was added. <sup>f</sup>MeCN solvent was used. <sup>g</sup>Fe(OH)<sub>3</sub> (10 mol%) was used as catalyst.

catalytic bases were added to increase the concentration of the aldehyde form from the hemiacetal form.<sup>9</sup> The addition of 2,6-di-*tert*-butylpyridine increased the reactivity (entry 8), and the addition of 2-hydroxypyridine further improved the reactivity (entry 9). Finally, we found that 2-mercaptopyridine was the best additive to afford **7aa** in 99% yield (entry 10).<sup>10</sup> Although reactivity decreased dramatically, the reaction could be conducted in water, which highlighted the tolerance of the catalytic system to free OH groups (entry 11). We assumed that the significant improvement in reactivity following the addition of 2-mercaptopyridine was due to its ambiphilic acid/base nature. The pyridine moiety of 2-mercaptopyridine can function as a Brønsted base to deprotonate the anomeric hydroxy group of **6a**, and the thiol moiety can function as a proton donor for the endocyclic oxygen atom (**A**). This synchronous activation of the lactol would facilitate the formation of the aldehyde form from the lactol form.<sup>11</sup>

Under these optimized conditions, we next investigated the substrate scope (Table 2).<sup>12</sup> Non-substituted 5-, 6-, and 7-membered simple lactols<sup>13</sup> were good substrates for this reaction, and the corresponding products were obtained in moderate to high yield (entries 1-3). Our examination of substituted lactols (entries 4-7) revealed that the position of the hydroxy groups markedly affected the reactivity. When an additional hydroxy group was introduced at the C4 position (**6e**), the reaction proceeded smoothly to afford product **7ae** in 64% yield (entry 5). A hydroxy group at the C2 position (**6f**), however, significantly hampered the reaction, and product **7af** was obtained in only 21% yield (entry 6). Notably, erythrose **6g** could be utilized as a substrate for this reaction, producing multi-hydroxylated product **7ag** in 24% yield with 11:1 diastereoselectivity. This result indicated that the current reaction conditions could be applied to a facile synthesis of multi-functional isotetronic acids, although the yield requires further improvement. We also investigated oligomerized aldehydes (entries 8-10), and the products were obtained in moderate yield. The scope of the pyruvic acid derivatives was also examined. A free phenol moiety did not affect the reaction (entry 11), which again supported the functional group tolerance of this reaction. The sterically demanding substrate **5c** containing an *ortho*-nitrophenyl group also reacted without problem. An  $\alpha$ -methylpyruvic acid derivative, however, did not react at all under the optimized conditions. Further investigation of iron sources indicated that the use of  $\text{Fe}(\text{OH})_3$ <sup>14</sup> instead of the iron trifluoroacetate complex afforded the product in low yield (entry 13). The use of pyruvic acid itself did not afford the desired product even in the presence of  $\text{Fe}(\text{OH})_3$ .

We next turned our attention to the development of an asymmetric variant. Based on the assumed mechanism of 2-mercaptopyridine to facilitate the conversion of the lactol form to the aldehyde form (Table 1, **A**), the resulting aldehyde would coordinate to 2-mercaptopyridine during the subsequent C-C bond-formation step. Hence, chiral 2-mercaptopyridine analogs would lead to asymmetric induction. We selected binaphthyl phosphates as candidates for such analogs.<sup>15</sup> A simple binaphthyl phosphate **8a** was

examined first (Table 3). Although the yield was low, enantioselectivity was high (78% ee).<sup>16</sup> In contrast, the use of (2*R*,3*R*)-tartaric acid, (*R*)-BINOL, and (*R*)-camphorsulfonic acid as asymmetric catalysts produced no significant enantioselectivity (entries 2-4). Both reactivity and enantioselectivity were dramatically affected by the electronic characteristics of the chiral phosphates. Introduction of electron-withdrawing bromide atoms at the 6,6'-positions of the binaphthyl core (**8b**) dramatically decreased the yield and enantioselectivity to 10% yield and 25% ee, respectively (entry 5). In contrast, introduction of electron-donating methoxy groups (**8c**) improved the yield and enantioselectivity (entry 6).

**Table 3.** Screening of chiral acid catalysts

entry	additive	yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	<b>8a</b>	17	78
2	(2 <i>R</i> ,3 <i>R</i> )-tartaric acid	10	4
3	( <i>R</i> )-BINOL	18	0
4	( <i>R</i> )-camphor-10-sulfonic acid	4	—
5	<b>8b</b>	10	25
6	<b>8c</b>	44 <sup>c</sup>	89

R = H: **8a**  
R = Br: **8b**  
R = OMe: **8c**

<sup>a</sup>Determined by <sup>1</sup>H NMR using *t*BuOMe as an internal standard. <sup>b</sup>Enantiomeric excess was determined by chiral HPLC. <sup>c</sup>Isolated yield.

The substrate scope of the asymmetric reaction was examined under the optimized conditions (Table 4).<sup>12</sup> Consistent with the results of the racemic variant, 5-membered lactol **6b** exhibited high reactivity and enantioselectivity (70% yield and 91% ee). In the case of 7-membered lactol **6c**,<sup>13</sup> however, the enantiomeric excess was significantly decreased to 22% ee. The sharp difference in enantioselectivity depending on the substrate ring size is likely due to the relative concentration between the lactol form and the aldehyde form. The 7-membered lactol **6c** preferred the aldehyde form rather than the lactol form. This preference was opposite that of the 5- and 6-membered lactols **6a** and **6b**. Thus, the background reaction without interaction of the chiral phosphate proceeded smoothly in the case of **6c**, resulting in low enantioselectivity. It is noteworthy that 3-phenyl substituted lactol **6d** reacted more smoothly under the asymmetric reaction conditions than under the racemic reaction conditions (Table 2, entry 4 vs. Table 4, entry 4). This result indicates that proper selection of the lactol-activating agent based on each substrate is important to realize high reactivity. The scope of pyruvic acid derivatives was also examined using

5-membered lactol **6b**. Pyruvates **5b** and **5c** containing *p*-OH and *o*-NO<sub>2</sub> substituents on the aromatic rings, respectively, exhibited high reactivity, but only moderate enantiomeric excess (entries 5 and 6). When  $\alpha$ -methyl substituted pyruvic acid **5d** was used, the yield was only 19% and the enantiomeric excess was 32% (entry 7).

**Table 4.** Substrate scope under catalytic asymmetric reaction conditions

6,6'-diMeO-binaphtyl phosphate (**8c**)

entry	R	electrophile	product	yield (%) <sup>a</sup>	ee (%) <sup>b</sup>	entry	R	electrophile	product	yield (%)	ee (%)
1	Ph <b>5a</b>			70	91	5	<i>p</i> -OH-C <sub>6</sub> H <sub>4</sub> <b>5b</b>			82	64
2	Ph <b>5a</b>			44	89	6	<i>o</i> -NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> <b>5c</b>			82	57
3	Ph <b>5a</b>			58	22	7 <sup>d</sup>	Me <b>5d</b>			19	32
4	Ph <b>5a</b>			68 (1.2:1) <sup>c</sup>	74/85						

<sup>a</sup>Isolated yield. <sup>b</sup>Enantiomeric excess was determined by chiral HPLC. <sup>c</sup>Diastereomeric ratio was determined by crude <sup>1</sup>H NMR analysis. <sup>d</sup>Fe(OH)<sub>3</sub> was used as catalyst.

In conclusion, we developed a novel catalytic method to construct functionalized isotetronic acid derivatives. The combined use of iron complex and 2-mercaptopyridine was crucial to obtain high reactivity. In addition, the developed method could be extended to an asymmetric variant by using chiral

binaphthyl phosphate **8c** instead of 2-mercaptopyridine. Further investigation to expand the substrate scope of this protecting group-minimal C–C bond-formation is on-going in our laboratory.

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  12. Typical procedure of the nucleophilic addition of  $\alpha$ -keto acids to lactols;  
racemic reaction: Tetrahydrofuran-2-ol (**6b**) (12.2  $\mu$ L, 150  $\mu$ mol) was added to a suspension of iron trifluoroacetate complex (3.1 mg, 3.3  $\mu$ mol), phenylpyruvic acid (**5a**) (16.4 mg, 100  $\mu$ mol), and 2-mercaptopyridine (1.1 mg, 10  $\mu$ mol) in dry DCE (400  $\mu$ L). This suspension was stirred for 24 h at 60 °C. To this mixture, DCE (2 mL), MeOH (500  $\mu$ L) and DOWEX 50WX8 (400 mg) were added, and the mixture was stirred for additional 30 min. The mixture was filtered, and the filtrate was evaporated. The crude product was purified by flash chromatography (silica gel, DCM/MeOH = 100/1 to 50/1) to afford **7ab** (18.3 mg, 78% yield) as white solid.  
asymmetric reaction: Tetrahydrofuran-2-ol (**6b**) (12.2  $\mu$ L, 150  $\mu$ mol) was added to a suspension of iron trifluoroacetate complex (3.1 mg, 3.3  $\mu$ mol), phenylpyruvic acid (**5a**) (16.4 mg, 100  $\mu$ mol) and **8c** (8.2 mg, 20  $\mu$ mol) in dry DCE (400  $\mu$ L). This suspension was stirred for 24 h at 60 °C. To this mixture, DCE (2 mL), MeOH (500  $\mu$ L) and DOWEX 50WX8 (400 mg) were added, and the mixture was stirred for additional 30 min. The mixture was filtered, and the filtrate was evaporated. The crude product was purified by flash chromatography (silica gel, DCM/MeOH = 100/1 to 50/1) to afford **7ab** (16.4 mg, 70% yield) as white solid. Enantiomeric excess was determined to be 91% by chiral HPLC analysis. DICEL CHIRALPAK IC, hexane/2-propanol 9/1, 1 mL/min.  $t_R$  28.2 min. (major), 34.9 min. (minor).  $[\alpha]_D^{25}$  -84.4 ( $c$  0.91, MeOH) for 76% ee.
  13. 7-Membered (**6c**) lactol mainly exists as aldehyde form.



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16. Absolute configuration was determined by the Mosher ester analysis (I. Ohtani, T. Kusumi, Y. Kashman, and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092) of **11**, which was derivatized from **7ab** in 4 steps as shown below. Esterification of **10** with (*R*)- and (*S*)-MTPA-Cl gave the (*S*)- and (*R*)-MTPA esters (**11a** and **11b**) respectively.

