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Asymmetric synthesis of 9-alkyl tetrahydroxanthenones *via* tandem asymmetric Michael/cyclization promoted by chiral phosphoric acid†

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A tandem asymmetric Michael-addition/cyclization of cyclic 1,3-dicarbonyl compounds to β,γ-unsaturated α-ketoesters catalyzed by chiral phosphoric acid is presented. This protocol provides a facile approach for the construction of enantioenriched 9-alkyl tetrahydroxanthenones, an ubiquitous framework found in a number of natural products and pharmaceutical molecules, in high yields with good to high enantioselectivities.

The xanthene is an important skeleton since it is present in numerous natural products and pharmaceutical molecules (*e.g.* callistrilone A, myrtucomvalone E and rhodomyrtone, Fig. 1a), which exhibit various biological activities, *e.g.*, antioxidant, analgesic, antibacterial, anti-inflammatory, anticancer and antiviral properties.[1,2] In this regard, 9-substituted tetrahydroxanthenone derivatives have been evaluated as an orally active neuropeptide Y5 receptor antagonist.[3] Moreover, tetrahydroxanthenones also showed unique physical properties, which have been widely utilized as fluorescent materials or dyes.[4] Therefore, a great of efforts have been devoted to the construction of such scaffold.[5–7] However, the asymmetric synthetic protocols are scarcely documented.[6,7] In this context, Xu described an enantioselective cascade Oxa-Michael/Michael reaction of 2-hydroxynitrostyrenes with enones catalyzed by prolinol thioether enabled the asymmetric synthesis of 9-alkyl hexahydroxanthenone.[6] Enders exploited a thiourea catalyst for the asymmetric synthesis of 9-nitromethyl tetrahydroxanthenone **3** in good to excellent enantioselectivities from 2-(nitrovinyl)phenol **1** and 1,3-dicarbonyl compounds **2** (Fig. 1b).[7a] Rueping and Schneinder respectively reported the tandem nucleophilic addition/cyclization of *ortho*-quinone methide (*o*-QM), *in situ* generated from diaryl methanol **4**, with cyclohexan-1,3-dione **2a** promoted by chiral phosphoric acid (CPA) to deliver chiral 9-aryl tetrahydroxanthenone **5** in good to excellent enantioselectivities (Fig. 1c).[7b,c] Subsequently, CPA catalyzed nucleophilic addition/cyclization of enamine to *in situ* generated *o*-QM or *p*-QM to build up enantioenriched 9-substituted tetrahydroxanthenone were also reported. However, this strategy could only enable the construction of enantioenriched 9-aryl or alkynyl tetrahydroxanthenone and the asymmetric synthesis of 9-alkyl tetrahydroxanthenone catalyzed by CPA remains elusive.

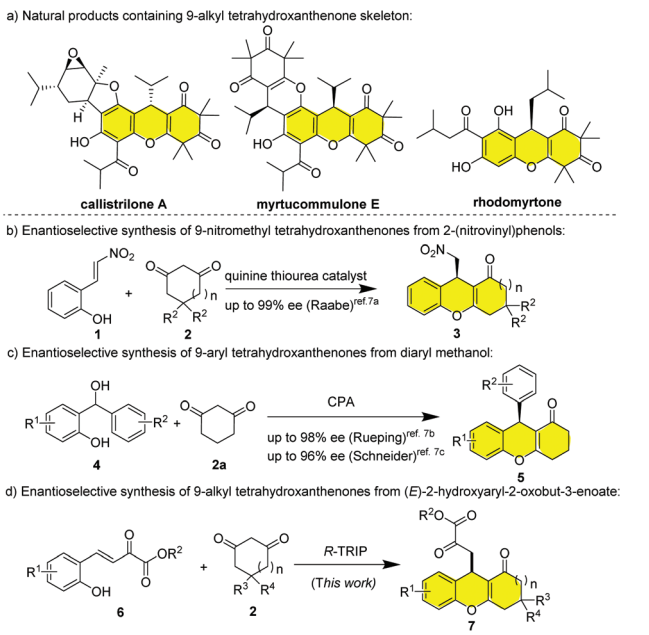

Fig. 1 Representative tetrahydroxanthenone natural products and chiral phosphoric catalyzed synthesis of enantioenriched tetrahydroxanthenone.

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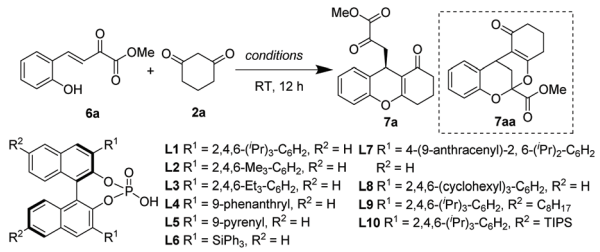
Undoubtedly, Michael addition of nucleophiles to electron-deficient alkenes is one of the most efficient strategies for the C–C bond formation. Particularly, asymmetric Michael additions of 1,3-dicarbonyl compounds to enones have been extensively employed for the construction of the core skeletons of natural products and biologically active molecules.[8,9] On the other hand, cascade reactions have provided competent tools for quick increasing molecular complexity from simple starting materials.[10] In this regard, enantioselective domino reactions have emerged for the asymmetric construction of ring framework *via* different type of domino reactions initiated with Michael addition, *e.g.* Michael-aldol,[11] Michael–Michael,[12] Michael–Darzens,[13] Michael–Knoevenagel,[14] Michael-alkylation,[15] Michael-lactamization[16] and Michael-acetalization[17] cascade reactions.

Since the seminal reports of Akiyama and Terada in 2004,[18] chiral phosphoric acids catalyzed reactions have witnessed enormous advances. This could be ascribed to finely tunable chiral pocket and its bifunctional catalytic activity. To date, over 100 asymmetric reactions, such as Michael addition, cycloaddition, Friedel–Crafts, C–H insertion, dearomatization, Fischer indolization and desymmetrization are realized by employing CPAs as promoter.[19] In line with our interests in the synthesis of polycyclic heterocycles,[20] herein we would like to report a *R*-TRIP catalyzed tandem Michael addition/cyclization reaction of (*E*)-2-hydroxyphenyl-2-oxobut-3-enoates with cyclo-1,3-diones to give enantioenriched 9-alkyl tetrahydroxanthenones *via* tandem Michael addition/cyclization process (Fig. 1d).

On the outset, the reaction of methyl (*E*)-4-(2-hydroxyphenyl)-2-oxobut-3-enoate **6a** with cyclo-1,3-dione **2a** was assessed to prepare 2,8-dioxabicyclo[3.3.1]nonane **7aa** by employing our previous reaction conditions.[20a] To our surprise, tetrahydroxanthenone **7a** instead of **7aa** was obtained (Table 1, entry 1). In a control experiment (Table 1, entry 2), the same result were obtained without the irradiation of blue LEDS, indicating the reaction might proceed through a different pathway (*vide infra*). We then began to optimize the reaction conditions. After the evaluation of various reaction mediums, we found that CCl_4 was the optimal solvent for both better yield and enantioselectivity (Table 1, entry 3). The reaction also proceeded smoothly in toluene and other halogenated solvents (*e.g.* DCE and $CHCl_3$) with slightly decreased enantioselectivities being observed (Table 1, entries 4 to 6). By contrast, no product could be obtained both in MeCN and THF and using hexane also led to inferior isolated yield (Table 1, entries 7 to 9). Subsequently, the reaction was investigated by screening an array of chiral phosphoric acids in CCl_4. Amongst all the used CPAs, *R*-TRIP was proved to be the optimal catalyst for this reaction, affording **7a** in 98% yield with 92% ee (Table 1, entries 10 to 18). In addition, the yield of **7a** was decreased when the concentration of reaction mixture increased (Table 1, entries 19 and 20).

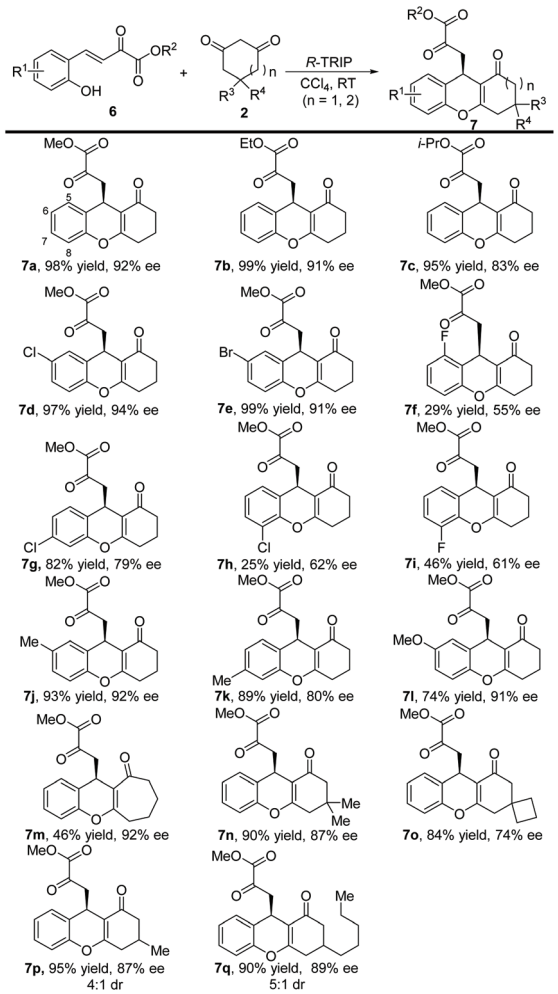
With the optimal condition in hand (Table 1, entry 2), the substrate scope was subsequently investigated (Scheme 1). Firstly, substrates with ethyl and isopropyl groups on the ester moiety (R^2) gave tetrahydroxanthenones **7b** and **7c** in 91% and 83% ee respectively. Additionally, a variety of substituted β,γ-unsaturated α-ketoesters were prepared and subjected enones with electron-withdrawing groups at C-6 on the aromatic ring (R^1 = 6-Cl, 6-Br) gave the desired products **7d** and **7e** in excellent yields and high enantioselectivities (94% ee and 91% ee). However, electron-withdrawing groups at C-5, C-7 and C-8 on the aromatic ring were unfavorable for this reaction and noticeable decrease in yields and enantioselectivities were observed of the corresponding products **7f** to **7i**. Furthermore, electron-donating groups such as methoxy and methyl on the aromatic ring reacted smoothly with cyclo-1,3-dione **2a**, and good results were achieved (**7j** to **7l**, 80–92% ee). In addition, the scope of cyclo-1,3-dione was also evaluated. Cycloheptane-1,3-dione gave comparable enantioselectivity (**7m**, 92% ee), while 5,5-disubstituted cyclohexane-1,3-dione led to lower enantioselectities (87% ee for **7n** and 74% ee for **7o**). Furthermore, 5-monosubstituted cyclohexane-1,3-dione was converted to the desired products **7p** and **7q** in high yields (95% and 90%) with good enantioselectivities (87% and 89% ee) and reasonable diastereoselectivities (4 : 1 and 5 : 1 dr).

Table 1 Survey of the reaction conditions[a]



Entry	Catalyst	Solvent	Yield[b] (%)	ee[c] (%)
1[d]	**L1**	CH_2Cl_2	58	87
2	**L1**	CH_2Cl_2	56	88
3	**L1**	CCl_4	98	92
4	**L1**	CH_2ClCH_2Cl	64	90
5	**L1**	$CHCl_3$	53	85
6	**L1**	$PhCH_3$	72	86
7	**L1**	MeCN	ND	
8	**L1**	THF	ND	
9	**L1**	Hexane	16	86
10	**L2**	CCl_4	40	72
11	**L3**	CCl_4	70	82
12	**L4**	CCl_4	34	11
13	**L5**	CCl_4	32	39
14	**L6**	CCl_4	16	4
15	**L7**	CCl_4	76	48
16	**L8**	CCl_4	48	71
17	**L9**	CCl_4	90	91
18[e]	**L10**	CCl_4	88	88
19[f]	**L1**	CCl_4	89	90
20	**L1**	CCl_4	84	90

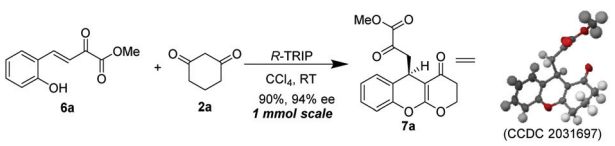
[a] Reaction conditions: To a mixture of hydroxyl (*E*)-2-hydroxyphenyl-2-oxobut-3-enoates **6a** (0.1 mmol), 1,3-cyclohexanedione **2a** (0.12 mmol) and catalyst (0.01 mmol) was added solvent (3 mL). The reaction mixture was stirred at room temperature overnight. [b] Isolated yields. [c] Determined by chiral HPLC on ChiralPak AD-H column. [d] Under the irradiation of blue LEDs. [e] 1 mL CCl_4 was added. [f] 0.5 mL CCl_4 was added.



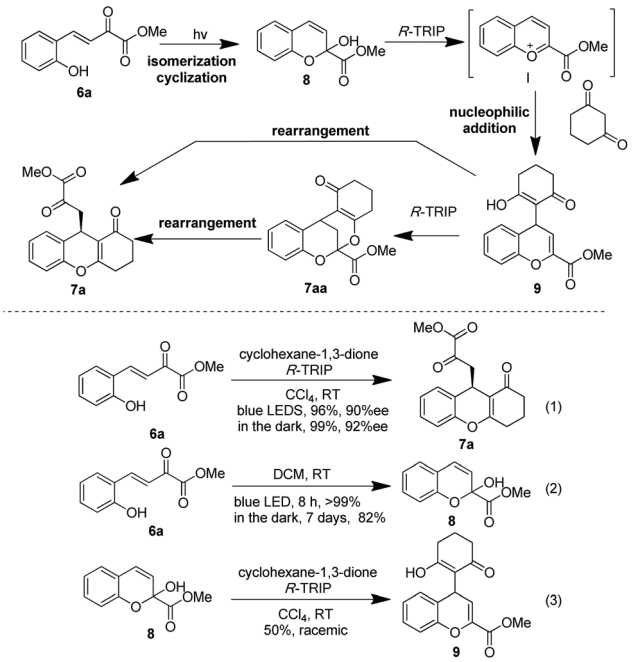
Scheme 1 Substrate scope.

To demonstrate the synthetic practicality of this protocol (Scheme 2), the reaction of methyl (*E*)-4-(2-hydroxyphenyl)-2-oxobut-3-enoate **6a** with cyclo-1,3-dione **2a** was carried out on 1 mmol scale, which afforded **7a** in 90% yield with 94% ee. A single crystalline of **7a** was fortunately obtained, which undoubtedly determined the absolute configuration of **7a** to be (*R*) (Scheme 2).

As our previous work indicated that 2-hydroxychalcone could be converted to flavylium **I** under the irradiation of visible light in the presence of Brønsted acid, which would engage in nucleophilic addition to afford flavonoids **9** or **7aa** (Scheme 3).[20a] We spelculated that acid-catalyzed skeleton rearrangement of flavonoids **9** or **7aa** might generate **7a** *via*



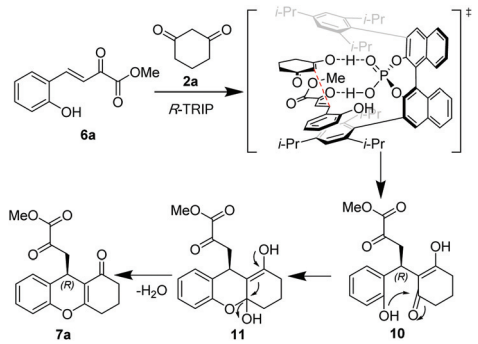
Scheme 2 1 mmol scale synthesis and X-ray crystallography of **7a**.



Scheme 3 The cycloisomerization/nucleophilic addition/skeleton rearrangement pathway.

ring opening/cyclization process. Therefore, two control reactions were carried out using the standard reaction conditions except that one was run under the irradiation of blue LEDs and the other was performed in the dark (Scheme 3). To our surprise, those two reactions only produced tetrahydroxanthenones **7a** in comparable yield and enantioselectivities. On the other hand, (*E*)-4-(2-hydroxyphenyl)-2-oxobut-3-enoate **6a** was slowly transferred to hemiketal **8** in quantitative yields under the irradiation of blue LEDs (eight hours) or in the dark (seven days). However, when hemiketal **8** was retreated with cyclo-1,3-dione **2a** under the standard reaction conditions, only racemic hybrid flavonoids **9** was isolated in 50% yield and no **7a** or **7aa** was detected even with extension of the reaction time. Based on these observations, the cycloisomerization/nucleophilic addition/skeleton rearrangement pathway was thus ruled out.

Based on the mechanistic studies and previous reports on CPA catalyzed Michael reactions,[7b,c,17,19] we proposed a tandem Michael addition/cyclization pathway for this reaction (Scheme 4). The phosphoric acid promoted the Michael addition of cyclohexa-1,3-dione **2a** to methyl (*E*)-4-(2-hydroxyphenyl)-2-oxobut-3-enoate **6a** *via* a hydrogen-bond network exerted by *R*-TRIP (Scheme 4). Hydrogen bonding between the keto-moiety of **6a** with *R*-TRIP together with plausible π–π stacking of the phenol fragment of **6a** with the side aromatic ring of *R*-TRIP made the *Si*-face of the enone available for the incoming nucleophilic attack of cyclohexa-1,3-dione,[21] which produced Michael adduct **10** with *R*-configuration. Subsequently, intramolecular cyclization of phenol to the dione moiety *via* nucleophilic addition/dehydration gave the resulting tetrahydroxanthenone **7a**.



Scheme 4 Proposed reaction pathway.

Conclusions

In summary, an asymmetric synthesis of 9-alkyl tetrahydroxanthenone scaffold from (*E*)-2-hydroxyaryl-2-oxobut-3-enoates *via* tandem Michael addition/cyclization with cyclo-1,3-diones catalyzed by *R*-TRIP was developed. This process provided a facile entry to a series of 9-alkyl tetrahydroxanthenones in high yields with good to high enantioselectivities. The application of this methodology in the asymmetric synthesis of natural products is currently pursued in our laboratory and the results will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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