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## Efficient Construction of Drug-like Bispriocyclic Scaffolds via Organocatalytic Cycloadditions of $\alpha$ -Imino $\gamma$ -Lactones and Alkylidene Pyrazolones

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**TITLE:**

Efficient Construction of Drug-like Bispriocyclic Scaffolds via Organocatalytic Cycloadditions of  $\alpha$ -Imino  $\gamma$ -Lactones and Alkylidene Pyrazolones

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**KEYWORDS:**

asymmetric synthesis, organocatalysis, bispriocyclic compounds, cycloaddition, lactones, pyrazolones

**SUMMARY:**

Enantiomerically enriched bispiro[ $\gamma$ -butyrolactone-pyrrolidin-4,4'-pyrazolone] skeletons are asymmetrically synthesized through a simple organocatalytic 1,3-dipolar cycloaddition reaction.

**ABSTRACT:**

Bispriocyclic scaffolds are one of the important structural subunits in many natural products that exhibit diverse and attractive biological activities. Recently, we have developed an efficient organocatalytic strategy, which provides facile access to a variety of enantiomerically enriched bispiro[ $\gamma$ -butyrolactone-pyrrolidin-4,4'-pyrazolone] skeletons. In this paper, we demonstrate a detailed protocol for the asymmetric synthesis of drug-like bispriocyclic compounds with two spirocyclic carbon centers via an organocatalytic 1,3-dipolar cycloaddition reaction. Spirocyclization synthons  $\alpha$ -imino  $\gamma$ -lactones and alkylidene pyrazolones are prepared first, which are then subjected to a cycloaddition reaction in the presence of a bifunctional squaramide organocatalyst to afford the desired bispriocycles in high yields and excellent stereoselectivities. Chiral high-performance liquid chromatography (HPLC) is carried out to determine the enantiomeric purity of the products, and the d.r. value is examined by proton nuclear magnetic resonance (<sup>1</sup>H NMR). The absolute configuration of the product is assigned according to an X-ray crystallographic analysis. This synthetic strategy allows scientists to prepare a diversity of bispriocyclic scaffolds in high yields and excellent diastereo- and enantioselectivities.

**INTRODUCTION:**

Chiral spirocyclic compounds found prevalent in natural products, chiral ligands and

organometallic complexes have emerged as attractive synthetic targets due to their structural complexity and biological activity<sup>1–3</sup>. Specifically, bispirocyclic scaffolds, featured by three rings with two rigid spirocenters, are structural subunits in many natural products with important biological activities<sup>4,5</sup>. Consequently, the construction of compounds with stereocontrolled, optically pure bispirocyclic skeletons has drawn great attention over the last few decades. A large number of spirocyclic compounds and their derivatives have been synthesized successfully through organometallic approaches and organocatalytic approaches, for example, asymmetric cycloadditions such as 1,3-dipolar cycloadditions and Diels–Alder reactions<sup>6–8</sup>. However, these molecules are mostly monospirocyclic structures, while bispirocyclic structures are less reported on and limited to the construction of indole-based bispirocycles.

In order to obtain more structurally diverse bispirocyclic compounds, the versatility of cycloaddition synthons for the asymmetric construction of spirocyclic centers has been explored<sup>9–11</sup>. Especially with bifunctional squaramide organocatalysts, azomethine ylide<sup>12–14</sup>, such as  $\alpha$ -imino  $\gamma$ -lactones, and dipolarophiles, such as alkylidene pyrazolones<sup>15–17</sup>, are able to undergo a simple 1,3-dipolar cycloaddition to construct bispirocyclic skeletons with multiple stereocenters, making them the perfect spirocyclization synthons (**Figure 1**). After the optimization of the structure of organocatalyst and reaction solvent, this cycloaddition process efficiently affords the desired product with high yields and excellent enantio- and diastereoselectivity. Moreover, this reaction exhibits a relatively high structural tolerance on a broad scope of cycloaddition synthons with diverse functional groups<sup>18</sup>. This new method provides an efficient access to a variety of highly functionalized drug-like compounds with two quaternary spirocenters via a simple organocatalytic cycloaddition, shining lights on its application in the structural diversity-oriented synthesis of this intriguing class of compounds.

## PROTOCOL:

CAUTION: Please consult all relevant material safety data sheets (MSDS) before use. Chemicals and solvents used were of reagent grade and were used without further purification. All reactions involving air or moisture-sensitive reagents or intermediates were performed under an argon atmosphere.

### 1. Preparation of $\alpha$ -Arylidene Pyrazolinone Species

#### 1.1. Preparation of pyrazolones

1.1.1. Add 40 mL of glacial acetic acid to a 250 mL round-bottom flask from a graduated cylinder at room temperature. Stir the solution while adding hydrazine (1 equivalent, 1.58 mol/L) and methyl acetoacetate (1 equivalent, 1.58 mol/L). Equip the flask with a reflux condenser.

NOTE: This concentration is used because a lower concentration leads to a slower reaction rate.

1.1.2. Heat the reaction flask to 120 °C in an oil bath while stirring for 3 h. After cooling the reaction flask down to ambient temperature, remove the magnetic stir bar, using a stir bar

retriever. Concentrate the reaction mixture, using a rotary evaporator at 60 °C. Avoid spilling the reaction mixture because of negative pressure.

1.1.3. Add 20 mL of deionized water to the reaction flask and transfer the solution into a separatory funnel. Extract the aqueous layer 3x with ethyl acetate (30 mL). Combine the organic layers in the separatory funnel and wash them 2x with brine (50 mL).

1.1.4. Dry the combined organic layers over anhydrous sodium sulfate for 1 h and, then, remove the sodium sulfate by gravity filtration.

1.1.5. Remove the solvent on a rotary evaporator at reduced pressure and at 35 °C.

1.1.6. After removing all the solvent, apply the pyrazolone species when performing section 4.

## 1.2. Preparation of $\alpha$ -Arylidiene Pyrazolinones

1.2.1. Add pyrazolone (1 equivalent, 0.49 mol/L), benzaldehyde (1 equivalent, 0.49 mol/L), magnesium oxide (0.5 g, 0.6 equivalent), and a magnetic stir bar into an oven-dried 100 mL round-bottom flask under N<sub>2</sub> atmosphere.

1.2.2. Add anhydrous acetonitrile (40 mL) to the reaction flask, using an airtight syringe, and then, equip the flask with a reflux condenser. Heat the reaction flask to 120 °C in an oil bath while stirring for 12 h.

1.2.3. Monitor the progress of the reaction by thin layer chromatography (TLC), using petroleum ether:ethyl acetate (2:1 [v/v], retention factor R<sub>f</sub> = 0.86) as an eluent.

1.2.4. After the complete consumption of pyrazolone, cool the reaction flask down to room temperature. Filter off the magnesium oxide through a Celite plug.

1.2.5. Remove the excess acetonitrile by using a rotary evaporator under reduced pressure and at 35 °C. Purify the residue by column chromatography on silica gel eluting with petroleum ether:ethyl acetate (10:1 to 8:1 [v/v]) to provide the crude product.

1.2.6. Add the crude product into a 100 mL Erlenmeyer flask equipped with a magnetic stir bar, and then, add a minimum volume of 95% ethanol. Place the flask on a hot plate and bring it to a gentle boil until the entire solid is just dissolved. Take the flask off the hot plate and cool it slowly without any agitation.

NOTE: When the mixture is cooled to room temperature, the corresponding  $\alpha$ -arylidiene pyrazolinone is formed as pure crystals.

## 2. Synthesis of $\alpha$ -imino $\gamma$ -lactones species

2.1. Add  $\alpha$ -amino- $\gamma$ -butyrolactone hydrobromide (1 equivalent, 0.41 mol/L), magnesium sulfate (1 equivalent, 0.41 mol/L), triethylamine (1 equivalent, 0.41 mol/L), and a magnetic stir bar into an oven-dried 100 mL round-bottom flask under N<sub>2</sub> atmosphere.

2.2. Add 36 mL of anhydrous dichloromethane to the reaction flask, using an airtight syringe. Stir the reaction mixture at room temperature for 1 h. Add the corresponding thiophene-2-carbaldehyde (1.1 equivalent, 0.45 mol/L) to the solution and stir for another 12 h.

2.3. Monitor the progress of the reaction by TLC, using petroleum ether:ethyl acetate (4:1 [v/v]) as an eluent until the complete consumption of the lactone species has occurred, and then, filter off the reaction mixture, using a filter paper with a pore size of 30–50  $\mu$ m.

2.4. Add 5 mL of deionized water to the resulting mixture and separate the organic layer from the aqueous phase. Extract the aqueous phase 2x with dichloromethane (30 mL). Combine the organic layers in the separatory funnel and wash them 2x with brine (50 mL).

2.5. Dry the combined organic layers over anhydrous sodium sulfate for 1 h, and then, remove the sodium sulfate by gravity filtration. Remove the solvent on a rotary evaporator at reduced pressure and at 35 °C.

2.6. After removing all the solvent, apply the  $\alpha$ -Imino  $\gamma$ -lactones species when performing section 4.

### 3. Synthesis of bifunctional squaramide catalyst C5<sup>19</sup>

NOTE: For the synthesis of organocatalysts 5C, see Figure 2.

#### 3.1. Preparation of 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (compound 1)

3.1.1. Add 3,4-dimethoxycyclobut-3-ene-1,2-dione (1 equivalent, 0.63 mol/L), 3,5-bis(trifluoromethyl)aniline (1.1 equivalent, 0.69 mol/L), 20 mL of methanol, and a magnetic stir bar into an oven-dried 100 mL round-bottom flask under N<sub>2</sub> atmosphere.

3.1.2. Stir the mixture at room temperature for 48 h. The formation of yellow precipitate is an indication that the reaction is taking place.

3.1.3. Filter the reaction solution through a funnel fitted with filter paper and wash the solid product 3x with methanol (15 mL). Dry the yellow solid in vacuo overnight to afford the final products as yellow solid.

#### 3.2. Synthesis of catalyst C5

3.2.1. Add 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione

(compound 1; 1 equivalent, 0.2 mol/L) and (S)-(6-methoxyquinolin-4-yl)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methanamine (compound 2; 1 equivalent, 0.2 mol/L) and a magnetic stir bar into a 25 mL round-bottom flask under N<sub>2</sub> atmosphere.

3.2.2. Add anhydrous dichloromethane (5 mL), using an airtight syringe. Stir the mixture at room temperature for 48 h.

3.2.3. Monitor the progress of the reaction by TLC, using dichloromethane:methanol (10:1 [v/v], R<sub>f</sub> = 0.49) as an eluent. After the reaction is completed, concentrate the reaction mixture, using a rotary evaporator at 40 °C.

3.2.4. Purify the residue by column chromatography on silica gel eluting with dichloromethane:methanol (20:1 [v/v]) to provide the desired product.

#### 4. Asymmetric synthesis of bispirocyclic compounds

4.1. Dry a 50 mL round-bottom reaction flask containing a magnetic stir bar. Remove the flask from the oven and cool it to room temperature by blowing on it with inert gas before use.

4.2. Add  $\alpha$ -arylidene pyrazolinone (1 mmol, 1 equivalent, 0.1 mol/L) and  $\alpha$ -imino  $\gamma$ -lactones (1.2 mmol, 1.2 equivalent, 0.12 mol/L) to the 50 mL round-bottom flask under N<sub>2</sub> atmosphere.

4.3. Add anhydrous ethyl ether (10 mL) to the reaction flask, using an airtight syringe. Then, add the corresponding organocatalyst (0.1 equivalent, 0.01 mol/L) to the solution and stir the reaction mixture at 40 °C.

4.4. Monitor the progress of the reaction by TLC, using petroleum ether:ethyl acetate (4:1 [v/v], R<sub>f</sub> = 0.51) as an eluent.

NOTE: The spots of the starting materials and products were visualized using a hand-held 254 nm UV lamp.

4.5. After the reaction was completed, concentrate the reaction mixture, using a rotary evaporator at 40 °C.

4.6. Purify the residue by column chromatography on silica gel eluting with petroleum ether:ethyl acetate (4:1 [v/v]) to provide the final product.

4.7. Characterize the final product by <sup>1</sup>H and <sup>13</sup>C NMR spectra, using a 400 MHz NMR spectrometer. Determine the ee values of the product, using a chiral column.

#### REPRESENTATIVE RESULTS:

Various hydrogen-bond donor bifunctional organocatalysts were examined in the presence of organocatalysts in dichloromethane (DCM) at 25 °C (Table 1). The representative synthetic

process of organocatalysts is shown in **Figure 1**. The screening of different organocatalysts (**Table 1**, entries 1–6) resulted in **C5** with excellent stereoselectivity (94% ee, >20:1 d.r., entry 5) and the best yield (85% yield). A further optimization of the solvents (**Table 1**, entries 7–11) suggested that Et<sub>2</sub>O was preferable in this synthetic process.

Significantly, to examine the generality of the reaction, a variety of substituents of two spirocyclization synthons with different functional groups were tested successfully using the optimized model reaction conditions, resulting in the desired bispirocycles with good to excellent yields and stereoselectivity. The scope of the pyrazolinone **1a** includes a replacement of the phenyl group on  $\alpha$ -aryldiene with a wide range of aryl, naphthyl, and thienyl groups, substrates with different substituents such as ethyl, decyl, *tert*-butyl, and benzyl group at 3-position, and substituents with different electronic properties on the aryl ring at 1-position. Besides, to explore the substrate scope of imino lactone **2a**, the cyclic imino ester moiety was substituted with a 5-methylthiophenyl, a phenyl or 2-naphthyl group, providing bispirocycles with similar yields and considerable stereoselectivities.

The structure of bispirocyclic products was confirmed by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy. To characterize the optical purity and stereoselectivity of the stereoisomer products, the ee values were determined using chiral HPLC and the d.r. values were determined by 400 MHz <sup>1</sup>H NMR. Reprehensive HPLC characterization results of compound **3e** are given in **Figure 3**. To explore the structural relativity, X-ray crystallography was used to analyze **3e**, revealing the absolute configuration of the product **3e** as (5*S*,6*R*,7*R*,13*R*). The single-crystal structure of **3e** is shown in **Figure 4**. CCDC 1590396 contains the crystallographic data of **3e**, which can be obtained free of charge from the Cambridge Crystallographic Data Centre ([www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif)).

For example, the characterization data for bispirocyclic product (**3e**) were as follows: R<sub>f</sub> = 0.51 (4:1 [v/v], petroleum ether/EtOAc); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.55 (d, *J* = 7.2 Hz, 2H), 7.35–7.31 (m, 2H), 7.26–7.22 (m, 2H), 7.19–7.15 (m, 2H), 6.98–6.93 (m, 3H), 6.90–6.88 (m, 1H), 5.03 (d, *J* = 11.6 Hz, 1H), 4.57 (s, 1H), 4.46–4.40 (m, 1H), 4.09 (td, *J* = 8.8, 2.0 Hz, 1H), 3.80 (d, *J* = 11.6 Hz, 1H), 2.67–2.61 (m, 1H), 2.35–2.27 (m, 4H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  178.8, 171.9, 163.9, 161.4, 158.5, 137.1, 136.0, 131.3, 131.2, 128.8, 127.0, 125.8, 125.4, 125.0, 119.7, 116.3, 116.1, 70.8, 67.4, 66.0, 64.1, 57.5, 34.6, 13.6; <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  112.8. The ee value was determined by HPLC analysis, hexane/2-propanol 80/20, flow rate = 1.0 mL/min, 254 nm, tr = 8.63 min (major); HRMS (ESI) Calcd for C<sub>26</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub>SF<sup>+</sup> [M+H]<sup>+</sup> 476.1439, found 476.1446.

## FIGURE AND TABLE LEGENDS:

**Table 1: Optimization of the reaction condition.** The table has been modified from Chen et al.<sup>18</sup>.

**Figure 1: Model reaction between 1a and 2a.** Structures of bifunctional organocatalysts (**C1–C6**) are listed. This figure shows reactions performed with **1a** (0.10 mmol), **2a** (0.12 mmol), and catalyst (10 mol%) in solvent (1 mL) at room temperature for 8–72 h. For detailed experimental procedures, see the protocol. This figure has been modified from Chen et al.<sup>18</sup>.

**Figure 2: Synthesis of organocatalyst 5C.** The top panel is the synthesis of compound **1**, and the bottom panel is the synthesis of **5C** from compound **1** and compound **2**.

**Figure 3: HPLC spectra of racemic and chiral product 3e.** The top panel is the HPLC spectrum of racemic product **3e**, and the bottom panel is the HPLC spectrum of chiral **3e**.

**Figure 4: Single-crystal structure of 3e.** The left structure is the single-crystal structure of **3e**, and the right structure is **3e** with the stereochemistry of each atom properly designated.

## DISCUSSION:

The successful preparation of bispiro[ $\gamma$ -butyrolactone-pyrrolidin-4,4'-pyrazolone] skeletons is dependent on a number of factors.

The key step of this one-step asymmetric cycloaddition process is the synergistical activation of the  $\alpha$ -aryliene pyrazolinone **1a** and cyclic imino ester **2a** by the bifunctional squaramide catalyst. It is achieved by the formation of multiple intermolecular hydrogen bonds between catalyst as a hydrogen-bond donor and two reaction substrates. Accordingly, with large steric hindrance, **C5**, out of all the hydrogen-bond donor bifunctional organocatalysts screened, exhibited the best stereoselectivity. The noted protocol uses 10 mol% catalyst in the model reaction. Besides, the requirement of high solubility of both substrates and catalyst is essential. As a result, the use of Et<sub>2</sub>O as the optimal solvent not only ensures that both substrates and catalyst are fully dissolved at room temperature but that they undergo a smooth cycloaddition with high yields and stereoselectivities as well. Notably, water in the reaction system would lead to poor stereoselectivity. In order to ensure a successful synthesis, it is critical to check the dryness of all of the reagents and solvent before starting the reaction.

The cycloaddition is compatible with a wide variety of substituted  $\alpha$ -aryliene pyrazolinone. Specifically, substituents with a different aryl group on  $\alpha$ -aryliene are well tolerated. Electron withdrawing aryl groups, due to their increased electrophilicity during 1,3-dipolar cycloaddition, are preferred in terms of yields and stereoselectivity. Also, substrates such as 3-position, replaced by ethyl, decyl, *tert*-butyl, and benzyl groups, and 1-position, functionalized by different electronic aryl rings, are highly tolerated. Moreover, substituents of the cyclic imino ester moiety on imino lactone with phenyl, thiophenyl, or naphthyl groups are also compatible with the reaction. It is notable that, in order to ensure a successful reaction, a small excess of imino lactone (1.2 equivalent) is required. In most cases, the concentrations of substrates are kept at a 0.1–0.12 mol/L scale in 1 mL of solvent. Depending on the types of substrates and catalysts, the one-step cycloaddition reaction may take 8–72 h at room temperature.

It is worth noting that this cycloaddition provided a high level of stereoselectivity when the R<sup>4</sup> substituent of imino lactone **2** was a thiophenyl, 5-methylthiophenyl, or 2-naphthyl group. However, when the R<sup>4</sup> substituent was replaced with other alkyl substituents or heterocyclic substituents, either a low stereoselectivity or a low reaction yield was achieved.



In summary, the presented protocol allows the direct asymmetric construction of bispiro[ $\gamma$ -butyrolactone-pyrrolidin-4,4'-pyrazolone] using an efficient one-step organocatalytic 1,3-dipolar cycloaddition reaction in excellent yields and a high level of stereoselectivity. Moreover, this new methodology is compatible with two synthons bearing versatile functional groups and should be useful for the synthesis of diverse therapeutic agents with bispirocyclic scaffolds.

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#### DISCLOSURES:

The authors have nothing to disclose.

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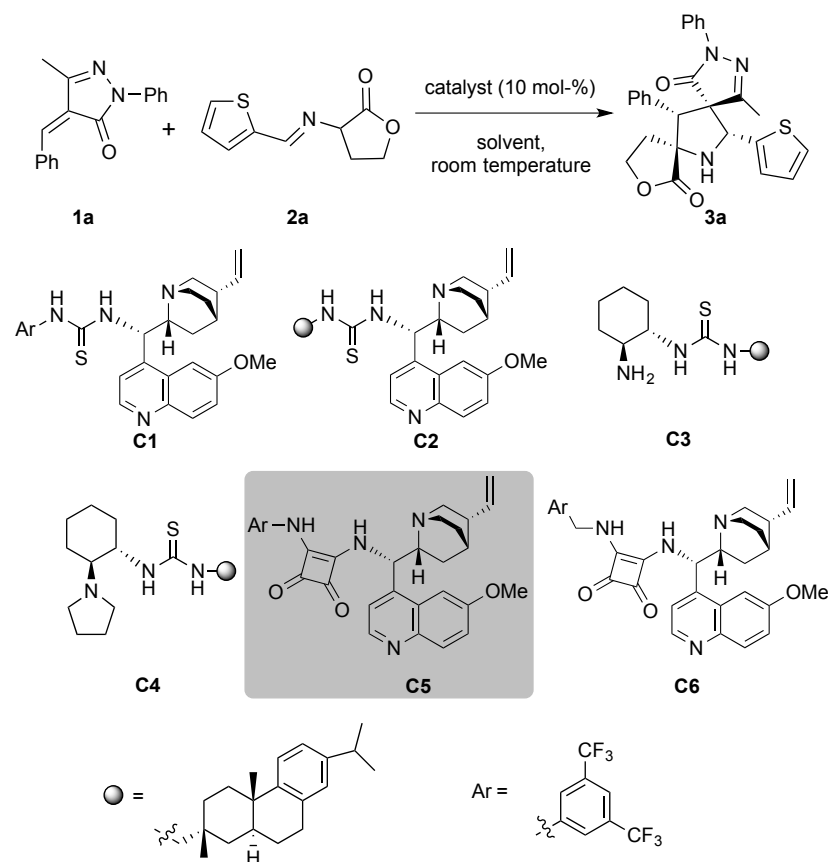
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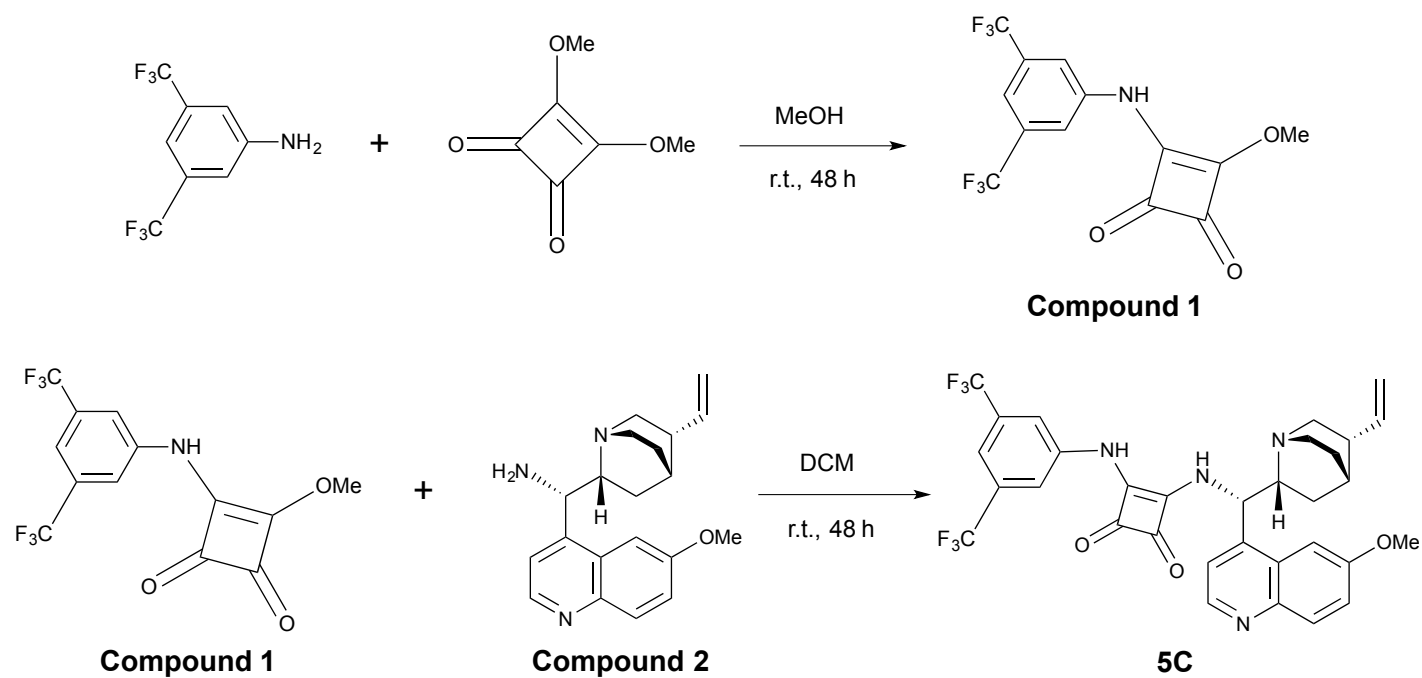
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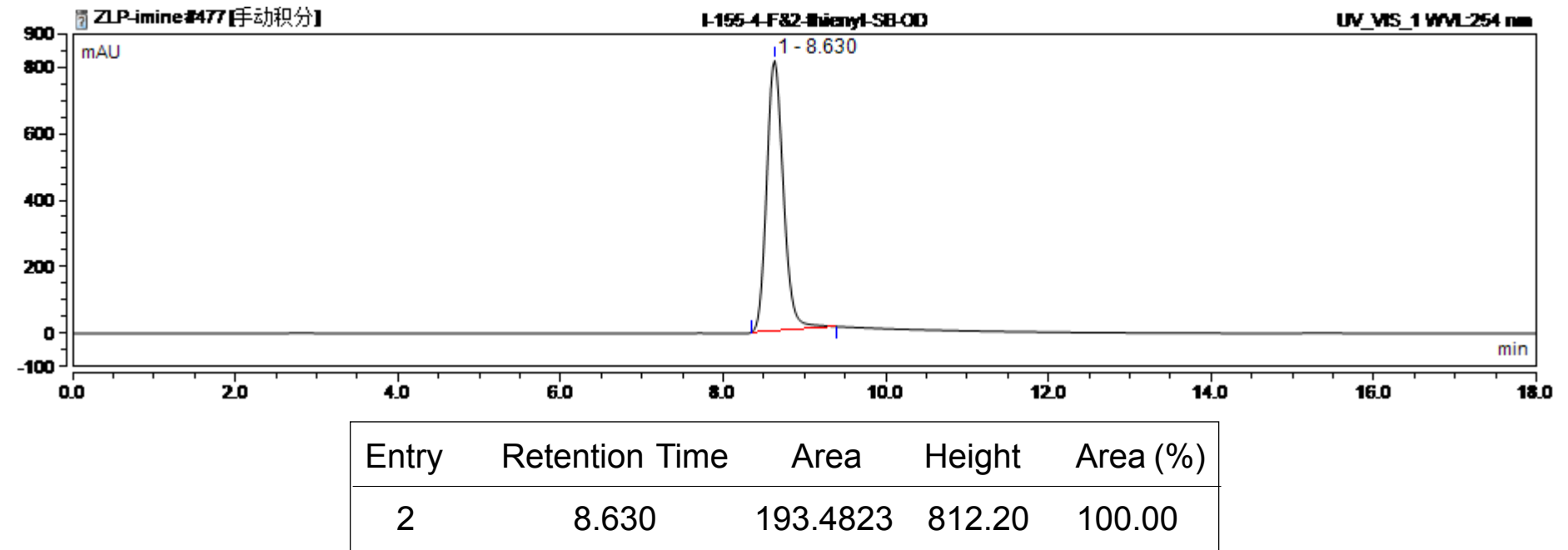
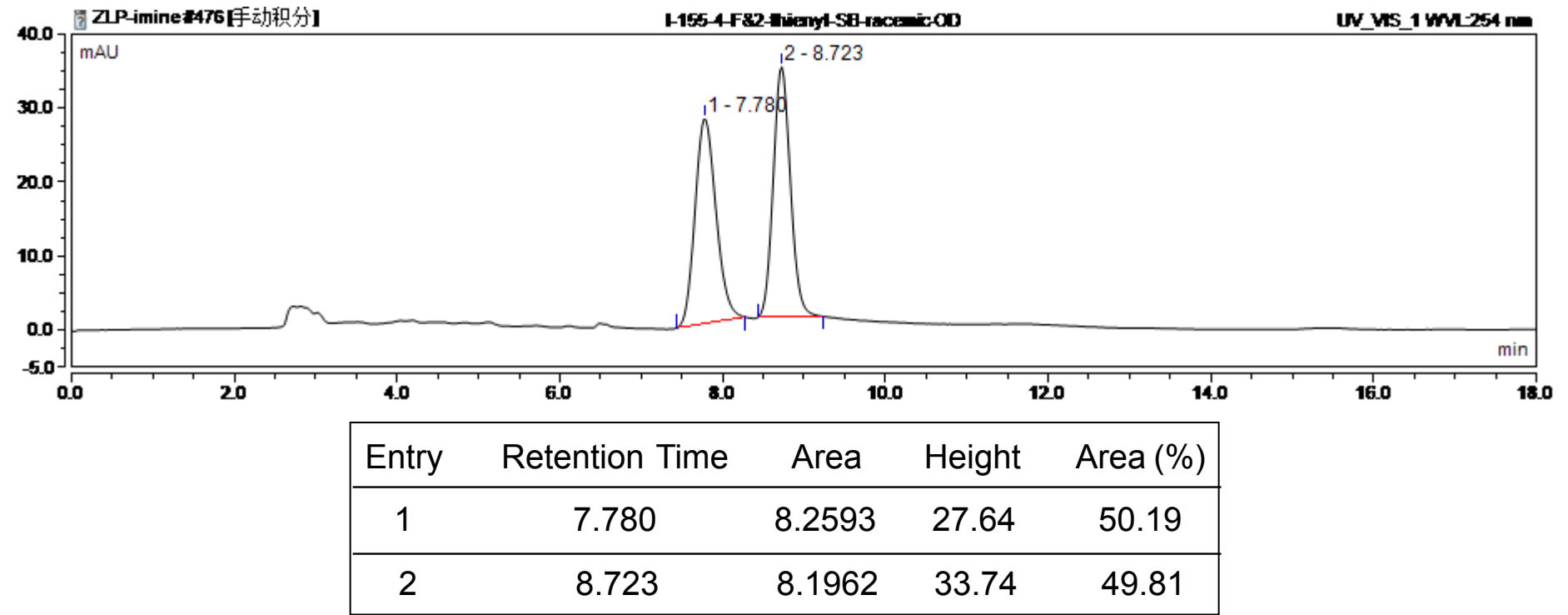
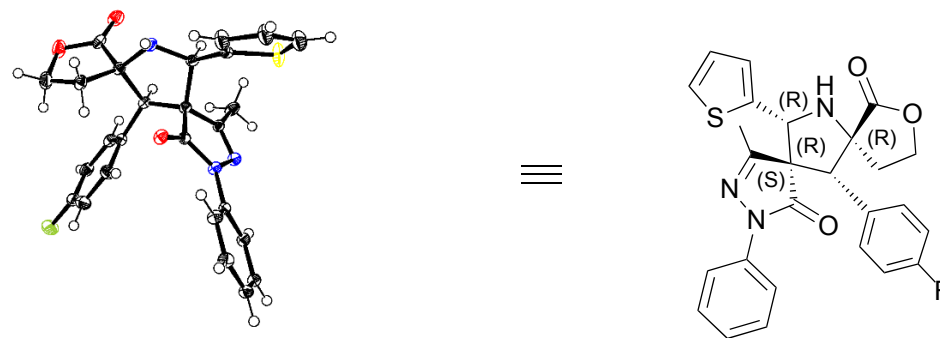


Figure 4



Name of Material/ Equipment	Company	Catalog Number
Acetonitrile, anhydrous, 99.9%	Innochem (China)	A0080
$\alpha$ -amino- $\gamma$ -butyrolactone hydrobromide, 98%	Alfa Aesar	B23148
3,5-bis(trifluoromethyl)aniline, 98+%	Adamas	48611B
Dichloromethane, 99.5%	Greagent	G81014H
3,4-dimethoxycyclobut-3-ene-1,2-dione, 98+%	Leyan (China)	1062550
Ethanol, 99.5%	Greagent	G73537B
Ethyl acetate, 99.5%	Greagent	G23272L
Ethyl ether, anhydrous, 99.5%	Greagent	G69159B
Ethyl 3-oxobutanoate, 98%	TCI	A0649
4-fluorobenzaldehyde, 98%	Innochem (China)	A24295
Glacial acetic acid, 99.5%	Greagent	G73562B
Magnesium oxide, 99+%	Alfa Aesar	44733
Magnesium sulfate, 98%	Greagent	G80872C
Methanol, 99.5%	Greagent	G75851A
Petroleum ether	Greagent	G84208D
Phenylhydrazine, 98%	Innochem (China)	A57671
(S)-(6-methoxyquinolin-4-yl)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methanamine	DAICEL Group	111240
Sodium sulfate, anhydrous, 99%	Greagent	G82667A
Thiophene-2-carbaldehyde, 98%	J & K scientific (China)	124605
Triethylamine, 99%	J & k scientific (China)	432915



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Author(s):	Yani Zhou, Nannan Chen, Yaping Cheng, Xiaoqing Cai

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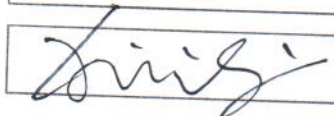
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Dear Editor,

Re: JoVE submission JoVE59155R1

Thank you for considering our manuscript entitled “*Efficient Construction of Drug-like Bispriocyclic Scaffolds via Organocatalytic Cycloadditions of  $\alpha$ -Imino  $\gamma$ -Lactones and Alkylidene Pyrazolones*” for publication in the *Journal of Visualized Experiments*. Below we have addressed your feedback in a point-by-point fashion. We have also highlighted all our corrections in our revised manuscript.

**<Editorial Comments>**

We have also attended to all editorial requirements as follows:

1. Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammar issues.

**Reply:** We have thoroughly proofread the manuscript to ensure that there are no spelling or grammar issues.

2. Figure 2: Please provide a short description of the figure in addition to the figure title in Figure Legend.

**Reply:** For Figure 2, we have added the following sentence to provide more details: “The top panel is the synthesis of compound **1**, and the bottom panel is the synthesis of **5C** from compound **1** and compound **2**.”

3. For in-text referencing, please put the reference number before a comma or period.

**Reply:** We have proofread the manuscript, and put all the reference number before a comma or period.

4. Step 1.1.6: Please write this step in imperative tense.

**Reply:** We have now rewritten this step in imperative tense.

5. Step 2.6: Please write this step in imperative tense.

**Reply:** We have now rewritten this step in imperative tense.

6. Unfortunately, there are a few sections of the manuscript that show significant overlap with previously published work. Though there may be a limited number of ways to describe a technique, please use original language throughout the manuscript. Please check the iThenticateReport attached to this email.

**Reply:** We have checked the iThenticateReport, and have now rewritten all the possible overlap sections of our manuscript.

With the additions/changes/corrections, we now believe our paper is acceptable for publication in *Journal of Visualized Experiments*.

Sincerely,

Professor Xiaoqing Cai, Ph.D.  
School of Pharmaceutical Sciences  
University of Sun Yat-sen University  
Guangzhou, China

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Sent: Samstag, 27. Oktober 2018 12:43

To: EurJOC <[eurjoc@wiley-vch.de](mailto:eurjoc@wiley-vch.de)>

Subject: Re: for your records: AW: Manuscript ejoc.201800404R1 for European Journal of Organic Chemistry: Legal statement now complete - [EMID:984d1744278a12fd]

Dear Editorial Office,

We have just published our article entitled "Asymmetric Synthesis of Bispiro [ $\gamma$ -butyrolactone-pyrrolidin-4,4'-pyrazolone] Scaffolds Containing Two Quaternary Spirocenters via an Organocatalytic 1,3-Dipolar Cycloaddition" in Eur JOC early this year (Eur. J. Org. Chem. 2018, 2939-2943).

We are now submitting a related paper to Journal of Visualized Experiments (JoVE) with an emphasis on video demonstrations and detailed protocols. We have already entered the revision session for our submission. We are hoping to use some of the data from Table 1 of our publication in Eur JOC (Eur. J. Org. Chem. 2018, 2939-2943), as well as two HPLC spectra from the supporting information. Accordingly, the editor from JoVE asked us for an explicit copy permission from the editor of Eur JOC to reuse figures from our previous publication.

So, I am writing to ask for copyright permission from the editor to reuse Table 1 and some data from the supporting information in our Eur JOC paper. If we can get the copyright permission from Eur JOC, we will cite the data in the Figure Legend in our JoVE paper: "This figure has been modified from [citation]".

Please let me know if additional information is needed. Thank you very much for your assistance!

I look forward to your reply.

Yours sincerely,

Xiaoqing Cai, Ph.D.  
Associate Professor  
Sun Yat-sen University  
Guangzhou, China

Entry	Catalyst	Solvent	Yield <sup>[a]</sup> (%)	d.r. <sup>[c]</sup>	ee <sup>[d]</sup> (%)
1	C1	DCM	81	>20:1	94
2	C2	DCM	82	12:1	90
3	C3	DCM	30	9:1	0
4	C4	DCM	78	>20:1	71
5	C5	DCM	85	>20:1	94
6	C6	DCM	70	12:1	93
7	C5	Toluene	79	>20:1	95
8	C5	THF	73	15:1	89
9	C5	CHCl <sub>3</sub>	71	>20:1	93
10	C5	DCE	81	18:1	91
11	C5	Et <sub>2</sub> O	88 (83 <sup>[b]</sup> )	>20:1	98

<sup>[a]</sup> The yields were determined by <sup>1</sup>H NMR analysis of crude product using 4-iodoanisole as the internal standard.

<sup>[b]</sup> Isolated yield.

<sup>[c]</sup> Ratio is determined by <sup>1</sup>H NMR.

<sup>[d]</sup> Determined by chiral HPLC.