JOC The Journal of Organic Chemistry

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Enantioselective Synthesis of 3,4-Dihydropyran Derivatives via Organocatalytic Michael Reaction of α,β-Unsaturated Enones

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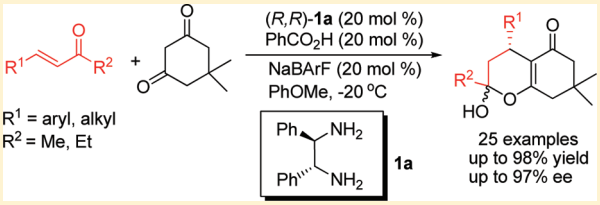
Supporting Information

ABSTRACT: A simple chiral diamine catalyst (**1a**) was successfully applied in the asymmetric Michael reaction between cyclic dimedone and α,β-unsaturated ketones. Both acyclic enones with aryl or alkyl β-substituents and cyclic enones were tolerated well in the reaction. The desired adducts were obtained in high yields (up to 98%) with excellent enantioselectivities (up to 97% ee). The additives were found to increase the reactivity dramatically. The biologically active 2,4-disubstituted polyhydroquinoline scaffold was conveniently prepared through an ammoniation from the generated 3,4-dihydropyran product.



The asymmetric Michael reaction of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated carbonyl compounds is one of the most powerful tools for the construction of biologically active compounds and has attracted growing attention in recent years.[1] Since the first example of such an asymmetric process reported by the Jørgensen group using chiral bisoxazoline−Cu(II) complexes,[2] a series of Michael acceptors and donors subsequently have been extended by many research groups.[3] Among them, the asymmetric Michael reaction of cyclic 1,3-dicarbonyl compounds to α,β-unsaturated enones provides an efficient method to synthesize chiral compounds possessing considerable bioactivities. For example, the chiral anticoagulant drug warfarin has been successfully prepared from the direct asymmetric reaction between 4-hydroxycoumarin and α,β-unsaturated ketones.[3c,4] In addition, aliphatic cyclic 1,3-diketone is a useful nucleophile to perform the Michael cyclization reaction. The resulted dihydropyran derivatives could be conveniently converted into a chiral 2,4-disubstituted polyhydroquinoline scaffold, which is a common structure with a number of biological activities such as antihypertensive, antidyslipidemic, and antidiabetic.[5] Recently, Calter's and our group reported such a procedure of β,γ-unsaturated α-ketoesters by cinchona alkaloid derived pyrimidine organocatalysts and *N*,*N*′-dioxide−Cu(OTf)$_2$ complex, respectively.[6] Yu's group utilized a fluorinated diarylprolinol silyl ether catalyst for the reaction of α,β-unsaturated aldehydes.[7] Despite good yield and enantioselectivity obtained, it is worth pointing out that α,β-unsaturated ketones, the common Michael acceptor, have not been applied in this kind of reaction as a consequence of the relatively low reactivity. Therefore, the development of efficient catalysts to realize asymmetric Michael cyclization of aliphatic cyclic 1,3-diketones with unactivated α,β-unsaturated enones is still in high demand.

C_2-Symmetric 1,2-diphenylethylenediamine (Dpen) is commercially inexpensive and air- and moisture-stable. Dpen as ligand and organocatalyst has shown high performance in many asymmetric transformations.[8] Chin and Mlynarski utilized vicinal diamine in the Michael reaction between 4-hydroxycoumarin and *trans*-4-phenyl-3-buten-2-one.[4a,d] On the basis of previous reports,[9] we considered that Dpen as a typical primary amine could activate both α,β-unsaturated enones via an iminium intermediate and 1,3-diketones via an enamine intermediate at the same time.[10] Herein, we describe the chiral 1,2-diphenylethylenediamine as an efficient catalyst for the asymmetric Michael cyclization of 1,3-dicarbonyl compounds with unactivated α,β-unsaturated ketones. The additives could greatly enhance the reaction activity. Good yields and enantioselectivities were achieved for aryl and alkyl β-substituted enones.

The addition of dimedone **3a** and cinnamone **2a** was used as a model reaction to screen the optimal conditions in the presence of chiral diamine catalysts **1a**−**1f** (Figure 1). Initially,

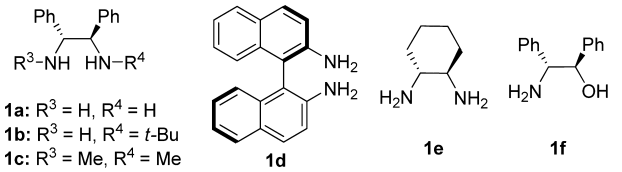


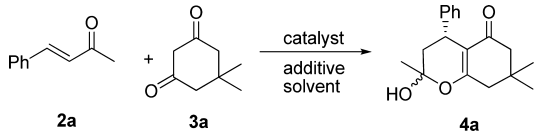
Figure 1. Chiral organocatalysts used for the reaction.

(*R*,*R*)-1,2-diphenylethylenediamine (Dpen) **1a** was used as the organocatalyst in toluene, but low yield was obtained (Table 1, entry 1).[11] Then, protonic acid was added to improve the reaction activity since it may facilitate the formation of the ketimine cation intermediate from cinnamone **2a**. Delightly, optically active **4a** was formed in a slightly improved yield and enantioselectivity in the presence of Dpen **1a** and benzoic acid

Received: February 4, 2012
Published: March 20, 2012

dx.doi.org/10.1021/jo3001047 | J. Org. Chem. 2012, 77, 4136−4142

Table 1. Screening of Catalysts for the Asymmetric Michael Reaction



2a 3a 4a

entry[a]	catalyst	solvent	additive	T (°C)	yield[b] (%)	ee[c] (%)
1	**1a**	PhMe		rt	10	80
2	**1a**	PhMe	$PhCO_2H$	rt	30	92
3	**1b**	PhMe	$PhCO_2H$	rt	20	59
4	**1c**	PhMe	$PhCO_2H$	rt	trace	nd
5	**1d**	PhMe	$PhCO_2H$	rt	15	80
6	**1e**	PhMe	$PhCO_2H$	rt	trace	nd
7	**1f**	PhMe	$PhCO_2H$	rt	trace	nd
8	**1a**	PhMe	TFA	rt	15	71
9	**1a**	PhMe	AcOH	rt	24	90
10	**1a**	PhMe	$PhCO_2H$	40	10	82
11	**1a**	PhMe	$PhCO_2H$	0	35	92
12	**1a**[d]	PhMe	$PhCO_2H$	0	52	92
13	**1a**[d]	PhMe	$PhCO_2H$/NaBArF	0	70	90
14	**1a**[d]	PhMe	$PhCO_2H$/NaBArF	−20	72	94
15	**1a**[d]	DCM	$PhCO_2H$/NaBArF	−20	45	94
16	**1a**[d]	Et_2O	$PhCO_2H$/NaBArF	−20	80	93
17	**1a**[d]	PhOMe	$PhCO_2H$/NaBArF	−20	94	95

[a]For entries 1−11, the reactions were performed with **2a** (0.15 mmol), **3a** (0.1 mmol), the indicated catalysts **1** (10 mol %), and additives (10 mol %) in solvent (1.0 mL) at room temperature for 48 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]With **1a** (20 mol %) and additives (20 mol %) in solvent (0.5 mL) for 96 h. NaBArF = Na[B(3,5-(CF3)2C6H3)4], nd = not detected.

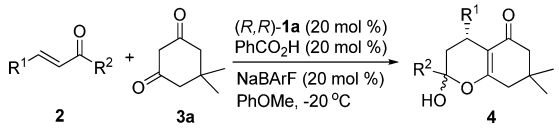
(30% yield, 92% ee; Table 1, entry 1 vs entry 2). However, diamine catalyst **1b** and **1c**, formed by modification of the primary diamine, proved to be inferior to the precursor **1a** (Table 1, entries 3 and 4 vs entry 2). It indicated the importance of the primary diamine subunits on the catalytic reaction. Next, chiral primary diamine catalysts bearing different backbones were investigated. The dihedral angle of the catalyst seemed to be another linchpin. Neither axial chiral binaphthyl diamine **1d** nor cyclohexylenediamine **1e** afforded satisfactory results (Table 1, entries 5 and 6). The use of chiral amino alcohol **1f** as the catalyst resulted in a trace amount of the product (Table 1, entry 7), which indicated the activation of both the enone and dimedone of concern was crucial for the yield and enantioselectivity of the reaction. To further improve the reactivity of the reaction, a series of additives was investigated. Acids, such as TFA, AcOH, had no improvement on the yield (Table 1, entries 8 and 9).[12] The catalyst loading of **1a** and the reaction temperature were also adjusted to enhancing the yield. Lowering the reaction temperature to 0 °C was more suitable for this process compared with raising the temperature to 40 °C (Table 1, entries 10 and 11). When the loading of the catalyst **1a** was increased to 20 mol % at 0 °C, the yield of the reaction was smoothly improved (Table 1, entry 12). Strikingly, adding 20 mol % of $PhCO_2H$/NaBArF at the same time achieved a 70% yield with little loss of the enantioselectivity (Table 1, entry 13).[13] In addition, the enantioselectivity was further raised to 94% ee at −20 °C with maintained yield (Table 1, entry 14). Solvent investigation showed that the enantioselectivity and yield increased in PhOMe (Table 1, entries 15−17). Hence, the optimal conditions were 20 mol % of **1a** with equivalent catalyst amounts of $PhCO_2H$ and NaBArF in PhOMe at −20 °C, which afforded the product **4a** with 94% yield and 95% ee.

The organocatalytic asymmetric Michael cyclization reaction under the optimal conditions was extended to various α,β-unsaturated enones, and the results are given in Table 2. A number of acyclic α,β-unsaturated enones with either various aryl substituents or alkyl substituents at the β-position of the enone **2** proceeded smoothly with dimedone **3a**, delivering the corresponding product **4** in high yields and enantioselectivities. The electronic properties and steric hindrance of the substituents at the aromatic ring had no apparent effect on the enantioselectivity (Table 2, entries 1−14). In general, cinnamone derivatives with electron-withdrawing substituents on the aromatic ring showed higher reactivity than the substrates with electron-donating substituents. Especially, hydroxyl substituted enone **2o**, which was rarely investigated, also was well tolerated in this reaction. Although the yield of the Michael adduct **4o** was slightly reduced, excellent enantioselectivity was maintained (66% yield, 94% ee; Table 2, entry 15). In the case of *o*-methoxyl substituted enone **2p**, relatively lower yield was obtained as a consequence of 1,2-addition side reaction (Table 2, entry 16).[7] The disubstituted aromatic α,β-unsaturated ketones could also be successfully extended, affording the products in moderate yields with 94−95% ee (Table 2, entries 17 and 18). Fused-ring enone **2s** and heteroaromatic enone **2t** were suitable substrates to give the corresponding products **4s** and **4t** with 95% ee and 94% ee, respectively (Table 2, entries 19 and 20). In addition, β-alkyl substituted enones **2u** and **2v** were also investigated and well tolerated (Table 2, entries 21 and 22). Notably, the best enantioselectivity (97% ee) was achieved in the case of (*E*)-1-phenylpent-1-en-3-one **2w** (Table 2, entry 23).

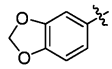
Moreover, we successfully achieved the asymmetric Michael reaction of 2-cyclohexen-1-one **2x** to synthesize bridged-ring compound **4x** (Scheme 1a, 70% yield, 90% ee). Gratifyingly, optically active anticoagulant warfarin **4y** was formed by one

dx.doi.org/10.1021/jo3001047 | J. Org. Chem. 2012, 77, 4136−4142

Table 2. Substrate Scope for the Catalytic Asymmetric Michael Cyclization Reaction

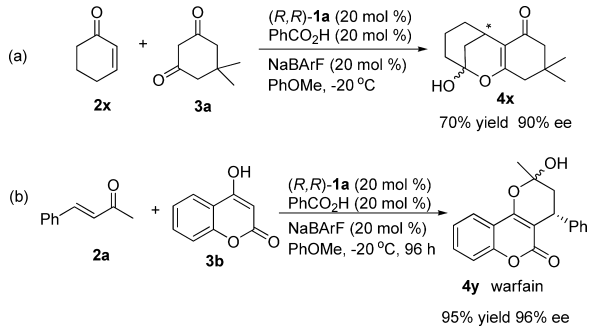


2 3a 4

entry[a]	R^1	R^2	4	yield[b] (%)	ee[c] (%)
1	Ph	Me	**4a**	94	95
2	4-FC_6H_4	Me	**4b**	96	93
3[d]	4-ClC_6H_4	Me	**4c**	95	94(*R*)
4	4-BrC_6H_4	Me	**4d**	91	94
5	4-CNC_6H_4	Me	**4e**	90	94
6	4-$NO_2C_6H_4$	Me	**4f**	86	94
7	4-$MeOC_6H_4$	Me	**4g**	78	95
8	4-$BnOC_6H_4$	Me	**4h**	80	95
9	4-PhC_6H_4	Me	**4i**	89	91
10	3-ClC_6H_4	Me	**4j**	98	94
11	3-$CF_3C_6H_4$	Me	**4k**	96	93
12	3-$NO_2C_6H_4$	Me	**4l**	90	93
13	3-$MeOC_6H_4$	Me	**4m**	90	93
14	3-MeC_6H_4	Me	**4n**	92	93
15	3-HOC_6H_4	Me	**4o**	66	94
16	2-$MeOC_6H_4$	Me	**4p**	70	94
17	2,3-$(MeO)_2C_6H_3$	Me	**4q**	70	95
18		Me	**4r**	80	94
19	2-naphthyl	Me	**4s**	93	95
20[e]	2-furyl	Me	**4t**	86	94
21[e]	*n*-Pr	Me	**4u**	73	82
22[e]	*i*-Pr	Me	**4v**	62	86
23	Ph	Et	**4w**	65	97

[a]Unless otherwise noted, the reaction was performed with **2** (0.15 mmol), **3a** (0.1 mmol), and catalyst **1a**/ $PhCO_2H$/NaBArF (20 mol %, 1/1/1) in PhOMe (0.5 mL) at −20 °C for 96 h. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]The absolute configuration of **4c** was *R* as determined by X-ray analysis. [e]With catalyst **1a**/$PhCO_2H$/NaBArF (30 mol %, 1:1:1)

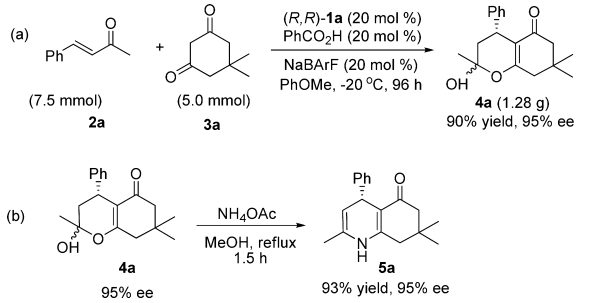
Scheme 1. Michael Cyclization Reaction between Cyclic 1,3-Dicarbonyl Compounds and α,β-Unsaturated Ketones



step in 95% yield and 96% ee in the presence of catalytic amounts of additives (Scheme 1b).[4]

In order to show the synthetic utility of the catalyst system, a gram-scale synthesis of the chiral dihydropyran derivative **4a** was performed. As shown in Scheme 2, by treatment of 1.1 g of

Scheme 2. Scaled-Up Version of the Michael Reaction and Conversion into 2,4-Disubstituted Polyhydroquinoline



2a (7.5 mmol) and 0.7 g of **3a** (5.0 mmol) under the optimal reaction conditions, the desired product **4a** was obtained in 90% yield with 95% ee (Scheme 2a). Notably, through a simple ammoniation, product **4a** was successfully converted into 2,4-disubstituted polyhydroquinoline scaffold **5a** in 93% yield without any loss of enantioselectivity (Scheme 2b).

The absolute configuration of the product **4c** was determined to be *R* by utilizing single-crystal X-ray diffraction (Figure 2).[14]

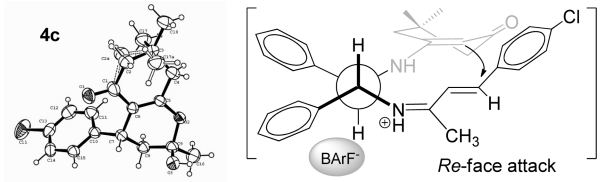


Figure 2. X-ray crystallographic structure of **4c** and proposed catalytic model.

Considering the influence of the catalyst structure on the reaction outcomes, we proposed a possible catalytic model as shown in Figure 2. For the chiral primary diamine catalyst **1a**, an iminium ion generated from enone **2c** and an enamine intermediate from dimedone **3a** can be envisaged in the process. The combined action of benzoic acid and NaBArF is the generation of sterically hindered $BArF^-$ anion around the iminium ion (see Supporting Information for details), and the *α,β*-unsaturated iminium ion adopts such an arrangement that facilitates the attack of the neighboring enamine from its *β-re* face. Therefore, the desired *R*-configured product **4c** was generated. The model can also be used to explain the best enantioselectivity obtained from enone **2w** with a bulky carbonyl substituent (Table 2, entry 23).

In conclusion, we have successfully demonstrated that simple unmodified chiral (*R,R*)-diphenylethylenediamine was an excellent organocatalyst for the enantioselective Michael reaction of aliphatic cyclic dimedone with unactivated *α,β*-unsaturated ketones under mild conditions. A variety of substituted *α,β*-unsaturated ketones were tolerated well in the presence of combined additives, delivering the products with high yields and excellent enantioselectivities. Further expansions of other nucleophiles and electrophiles using this catalyic system are under way.

dx.doi.org/10.1021/jo3001047 | J. Org. Chem. 2012, 77, 4136−4142

EXPERIMENTAL SECTION

General Details. Unless otherwise noted, ^{1}H and ^{13}C NMR spectra are internally referenced to residual solvent signals (^{1}H, 600 MHz, $CDCl_3$; ^{13}C 150 MHz, $CDCl_3$). Spectra were reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Enantiomeric excesses (ee) were determined by HPLC analysis using chiralpak columns. Optical rotations were reported as follows: $[\alpha]^{20}_D$ (c g/100 mL, CH_2Cl_2). HRMS was recorded on a commercial apparatus (ESI Source).

General Procedure for Asymmetric Michael Cyclization Reaction. The α,β-unsaturated ketones **2** (0.15 mmol, 1.5 equiv), cyclic 1,3-diketones **3** (0.1 mmol), catalyst **1a** (20 mol %, 4.2 mg), $PhCO_2H$ (20 mol %, 2.4 mg), and NaBArF (20 mol %, 17.7 mg) were added into a test tube. Then, PhOMe (0.5 mL) was added under nitrogen, and the mixture was stirred for 96 h at −20 °C. The product **4** was isolated via column chromatography (1/1/2.5, EtOAc/CH_2Cl_2/petroleum ether).

2-Hydroxy-2,7,7-trimethyl-4-phenyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4a). Yield 27.0 mg, 94%; white solid, mp 114−116 °C; $[\alpha]^{20}_D$ = +17.1 (c 0.54, CH_2Cl_2); HPLC Daicel chiralpack IA, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 5.93 min, $t_{R(minor)}$ 8.41 min; ^{1}H NMR (600 MHz, DMSO) δ 7.17−7.28 (m, 3H), 7.12−7.08 (m, 2H), 4.69 (t, J = 7.6 Hz, 0.3H), 3.73 (dd, J = 19.3, 9.1 Hz, 0.7H), 3.42−3.36 (m, 0.4H), 3.23−3.14 (m, 0.6H), 2.39−2.05 (m, 6H), 1.69 (dd, J = 13.3, 11.1 Hz, 0.54H), 1.42 (s, 2.45H), 1.13 (d, J = 3.5 Hz, 2H), 1.04 (s, 2.2H), 0.95 (s, 1.8H); ^{13}C NMR (150 MHz, DMSO) δ 207.9, 195.7, 195.5, 169.4, 168.5, 146.2, 146.0, 145.0, 128.4, 128.1, 127.8, 127.6, 127.3, 125.6, 125.5, 115.9, 112.5, 111.3, 100.3, 98.5, 65.4, 50.9, 46.3, 43.8, 42.8, 35.5, 34.4, 34.3, 31.9, 31.7, 30.1, 29.4, 28.8, 28.2, 28.1, 27.9, 27.6, 25.9, 15.6; ESI-HRMS calcd for $[C_{18}H_{22}O_3 + Na^+]$: 309.1461, found 309.1471.

4-(4-Fluorophenyl)-2-hydroxy-2,7,7-trimethyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4b). Yield 29.2 mg, 96%; colorless oil; $[\alpha]^{20}_D$ = +15.9 (c 0.58, CH_2Cl_2); HPLC Daicel chiralcel OD-H, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 6.34 min, $t_{R(minor)}$ 5.68 min; ^{1}H NMR δ 7.12 (dd, J = 8.4, 5.4 Hz, 0.88H), 7.07 (d, J = 3.0 Hz, 1.12H), 6.90−6.96 (m, 2H), 4.09 (s, 0.5H), 3.93 (t, J = 5.3 Hz, 0.41H), 3.80 (dd, J = 27.5, 18.7 Hz, 0.5H), 3.56 (s, 0.38H), 3.53−3.46 (m, 0.21H), 2.04−2.38 (m, 6H), 1.46 (d, J = 7.5 Hz, 3H), 1.17 (s, 1.3H), 1.14 (s, 1.7H), 1.09 (s, 1.3H), 1.07 (s, 1.7H); ^{13}C NMR δ 210.5, 197.3, 197.0, 169.6, 168.7, 162.1, 161.8, 160.5, 160.2, 140.6, 139.1, 139.0, 129.2, 128.6, 128.5, 128.3, 115.5, 115.3, 115.1, 115.0, 114.6, 114.5, 113.0, 110.7, 99.7, 98.1, 65.8, 50.7, 46.1, 42.9, 42.8, 40.6, 33.6, 33.4, 32.6, 32.0, 31.5, 31.4, 30.0, 29.7, 29.5, 28.6, 28.4, 27.9, 27.4, 27.1, 15.2; ESI-HRMS calcd for $[C_{18}H_{21}FO_3 + H^+]$: 305.1547, found 305.1560.

4-(4-Chlorophenyl)-2-hydroxy-2,7,7-trimethyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4c). Yield 30.7 mg, 95%; white solid, mp 123−124 °C; $[\alpha]^{20}_D$ = −3.4 (c 0.61, CH_2Cl_2); HPLC Daicel chiralcel OD-H, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 7.49 min, $t_{R(minor)}$ 5.49 min; ^{1}H NMR δ 7.16−7.22 (m, 2H), 7.02−7.09 (m, 2H), 4.28−4.40 (m, 0.6H), 3.96−3.75 (m, 1.4H), 2.39−2.12 (m, 6H), 1.51−1.40 (m, 3H), 1.17 (s, 1.2H), 1.13 (s, 1.8H), 1.09 (s, 1.2H), 1.06 (s, 1.8H); ^{13}C NMR δ 197.4, 197.1, 169.9, 169.1, 143.7, 142.3, 131.7, 131.2, 129.2, 128.6, 128.4, 128.3, 127.9, 115.4, 115.3, 115.1, 115.0, 112.8, 110.6, 99.7, 98.1, 50.7, 50.6, 42.9, 42.6, 40.6, 33.6, 33.4, 33.1, 32.7, 32.0, 31.5, 29.5, 28.6, 28.4, 27.9, 27.4, 27.0, 26.9, 22.6, 14.1; ESI-HRMS calcd for $[C_{18}H_{21}{}^{35}ClO_3 + H^+]$: 321.1252, found 321.1254.

4-(4-Bromophenyl)-2-hydroxy-2,7,7-trimethyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4d). Yield 33.4 mg, 91%; colorless oil; $[\alpha]^{20}_D$ = −8.5 (c 0.66, CH_2Cl_2); HPLC Daicel chiralcel OD-H, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 8.19 min, $t_{R(minor)}$ 5.58 min; ^{1}H NMR δ 7.31−7.36 (m, 2H), 7.06−6.96 (m, 2H), 4.31−4.40 (m, 0.55H), 3.75−3.89 (m, 1.43H), 2.37−2.08 (m, 6H), 1.44(s, 1.3H), 1.43 (s, 1.7H), 1.16 (s, 1.2H), 1.13 (s, 1.8H), 1.09 (s, 1.2H), 1.06 (s, 1.8H); ^{13}C NMR δ 210.0, 197.4, 197.1, 169.9, 169.1, 144.2, 142.9, 131.5, 131.3, 130.9, 129.7, 129.0, 128.8, 128.6, 128.4, 119.8, 119.3, 112.8, 110.6, 99.7, 98.1, 50.6, 42.9, 42.6, 33.7, 33.2, 32.0, 31.5, 29.5, 28.6, 28.4, 27.9, 27.4, 26.9, 22.6, 14.1; ESI-HRMS calcd for $[C_{18}H_{21}{}^{79}BrO_3 + H^+]$: 365.0747, found 365.0753.

4-(2-Hydroxy-2,7,7-trimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromen-4-yl)benzonitrile (4e). Yield 28.1 mg, 90%; colorless oil; $[\alpha]^{20}_D$ = −24.0 (c 0.50, CH_2Cl_2); HPLC Daicel chiralcel OD-H, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 9.99 min, $t_{R(minor)}$ 7.47 min; ^{1}H NMR δ 7.51 (dd, J = 11.3, 8.3 Hz, 2H), 7.25 (dd, J = 16.7, 8.1 Hz, 2H), 5.16 (s, 0.55H), 4.73 (s, 0.35H), 3.86 (dd, J = 12.5, 6.9 Hz, 1H), 3.49 (q, J = 7.0 Hz, 0.1H), 2.40−2.00 (m, 6H), 1.43 (d, J = 13.3 Hz, 3H), 1.15 (d, J = 12.5 Hz, 3H), 1.08 (d, J = 11.6 Hz, 3H); ^{13}C NMR δ 208.8, 197.5, 197.2, 170.7, 170.1, 151.6, 150.6, 132.1, 131.8, 128.4, 127.9, 119.1, 112.2, 110.2, 109.1, 99.6, 98.1, 65.8, 50.6, 50.5, 42.9, 42.4, 40.4, 34.6, 34.5, 32.0, 31.5, 29.5, 28.5, 28.3, 27.6, 27.3, 26.7, 22.6, 15.2, 14.1; ESI-HRMS calcd for $[C_{19}H_{21}NO_3 + H^+]$: 312.1594, found 312.1602.

2-Hydroxy-2,7,7-trimethyl-4-(4-nitrophenyl)-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4f). Yield 28.4 mg, 86%; colorless oil; $[\alpha]^{20}_D$ = −40.3 (c 0.52, CH_2Cl_2); HPLC Daicel chiralcel IA, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 13.84 min, $t_{R(minor)}$ 26.06 min; ^{1}H NMR δ 8.11 (dd, J = 11.8, 8.7 Hz, 2H), 7.32−7.28 (m, 2H), 3.99 (t, J = 5.7 Hz, 0.4H), 3.93 (dd, J = 11.5, 6.7 Hz, 0.6H), 3.75 (t, J = 6.5 Hz, 0.55H), 3.19 (s, 0.45H), 2.39−2.17 (m, 6H), 1.55 (s, 2H), 1.51 (s, 1H), 1.19 (s, 1H), 1.15 (s, 2H), 1.11 (s, 1H), 1.09 (s, 2H); ^{13}C NMR δ 197.0, 196.5, 169.6, 168.9, 153.4, 152.3, 146.1, 128.3, 127.7, 123.8, 123.5, 112.4, 110.3, 99.2, 97.8, 67.9, 65.8, 50.7, 50.6, 42.9, 42.8, 42.0, 39.9, 34.4, 33.8, 32.0, 31.6, 30.3, 29.4, 28.7, 28.3, 28.2, 27.5, 27.4, 25.6, 15.2; ESI-HRMS calcd for $[C_{18}H_{21}NO_5 + H^+]$: 332.1492, found 332.1497.

2-Hydroxy-4-(4-methoxyphenyl)-2,7,7-trimethyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4g). Yield 24.6 mg, 78%; colorless oil; $[\alpha]^{20}_D$ = +8.2 (c 0.49, CH_2Cl_2); HPLC Daicel chiralcel IA, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 7.72 min, $t_{R(minor)}$ 12.61 min; ^{1}H NMR δ 7.08 (dd, J = 29.8, 8.6 Hz, 2H), 6.81 (dd, J = 19.5, 8.6 Hz, 2H), 4.00 (s, 0.6H), 3.82−3.78 (m, 0.4H), 3.76 (d, J = 2.2 Hz, 3H), 3.40 (t, J = 9.8 Hz, 0.4H), 3.25 (s, 0.6H), 2.42−2.10 (m, 6H), 1.48 (s, 3H), 1.20 (s, 1.8H), 1.15 (s, 1.2H), 1.11 (s, 1.8H), 1.07 (s, 1.2H); ^{13}C NMR δ 197.1, 196.7, 169.1, 167.8, 158.3, 157.6, 136.8, 134.4, 128.0, 127.9, 114.5, 113.8, 113.3, 110.5, 99.7, 98.1, 55.2, 55.1, 50.8, 43.0, 42.8, 42.7, 40.1, 33.2, 32.0, 31.6, 31.5, 31.4, 29.5, 28.9, 28.3, 28.0, 27.5, 22.6, 14.1; ESI-HRMS calcd for $[C_{19}H_{24}O_4 + H^+]$: 317.1747, found 317.1746.

4-(4-(Benzyloxy)phenyl)-2-hydroxy-2,7,7-trimethyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4h). Yield 30.0 mg, 80%; yellow solid, mp 126−128 °C; $[\alpha]^{20}_D$ = −0.5 (c 0.60, CH_2Cl_2); HPLC Daicel chiralcel IA, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 9.83 min, $t_{R(minor)}$ 16.92 min; ^{1}H NMR δ 7.39 (dt, J = 14.7, 7.6 Hz, 4H), 7.31 (t, J = 7.1 Hz, 1H), 7.08 (dd, J = 27.3, 8.5 Hz, 2H), 6.91−6.87 (m, 2H), 5.00 (s, 2H), 4.01 (d, J = 4.1 Hz, 0.5H), 3.80 (d, J = 9.0 Hz, 0.3H), 3.70 (s, 0.4H), 3.24−3.13 (m, 0.8H), 2.45−1.98 (m, 6H), 1.48 (s, 3H), 1.17 (d, J = 26.0 Hz, 3H), 1.09 (d, J = 19.0 Hz, 3H); ^{13}C NMR δ 197.0, 196.7, 196.6, 169.1, 157.6, 157.0, 137.3, 137.0, 128.6, 128.5, 128.0, 127.9,127.8, 127.5, 127.4, 115.5, 114.7, 113.3, 100.0, 99.7, 98.1, 70.0, 69.9, 67.1, 50.8, 42.9, 42.8, 40.0, 33.2, 32.0, 31.5, 31.3, 29.5, 28.9, 28.3, 28.0, 27.6, 27.5, 22.6, 15.6; ESI-HRMS calcd for $[C_{25}H_{28}O_4 + Na^+]$: 415.1880, found 415.1878.

4-(Biphenyl-4-yl)-2-hydroxy-2,7,7-trimethyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4i). Yield 32.2 mg, 89%; colorless oil; $[\alpha]^{20}_D$ = −24.0 (c 0.60, CH_2Cl_2); HPLC Daicel chiralcel IA, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 7.86 min, $t_{R(minor)}$ 12.46 min; ^{1}H NMR δ 7.51 (ddd, J = 27.9, 15.3, 8.0 Hz, 4H), 7.40 (td, J = 7.6, 3.6 Hz, 2H), 7.34−7.28 (m, 1H), 7.26−7.24 (m, 1.12H), 7.20 (d, J = 8.1 Hz, 0.88H), 4.07 (s, 0.48H), 3.91−3.87 (m, 0.40H), 3.75 (t, J = 6.4 Hz, 0.28H), 3.48 (q, J = 7.0 Hz, 0.43H), 3.27 (s, 0.42H), 2.40−2.19 (m, 6H), 1.50 (s, 3H), 1.21 (s, 1.69H), 1.17 (s, 1.29H), 1.11 (s, 1.56H), 1.08 (s, 1.43H); ^{13}C NMR δ 197.1, 196.8, 169.3, 168.3, 144.1, 142.0, 141.2, 140.8, 139.6, 138.7, 135.8, 128.7, 128.6, 127.7, 127.4, 127.2, 127.1, 127.0, 126.8, 125.5, 113.1, 110.5, 99.7, 98.1, 68.0, 65.8, 50.8, 43.0, 42.9, 42.7, 40.3, 34.2, 33.8, 32.3, 32.0, 31.5, 30.3, 29.5, 28.8, 28.3, 28.1, 27.5, 27.4, 25.6, 15.2; ESI-HRMS calcd for $[C_{24}H_{26}O_3 + Na^+]$: 385.1774, found 385.1779.

4-(3-Chlorophenyl)-2-hydroxy-2,7,7-trimethyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4j). Yield 32.0 mg, 98%; white

dx.doi.org/10.1021/jo3001047 | J. Org. Chem. 2012, 77, 4136−4142

solid, mp 102−104 °C; $[\alpha]^{20}_D$ = +1.3 (*c* 0.64, CH_2Cl_2); HPLC Daicel chiralcel IA, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 6.39 min, $t_{R(minor)}$ 9.01 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17−7.06 (m, 3H), 7.00 (q, *J* = 7.4 Hz, 1H), 4.61 (s, 0.59H), 3.87 (t, *J* = 5.5 Hz, 0.40H), 3.82−3.77 (m, 0.51H), 3.73 (d, *J* = 5.9 Hz, 0.49H), 2.41−2.04 (m, 6H), 1.43 (d, *J* = 4.2 Hz, 3H), 1.16 (d, *J* = 9.6 Hz, 3H), 1.07 (d, *J* = 8.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 197.1, 170.0, 169.3, 147.4, 146.1, 134.2, 134.0, 129.6, 129.5, 129.1, 128.0, 127.5, 127.1, 126.3, 126.0, 125.4, 125.3, 112.6, 110.5, 99.7, 98.2, 67.9, 65.8, 50.7, 50.6, 43.0, 42.9, 42.6, 40.7, 34.0, 33.6, 32.0, 31.6, 30.3, 30.0, 29.7, 29.5, 29.3, 28.6, 28.4, 27.8, 27.4, 26.8, 25.6, 22.7, 15.2; ESI-HRMS calcd for $[C_{18}H_{21}{}^{35}ClO_3 + H^+]$: 321.1252, found 321.1259.

2-Hydroxy-2,7,7-trimethyl-4-(3-(trifluoromethyl)phenyl)-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4k). Yield 34.2 mg, 96%; colorless oil; $[\alpha]^{20}_D$ = +7.6 (*c* 0.68, CH_2Cl_2); HPLC Daicel chiralcel IA, *n*-hexane/*i*-PrOH 90/10, 1.0 mL/min, $t_{R(major)}$ 11.23 min, $t_{R(minor)}$ 18.74 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 15.1 Hz, 2H), 7.32 (d, *J* = 5.7 Hz, 2H), 4.07 (s, 0.3H), 3.98−3.84 (m, 1H), 3.74 (t, *J* = 6.1 Hz, 0.4H), 3.54−3.37 (m, 0.3H), 2.37−2.08 (m, 6H), 1.42 (s, 3H), 1.17 (s, 1.2H), 1.14 (s, 1.8H), 1.09 (s, 1.3H), 1.06 (s, 1.7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 197.1, 170.1, 169.4, 146.3, 145.2, 130.8, 130.6, 130.5, 130.3, 130.2, 128.7, 128.6, 125.8, 125.6, 125.5, 124.2, 123.7, 123.6, 123.0, 122.9, 122.6, 112.6, 110.6, 99.7, 98.1, 67.9, 65.8, 50.6, 50.5, 43.0, 42.9, 42.6, 40.7, 34.2, 34.0, 32.0, 31.5, 30.3, 29.7, 29.5, 28.5, 28.2, 27.8, 27.1, 26.8, 25.5, 15.2; ESI-HRMS calcd for $[C_{19}H_{21}F_3O_3 + Na^+]$: 377.1335, found 377.1316.

2-Hydroxy-2,7,7-trimethyl-4-(3-nitrophenyl)-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4l). Yield 29.8 mg, 90%; colorless oil; $[\alpha]^{20}_D$ = −11.1 (*c* 0.54, CH_2Cl_2); HPLC Daicel chiralcel IA, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 11.68 min, $t_{R(minor)}$ 14.80 min; ^{1}H NMR δ 8.04−7.96 (m, 2H), 7.50 (s, 1H), 7.40 (dt, *J* = 12.4, 7.8 Hz, 1H), 4.02−3.90 (m, 1H), 3.74 (s, 0.6H), 3.15 (s, 0.4H), 2.43−2.13 (m, 6H), 1.52 (d, *J* = 18.2 Hz, 3H), 1.19 (d, *J* = 23.2 Hz, 3H), 1.10 (d, *J* = 14.8 Hz, 3H); ^{13}C NMR δ 197.1, 196.6, 181.9, 169.7, 169.1, 148.4, 147.5, 146.4, 140.2, 134.0, 133.7, 129.1, 128.9, 125.5, 122.6, 121.6, 121.0, 112.4, 110.3, 99.2, 97.9, 67.9, 50.6, 42.9, 42.3, 40.0, 34.2, 33.4, 32.0, 31.6, 30.3, 29.5, 28.6, 28.3, 28.1, 27.6, 27.4, 25.5, 18.8; ESI-HRMS calcd for $[C_{18}H_{21}NO_5 + H^+]$: 332.1492, found 332.1495.

2-Hydroxy-4-(3-methoxyphenyl)-2,7,7-trimethyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4m). Yield 28.5 mg, 90%; colorless oil; $[\alpha]^{20}_D$ = +6.5 (*c* 0.57, CH_2Cl_2); HPLC Daicel chiralcel IA, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 7.66 min, $t_{R(minor)}$ 10.69 min; ^{1}H NMR δ 7.18 (dt, *J* = 24.6, 7.8 Hz, 1H), 6.79−6.67 (m, 3H), 4.00 (s, 0.56H), 3.94−3.77 (m, 1H), 3.75 (s, 3H), 3.48 (dd, *J* = 14.0, 7.0 Hz, 0.45H), 2.43−2.01 (m, 6H), 1.46 (d, *J* = 9.1 Hz, 3H), 1.18 (d, *J* = 20.9 Hz, 3H), 1.09 (d, *J* = 19.6 Hz, 3H); ^{13}C NMR δ 197.1, 169.4, 160.1, 146.7, 144.7, 130.1, 129.2, 119.5, 119.0, 113.0, 112.8, 112.0, 111.1, 110.3, 99.7, 98.1, 55.1, 50.7, 42.8, 40.3, 34.1, 32.5, 32.0, 31.6, 31.5, 29.5, 28.8, 28.4, 28.0, 27.3, 22.6, 14.1; ESI-HRMS calcd for $[C_{19}H_{24}O_4 + Na^+]$: 339.1567, found 339.1571.

2-Hydroxy-2,7,7-trimethyl-4-m-tolyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4n). Yield 27.6 mg, 92%; colorless oil; $[\alpha]^{20}_D$ = +19.2 (*c* 0.59, CH_2Cl_2); HPLC Daicel chiralcel IA, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 7.66 min, $t_{R(minor)}$ 10.69 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (dd, *J* = 14.5, 7.4 Hz, 1H), 7.01−6.89 (m, 3H), 4.00 (s, 0.5H), 3.85−3.76 (m, 0.6H), 3.48 (q, *J* = 7.0 Hz, 0.5H), 3.42 (s, 0.4H), 2.42−2.12 (m, 9H), 1.46 (d, *J* = 7.7 Hz, 3H), 1.18 (d, *J* = 16.8 Hz, 3H), 1.09 (d, *J* = 14.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1, 196.8, 169.3, 168.1, 144.9, 142.8, 138.7, 137.7, 129.0, 128.2, 127.8, 127.6, 126.6, 124.0, 123.7, 113.2, 110.4, 99.8, 98.1, 67.0, 65.8, 50.8, 43.0, 42.9, 40.4, 34.0, 32.4, 32.0, 31.5, 29.6, 28.8, 28.4, 28.0, 27.4, 27.3, 21.5, 15.2; ESI-HRMS calcd for $[C_{19}H_{24}O_3 + H^+]$: 301.1798, found 301.1809.

2-Hydroxy-4-(3-hydroxyphenyl)-2,7,7-trimethyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4o). Yield 20.0 mg, 66%; colorless oil; $[\alpha]^{20}_D$ = +36.1 (*c* 0.40, CH_2Cl_2); HPLC Daicel chiralcel IA, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 6.76 min, $t_{R(minor)}$ 9.13 min; ^{1}H NMR δ 7.02 (dt, *J* = 11.5, 7.9 Hz, 1H), 6.66−6.49 (m, 3H), 4.68 (s, 0.33H), 4.12 (d, *J* = 7.1 Hz, 0.3H), 3.89 (d, *J* = 30.2 Hz, 0.7H), 3.78−3.73 (m, 0.45H), 3.49 (q, *J* = 7.0 Hz, 0.56H), 2.37−2.04 (m, 6H), 1.45 (s, 3H), 1.14 (d, *J* = 13.3 Hz, 3H), 1.06 (d, *J* = 22.7 Hz, 3H); ^{13}C NMR δ 211.6, 198.4, 171.4, 170.6, 169.9, 157.0, 156.2, 146.3, 144.5, 130.0, 129.3, 118.0, 117.9, 115.0, 114.5, 114.2, 113.2, 113.0, 110.5, 100.1, 98.5, 65.8, 60.5, 50.6, 50.5, 43.0, 42.9, 42.5, 40.3, 33.8, 32.6, 32.0, 31.5, 29.4, 28.8, 28.1, 27.8, 27.5, 27.1, 21.0, 15.2, 14.1; ESI-HRMS calcd for $[C_{18}H_{22}O_4 + H^+]$: 303.1591, found 303.1602.

2-Hydroxy-4-(2-methoxyphenyl)-2,7,7-trimethyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4p). Yield 22.0 mg, 70%; colorless oil; $[\alpha]^{20}_D$ = +39.1 (*c* 0.44, CH_2Cl_2); HPLC Daicel chiralcel OD-H, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 5.96 min, $t_{R(minor)}$ 8.32 min; ^{1}H NMR δ 7.19−7.10 (m, 1H), 6.98−6.92 (m, 1H), 6.89−6.80 (m, 2H), 4.22−4.28 (m, 0.8H), 3.87 (d, *J* = 5.8 Hz, 0.7H), 3.86 (s, 2H), 3.82 (s, 1H), 3.55 (s, 0.5H), 2.43−2.00 (m, 6H), 1.45 (s, 2H), 1.42 (s, 1H), 1.19 (s, 2H), 1.16 (s, 1H), 1.10 (s, 2H), 1.06 (s, 1H); ^{13}C NMR δ 209.3, 198.2, 196.8, 196.5, 171.2, 169.3, 157.0, 156.7, 155.4, 132.6, 130.5, 130.4, 129.2, 128.1, 127.3, 126.8, 126.2, 121.3, 120.8, 120.4, 115.0, 113.0, 111.1, 110.6, 110.4, 110.3, 100.0, 99.9, 98.4, 65.8, 55.8, 55.4, 55.2, 51.3, 50.9, 50.8, 45.8, 43.0, 42.9, 40.0, 37.3, 32.0, 31.6, 31.5, 31.1, 30.1, 29.5, 29.06, 28.4, 28.3, 28.2, 27.9, 27.8, 27.7, 27.6, 27.4, 22.6, 15.2, 14.1; ESI-HRMS calcd for $[C_{19}H_{24}O_4 + H^+]$: 317.1747, found 317.1756.

4-(2,3-Dimethoxyphenyl)-2-hydroxy-2,7,7-trimethyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4q). Yield 24.0 mg, 70%; colorless oil; $[\alpha]^{20}_D$ = −17.9 (*c* 0.48, CH_2Cl_2); HPLC Daicel chiralcel IB, *n*-hexane/*i*-PrOH = 80/20, 1.0 mL/min, $t_{R(major)}$ 8.19 min, $t_{R(minor)}$ 6.53 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (td, *J* = 8.0, 5.4 Hz, 1H), 6.79−6.70 (m, 1H), 6.61 (d, *J* = 7.7 Hz, 0.55H), 6.53 (d, *J* = 7.8 Hz, 0.45H), 4.26 (t, *J* = 8.7 Hz, 1H), 4.07 (s, 0.55H), 3.94 (d, *J* = 3.8 Hz, 3H), 3.84 (d, *J* = 3.3 Hz, 3H), 3.71 (s, 0.45H), 2.35−2.11 (m, 6H), 1.47 (d, *J* = 10.3 Hz, 3H), 1.17 (d, *J* = 10.0 Hz, 3H), 1.08 (d, *J* = 10.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.5, 198.4, 196.8, 196.5, 171.8, 169.3, 168.1, 153.2, 152.6, 152.0, 146.8, 146.4, 144.3, 138.9, 137.0, 136.4, 125.0, 124.3, 124.0, 120.3, 118.5, 118.0, 115.4, 113.4, 111.1, 110.6, 110.3, 109.8, 99.9, 98.1, 65.8, 61.4, 60.4, 55.7, 55.6, 51.5, 50.8, 46.4, 43.1, 43.0, 42.9, 41.3, 38.9, 32.0, 31.6, 31.1, 30.3, 29.5, 29.2, 29.0, 28.5, 28.2, 28.0, 27.7, 27.6, 27.4, 27.0, 22.6, 15.2, 14.1; ESI-HRMS calcd for $[C_{20}H_{26}O_5 + H^+]$: 347.1853, found 347.1862.

4-(Benzo[*d*][1,3]dioxol-4-yl)-2-hydroxy-2,7,7-trimethyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4r). Yield 26.4 mg, 80%; colorless oil; $[\alpha]^{20}_D$ = +2.5 (*c* 0.52, CH_2Cl_2); HPLC Daicel chiralcel IA, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 8.92 min, $t_{R(minor)}$ 13.23 min; ^{1}H NMR δ 6.70 (dd, *J* = 8.0, 3.4 Hz, 1.6H), 6.64−6.60 (m, 1.4H), 5.90 (d, *J* = 12.9 Hz, 2H), 3.96 (s, 0.5H), 3.79−3.74 (m, 0.4H), 3.55−3.44 (m, 0.6H), 3.38 (d, *J* = 9.4 Hz, 0.5H), 2.41−2.00 (m, 6H), 1.49 (d, *J* = 3.7 Hz, 3H), 1.19 (s, 1.7H), 1.15 (s, 1.3H), 1.10 (s, 1.7H), 1.07 (s, 1.3H); ^{13}C NMR δ 197.1, 196.8, 169.2, 168.1, 148.3, 147.5, 146.4, 145.5, 138.9, 136.9, 120.0, 119.4, 113.2, 110.5, 108.6, 108.2, 107.8, 107.3, 101.0, 100.7, 99.7, 98.1, 65.8, 50.8, 43.0, 42.8, 40.2, 33.8, 32.1, 32.0, 31.6, 31.5, 29.4, 29.0, 28.2, 28.0, 27.6, 27.5, 22.6, 15.2, 14.1; ESI-HRMS calcd for $[C_{19}H_{22}O_5 + H^+]$: 331.1540, found 331.1551.

2-Hydroxy-2,7,7-trimethyl-4-(naphthalen-2-yl)-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4s). Yield 31.3 mg, 93%; colorless oil; $[\alpha]^{20}_D$ = −29.7 (*c* 0.62, CH_2Cl_2); HPLC Daicel chiralcel IA, *n*-hexane/*i*-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 8.25 min, $t_{R(minor)}$ 13.38 min; ^{1}H NMR δ 7.78−7.69 (m, 3H), 7.55 (d, *J* = 20.3 Hz, 1H), 7.44−7.32 (m, 3H), 4.15 (s, 0.55H), 4.01−3.97 (m, 0.45H), 3.79−3.54 (m, 0.5H), 3.37 (t, *J* = 45.0 Hz, 0.5H), 2.44−2.08 (m, 6H), 1.44 (d, *J* = 21.8 Hz, 3H), 1.24 (s, 1.6H), 1.18 (s, 1.4H), 1.12 (s, 1.6H), 1.06 (s, 1.4H); ^{13}C NMR δ 214.5, 197.2, 169.6, 140.6, 133.6, 133.5, 132.4, 132.1, 129.0, 128.0, 127.7, 127.6, 126.2, 125.8, 125.7, 125.6, 125.5, 125.0, 124.9, 113.1, 110.5, 99.8, 98.2, 50.8, 43.0, 42.9, 42.6, 40.0, 34.2, 32.9, 32.1, 31.6, 31.5, 29.5, 28.8, 28.4, 28.0, 27.5, 27.3, 22.6, 14.1; ESI-HRMS calcd for $[C_{22}H_{24}O_3 + H^+]$: 337.1798, found 337.1803.

4-(Furan-2-yl)-2-hydroxy-2,7,7-trimethyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4t). Yield 23.7 mg, 86%; colorless oil; $[\alpha]^{20}_D$ = +20.9 (*c* 0.47, CH_2Cl_2); HPLC Daicel chiralcel AD-H, *n*-hexane/*i*-PrOH 95/5, 1.0 mL/min, $t_{R(major)}$ 30.75 min, $t_{R(minor)}$ 38.48 min; ^{1}H NMR δ 7.33 (s, 0.68H), 7.25 (s, 0.32H), 6.27 (m, 1H), 5.99 (dd, *J* = 10.9, 2.7 Hz, 0.86H), 5.94 (d, *J* = 2.9 Hz, 0.21H), 4.12 (dd, *J* =

dx.doi.org/10.1021/jo3001047 | *J. Org. Chem.* 2012, 77, 4136−4142

8.4, 6.1 Hz, 1H), 4.04 (m, 0.9H), 2.26 (m, 6H), 1.53 (s, 2.34H), 1.40 (s, 0.64H), 1.14 (d, J = 5.8 Hz, 3H), 1.08 (d, J = 9.2 Hz, 3H); ^{13}C NMR δ 196.7, 169.0, 155.5, 142.0, 140.4, 130.0, 128.4, 110.6, 110.3, 108.4, 106.1, 105.3, 98.9, 60.4, 50.7, 42.9, 36.0, 32.1, 28.6, 28.2, 27.9, 27.7, 26.1; ESI-HRMS calcd for [$C_{16}H_{20}O_4$ + Na^+]: 299.1254, found 299.1248.

2-Hydroxy-2,7,7-trimethyl-4-propyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4u). Yield 18.3 mg, 73%; colorless oil; $[\alpha]^{20}_D$ = +16.1 (c 0.25, CH_2Cl_2); HPLC Daicel chiralcel IC, n-hexane/i-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 6.12 min, $t_{R(minor)}$ 12.08 min; ^{1}H NMR δ 3.68 (d, J = 35.1 Hz, 0.47H), 3.18−3.09 (m, 0.39H), 3.00 (s, 0.35H), 2.63 (d, J = 19.2 Hz, 0.8H), 2.42−2.01 (m, 6H), 1.62−1.35 (m, 4H), 1.22 (d, J = 48.2 Hz, 3H), 1.08−1.00 (m, 6H), 0.88 (d, J = 32.5 Hz, 3H); ^{13}C NMR δ 213.5, 198.7, 198.0, 171.7, 167.4, 167.1, 125.5, 115.6, 114.3, 113.9, 99.5, 98.1, 51.2, 48.2, 43.3, 43.0, 42.9, 38.3, 35.3, 34.7, 34.4, 31.8, 31.3, 31.0, 30.3, 29.8, 29.7, 29.5, 28.4, 28.2, 28.1, 28.0, 27.9, 27.1, 26.7, 21.3, 20.2, 19.5, 14.3, 14.1, 13.9; ESI-HRMS calcd for [$C_{15}H_{24}O_3$ + Na^+]: 275.1618, found 275.1615.

2-Hydroxy-4-isopropyl-2,7,7-trimethyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4v). Yield 15.5 mg, 62%; colorless oil; $[\alpha]^{20}_D$ = +15.4 (c 0.31, CH_2Cl_2); HPLC Daicel chiralcel IC, n-hexane/i-PrOH 90/10, 1.0 mL/min, $t_{R(major)}$ 12.07 min, $t_{R(minor)}$ 14.72 min; ^{1}H NMR δ 3.20−3.15 (m, 0.39H), 3.05 (s, 0.21H), 2.94 (s, 0.38H), 2.68 (d, J = 8.5 Hz, 0.28H), 2.64−2.59 (m, 0.72H), 2.36−2.04 (m, 6H), 1.98 (ddd, J = 13.1, 11.8, 4.9 Hz, 1H), 1.57 (s, 0.8H), 1.51 (s, 1H), 1.43 (s, 1.2H), 1.26 (s, 6H), 1.05 (d, J = 3.6 Hz, 3H), 0.93−0.87 (m, 3H); ^{13}C NMR δ 213.8, 198.6, 197.8, 171.6, 167.0, 166.6, 125.5, 115.7, 114.2, 113.9, 99.3, 98.0, 51.3, 51.2, 48.2, 43.2, 43.0, 42.8, 38.2, 35.0, 34.7, 34.3, 31.9, 31.8, 30.9, 30.3, 29.8, 29.7, 29.6, 29.4, 29.3, 28.3, 28.2, 28.1, 28.0, 27.8, 27.1, 26.7, 22.6, 21.3, 20.2, 19.4, 14.2, 14.1, 13.8; ESI-HRMS calcd for [$C_{15}H_{24}O_3$ + Na^+]: 275.1618, found 275.1632.

2-Ethyl-2-hydroxy-7,7-dimethyl-4-phenyl-3,4,7,8-tetrahydro-2*H*-chromen-5(6*H*)-one (4w). Yield 19.4 mg, 65%; white solid, mp 124−126 °C; $[\alpha]^{20}_D$ = +14.7 (c 0.38, CH_2Cl_2); HPLC Daicel chiralcel IA, n-hexane/i-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 5.86 min, $t_{R(minor)}$ 9.60 min; ^{1}H NMR δ 7.29 (dd, J = 10.8, 4.3 Hz, 1H), 7.26−7.24 (m, 1H), 7.21−7.13 (m, 3H), 4.05 (s, 0.5H), 3.85−3.81 (m, 0.4H), 3.70 (d, J = 3.9 Hz, 0.1H), 3.24 (s, 0.4H), 3.11 (d, J = 23.4 Hz, 0.6H), 2.45−1.99 (m, 6H), 1.75−1.71 (m, 2H), 1.18 (d, J = 26.6 Hz, 3H), 1.09 (d, J = 20.3 Hz, 3H), 0.97−0.92 (m, 3H); ^{13}C NMR δ 197.0, 196.6, 169.4, 168.1, 145.1, 142.9, 129.0, 128.3, 126.9, 126.7, 125.8, 113.3, 110.5, 101.3, 99.8, 50.8, 42.9, 42.8, 40.3, 38.0, 33.9, 33.6, 33.1, 32.0, 31.5, 29.5, 28.9, 28.3, 27.5, 7.4, 7.3; ESI-HRMS calcd for [$C_{19}H_{24}O_3$ + Na^+]: 323.1618, found 323.1614.

4,4-Dimethylbi(cyclohexane)-2,3′,6-trione (4x). Yield 16.5 mg, 70%; white solid, mp 116−118 °C; $[\alpha]^{20}_D$ = −20.1 (c 0.33, CH_2Cl_2); HPLC Daicel chiralcel IC, n-hexane/i-PrOH 90/10, 1.0 mL/min, $t_{R(major)}$ 16.60 min, $t_{R(minor)}$ 14.82 min; ^{1}H NMR δ 3.74 (s, 1H), 3.19 (s, 1H), 2.32 (d, J = 4.9 Hz, 2H), 2.22 (s, 2H), 2.03 (d, J = 12.8 Hz, 1H), 1.92 (dd, J = 12.5, 2.6 Hz, 1H), 1.76−1.69 (m, 2H), 1.63 (d, J = 12.7 Hz, 2H), 1.46−1.40 (m, 2H), 1.07 (s, 6H); ^{13}C NMR δ 196.5, 170.8, 112.4, 101.2, 50.4, 42.0, 38.8, 36.3, 32.3, 28.5, 28.4, 28.2, 27.0, 19.3; ESI-HRMS calcd for [$C_{14}H_{20}O_3$ + H^+]: 237.1485, found 237.1490.

2-Hydroxy-2-methyl-4-phenyl-3,4-dihydropyrano[3,2-*c*]-chromen-5(2*H*)-one (4y). Yield 30.0 mg, 95%; white solid, mp 156−158 °C; $[\alpha]^{20}_D$ = +9.9 (c 0.46, CH_2Cl_2); HPLC Daicel chiralcel AD-H, n-hexane/i-PrOH 80/20, 1.0 mL/min, $t_{R(major)}$ 5.45 min, $t_{R(minor)}$ 8.21 min; ^{1}H NMR δ 7.92 (d, J = 11.7 Hz, 0.12H), 7.89 (d, J = 7.7 Hz, 0.38H), 7.80 (d, J = 5.7 Hz, 0.45H), 7.56 (t, J = 7.6 Hz, 0.39H), 7.47 (d, J = 5.2 Hz, 0.62H), 7.35−7.20 (m, 7.42H), 4.69 (s, 0.09H), 4.27 (s, 0.42H), 4.16 (dd, J = 11.0, 7.0 Hz, 0.50H), 3.84 (s, 0.12H), 3.61 (s, 0.38H), 3.31 (d, J = 18.8 Hz, 0.43H), 2.56−2.37 (m, 1.47H), 1.99 (t, J = 12.4 Hz, 0.54H), 1.69 (s, 1.54H), 1.67 (s, 1.47H); ^{13}C NMR δ 162.2, 161.4, 159.7, 158.9, 152.8, 143.2, 141.5, 132.0, 131.5, 129.2, 128.6, 127.2, 127.0, 126.9, 126.4, 123.9, 123.6, 123.0, 122.7, 116.6, 116.4, 115.9, 115.5, 104.1, 101.1, 100.5, 99.0, 42.5, 40.0, 35.3, 34.2, 28.1, 27.6; ESI-HRMS calcd for [$C_{19}H_{16}O_4$ + H^+]: 309.1121, found 309.1119.

2,7,7-Trimethyl-4-phenyl-4,6,7,8-tetrahydroquinolin-5(1*H*)-one (5a). To a solution of **4a** (0.15 mmol, 42.9 mg) in MeOH (0.6 mL) was added ammonium acetate (115.6 mg, 10 equiv). Then, the reaction was refluxed for 1.5 h. The solvent was evaporated, and the mixture was subjected to silica gel chromatography (1/1/2.5, EtOAc/CH_2Cl_2/petroleum ether) to provide a yellow solid **5a** (37.7 mg, 93% yield, mp 106−108 °C). $[\alpha]^{20}_D$ = +358.1 (c 0.13, CH_2Cl_2); HPLC Daicel chiralcel IA, n-hexane/i-PrOH 90/10, 1.0 mL/min, $t_{R(major)}$ 13.70 min, $t_{R(minor)}$ 12.25 min; ^{1}H NMR δ 7.28−7.22 (m, 4H), 7.11 (t, J = 7.0 Hz, 1H), 6.04 (s, 1H), 4.74 (d, J = 4.1 Hz, 1H), 4.54 (d, J = 4.6 Hz, 1H), 2.27−2.12 (m, 4H), 1.75 (s, 3H), 1.06 (s, 3H), 1.00 (s, 3H); ^{13}C NMR δ 195.4, 151.4, 148.3, 129.6, 128.1, 127.6, 125.8, 107.8, 105.7, 50.8, 41.7, 37.7, 32.4, 29.4, 27.4, 18.8; ESI-HRMS calcd for [$C_{18}H_{21}NO$ + Na^+]: 290.1515, found 290.1512.

Preparation of DPEN·HBArF Salt. DPEN (1.0 mmol), NaBArF (1.0 mmol), and $PhCO_2H$ (1.0 mmol) were added into a round bottomed flask. Then, CH_2Cl_2 (20 mL) was added, and the mixture was stirred for 3 h at rt. A white crystalline solid was smoothly precipitated. After filtration, the solution was concentrated to provide a white solid. The structure was conformed as DPEN·HBArF salt by ^{1}H NMR analysis. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 8H), 7.52 (s, 4H), 7.32 (m, 6H), 7.10 (dd, J = 6.3, 2.9 Hz, 4H), 4.18 (d, J = 15.1 Hz, 9H). ^{1}H NMR (400 MHz, $CDCl_3$-D_2O) δ 7.71 (s, 8H), 7.53 (s, 4H), 7.31 (dd, J = 4.9, 1.5 Hz, 6H), 7.13 (dd, J = 6.6, 2.7 Hz, 4H), 4.20 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.42, 161.93, 161.43, 160.94, 135.08, 134.79, 130.06, 129.95, 129.08, 128.80, 128.62, 125.91, 125.82, 123.20, 120.49, 117.60, 59.85.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full optimization details, ^{1}H and ^{13}C NMR spectra, and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (Nos. 21021001, 21072133) and the National Basic Research Program of China (973 Program: 2010CB833300) for financial support. We also thank Sichuan University Analytical & Testing Center for NMR and X-ray analysis.

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(11) According to previous reports and our experimental data, compound **4** was confirmed to exist as a mixtrue of anomers. The equilibrium of the anomers is so rapid that no pseudodiastereomers are observed during HPLC analysis. NMR spectroscopy show up as a mixture of ketone and hemiketal.

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(14) CCDC 860294 (**4c**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.