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Asymmetric Total Synthesis and Biological Evaluation of the Natural PDE4 Inhibitor Toddacoumalone

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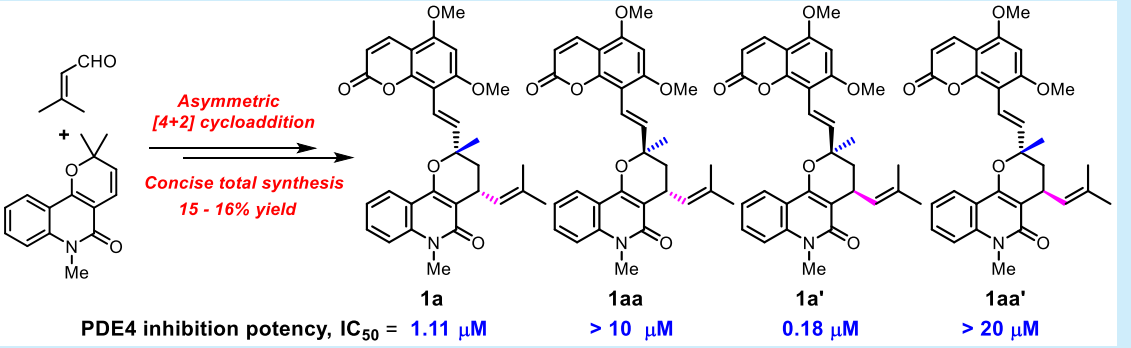

ABSTRACT: We describe herein the first asymmetric total synthesis and biological evaluation of the natural PDE4 inhibitor toddacoumalone and its stereoisomers. The key step of the total synthesis is a formal asymmetric [4 + 2] cycloaddition reaction catalyzed by chiral secondary amine catalysts. A variety of pyranoquinolinones and 3-methylcrotonaldehyde are well tolerated under the optimized reaction conditions, which paved the way for further SAR studies. Further biological evaluation showed **1a′** with the best PDE4 inhibitory activity (IC_{50} = 0.18 μM).

The phosphodiesterases (PDEs) families, consisting of 11 members (PDE1-PDE11), are responsible for regulating the cellular levels of the secondary signal messengers cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP).[1] Among all PDEs, phosphodiesterase-4 (PDE4) is the primary cAMP-specific hydrolase within cells and has proven to be a therapeutic target of high interest for pulmonary, dermatological, and severe neurological diseases.[2] Recently, PDE4 inhibitors roflumilast (for the treatment of chronic obstructive pulmonary disease), apremilast (for the treatment of psoriatic arthritis), and crisaborole (for the treatment of atopic dermatitis) have been approved by the FDA, respectively (Figure 1).[3−5] However, most of the PDE4 inhibitors, including those applied in the clinic, have severe dose-limiting gastric adverse effects, such as nausea, emesis, and gastrointestinal reactions.[6] Thus, the search for novel PDE4 inhibitors continues unabated.

In 1991, Ishikawa and co-workers reported the isolation and characterization of toddacoumalone (**1**) (Figure 1) with a 0.0077% yield in a racemic form from *Toddalia asiatica* (L.) Lam. (Rutaceae).[7] Later, toddacoumalone (**1**) was reported by the Luo and Yin group to inhibit PDE4 with an IC_{50} of 0.14 μM, which was more potent than the commonly used positive control rolipram (IC_{50} = 0.59 μM), by using tritium-labeled adenosine 3′, 5′-cyclic monophosphate ([^{3}H]-cAMP) as substrate for identifying its inhibitory activity.[8]

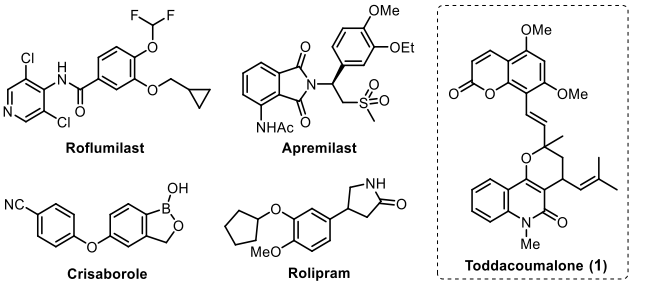

Figure 1. Representative PDE4 inhibitors and the natural isolated toddacoumalone (**1**).

Toddacoumalone is a highly potent PDE4 inhibitor with a unique structure and potential clinical applications. However, the scarce and extremely low abundance in nature limited its comprehensive studies. The structure of toddacoumalone was assigned by NMR analysis, which needs to be further verified. In addition, the total synthesis of this molecule has not been reported, which further prevented its development, including

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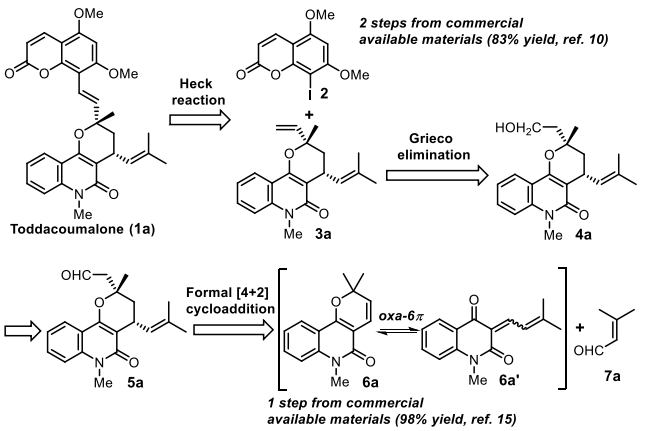
thorough biological evaluation, structure−activity relationship (SAR) study, etc. More importantly, toddacoumalone exists as a racemic form in nature. The two chiral centers within the molecule have not yet been established, which is one of the biggest obstacles for modern drug research, as all chiral centers need to be identified. Our research interests include the development of new synthetic strategies for bioactive molecules, followed by SAR studies in searching for lead structures with therapeutic purpose. Herein, we report a concise asymmetric total synthesis of toddacoumalone through the exploration of a formal catalytic asymmetric [4 + 2] cycloaddition reaction catalyzed by secondary amine catalysts, followed by investigating their inhibition potency on PDE4.

The retrosynthetic analysis of toddacoumalone (**1a**) is depicted in Scheme 1. Structurally, toddacoumalone was

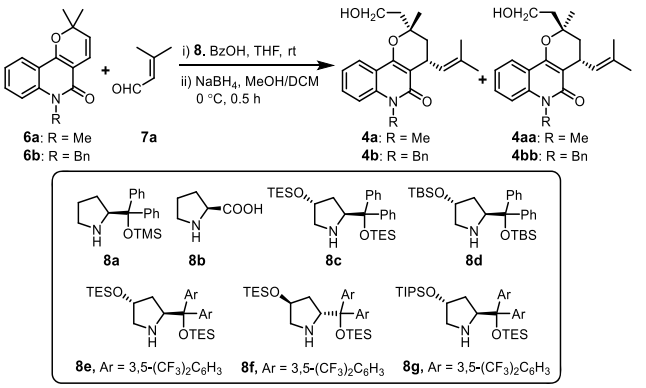
Scheme 1. Retrosynthetic Analysis of Toddacoumalone (1a)



characterized by a novel mixed dimer with a coumarin unit and quinolinone unit connected by an alkene. The quinolinone unit fused a chiral dihydropyran moiety which contains one quaternary and one tertiary carbon chiral center. We proposed that toddacoumalone (**1a**) could be obtained from coumarin derivative **2** and quinolinone derivative alkene **3a** through Heck reaction as the final step.[9] Coumarin derivative **2** could be prepared in two steps from commercially available materials according to the reported methods.[10] The terminal olefin group in the key intermediate **3a** was envisioned to be transformed from primary alcohol **4a** via Grieco elimination.[11] **4a** could be derived from the aldehyde **5a** by a simple reduction reaction. Thus, the preparation of quinolinone fused dihydropyran aldehyde **5a** was the key step in the total synthesis of toddacoumalone. Inspired by the dienamine catalyzed inverse-electron-demand Diels−Alder (IEDDA) reactions, especially, the pioneering work by Jørgensen and Chen,[12] we proposed that the chiral dihydropyran moiety could be constructed through a formal [4 + 2] cycloaddition reaction by dienamine catalysis from quinolinone derived diene **6a′** and commercially available 3-methylcrotonaldehyde **7a**.[13] We noticed that the nonisolable diene **6a′** exists in the form of stable and isolable ring closing pyranoquinolinone **6a**, which could be in equilibrium with **6a′** through an oxa-6π electrocyclic pathway.[14] It is worth noting that **6a** could be easily prepared by one step from commercial starting materials.[15] Because the examples of using **6a** in asymmetric catalysis are rare, we first set out to explore the possibility of accessing chiral quinolinone fused dihydropyran aldehyde **5a** through a chiral secondary amine catalyzed reaction of **6a** and **7a**.

In the initial screening studies, **6a** was treated with **7a** in the presence of the L-proline derived catalyst **8a** in THF at room temperature (Table 1, entry 1). To our delight, diastereoisomers **5a** and **5aa** were isolated after 3 days, which were reduced to the corresponding alcohols **4a** and **4aa** to facilitate further characterizations. **4a** and **4aa** were obtained in moderate yield with low enantioselectivity and poor diastereoselectivity (Table 1, entry 1). Several frequently used solvents were screened, and THF was witnessed to be the suitable solvent (see Supporting Information, Table S1). The addition of H_2O or 4 Å MS did not improve the reaction outcomes (Table 1, entries 2−3). Use of different acid additives did not result in significant improvement (see Supporting Information, Table S1). With the purpose of improving the enantioselectivity and poor diastereoselectivity, L-proline **8b** and some of its known derivatives were tried, but none of them gave remarkable better results compared with **8a** (see Supporting Information, Table S1). To further improve the reaction results, catalysts **8c−8g** were synthesized by a similar reported synthetic process with the purpose of increasing the steric hindrance, by fine-tuning the protecting groups on the two hydroxyl groups.[16] In general, **8c−8g** with bulky substituents displayed superior results to **8a** (Table 1,

Table 1. Optimization of the Reaction Conditions[a]



entry	8	6	time (d)	yield (%)[b]	dr[c] (4a:4aa or 4b:4bb)	ee[c] (4a:4aa or 4b:4bb)
1	8a	6a	3	40	55:45	44/44
2[d]	8a	6a	3	38	52:48	44/43
3[e]	8a	6a	3	trace	–	–
4	8b	6a	3	35	51:49	1/0
5	8c	6a	3	42	55:45	68/82
6	8d	6a	3	40	51:49	73/81
7	8e	6a	3	41	51:49	91/91
8	8f	6a	3	42	52:48	−91/−91
9	8g	6a	3	39	53:47	88/90
10	8e	6b	3	46	52:48	93/93
11	8f	6b	3	45	52:48	−93/−93
12[f]	8e	6b	2	70	52:48	93/93

[a]Unless otherwise noted, reactions were performed with **6** (0.1 mmol), **7a** (0.15 mmol), catalyst **8** (20 mol %), and BzOH (20 mol %) in 1 mL of THF under room temperature. [b]Combined isolated yield of **4a** and **4aa** or **4b** and **4bb**. [c]Determined by chiral HPLC analysis of **4a** and **4aa** or **4b** and **4bb**. [d]Adding 0.1 mL of H_2O. [e]Adding 50 mg of 4 Å MS. [f]With **6b** (0.25 mmol), **7a** (0.375 mmol), **8e** (20 mol %), and BzOH (20 mol %) in 0.25 mL of THF.

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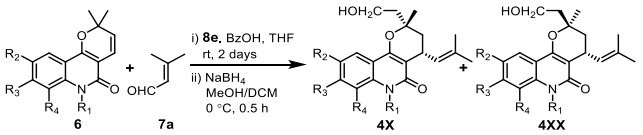
entries 5−9). Luckily, catalyst **8e** gave the best results and delivered **4a** and **4aa** in moderate yield (41%) and high ee value (91%), albeit with dissatisfactory diastereoselectivity (Table 1, entry 7). Perhaps not surprisingly, catalyst **8f**, which is the enantiomer of **8e**, gave **4a** and **4aa** in almost identical yield and completely opposite enantioselectivity (Table 1, entry 8). In addition, better results were obtained for alcohol **4b** and **4bb** by using **6b** with a benzyl group on the nitrogen atom (entries 10−11). Further optimization, including screening the reaction concentration, temperature, and reaction time (see Supporting Information, Table S1), led to establishing the optimal reaction conditions (Table 1, entry 12). Although poor diastereoselectivities were observed for the reaction, this set of conditions provided the opportunity to synthesize all possible stereoisomers of the key intermediate **4**, which could be applied to prepare the isomers of toddacoumalone.

With the optimized reaction conditions in hand, the scope of the pyranoquinolinones **6a−6o** to react with **7a** was then explored. As shown in Table 2, **6a−6c** bearing different

Table 2. Substrate Scope of the Reaction[a]



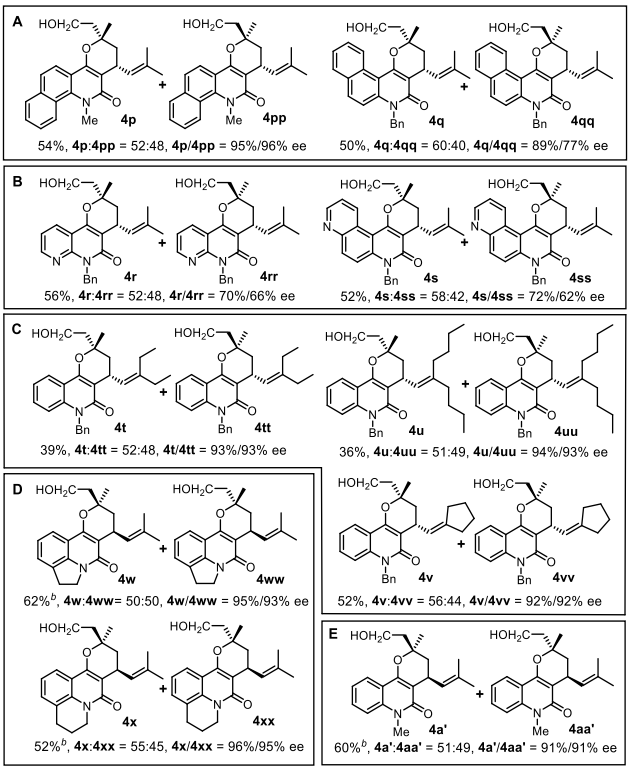
entry	6	R_1, R_2, R_3, R_4	yield[b] (%)	dr[b] (4X:4XX)	ee[c] (4X:4XX)
1	**6a**	Me, H, H, H	60	51:49	91/91
2	**6b**	Bn, H, H, H	70	52:48	93/93
3	**6c**	Ph, H, H, H	55	51:49	94/94
4	**6d**	Bn, F, H, H	60	52:48	84/85
5	**6e**	Bn, Cl, H, H	61	55:45	85/85
6	**6f**	Bn, Br, H, H	73	51:49	87/87
7	**6g**	Bn, CF_3, H, H	73	54:46	89/87
8	**6h**	Bn, NO_2, H, H	45	55:45	73/68
9	**6i**	Bn, Me, H, H	64	50:50	90/90
10	**6j**	Bn, iPr, H, H	56	52:48	93/87
11	**6k**	Bn, tBu, H, H	51	55:45	91/85
12	**6l**	Bn, Ph, H, H	58	56:44	92/85
13	**6m**	Bn, MeO, H, H	68	53:47	90/83
14	**6n**	Bn, H, H, MeO	63	53:47	91/91
15	**6o**	Bn, MeO, MeO, H	54	55:45	81/79

[a]For reaction conditions, please see Table 1, entry 12. [b]The dr was determined by the separated diastereomers of **4X** and **4XX**. [c]The ee was determined by chiral HPLC analysis of the separated **4X** and **4XX**.

substituents on the nitrogen atom participated well in the reaction and provided the desired products with high enantioselectivities (Table 2, entries 1−3). A range of the pyranoquinolinones bearing either electron-donating or electron-withdrawing groups on the benzene ring, ranging from the 6-position to 8-position, participated well in the reaction to give the desired products in moderate to good yield and high enantioselectivities (entries 4−7 and 9−14), although the 6-NO_2-pyranoquinolinone (**6h**) and 6,7-$(MeO)_2$-pyranoquinolinone (**6o**) gave the products with slightly reduced enantioselectivities (entries 8 and 15).

To further demonstrate the generality of this reaction, more pyranoquinolinones (**6p−6x**, see Supporting Information Figure S2) were examined, and the products were outlined in Scheme 2. **6p** gave the highest ee value up to 96%, while **6q**

Scheme 2. Substrate Scope of the Reaction[a,b,c,d]



[a]For reaction conditions, please see Table 1, entry 12. [b]With catalyst **8f**. [c]The dr was determined by the separated diastereomers of **4X** and **4XX**. [d]The ee was determined by chiral HPLC analysis of the separated **4X** and **4XX**.

gave slightly deterious results (Scheme 2A). As the nitrogen atom exists in most of the pharmaceuticals and bioactive molecules, we tried to incorporate additional nitrogen atom into the pyranoquinolinone to explore the substrate diversity. **6r** and **6s** smoothly delivered the products, despite only moderate enantioselectivities were observed (Scheme 2B). **6t−6v**, where a long alkyl chain or cycloalkane substitution was readily tolerated, gave the corresponding products with good ee and slightly reduced yield, which might be due to the increased steric hindrance (Scheme 2C). Finally, the generality of our catalytic system was also surveyed by using catalyst **8f**, as it can deliver the cycloadducts with different enantiomers compared with catalyst **8e**. **6w** and **6x**, which present new types of pyranoquinolinones, were well tolerated, and high enantioselectivities were detected (Scheme 2D). In addition, **4a′** and **4aa′**, enantiomers of **4a** and **4aa**, could also be obtained with high ee values by the catalysis of **8f**, as they are key intermediates for the synthesis of stereoisomers of toddacoumalone (Scheme 2E).

After successfully preparing the key intermediates **4a**, **4aa**, **4a′**, and **4aa′**, we then set our attention toward completing the total synthesis of toddacoumalone (Scheme 3A). According to the Grieco protocol,[11] the primary alcohol **4a** first reacted with *o*-nitrophenylselenocyanate and tributylphosphine to form a selenide intermediate through the nucleophilic substitution on the electron-deficient selenium, followed by treatment with hydrogen peroxide to obtain the terminal alkene **3a** in an 85% overall yield with retained ee. As the final step, the two fragments coumarin-derivative **2** and alkene **3a** were coupled through a Heck reaction in the presence of $Pd(OAc)_2$,

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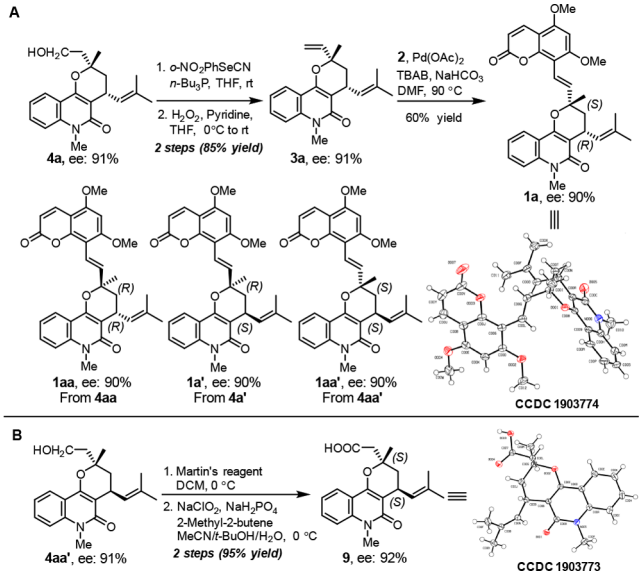
Scheme 3. Total Synthesis and Structure Confirmation of Toddacoumalone



tetrabutylammonium bromide (TBAB), and $NaHCO_3$ to accomplish the total synthesis of **1a** in 60% yield. Gratifyingly, high stereoselectivity was still obtained, even under such harsh reaction conditions. By employing the same strategy, **1aa**, **1a′**, and **1aa′**, the other stereoisomers of **1a**, could also be obtained from intermediates **4aa**, **4a′**, and **4aa′**, respectively. Thus, we achieved the first asymmetric total synthesis of toddacoumalone and its stereoisomers with the overall yields ranging from 15% to 16% starting from **6a**.

4a and **4aa** are diastereoisomers. The absolute configuration of **4a** derived toddacoumlone **1a** was unequivocally assigned by single-crystal X-ray analysis (CCDC 1903774, Scheme 3A). Thus, the absolute configuration of **4a** and its enantiomer **4a′** were assigned. **4aa** and **4aa′** are enantiomers. The absolute configuration of **4aa′** was unambiguously assigned on the basis of the single-crystal X-ray analysis of acid **9** (CCDC 1903773), which was derived from **4aa′** by converting the corresponding alcohol to aldehyde, followed by using the Pinnick oxidation to obtain the carboxylic acid **9** (Scheme 3B).[17] Thus, the absolute configuration of **4a**, **4aa**, **4a′**, and **4aa′** were all assigned. Accordingly, the absolute configuration of **1a** (from **4a**), **1aa** (from **4aa**), **1a′** (from **4a′**), and **1aa′** (from **4aa′**) were also all assigned. After careful analysis of the NMR data of **1a**, **1aa**, **1a′**, and **1aa′**, and comparison of the NMR data with NMR of the natural isolated toddacoumalone (**1**),[7,8] we confirmed that the natural toddacoumalone (**1**) was composed of enantiomer **1a** and **1a′**. As there were no crystal structure of toddacoumalone reported, the single-crystal X-ray analysis of **1a** not only established the absolute configuration of the two chiral centers but also confirmed the structure of toddacoumalone.

Having the desired four stereoisomers of the synthesized toddacoumalone in hand, we then investigated their inhibition potency on PDE4 (Table 3). The inhibition potency on PDE4D2 of the four compounds was determined using the well-known PDE4 inhibitor rolipram as the reference compound.[18] The results of bioassay showed that compound **1a** was potent with the IC_{50} values around 1 μM. **1a′** was the most potent compound among its stereoisomers, with IC_{50} values around 0.18 μM, which was more potent than rolipram and almost identical to the natural isolated toddacoumalone.[8]

Table 3. IC_{50} Values of the Active Compounds against PDE4D2

compound	IC_{50} (μM)	compound	IC_{50} (μM)
1a	1.11 ± 0.14	**1aa**	>10
1a′	0.18 ± 0.009	**1aa′**	>20

Interestingly, **1aa** and **1aa′**, the stereoisomers of **1a** and **1a′**, did not show remarkable inhibition activity, even when the concentration was up to 10 μM or 20 μM, indicating that the stereocenters within those molecules are critical for their bioactivity on PDE4. Importantly, compound **1a′**, which showed at least 6-, 50-, and 100-fold potency over its stereoisomers **1a**, **1aa**, and **1aa′**, shed light on the primary SAR information of how to further develop this compound. The inhibitory curves of the two most active compounds (**1a** and **1a′**, IC_{50} = 1.11 and 0.18 μM) are represented in Figure 2.

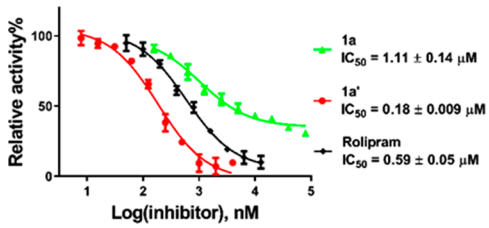


Figure 2. Inhibitory curves of compounds **1a**, **1a′**, and rolipram (positive control) against PDE4D2.

The yields of this asymmetric [4 + 2] cycloaddition reaction which were not satisfactory might be due to the slow isomerization rate from oxa-6π electrocyclic ring closing pyranoquinolinone **6a** to ring opening **6a′**. On the basis of the stereochemistry of the obtained products, we also looked into the poor diasteroselectivity of this reaction. As most of the IEDDA reactions generally gave excellent diastereoselectivities,[19] we speculated that this reaction did not occur as an IEDDA reaction, but might be a step-wise formal [4 + 2] cycloaddition reaction (a proposed transition state model was provided; please see the Supporting Information, Figure S4). Further mechanistic studies to fully explain the reaction mechanism are currently underway.

In summary, we have achieved the first concise asymmetric total synthesis of toddacoumalone and its stereoisomers by developing diastereodivergent asymmetric [4 + 2] cycloaddition reactions catalyzed by secondary amine catalysts, with the overall yield ranging from 15% to 16% starting from **6a**. A diverse range of pyranoquinolinones and 3-methylcrotonaldehyde were well tolerated under the optimized reaction conditions. We also confirmed the structure of todacoumalone and identified **1a′** to be most potent with an IC_{50} around 0.18 μM. Our study not only provided the primary SAR information on these molecules but also clarified the stereochemistry is critical for the bioactivities. Further investigations on the reaction mechanism and medicinal chemistry studies of **1a′** to develop the highly potent PDE4 inhibitor in search of lead structures are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04355.

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Complete experimental procedures and characterization of new products; NMR spectra and HPLC chromatograms (PDF)

Accession Codes

CCDC 1903773−1903774 and 1952168 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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