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PII:	S0040-4039(20)30742-5
DOI:	https://doi.org/10.1016/j.tetlet.2020.152275
Reference:	TETL 152275
To appear in:	Tetrahedron Letters
Received Date:	16 June 2020
Revised Date:	14 July 2020
Accepted Date:	19 July 2020



Please cite this article as: Takabatake, T., Fujiwara, K., Okamoto, S., Kishimoto, R., Kagawa, N., Toyota, M., Discovery of orthogonal synthesis using artificial intelligence: Pd(OAc)<sub>2</sub>-catalyzed one-pot synthesis of benzofuran and bicyclo[3.3.1]nonane scaffolds, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet. 2020.152275

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# Discovery of orthogonal synthesis using artificial intelligence: Pd(OAc)<sub>2</sub>catalyzed one-pot synthesis of benzofuran and bicyclo[3.3.1]nonane scaffolds

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#### ARTICLE INFO

Article history: Received Received in revised form Accepted Available online

*Keywords:* Artificial intelligence Pd(OAc)<sub>2</sub> catalyst benzofuran bicyclo[3.3.1]nonane

#### ABSTRACT

A synthetic route for the common intermediate, methyl 2-formylbenzofuran-7-carboxylate (7a), to efficiently assemble three bioactive benzofurans 4-6 was explored using the artificial intelligence system SYNSUP. Among the routes proposed by SYNSUP, we investigated a three-step synthesis of 7a using methyl 4-ally-3-oxohept-6-enoate (10). A new catalytic reaction was found in which 7a was directly obtained from 10 in a single step with a yield of 24%. It was found that this chemical yield could be increased to 74% when methyl 3-allyl-2-hydroxybenzoate (9a), an intermediate of the above one-pot transformation, was subjected to the catalytic process. In addition, in this catalytic process, 8a (76%) and 11 (77%) were each selectively synthesized from 10 by changing only the solvent. Therefore, we created a novel orthogonal synthesis of methyl 2-methylbenzofuran-7-carboxylate (8a) and methyl 9-oxobicyclo[3.3.1]nona-3,6-diene-1-carboxylate (11). Finally, the total syntheses of bioactive benzofurans 4-6 were completed smoothly using 7a and 8a.

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### Introduction

Artificial intelligence (AI) is defined as the ability of machines to interpret data, make decisions, and carry out tasks in a way similar to humans.<sup>1</sup> AI is already widely used in many commercial and scientific fields. Algorithms predict what we like, anticipate our behavior, and diagnose medical conditions with impressive speed. AI is also being used to identify diseases, and can even outperform human experts when it comes to diagnosing disease.<sup>2</sup> We are entering a world where conversation with machines is going to be both enlightening and more efficient in many areas. How is AI going to change our world? There are no certain answers to that question at the present time. In contrast, the first introduction of AI into the field of synthetic organic chemistry was more than 50 years ago, however, the evolution of AI in this field has been extremely slow.<sup>3</sup> One of the reasons is that it takes a significant amount of time to experimentally evaluate proposed synthetic routes using AI. Our laboratory has been engaged in the evolution of SYNSUP (an AI program)<sup>4</sup> since 2007. Recently, we have succeeded in the stereoselective synthesis of SCH 47949 (3), which inhibits the absorption of cholesterol from the small intestine, using SYNSUP (Scheme 1).<sup>5</sup> After tuning a part of the reaction substrate structure proposed by SYNSUP, basic treatment of **1** in the presence of two silulation reagents provided *trans*  $\beta$ lactam 2 in a stereoselective manner. Finally, the five-step transformation of 2 proceeded smoothly and the desired SCH 47949 (3) was obtained in a reasonable chemical yield (Scheme 1). It is worth noting that the present functional group manipulation for the synthesis of 3 was identical to the synthetic routes proposed by SYNSUP.





As part of our drug synthesis program using SYNSUP, we embarked on the creation of a potential intermediate to concisely synthesize bioactive benzofuran analogs. Not surprisingly, some rather simple benzofuran derivatives showed a wide variety of significant bioactivities. Among them, we especially became interested in unnatural bioactive products **4-6** (Figure 1).<sup>6</sup>



Figure 1. Structures of known bioactive benzofuran analogs 4-6.

routes were searched using STINSOP. As a result, 50 synthetic routes were proposed in a short time (see Supporting Information-1). We attempted to determine a method of synthesis of **7a** from methyl 4-allyl-3-oxohept-6-enoate (**10**), since this proposed route, shown below, involved a catalytic reaction reported by our laboratory (Scheme 2).<sup>7</sup>



Scheme 2. Retrosynthetic route for 7a proposed by SYNSUP.

#### **Results and Discussion**

First, we investigated the transformation of **10** into **9a** using Orellana's protocol.<sup>8</sup> A PdCl<sub>2</sub>(MeCN)<sub>2</sub>-catalyzed cyclization of **10** followed by oxidation with two equivalent chloranil provided **9a** in an 18% yield, which was subjected to PdCl<sub>2</sub>-catalyzed cyclization<sup>9</sup> to afford **8a** (62%). Finally, an allylic oxidation of **8a** was performed with IBX<sup>10</sup> to give the desired intermediate **7a** in a 9% yield. Accordingly, the total yield of the preparation of **7a** from **10** was only 1%. The extremely low chemical yield of the IBX oxidation at the allylic position in **8a** was the biggest problem with this process, and the transformation of **10** to **9a** was the first stumbling block. Incidentally, an allylic oxidation of **8a** using SeO<sub>2</sub> was completely unsuccessful (Scheme 3).

	(1) 10 mol % PdCl <sub>2</sub> (MeCN) <sub>2</sub>		2 mol % PdCl <sub>2</sub>			
	10 mol % CuCl <sub>2</sub>		3 equiv Cu(OAc) <sub>2</sub>		5 equiv IBX	-
10	10 mol % HCl	9a	3 equiv LiCl	8a	80 °C 24 b	/a
	70 °C, 48 h	18%	100 °C, 41 h	62%	00 0,2411	9%
	(2) 2 equiv chloranil	(z steps)				
	100 °C, 18 h					

Scheme 3. Linear synthesis of 7a from 10.

Next, we applied  $Pd(OAc)_2$ -catalyzed cycloaromatization<sup>7</sup> to methyl 4-allyl-3-oxohept-6-enoate (**10**). Perhaps because the reactivity of substrate **10** to Pd (II) was extremely high, subtle differences in the reaction solvent, additive, reaction temperature, reaction time, and work-up method greatly affected the isolation yields of each product and the reproducibility of this process. Therefore, we tested the reaction conditions using 10 mol % Pd(OAc)<sub>2</sub> with a purity of 99.98% for the following investigations. Among various studies on the reaction conditions, some characteristic results are summarized in Table 1. When this reaction was carried out without either Cu(OAc)<sub>2</sub> or oxygen e-proofs ned.

When substance 10 was treated with 10 mol %  $Pd(OAc)_2$  in dimethyl sulfoxide (DMSO) in the presence of 20 mol % Cu(OAc)<sub>2</sub> at room temperature under one atmosphere of oxygen for 21 hours, methyl 9-oxobicyclo[3.3.1]nona-3,6-diene-1carboxylate  $(11)^{11}$  was obtained in a 43% yield, together with a 14% yield of methyl 3-allyl-2-hydroxybenzoate (9a) and an 8% methyl 3-allyl-2-hydroxycyclohexa-1,4-diene-1yield of carboxylate (13) (Table 1, entry 1). This result suggested that both 9a and 11 were produced from the common intermediate 13. Samples were continuously taken from the reaction and monitored by TLC analysis. As a result, the first catalytic cyclization consumed approximately 7 hours and only the intermediate 13 was obtained in a 62% yield (Table 1, entry 2). To obtain methyl 2methylbenzofuran-7-carboxylate (8a) as a major product, the amount of Cu(OAc)<sub>2</sub> was increased to 3 equivalents.<sup>12, 13</sup> Unfortunately, only 2-hydroxybenzoate 9a was isolated in a 78% yield (Table 1, entry 3). At this point, we expected that heating must be required for the cyclization of phenol 9a. On heating 9a with 10 mol % Pd(OAc)<sub>2</sub> and 3 equivalents of Cu(OAc)<sub>2</sub> at 60 °C, it was found that the target molecule, methyl 2-formylbenzofuran-7-carboxylate (7a), was directly produced, although at a low yield (24%), along with a 13% yield of methyl 2-methylbenzofuran-7carboxylate (8a) and a 21% yield of bicyclic compound 11 (Table 1, entry 4). The structure of 7a was determined by NMR techniques (COSY, HMBC, HMQC). To efficiently obtain 7a, the catalytic amount of Pd(OAc)<sub>2</sub> was increased to 20 mol %. Interestingly, not only were the chemical yields of 7a, 8a, and 11 decreased, but methyl 2H-chromene-8-carboxylate (12) was also produced via a 6-endo-trig cyclization mode in a 10% yield (Table 1, entry 5).<sup>14</sup> When the reaction solvent was changed to MeCN, only benzofuran 8a was obtained, in a 44% yield (Table 1, entry 6). The reaction was conducted using 10 mol % Pd(OAc)<sub>2</sub> and 1 equivalent Cu(OAc)<sub>2</sub> in MeCN at 50 °C in the presence of 2 equivalent DMSO<sup>13</sup> to furnish benzofuran 8a in a 76% yield (Table 1, entry 7). To our surprise, changing MeCN to THF gave rise to bicyclo[3.3.1]nonane 11 in a 77% yield as a single isomer (Table 1, entry 7). It is worth mentioning that only Snider's group has reported the one-step preparation of 11 from 10 using radical reaction conditions; however, the chemical yield was 11% as a 2:1 mixture of the olefin isomers.<sup>11</sup> Because bicyclic compound 11 is highly functionalized, 11 could be used as a synthon for the



Table 1. Cyclization of methyl 4-allyl-3-oxohept-6-enoate (10).

ontra	Cu(OAc) <sub>2</sub> (mol %) solevent	Additive	temp	time	yield (%)						
entry		solevent	(equiv)	(°C)	(h)	7a	8a	9a	11	12	13
1	20	DMSO	none	Rt	21	0	0	14	43	0	8
2	20	DMSO	none	Rt	7	0	0	0	0	0	62
3	300	DMSO	none	Rt	37	0	0	78	0	0	0
4	300	DMSO	none	60	23	24	13	0	21	0	0
5 <sup>a</sup>	300	DMSO	none	60	24	10	10	0	5	10	0
6	300	MeCN	none	60	22	0	44	0	0	0	0
7	100	MeCN	DMSO (2)	50	26	0	76	0	0	0	0
8	20	THF	DMSO (2)	50	20	0	0	11	77	0	0
9	20	THF	none	50	24	0	0	16	19	0	0
10 <sup>b</sup>	None	DMSO	none	60	24	0	0	0	0	0	53
11 <sup>c</sup>	none	DMSO	none	60	24	0	0	0	0	0	65

 (a) 20 mol % Pd(OAc)<sub>2</sub> was used.
 (b) 10 mol % Pd(TFA)<sub>2</sub> was used.
 (c) 10 mol % PdCl<sub>2</sub> was used. synthesis of terpenes, such as upial<sup>15</sup> and trifarienols.<sup>16</sup> It is compound **14a**, but neither compound produced 2obvi Journal Pre-proofs

to Pd(II) (Table 1, entry 9). Both Pd(TFA)<sub>2</sub> and PdCl<sub>2</sub> provided methyl 3-allyl-2-hydroxycyclohexa-1,4-diene-1-carboxylate (**13**), respectively, in a moderate yield (Table 1, entries 10 and 11). The cyclization reaction using other solvents such as DMF, CH<sub>2</sub>Cl<sub>2</sub>, and 1,4-dioxane was also investigated, but the chemical yield of each product was drastically reduced.

Since the direct conversion of 10 into 7a was difficult, a detour route via the easily obtainable 9a was examined. Scheme 4 summarizes the results of a Pd(OAc)<sub>2</sub>-catalyzed one-pot synthesis of 2-formylbenzofuran 7a using 2-allylphenol 9a and the substrate scope. The electron-withdrawing group next to the hydroxyl group in 9a resulted in an improvement in yield. For example, when 9a was heated with 10 mol % Pd(OAc)<sub>2</sub> and 20 mol % Cu(OAc)<sub>2</sub> at 100 °C in DMSO under one atmosphere of oxygen for 23 hours, 7a was isolated in a 73% yield, together with 8a (11%) and acetate 14a (2%). Substrate 9b with an electron-withdrawing chloride at the para position of the benzene ring afforded the desired aldehyde 7b, in a 68% yield, as well as 8b (13%) and 14b (3%). Unsubstituted 2-allylphenol 9c furnished 7c in a moderate yield, and also produced 8c (10%) and 14c (3%). On the other hand, substrate 9d with an electron-donating group at the ortho position of the benzene ring produced 7d in a 52% yield with 8d (14%) and 14d (5%). The methylenedioxy group in 9e survived under the reaction conditions to give rise to 7e (51%), 8e (17%), and 14e (6%). In this reaction, the electron-donating group tends to reduce the yield. All of the above products were easily isolated by flash column chromatography. It is worth emphasizing that there are no reports of a one-step conversion of 2-allylphenols 9 to 2formylphenols 7.

Scheme 4. Pd(OAc)<sub>2</sub>-catalyzed one-pot synthesis of 2-formylbenzofurans 9a-e.



Additional experiments were conducted as shown below to estimate the reaction mechanism of the cyclization reaction of compound **10**. By changing the reaction conditions, compounds **8a** and **11** can clearly be produced separately from the reaction intermediate **13** (Scheme 5). Additionally, the reaction conditions shown in entry 4 of Table 1 were applied to compound **8a** and



Scheme 5. Orthogonal cyclizations of 1,4-cyclohexadiene 13.



#### Scheme 6. Transformational examination of 8a and 14a.

According to the experimental results, we proposed the reaction mechanism shown in Scheme 7. 2-Allylphenol 9a and bicyclic compound 11 were produced via the monocyclization intermediate 13.<sup>17</sup> By properly selecting the reaction temperature and the reaction solvent, 9a and 11 can be produced separately. When the catalytic reaction of 10 was conducted in MeCN at 50 °C in the presence of 2 equivalents of DMSO, 8a was obtained via 9a as the sole product. The initial target molecule 7a was directly obtained from acyclic compound 10, although at a low yield of 24%. Based on the experimental results of Schemes 4-6, we considered how 7a was generated. After a regioselective acetoxypalladation on the olefinic moiety in 9a, intramolecular oxypalladation of 15 proceeded to lead to 16 as a mixture of stereoisomers.<sup>18</sup> Reductive elimination of 16 gave diacetate 18, which was hydrolyzed to 7a.<sup>19</sup> On the other hand, generation of the palladium-hydride species 17 followed by reductive elimination gave 18, which isomerized to thermodynamically stable 14a.<sup>19, 18b.</sup> The Pd(0) species produced in this process were reoxidized to Pd(OAc)<sub>2</sub> by Cu(OAc)<sub>2</sub> in the presence of oxygen. Additionally, since there might be oxidizing agents generated in the system, we cannot rule out that Pd(IV) is involved in the reaction mechanism.



Scheme 7. Plausible reaction mechanism.

With the desired compounds **7a** and **8a** in hand, we attempted to complete the total syntheses of bioactive benzofurans **4-6**. Ester

aldehyde 7a, obtained from 10 by a two-step process in 57% over Journal

oxidation to arrord dialdenyde **20** (80% for two steps). Subsequent dimethylation and MnO<sub>2</sub> oxidation gave rise to diacetate **4** in an 88% yield through two steps. 2-Methylbenzofuran **8a** was transformed into the corresponding tropine ester **5** in an 85% overall yield utilizing hydrolysis followed by a Schottem– Baumann reaction. On the other hand, another tropine ester, **6**, was synthesized via **21**. Acidic reduction of the furan component in **8a** was conducted at 0 °C using TFA and Et<sub>3</sub>SiH to furnish **21** in an 81% yield. Hydrolysis of **21** and a Schottem–Baumann reaction provided tropine ester **6** as a mixture of two diastereoisomers in an 80% overall yield. The spectroscopic properties of synthetic benzofurans **4-6** were identical with those reported for **4-6**, respectively (Scheme 8).<sup>6</sup>



Scheme 8. Total syntheses of bioactive benzofurans 4-6.

#### Acknowledgements

We would like to thank Sumitomo Chemical for allowing us to use SYNSUP. We would also like to thank Professor Barry M. Trost (Stanford University) for the fruitful discussions regarding the reaction mechanism.

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