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Highly enantioselective synthesis of warfarin and its analogs by means of cooperative $LiClO_4$/DPEN-catalyzed Michael reaction: enantioselectivity enhancement and mechanism

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ABSTRACT

The highly enantioselective synthesis of warfarin and its analogs was reported in this manuscript. And a cooperative catalysis was observed in asymmetric primary amine-catalyzed Michael reaction for the enantioselective synthesis of warfarin and its analogs, which led to the finding of several cooperative catalyst systems combined with Lewis acid and primary amine, such as $LiClO_4$/DPEN. In this Michael reaction of 4-hydrocoumarin, the cooperative catalyst system ($LiClO_4$/DPEN) resulted in higher levels of stereoselectivity (up to 94%ee). Additionally, the mechanism of the enantioselectivity enhancement in the cooperative catalytic Michael reaction has been investigated by using of ESI-MS and the study of nonlinear effect.

1. Introduction

The Michael reaction is one of the most important carbon–carbon and carbon–heteroatom bond-forming processes in organic synthesis,[1] and there is a continuing need for the development of enantioselective catalytic protocols for this reaction. The use of asymmetric Michael reactions to generate interesting and drug-like scaffolds has been actively investigated over the last decades. One successful example is straightforward production of chiral warfarin via the well established Michael addition of 4-hydrocoumarin to benzylideneacetone.[2]

Warfarin and sodium warfarin have been introduced for clinical use as Coumadin® and Marevan® to help prevent and treat blood clots in the legs, lungs and those associated with heart-value replacement or an irregular, rapid heartbeat. It is one of the most widely prescribed anti-thrombotics in North America over past decades. However, the active component of Coumadin® is a racemic mixture of warfarin, which results in decreased activity of clotting factors II, VII, IV, and X by inhibiting vitamin K epoxide reductase and thereby decreasing blood coagulation by preventing the vitamin K-dependent synthesis of blood-clotting proteins.[3] Further investigation showed considerable differences existed in the metabolic disposition of its two enantiomers.[4] Initially, enantiomerically pure *S*- or *R*-warfarin was obtained by chemical resolution[5] and chiral auxiliary-assisted synthesis strategy.[6] Although asymmetric hydrogenation[7] and hetereo-Diels–Alder cycloaddition reaction[8] have been reported as alternative process, highly enantioselective warfarin synthesis had rarely been achieved before 2003. Since the first example on the one-step synthesis of chiral warfarin through Michael addition reported by Jùrgensen in 2003,[2a,b] asymmetric organocatalytic Michael addition of 4-hydrocoumarin to benzylideneacetone has attracted considerable attention recently and allowed the straightforward access to chiral warfarin by using of easily available and inexpensive start materials. Chiral amines-based organocatalysts, especially primary amines,[9] have been showed to be good efficient in this asymmetric procedure. However, in most cases, 20 mol % or more catalyst loading was needed and the reaction time was long.[2d–f]

Despite the significant advances in this field, the synthesis of optically active warfarin and its analogs still represent a considerable synthetic challenge. Therefore it is still desirable to develop novel protocol or strategy for this important transformation. Herein, we wish to report a novel cooperative catalyst system that using metal salts and primary amine as combined catalysts in the enantioselective synthesis of chiral warfarin through the Michael reaction of 4-hydrocoumarin to benzylideneacetone, which leads to a significant increase in stereoselectivity and novel strategy for the synthesis of warfarin and its analogs. And in this report, anomalous nonlinear effects of catalysts provide a coherent mechanistic rationalization of the role of $LiClO_4$ in the primary amine-catalyzed Michael reaction.

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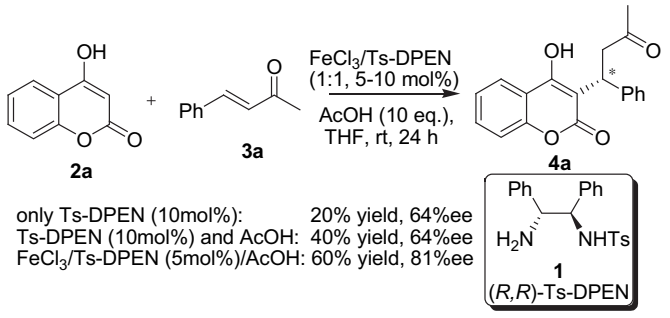
2. Results and discussion

In an earlier study, we have established that Noyori ligand, Ts-DPEN, could serve as enantioselective organocatalyst in the Michael addition of 1,3-dicarbonyl compounds to nitroolefins and indicated the importance of the primary amine group in controlling the enantioselectivity in this Michael reaction.[10] In an attempt to apply this catalyst to the asymmetric synthesis of chiral warfarin, however, only moderate enantioselectivity (64%ee) and low yield is obtained. As iron salts are convinced with the privileged chelation effects[11] and preparative advantages in the Michael addition of 1,3-dicarbonyl compounds, such as user-friendly, inexpensive, and virtually non-toxic metal catalysts, we hypothesized that iron salt would promote the reaction efficiently with higher enantioselectivity. As revealed in Scheme 1, the addition of catalytic amount



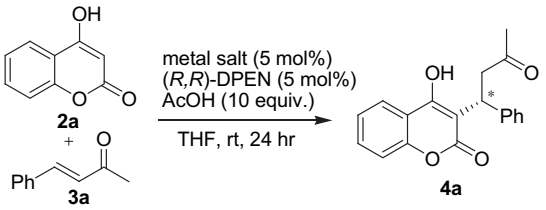
Scheme 1. Asymmetric synthesis of chiral warfarin catalyzed by cooperative iron/primary amine catalyst.

of $FeCl_3$ could improve the yield and enantioselectivity obviously, and we found that the decrease of catalytic amount of iron and primary amine to 5 mol %, acceptable yield and higher enantioselectivity (81%ee, Δ=+17%ee) was achieved in this reaction. Building on these results, we decided to carry out a first series experiments using (*R*,*R*)-1,2-diphenylethylenediamine (DPEN) as an organocatalyst under the optimal conditions,[12] while only varying the metal salts. Interestingly, significant variations in the stereoselectivity were observed depending on the nature of metal salts. The salts of Ca(II), Li(I), Mg(II), Sn(II), and In(III) gave promising enantioselectivities (>90%ee). When the salts of Bi(III), Cu(II), Ce (III), Ni(II), Ru(III), and Au(III) were used, no product or only a trace amount of the Michael adduct was detected even with larger amount of DPEN (10 mol %). Considering the comprehensive synergistic effect of metal salt and DPEN in conversion and enantioinduction, we were pleased to find that $LiClO_4$ led to preferential enantioselectivity and yield of chiral warfarin. This remarkable result obtained in THF with $LiClO_4$/DPEN exists a spectacular salt effect in comparison to that with only DPEN catalyst, which proved the concept of combining metal catalysis and organocatalysis is a promising strategy to improve the enantioselectivity (Table 1).[13]

We then studied the solvent effect in the enantioselective synthesis of chiral warfarin through Michael reaction of 4-hydrocoumarin to benzylideneacetone. As noted in Table 2, we observed significant solvent effects on both the overall yields and stereoselectivity of the reaction, and 1,4-dioxane provided the product with slight improvement in enantioselectivity (92%ee, Δ=+8%ee).

With these findings in hand, we turned our attention to the general Michael addition of substituted 4-hydrocoumarin to enones under the optimal reaction conditions. As shown in Table 3, the warfarin analogs were all obtained with excellent enantioselectivities (90–94%ee) in the presence of the simple cooperative $LiClO_4$/primary amine catalysts. Interestingly, although $NbCl_5$ gave a much higher yields than $LiClO_4$ for the examined substrates under the similar conditions, the enantioselectivities are not enough good (only 82–90%ee) (see Supplementary data, Table S-3).

Table 1
Effect of metal salts in enantioselective Michael reaction



MX_n	Yield%[a]	ee%[b]
—	47	84[c]
CuF_2	<5	—
$CaCl_2$	<20	90
$Bi(OTf)_3$	NR	—
$CeCl_3\cdot 7H_2O$	NR	—
AgF	50	88
$NbCl_5$	50	88
$LiClO_4\cdot 3H_2O$	64	90
$SbCl_3$	29	88
$Cu(TFA)_2$	NR	—
$Mg(ClO_4)_2$	32	94
$Pd(OAc)_2$	49	87
$InCl_3$	25	90
LiCl	68	85
LiOAc	68	49
$CuBr_2$	<10	88
$CuCl_2$	<10	86
$Ni(NO_3)_2\cdot 6H_2O$	<10	90
$Ni(OAc)_2\cdot 4H_2O$	NR	—
$Co(NO_3)_2\cdot 6H_2O$	<10	87
$RuCl_3$	NR	—
$HAuCl_4\cdot 4H_2O$	NR	—
$Mn(OAc)_2\cdot 4H_2O$	72	73
$SnCl_2\cdot 2H_2O$	53	90
$Bi(OTf)_3$	30	92[d]
$CeCl_3\cdot 7H_2O$	<10	92[d]
$NbCl_5$	83	90[d]
$ZnCl_2$	71	80[d]
LiBr	73	73
$LiClO_4\cdot 3H_2O$/additive[e]	92	47

[a] Isolated yields.
[b] Enantiomeric excess of warfarin was determined by HPLC analysis using a chiral phase column.
[c] No addition of any metal salts.
[d] DPEN (10 mol %) and metal salt (5 mol %) were used.
[e] The additive is acetophenone (5 mol %). And when the additive is benzaldehyde (5 mol %), the isolated yield and enantiomeric excess is 68% and 35%ee, respectively.

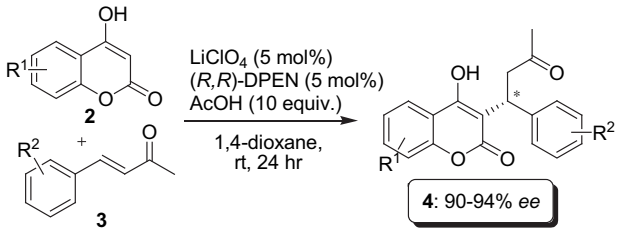
Table 2
Solvent effect on the enantioselective synthesis of warfarin

Entry[a]	Solvent	Yield%[b]	ee%[c]
1	$CHCl_3$	55	90
2	EtOAc	64	89
3	MeOH	39	72
4	1,4-Dioxane	61	92
5	Toluene	42	82
6	1,2-Dichloroethane	68	77
7	1,4-Dioxane/*t*-BuOH	54	89
8	THF	64	90(99)[d]

[a] Under standard conditions: 5 mol % of cocatalysts of $LiClO_4$/(*R*,*R*)-DPEN.
[b] Isolated yields.
[c] Enantiomeric excess of warfarin was determined by HPLC analysis using a chiral phase column.
[d] Warfarins (99%ee) could be obtained after crystallization.

To gain support for the hypothesis of cooperative effect of metal salt and primary amine catalysis in this Michael reaction, we made use of ESI-MS analysis and the nonlinear effect. The direct infusion eletrospray ionization mass spectrometry (ESI-MS) has been incorporated to the set of major techniques for mechanistic studies of organic reactions.[14] Therefore direct evidence of cooperative effect of $LiClO_4$/primary amine catalyst system was attained by ESI-MS

Table 3
Enantioselective synthesis of warfarin analogs via Michael addition



Entry	R^1	R^2	Yield%[a]	ee%[b]
1	H	*o*-OCH_3	**4b**: 52	91
2	H	*m*-OCH_3	**4c**: 64	90
3	H	*p*-CH_3	**4d**: 75	90
4	H	*p*-Cl	**4e**: 74	90
5	6-Cl	H	**4f**: 61	94
6	6-Cl	*o*-OCH_3	**4g**: 69	92
7	6-Cl	*p*-CH_3	**4h**: 62	91
8	6-Br	*o*-OCH_3	**4i**: 50	92

[a] Isolated yields.
[b] Enantiomeric excess of warfarin analogs were determined by HPLC analysis using a chiral phase column.

analysis of the ionic or ionized intermediates directly from the solutions of reaction mixture. In the cationic ESI spectra of reaction mixture obtained directly from solution to the gas phase (see Figs. 1 and 2 and Supplementary data), we 'fished' several important intermediates signals, such as the iminium salts of primary amine and benzylideneacetone (m/z=341.16 and 469.13). Thus these potential intermediates in the catalytic cycle showed the role of lithium salt and (*R*,*R*)-DPEN was different as coordinated Lewis acid and iminium-activated organocatalyst, and their combinational use resulted in the improved enantioselectivity in the Michael reaction of 4-hydrocoumarin with enones.

Since the pioneering studies of nonlinear stereochemical effect of catalyst enantiopurity on product enantiomeric excess by Kagan et al.,[15] observations of this phenomenon have an important diagnostic tool mechanistic studies of asymmetric reactions.[16] The

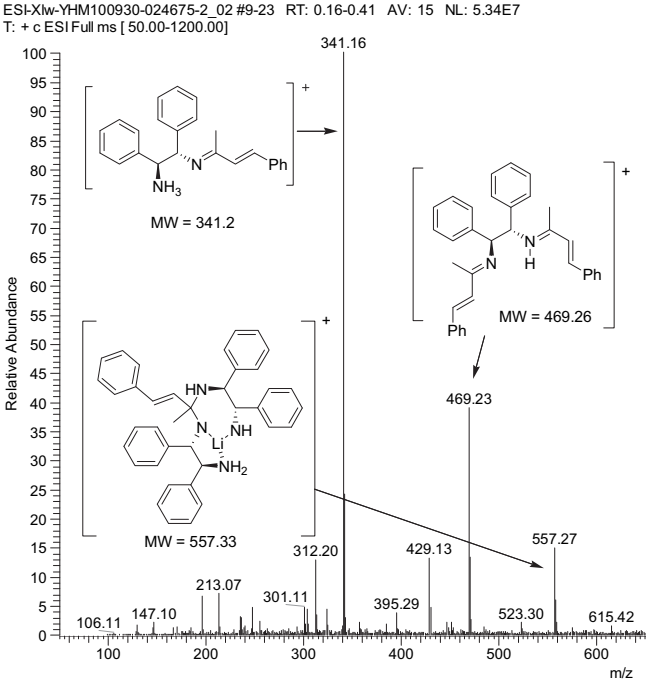


Fig. 1. ESI-MS spectrum of the mixture of $LiClO_4 \cdot 3H_2O$ (5 mol %), DPEN (5 mol %), benzylideneacetone (1.2 equiv), and AcOH (10 equiv) in THF.

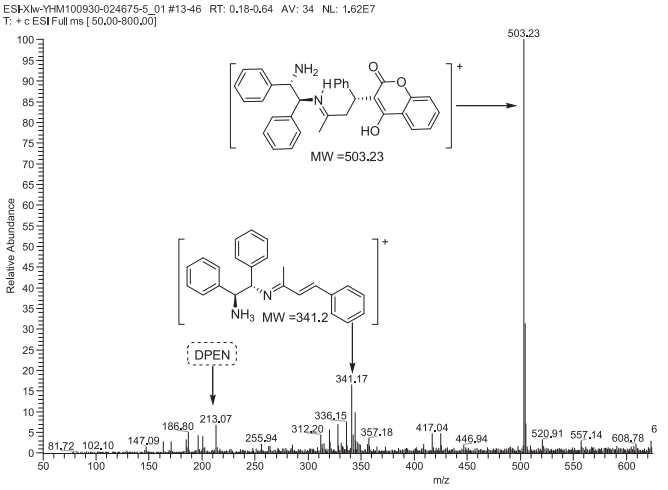


Fig. 2. ESI-MS spectrum of the Michael reaction mixture under standard conditions: $LiClO_4 \cdot 3H_2O$ (5 mol %), 4-hydrocoumarin (1 equiv), DPEN (5 mol %), benzylideneacetone (1.2 equiv), and AcOH (10 equiv) in THF.

results of this nonlinear study, graphically depicted in Fig. 3 clearly demonstrated the abnormal 'negative' nonlinear effect. The ee value of warfarin was, almost for all ee_{aux}, lower than it should be, and thus generates the multishaped curve in Fig. 3. It is negative in part but is positive partially. This abnormal (−)-NLE is a clear indication of a special behavior of the (*R*,*R*)-DPEN even when there are no $LiClO_4$ and AcOH as additive. The observed asymmetric depletion is interpreted as arising from the presence of two reactive chiral center of (*R*,*R*)-DPEN in the stereochemically determined transition structure. Additionally, we suggested that the aggregation of the intermediate of (*R*,*R*)-DPEN-based iminium ion is responsible for this effect, in which more complicated molecule, some like as ML_4 system described by Kagan, is formed. Accordingly, the presence of $LiClO_4$ resulted in the decomposition or restriction of such complex and then improved enantioselectivity of Michael addition.

Based on aforementioned experimental results and mechanistic studies, a detailed catalytic cycle for the Michael reaction with 4-hydrocoumarin and benzylideneacetone can be proposed in Scheme 2.

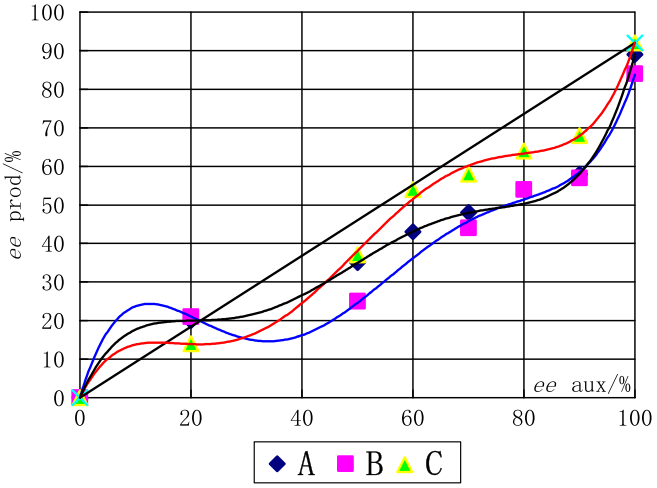
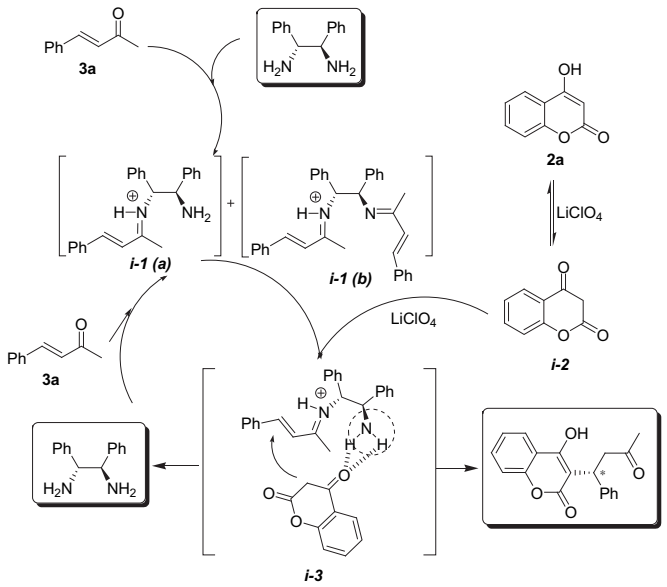


Fig. 3. Nonlinear effects in $LiClO_4$/DPEN/AcOH (5 mol %/5 mol %/10 equiv) mediated Michael reaction. Experimental ee_{prod} versus ee_{cat} with different catalytic system based on (*R*,*R*)-DPEN: (A) No addition of AcOH (◆: diamonds and black line); (B) No addition of $LiClO_4$ (■: squares and blue line); (C) Standard conditions with $LiClO_4$/DPEN/AcOH (5 mol %/5 mol %/10 equiv)(▲: uptriangles and red line).



Scheme 2. Possible catalytic cycle of cooperative catalysis with Lewis acid and organocatalyst in the combined $LiClO_4$/DPEN-catalyzed Michael reaction.

The 4-hydrocoumarin activated by a lithium-based Lewis acid would react with chiral iminium intermediate **i-1** in situ generated from α,β-unsaturated ketone and DPEN to provide enantioenriched **i-3**, in which the lithium plays positive Lewis acidic activation on the enhancement of enantioselectivity and reactivity.

3. Conclusions

In summary, we have described a Lewis acidic metal salt effect with cooperative catalysis when using primary amine as organocatalyst in the enantioselective synthesis of warfarin and its analogs through Michael reaction, which leads to the finding of several useful metal salts, such as $LiClO_4$, and give an increase in reactivity, and higher levels of stereoselectivity. Thus, by modifying the reaction conditions, we were able to obtain the warfarin with an excellent 94%ee under mild conditions. Finally, present example showed that further enhancements in the stereoselectivity and reactivity may be discovered with the novel cooperative strategy, in which the application of metal complexes or Lewis acid in tuning the reactivity of organic molecules-promoted reactions would be an efficient and privileged biomimic catalytic process in asymmetric catalysis.

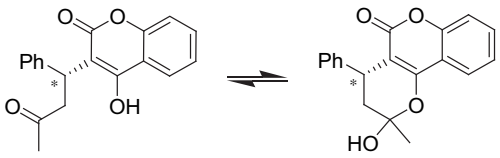
4. Experimental sections

4.1. General

General remarks: all reagents and solvents were used directly without purification. Flash column chromatography was performed over silica (200–300 mesh). ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on Advance (Brucker) 400 MHz Nuclear Magnetic Resonance Spectromer, and were referenced to the internal solvent signals. Thin layer chromatography was performed using silica gel; F_{254} TLC plates and visualized with ultraviolet light. HPLC was carried out with a Waters 2695 Millennium system equipped with a photodiode array detector. EI and CI mass spectra were performed on a Trace DSQ GC/MS spectrometer. Data are reported in the form of(m/z). The organocatalysts were commercial available and used directly. The Michael product, warfarin, was known and confirmed by GC/MS, and usual spectral methods (^1H NMR, ^{13}C NMR). The ESI-MS analysis of the samples was operated on an LCQ advantage mass spectrometer (ThermoFisher Company, USA), equipped with an ESI ion source in the positive ionization mode, with data acquisition using the Xcalibur software (Version 1.4).

4.2. General procedure for Michael addition of 4-hydrocoumarin to benzylideneacetone

A catalytic amount of (*R*,*R*)-DPEN (5 mol %) and $LiClO_4$ (5 mol %) were added to a vial containing 4-hydrocoumarin (1 mmol), AcOH (10 mmol), and benzylideneacetone (1.2 mmol) in THF or 1,4-dioxane (2 mL). After vigorous stirring at room temperature for the times shown in the Table, the reaction mixture was poured into an extraction funnel containing brine, diluted with distilled water, and EtOAc. The aqueous phase was extracted with EtOAc. The combined organic phases were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography to furnish the desired known warfarin and confirmed by GC/MS, NMR, the ees of the Michael products were determined by chiral-phase HPLC analysis using a Chiralcel AD-H column and the indicated eluent systems. The warfarin and its analogs were found to exist in rapid equilibrium with a pseudodiastereomeric hemiketal form in solution, which was determined by ^1H NMR spectroscopy. Interestingly, the equilibrium was so rapid that no pseudodiastereomers were observed during HPLC analysis. The warfarin and its analogs are known compounds, and their spectroscopic properties in accordance with those reported.[2]



4.2.1. Compound ***4a***. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm)=1.68 (s, 1.60H, CH_3, ketal), 1.72 (s, 1.37H, CH_3, ketal), 1.97–2.04 (t, 0.67H, CH_2, ketal), 2.30 (s, 0.46H, CH_3, ketal), 2.40–2.60 (m, 1.65H, CH_2, keto), 3.30–3.34 (d, J=19.2 Hz, 0.29H, CH_2, ketal), 3.83–3.39 (dd, J=19.2 Hz, 0.22H, CH_2, keto), 4.14–4.19 (m, 0.54H, CH, ketal), 4.28–4.30 (m, 0.43H, CH ketal), 4.70–4.72 (d, J=9.6 Hz, 0.20H, CH, keto), 7.23–7.30 (m, 7.37H, ArH), 7.50 (t, 0.72H, ArH), 7.80, 7.82 (d, J=7.6 Hz, 0.45H), 7.90, 7.91 (d, J=8, 0.41 Hz), 7.94–7.96 (d, J=7.6 Hz, 0.16H, ArH), 9.50 (s, 0.21H, OH keto); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=212.318, 171.166, 162.151, 161.384, 159.712, 158.897, 153.023, 152.902, 143.287, 141.410, 132.04, 131.60, 129.27, 128.65, 128.19, 127.99, 127.26, 127.05, 126.97, 126.53, 123.95, 123.65, 123.07, 122.72, 116.69, 116.56, 104.23, 101.13, 100.50, 98.96, 42.51, 39.97, 35.35, 34.13, 28.28, 27.78. IR (film): ν=3277.7, 1681.5, 1617.7, 1517.2, 1496.2, 1451.9, 1377.4, 1076.0, 995.9, 763.4, 700.1. GC m/z: 309 (M^+), 265(bp), 187, 120. HRMS(ESI): calcd for $C_{19}H_{16}O_4H^+$: [M+H] 309.1121; found 309.1125. HPLC: (Daicel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate=1.0 mL/min; λ=254 nm): t_{major}=6.3 min (major), t_{minor}=16.4 min (minor).

4.2.2. Compound ***4b***. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm)=9.13 (s, 0.34H), 7.88–8.01 (m, 1.49H), 7.53–7.83 (m, 1.70H), 7.44–7.49 (m, 0.96H), 7.29–7.36 (m, 1.13H), 6.98–7.07 (m, 1.09H), 6.82–6.98 (m, 2.00H), 4.96 (q, J=5.2, 8.0 Hz, 0.37H), 4.538 (q, J=1.6, 6.8 Hz, 0.86H), 3.94 (d, J=13.2 Hz, 3.18H), 3.701 (s, 0.61H), 3.36–3.42 (m, 0.60H), 2.66 (q, J=2.0, 14.4 Hz, 0.60H), 2.48 (q, J=6.8, 13.6 Hz, 0.35H), 2.30 (q, J=7.2, 14.4 Hz, 0.58H), 2.18 (s, 0.92H), 2.01–2.10 (m, 0.54H), 1.66 (d, J=12.0 Hz, 3.02H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=208.86, 162.03, 159.83, 157.13, 152.99, 131.87, 130.94, 129.17, 128.86, 128.75, 129.55, 126.37, 123.87, 123.04, 121.02, 116.643,116.09, 115.687, 111.283,

110.917, 110.803, 101.187, 100.727, 65.609, 55.358, 36.914, 31.959, 29.730, 29.691, 29.395, 28.193, 22.726. IR (film): ν=3373.6, 2938.1, 1684.5, 1620.4, 1572.0, 1492.9, 1457.2, 1439.2, 1251.0, 1182.2, 1064.1, 748.2. HRMS(ESI): calcd for $C_{20}H_{18}O_5H^+$: [M+H] 339.1227; found 339.1226. HPLC (Daicel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate=1.0 mL/min; λ=254 nm): t_{major}=8.53 min, t_{minor}=14.44 min.

4.2.3. Compound ***4c***. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)=1.64 (d, J=7.2 Hz, 3.0H), 1.93–2.03 (m, 0.74H), 2.25 (s, 0.30H), 2.34–2.52 (m, 1.50H), 3.74 (s, 3.05H), 4.11–4.15 (m, 0.56H), 4.20–4.23 (m, 0.38H), 6.72–6.84 (m, 2.87H), 7.18–7.21 (m, 2.12H), 7.51–7.53 (m, 1.19H), 7.57–7.61 (m, 1.00H), 7.76–7.79 (q, J=1.6, 8.4 Hz, 0.48H), 7.86–7.88 (q, J=1.2, 8 Hz, 0.46H), 8.08–8.10 (d, J=7.2 Hz, 0.55H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=212.303, 171.033, 162.288, 161.565, 160.222, 159.832, 152.964, 152.857, 145.059, 143.414, 133.645, 132.024, 131.528, 130.234, 130.162, 129.567, 128.464, 123.964, 123.643, 123.095, 122.792, 119.543, 119.050, 116.628, 116.442, 115.958, 115.587, 113.437, 113.220, 112.172, 111.535, 103.995, 101.155, 100.622, 99.187, 55.208, 55.159, 42.615, 40.078, 35.412, 34.403, 31.953, 29.732, 29.384, 27.979, 27.554, 22.717. IR (film): ν=3377.5, 2923.7, 2852.3, 1686.3, 1618.8, 1570.7, 1491.1, 1453.9, 1381.3, 1326.3, 1264.8, 1070.7, 903.0, 760.4, 677.0. HRMS(ESI): calcd for $C_{20}H_{18}O_5H^+$: [M+H] 339.1227; found 339.1226. HPLC (Daicel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate=1.0 mL/min; λ=254 nm): t_{major}=7.88 min, t_{minor}=22.24 min.

4.2.4. Compound ***4d***. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)= 7.795–8.107 (m, 1.59H), 7.468–7.583 (m, 1.51H), 7.292–7.359 (m, 1.15H), 7.18–7.225 (m, 3.96H), 4.251 (q, J=3.2, 6.8 Hz, 0.50H), 4.132 (q, J=6.8, 11.2 Hz, 0.55H), 2.306–2.552 (m, 1.30H), 2.83 (d, J=2.8 Hz, 2.95H), 1.962–2.049 (m, 0.78H), 1.705 (d, J=14 Hz, 3.04H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=212.617, 162.204, 101.338, 159.616, 158.723, 153.008, 152.922, 140.149, 138.252, 136.904, 135.957, 131.970, 131.504, 130.024, 129.367, 128.939, 128.471, 129.818, 126.937, 126.820, 123.923, 123.603, 123.078, 116.666, 116.512, 115.951, 115.619, 104.366, 101.320, 100.577, 99.059, 42.661, 39.994, 34.950, 33.752, 31.955, 29.726, 28.178, 27.758, 22.721, 21.045. IR (film): ν=3375.3, 2921.7, 2851.3, 1685.2, 1607.7, 1564.7, 1512.2, 1489.6, 1452.8, 1384.6, 1376.3, 1248.2, 1070.5, 766.8. HRMS(ESI): calcd for $C_{20}H_{18}O_4H^+$: [M+H] 323.1278; found 323.1273. HPLC (Daicel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate=1.0 mL/min; λ=254 nm): t_{major}=6.91min t_{minor}=17.84min.

4.2.5. Compound ***4e***. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)= 7.759–7.920 (m, 1.27H), 7.427–7.549 (m, 1.27H), 7.104–7.254 (m, 6.10H), 4.097–4.142 (m, 1.53H), 3.661–3.815 (m, 0.56H), 2.251–2.431 (m, 1.70H), 1.865–1.929 (dd, J=11.6, 14 Hz), 1.673 (d, J=11.2 Hz, 3.00H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=212.263, 162.287, 162.601, 159.943, 459.323, 152.897, 152.807, 141.931, 140.796, 132.392, 132.099, 132.032, 131.721, 129.459, 128.788, 128.740, 128.496, 128.230, 124.029, 123.782, 123.040, 122.820, 116.632, 116.461, 115.840, 115.564, 103.665, 101.290, 100.409, 99.133, 58.485, 45.200, 42.494, 40.067, 34.879, 34.445, 31.959, 29.730, 27.999, 27.558, 22.738. IR (film): ν=3378.0, 2922.0, 1686.0, 1608.5, 1565.6, 1690.5, 1454.2, 1410.8, 1385.8, 1327.6, 1273.2, 1250.0, 1071.6, 763.4. HRMS(ESI): calcd for $C_{19}H_{15}ClO_4H^+$: [M+H] 343.0732; found 343.0730. HPLC (Daicel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate=1.0 mL/min; λ=254 nm): t_{major}=7.13min, t_{minor}=22.51min.

4.2.6. Compound ***4f***. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)= 7.740–7.909 (m, 1.06H), 7.493 (dd, J=2.4, 8.8 Hz, 0.48H), 7.402 (dd, J=2.4, 8.8 Hz, 0.58H), 7.115–7.312 (m, 6.01H), 4.121–4.258 (m, 0.93H), 3.289–3.862 (m, 1.09H), 2.332–2.541 (m, 1.40H), 1.973 (q, J=11.6, 14 Hz, 0.63H), 1.671 (d, J=3.6 Hz, 3.00H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=203.787, 161.684, 160.892, 158.741, 157.904, 151.313, 151.208, 142.907, 141.284, 131.982, 131.465, 129.563, 129.180, 128.676, 128.259, 127.985, 127.250, 127.085 127.014 126.620, 122.683, 122.336, 118.121, 117.932, 117.103, 116.740, 105.171, 102.211, 100.925, 99.462, 42.506, 40.002, 35.432, 34.438, 29.721, 28.044, 27.639, 22.713. IR(film): ν=3350.7, 2929.3, 2853.9, 1697.6, 1621.9, 1569.2, 1485.1, 1453.3, 1418.7, 1378.3, 1261.2, 1165.1, 1116.2, 1067.4, 699.7. HRMS(ESI): calcd for $C_{19}H_{15}ClO_4H^+$: [M+H] 343.0732; found 343.0731. HPLC (Daicel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate=1.0 mL/min; λ=254 nm): t_{major}=6.08min, t_{minor}=16.44min.

4.2.7. Compound ***4g***. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)=9.25 (s, 0.33H), 7.64–7.86 (m, 1.48H), 7.38–7.50 (m, 1.26H), 7.13–7.26 (m, 0.94H), 6.98–7.04 (m, 1.00H), 6.82–6.94 (m, 1.88H), 4.94 (d, J=5.2, 8.4 Hz, 0.28H), 4.50–4.57 (m, 0.78H), 3.90 (d, J=10.8 Hz, 3.28H), 3.55 (s, 0.68H), 3.38 (q, J=5.2, 18.8 Hz, 0.33H), 2.62 (q, J=1.6, 14.4 Hz, 0.48H), 2.46 (q, J=6.8, 13.6 Hz, 0.31H), 2.29 (q, J=7.2, 14.4 Hz, 0.51H), 2.19 (s, 0.80H), 2.03 (t, J=12.4 Hz, 0.41H), 1.67 (d, J=7.2 Hz, 3.00H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=208.898, 161.470, 159.933, 158.790, 157.072, 156.919, 155.330, 151.318, 131.804, 131.544, 131.210, 129.199, 128.770, 128.137, 127.660, 126.453, 123.378, 122.651, 122.250, 121.744, 120.976, 120.828, 118.089, 117.908, 117.555, 116.853, 111.303, 110.829, 107.140, 105.414, 102.239, 101.073, 99.604, 56.197, 55.570, 55.392, 45.224, 39.645, 36.955, 30.230, 29.716, 29.289, 28.414, 28.112. HPLC (Daicel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate=1.0 mL/min; λ=254 nm): t_{major}=7.56min, t_{minor}=15.14min.

4.2.8. Compound ***4h***. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)= 7.719–7.888 (m, 1.13H), 7.346–7.483 (m, 1.20H), 7.086–7.226 (m, 5.14H), 4.194–4.219 (m, 0.46H), 4.087–4.132 (m, 0.57H), 2.400–2.521 (m, 1.10H), 2.296 (d, J=1.6 Hz, 3.05H), 1.918–2.035 (m, 0.94H), 1.647 (d, J=2.8 Hz, 3.00H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=212.695, 161.743, 160.945, 158.679, 157.849, 151.290, 151.168, 139.875, 138.082, 136.078, 131.926, 131.371, 129.966, 129.394, 129.123, 128.981, 126.969, 126.847, 122.679, 122.299, 118.097, 118.097, 117.884, 117.144, 116.769, 105.316, 102.328, 100.986, 99.532, 42.602, 39.959, 35.016, 33.970, 29.733, 27.956, 27.653, 21.107. HPLC (Daicel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate=1.0 mL/min; λ=254 nm): t_{major}=6.57min, t_{minor}=16.51min.

4.2.9. Compound ***4i***. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm)= 7.912–8.017 (m, 1.53H), 7.520–7.661 (m, 1.57H), 6.820–7.192 (m, 4.19H), 4.898–5.014 (m, 0.40H), 4.504–4.553 (m, 0.68H), 3.924 (d, J=10.8 Hz, 2.99H), 3.330–3.452 (m, 0.43H), 2.614 (q, J=2, 14.4 Hz, 0.60H), 2.441 (q, J=6.8, 14 Hz, 0.41H), 2.256–2.385 (m, 0.97H), 2.188 (s, 0.91H), 1.960–2.055 (m, 0.68H), 1.688 (d, J=10.4 Hz, 3.00H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm)=208.866, 162.233, 161.596, 161.365, 160.532, 159.811, 158.665, 157.076, 155.333, 151.810, 134.632, 128.805, 128.143, 127.686, 126.430, 125.695, 125.290, 121.750, 121.001, 118.397, 116.735, 111.318, 110.826, 107.161, 102.231, 101.076, 99.568, 56.200, 55.566, 55.388, 45.232, 39.596, 36.935, 30.225, 29.713, 19.276, 28.215, 28.151. IR (film): ν=3419.5, 2927.7, 1696.4, 1696.4, 1618.9, 1567.1, 1494.0, 1438.3, 1417.6, 1381.1, 1289.0, 1263.5, 1248.0, 1178.7, 1118.6, 1073.0, 751.1. HRMS(ESI): calcd for $C_{20}H_{17}BrO_5H^+$: [M+H] 417.0332; found 417.0325. HPLC (Daicel AD-H; 2-propanol/*n*-hexane, 20:80; flow rate=1.0 mL/min; λ=254 nm): t_{major}=7.71min, t_{minor}=17.30min.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.10.032. These data include MOL files and InChiKeys of the most important compounds described in this article.

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