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Catalytic asymmetric synthesis of 3-hydroxyl-2-oxindoles via enantioselective Morita–Baylis–Hillman reaction of isatins

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ABSTRACT

The enantioselective Morita–Baylis–Hillman reaction of acrylates to isatins was investigated for the first time, employing bifunctional phosphinothiourea organocatalysts based on chiral cyclohexane scaffold. The 3-hydroxyl-2-oxindole derivatives were obtained in excellent yields with moderate enantioselectivity (up to 69% ee) in the presence of 10 mol % catalyst **1b**.

1. Introduction

The oxindole motifs bearing C3-quaternary structures are widely distributed in many natural products and pharmaceutical molecules.[1] For example, the 3-substituted 3-hydroxyl-oxindole units are existed in various alkaloids, such as convolutamydines, dioxibrassinine and donaxaridine (Fig. 1).[1d,e] Over the past several years, the enantioselective synthesis of 3,3-disubstituted oxindoles has received considerable attention.[2] The nucleophilic addition to prochiral isatins is a very simple and straightforward approach for the preparation of optically active 3-substituted-3-hydroxyl-2-oxindole derivatives.[2b] Since Hayashi's pioneering work,[3a] several organometallic catalytic systems were developed for the asymmetric conjugate additions to isatins.[3] With the development of enantioselective organocatalysis,[4] the aldol reaction of isatins was also used to construct the chiral 3-hydroxyl-2-oxindole derivatives.[5]

The Morita–Baylis–Hillman (MBH) reaction is known to be a powerful tool for the construction of densely functionalized alcohols.[6] And isatin derivatives could serve as electrophiles in the MBH reaction.[7,8] To the best of our knowledge, enantioselective synthesis of 3-hydroxyl-2-oxindole derivatives is not known by MBH reaction. Herein we report the first enantioselective MBH reaction of isatins to provide chiral 3-hydroxyl-2-oxindole derivatives.[9]

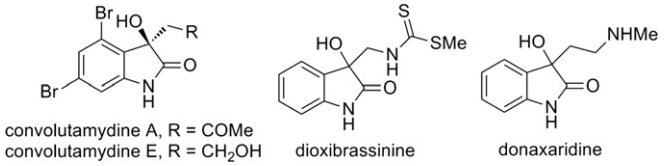

Fig. 1. Examples of natural products bearing 3-hydroxyl-2-oxindole moiety.

2. Result and discussion

In our previous work, we found the chiral bifunctional phosphinothioureas were highly efficient for the MBH reaction due to the nucleophilic activation by tertiary phosphine and the electrophilic activation by hydrogen-bonding.[10] Initially, we chose the MBH reaction of *N*-methyl isatin with methyl acrylate as a model reaction to evaluate the cyclohexane-based bifunctional catalysts (Fig. 2). The results are summarized in Table 1. In general, the aromatic thioureas provided better enantioselectivities but lower yields than the aliphatic thioureas (entries 2–4 vs 6–9). However, catalyst **1e** bearing strongly electron-withdrawing group resulted in racemic MBH adduct (entry 5). Comparable results were obtained when the urea derivative **1a** was used as catalyst, although it was ineffective in the MBH reaction of MVK with aldehyde (entry 1 vs 2).[10a] In term of both chemical yield and enantioselectivity, **1b** was selected for further study to optimize the reaction conditions.

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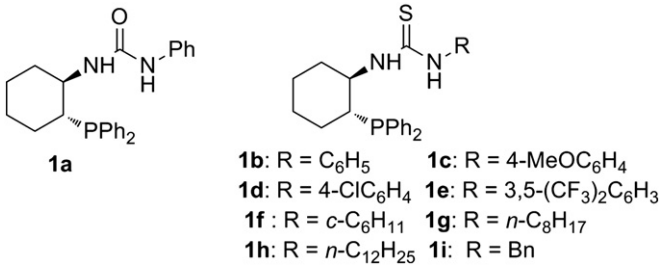
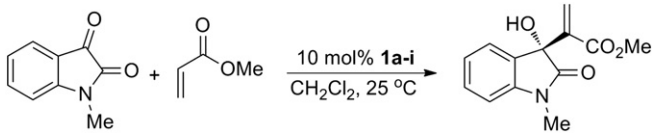


Fig. 2. Structures of the screened phosphinothiourea catalysts.

Table 1
Screening of catalysts for MBH reaction of *N*-methyl isatin with methyl acrylate[a]

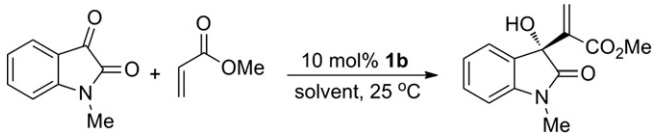


Entry	Catalyst	Time (d)	Yield (%) [b]	ee (%) [c]
1	**1a**	3	65	42
2	**1b**	3	75	43
3	**1c**	3	75	35
4	**1d**	3	62	44
5	**1e**	3	73	0
6	**1f**	3	84	23
7	**1g**	3	87	21
8	**1h**	3	89	17
9	**1i**	3	83	1

[a] The reactions were performed with 10 mol % of organocatalyst, 0.2 mmol *N*-methyl isatin and 2 equiv of methyl acrylate in 1 mL CH_2Cl_2 at 25 °C.
[b] Isolated yield after column chromatography.
[c] Determined by HPLC analysis using chiralcel OD-H column.

Next, the effect of reaction solvent was investigated using 10 mol % of **1b** as catalyst. As illustrated in Table 2, in ethyl acetate and various ethers, the MBH reaction was accomplished in a short time (3–5 h) and provided nearly quantitative yields, while the enantioselectivity was different (entries 4–9). In other solvents examined, the MBH reaction was relatively slower and a longer reaction time (at least one day) was required (entries 1–3, 10 and 11). On the whole, the enantioselectivity was moderate. The solvent survey indicated THF was the more suitable solvent, and the trace amount of water in the solvent had no effect on the MBH reaction (entry 4 vs 5).

Table 2
The survey of solvents for the MBH reaction of *N*-methyl isatin with methyl acrylate[a]

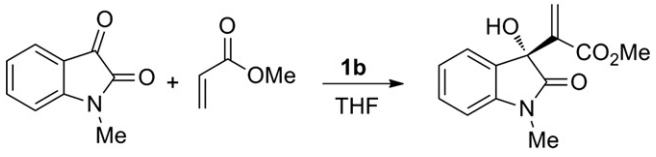


Entry	Solvent	Time (h)	Yield (%) [b]	ee (%) [c]
1	CH_2Cl_2	72	75	43
2	$CHCl_3$	48	84	41
3	PhMe	24	99	24
4[d]	THF	5	99	45
5[e]	THF	5	99	45
6	Ether	3	99	31
7	1,4-Dioxane	5	95	40
8	Dimethoxyethane	5	98	42
9	Ethyl acetate	5	99	33
10	CH_3CN	48	86	48
11	DMSO	24	98	40

[a] The reactions were performed with 10 mol % of organocatalyst **1b**, 0.2 mmol *N*-methyl isatin and 2 equiv of methyl acrylate in 1 mL solvent at 25 °C.
[b] Isolated yield after column chromatography.
[c] Determined by HPLC analysis using chiralcel OD-H column.
[d] Dry THF was used.
[e] Commercial available THF was used directly.

To improve the enantioselectivity of the MBH reaction, other aspects of this reaction, such as the reaction temperature, the substrate concentration, the loading of the catalyst and the additives were investigated (Table 3). The results indicated the higher reaction temperature resulted in shorter reaction time and lower enantioselectivity (entries 1–5). In the ranger from −15 to 40 °C, the suitable reaction temperature is 0 °C (entry 4, 99% yield with 52% ee). The substrate concentration has no effect on the chemical yield, and the influence on enantioselectivity is negligible (entries 6 and 7 vs 4). Similarly, the increase of methyl acrylate loading could not improve the enantioselectivity (entries 8 and 9 vs 4). The same enantioselectivity and yield was also observed as decreasing the catalyst loading, certainly longer reaction time was demanded (entries 10 and 11). In addition, different additives were examined.[11] The tertiary amines, such as imidazole, triethylamine and DABCO would decelerate the reaction with a slight decrement of enantioselectivity (entries 12–14 vs 4), probably due to the background reaction promoted by the tertiary amines. While benzoic acid was added, the reaction was quenched and no product was observed.

Table 3
Further optimization of reaction conditions[a]

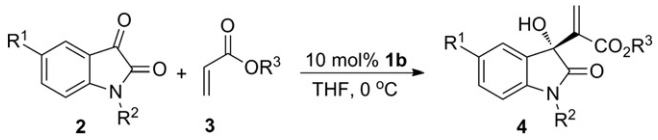


Entry	Temp (°C)	Concn (M)	Additive	**1b** (mol %)	Time (h)	Yield (%) [b]	ee (%)[c]
1	40	0.2	None	10	4	90	33
2	25	0.2	None	10	5	99	45
3	10	0.2	None	10	5	99	50
4	0	0.2	None	10	8	99	52
5	−15	0.2	None	10	48	99	52
6	0	0.1	None	10	12	99	52
7	0	0.3	None	10	8	99	50
8[d]	0	0.2	None	10	8	99	52
9[e]	0	0.2	None	10	8	99	52
10	0	0.2	None	5	48	99	52
11	0	0.2	None	1	216	99	52
12	0	0.2	Imidazole	10	24	99	50
13	0	0.2	Et_3N	10	24	99	50
14	0	0.2	DABCO	10	24	99	50
15	0	0.2	$PhCO_2H$	10	48	0	n.d.[f]

[a] Unless stated otherwise, the reactions were performed with organocatalyst **1b**, 0.2 mmol *N*-methyl isatin and 2 equiv of methyl acrylate in 1 mL THF.
[b] Isolated yield after column chromatography.
[c] Determined by HPLC using chiralcel OD-H column.
[d] 3 equiv of methyl acrylate was used.
[e] 5 equiv of methyl acrylate was used.
[f] Not determined.

Under the optimized reaction conditions (10 mol % of **1b** as catalyst, 2 equiv of acrylate, THF as solvent, 0 °C), the scope of substrates was probed. Firstly, various acrylates were applied as Michael donor to react with *N*-methyl isatin. The results summarized in Table 4 showed that the structure of acrylate had obvious effect on the reactivity (entries 1–6). Generally, the larger the alkyl group of acrylate, the longer the reaction time was required to achieve excellent yields. And the reaction with *tert*-butyl and phenyl acrylate afforded poor enantioselectivity probably due to steric hindrance. Therefore, methyl acrylate was selected to react with different isatin derivatives. As shown in Table 4, the *N*-substituents of isatins had a limited influence on both yields and enantioselectivity, and comparable results were obtained (entries 7–11 vs 1). The best enantioselectivity was achieved using *N*-benzyl

Table 4
The MBH reaction of isatins with different acrylates[a]

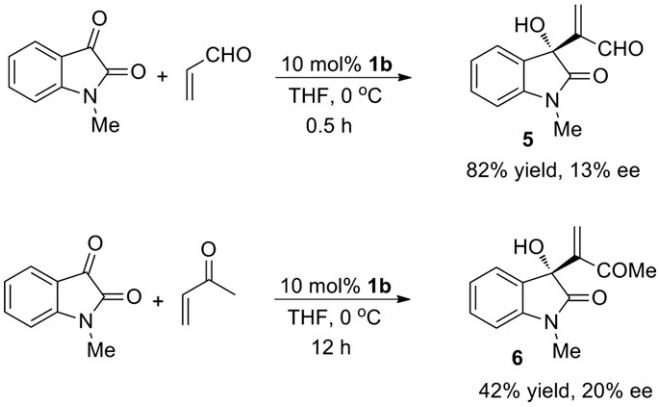


Entry	R^1	R^2	R^3	Time (h)	Yield (%) [b]	ee (%) [c]
1	H	Me	Me	8	99	52
2	H	Me	Et	18	99	49
3	H	Me	*n*-Bu	15	99	41
4	H	Me	*t*-Bu	103	99	10
5	H	Me	Bn	48	99	53
6	H	Me	Ph	48	99	14
7	H	Et	Me	12	99	53
8	H	*n*-Bu	Me	12	99	50
9	H	Bn	Me	8	98	69
10	H	n-$C_{12}H_{25}$	Me	12	99	49
11	H	H	Me	120	87	49
12	Me	Me	Me	24	99	56
13	Me	H	Me	120	85	56
14	Cl	Me	Me	24	99	8
15	Cl	H	Me	120	82	16
16	H	Bn	Ph	20	89	9
17	H	Bn	$CH(CF_3)_2$	36	15	38
18	H	Bn	Bn	24	99	35

[a] The reactions were performed with 10 mol % of organocatalyst **1b**, 0.2 mmol *N*-methyl isatin and 2 equiv of acrylate in 1 mL THF at 0 °C.
[b] Isolated yield after column chromatography.
[c] Determined by HPLC using chiral column.

isatin as an electrophile (entry 9, 69% ee with 98% yield). In addition, it appeared that the electronic property of the substituent on the phenyl moiety of isatin derivatives had an obvious effect on the enantioselectivity. The electron-rich substituent for the phenyl ring of isatins gave higher enantioselectivity than electron-deficient one (entries 11–15 and 1). It's notably that the *N*-protected group free isatin derivatives could provide the desired products in good chemical yields and comparative enantioselectivity (entry 11 vs 1, entry 13 vs 12, entry 15 vs 14). The absolute configuration of the BMH adducts were assigned as *R*- by comparing the optical rotation and the retention time of products **4p** and **4q** (entries 16 and 17) with those reported in the literature.[9b]

In addition, other nucleophiles were examined (Scheme 1). Acrolein is so reactive that the MBH reaction was completed in half an hour.[9a] And the MBH reaction between methyl vinyl ketone (MVK) and *N*-methyl isatin was accomplished in 12 h. The moderate yields resulted from side-reaction. However, cyclohex-2-one is inert under the typical reaction conditions.



Scheme 1. The MBH reactions of acrolein and MVK to isatin.

3. Conclusion

In summary, we have explored the first example of enantioselective Morita–Baylis–Hillman reaction using isatin derivatives as electrophiles catalyzed by chiral phosphinothioureas. In the presence of 10 mol % of phosphinothiourea **1b**, the Morita–Baylis–Hillman reaction of acrylates to isatins could proceed smoothly to afford 3-substituted-3-hydroxyl-oxindole derivatives in excellent yields (82–99%) and up to 69% ee.

4. Experimental

4.1. General methods

Melting points are taken without correction. Optical rotations were measured on a WZZ-2A digital polarimeter at the wavelength of the sodium D-line (589 nm) at 20 °C. ^{1}H and ^{13}C spectra were recorded on Bruker 400 spectrometer. ^{1}H NMR spectra were referenced to tetramethylsilane (δ 0.00 ppm) using $CDCl_3$ or DMSO-d_6 as solvent. ^{13}C NMR spectra were referenced to the solvent carbon (77.0 ppm for $CDCl_3$). IR spectra were recorded on Nicolet Magna-I 550 spectrometer. High Resolution Mass spectra (HRMS) were recorded on Micromass GCT spectrometer with Electron Ionization (ESI) resource. HPLC analysis was performed on Waters equipment using Daicel Chiralcel OD-H, Chiralpak AD-H or AS-H column.

THF was directly used without further purification. And other solvents were purified and dried according to standard methods prior to use.

4.2. General procedure for the Morita–Baylis–Hillman reaction

To a solution of phosphinothiourea **1b** (0.02 mmol) in THF (1.0 mL) was added acrylate (0.4 mmol) at 0 °C. After 10 min stirring at this temperature, isatin (0.2 mmol) was added. The reaction mixture was stirred at 0 °C (monitoring by TLC). Then the resulting solution was concentrated under reduced pressure and the residue was purified by a flash column chromatography on silica gel to afford the desired adducts and the ee values were determined by HPLC analysis with chiral column.

*4.2.1. Compound **4a** (Table 4, entry 1)*[12a]. Yield 99%, 52% ee, $[\alpha]_D$ +7.1 (*c* 0.49, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.33 (m, 1H), 7.20 (d, *J*=6.4 Hz, 1H), 7.05 (t, *J*=7.2 Hz, 1H), 6.88 (d, *J*=7.6 Hz, 1H), 6.57 (s, 1H), 6.42 (s, 1H), 3.65 (s, 3H), 3.59 (s, 1H), 3.26 (s, 3H). HPLC analysis (OD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=21.43 min (major), 12.75 min (minor).

*4.2.2. Compound **4b** (Table 4, entry 2)*[7a]. Yield 99%, 49% ee, $[\alpha]_D$ +15.4 (*c* 0.52, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.33 (m, 1H), 7.20 (d, *J*=6.8 Hz, 1H), 7.05 (t, *J*=7.2 Hz, 1H),6.87 (d, *J*=8.0 Hz, 1H), 6.59 (s, 1H), 6.40 (s, 1H), 4.10–4.01 (m, 2H), 3.55 (s, 1H), 3.26 (s, 3H), 1.14 (t, *J*=7.2 Hz, 3H). HPLC analysis (OD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=26.23 min (major), 16.35 min (minor).

*4.2.3. Compound **4c** (Table 4, entry 3).* Yield 99%, 41% ee, $[\alpha]_D$ +5.2 (*c* 0.58, CH_2Cl_2); IR (KBr, cm^{-1}): ν 3334, 2958, 1715, 1701, 1615, 1471, 1060, 750; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35–7.30 (m, 1H), 7.17 (d, *J*=6.4 Hz, 1H), 7.03 (t, *J*=8.0 Hz, 1H), 6.85 (d, *J*=7.6 Hz, 1H), 6.58 (s, 1H), 6.44 (s, 1H), 4.22 (s, 1H), 4.04–3.91 (m, 2H), 3.23(s, 3H), 1.50–1.43 (m, 2H), 1.24–1.18 (m, 2H), 0.853 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.4, 164.7, 144.5, 139.3, 130.1, 129.6, 127.9, 123.8, 123.0, 108.6, 64.9, 30.4, 26.4, 19.0, 13.7; HRMS (ESI) calcd for $C_{16}H_{19}NO_4$([M]$^+$) 312.1212, obsd 312.1211. HPLC analysis

(OD-H column, λ=254 nm, eluent: hexane/2-propanol=96/4, flow rate: 1.0 mL/min): t_R=12.68 min (major), 10.31 min (minor).

4.2.4. Compound ***4d*** *(Table 4, entry 4).* Yield 99%, 10% ee, $[\alpha]_D$ +6.0 (*c* 0.58, CH_2Cl_2); IR (KBr, cm^{-1}): *ν* 3333, 2967, 1716, 1614, 1495, 1058, 772; ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.35–7.30 (m, 1H), 7.18 (d *J*=6.8 Hz, 1H), 7.03 (t, *J*=7.2 Hz, 1H), 6.83 (d, *J*=8.0 Hz, 1H),6.50 (s, 1H), 6.30 (s, 1H), 4.16 (s, 1H), 3.20 (s, 3H), 1.22 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 176.2, 163.9, 144.3, 140.3, 129.9, 129.8, 127.3, 123.7, 122.9, 108.4, 81.7, 76.1, 27.6, 26.3; HRMS (ESI) calcd for $C_{16}H_{19}NO_4$([M]$^+$) 328.0951, obsd 328.0953. HPLC analysis (AS-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=7.34 min (major), 11.29 min (minor).

4.2.5. Compound ***4e*** *(Table 4, entry 5).* Yield 99%, 53% ee, $[\alpha]_D$ +8.6 (*c* 0.64, CH_2Cl_2); IR (KBr, cm^{-1}): *ν* 3319, 1713, 1699, 1614, 1470, 1058, 767; ^1H NMR (CDCl3, 400 MHz): *δ* 7.36–7.31 (m, 4H), 7.20 (d, *J*=6.8 Hz, 1H), 7.13–7.10 (m, 2H), 7.05 (t, *J*=7.6 Hz, 1H), 6.73 (d, *J*=8.0 Hz, 1H), 6.67 (s, 1H), 6.46 (s, 1H), 5.00 (d, *J*=12.4 Hz, 1H), 4.96 (d, *J*=12.4 Hz, 1H), 3.43 (s, 1H), 2.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 176.3, 164.4, 144.4, 139.1, 134.9, 130.1, 129.5, 128.6, 128.5, 128.4, 123.8, 123.0, 108.8, 76.1, 67.0, 26.1; HRMS (ESI) calcd for $C_{19}H_{17}NO_4$([M]$^+$) 324.1236, obsd 324.1231. HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=29.96 min (major), 27.30 min (minor).

4.2.6. Compound ***4f*** *(Table 4, entry 6).* Yield 99%, 14% ee, $[\alpha]_D$ +5.6 (*c* 0.62, CH_2Cl_2); IR (KBr, cm^{-1}): *ν* 3551, 3082, 1700, 1609, 1468, 1047, 770; ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.38–7.27 (m, 4H), 7.19 (t, *J*=7.6 Hz, 1H), 7.11–7.07 (m, 1H), 6.93–6.90 (m, 2H), 6.86–6.84 (m, 2H), 6.66 (s, 1H), 3.47 (s, 1H), 3.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 176.3, 163.1, 150.1, 144.6, 139.2, 130.3, 129.5, 129.4, 126.0, 123.8, 123.1, 121.4, 108.8, 76.2, 26.5; HRMS (ESI) calcd for $C_{18}H_{15}NO_4$([M]$^+$) 310.1079, obsd 310.1084. HPLC analysis (OD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=33.49 min (major), 22.34 min (minor).

4.2.7. Compound ***4g*** *(Table 4, entry 7)*[12b]. Yield 99%, 53% ee, $[\alpha]_D$ +6.7 (*c* 0.52, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.35–7.31 (m, 1H), 7.19 (d, *J*=6.4 Hz, 1H), 7.03 (t, *J*=7.6 Hz, 1H), 6.89 (d, *J*=8.0 Hz, 1H), 6.57 (s, 1H), 6.43 (s, 1H), 3.90–3.69 (m, 3H), 3.62 (s, 3H), 1.32 (t, *J*=8.0 Hz, 3H). HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=29.39 min (major), 54.48 min (minor).

4.2.8. Compound ***4h*** *(Table 4, entry 8).* Yield 99%, 50% ee, $[\alpha]_D$ +6.0 (*c* 0.58, CH_2Cl_2); IR (KBr, cm^{-1}): *ν* 3327, 2954, 1716, 1467, 1063, 767; ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.34–7.30 (m, 1H), 7.18 (d, *J*=6.4 Hz, 1H), 7.02 (t, *J*=7.6 Hz, 1H), 6.88 (d, *J*=8.0 Hz, 1H), 6.57 (s, 1H), 6.43 (s, 1H), 3.94 (s, 1H), 3.72 (m, 2H), 3.62 (s, 3H), 1.71 (m, 2H), 1.44 (m, 2H), 0.97 (t, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 176.2, 165.1, 144.0, 139.2, 130.1, 129.6, 127.8, 124.0, 122.8, 108.9, 76.2, 52.0, 40.1, 29.2, 20.2, 13.8; HRMS (ESI) calcd for $C_{16}H_{19}NO_4$([M]$^+$) 290.1392, obsd 290.1395. HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=19.62min (major), 23.87min (minor).

4.2.9. Compound ***4i*** *(Table 4, entry 9)*[8a]. Yield 98%, 69% ee, $[\alpha]_D$ +8.6 (*c* 0.64, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.39 (d, *J*=7.2 Hz, 2H), 7.33 (t, *J*=6.8 Hz, 2H), 7.28 (d, *J*=7.2 Hz, 1H), 7.23–7.18 (m, 2H), 7.00 (t, *J*=7.2 Hz, 1H), 6.72 (d, *J*=7.2 Hz, 1H), 6.60 (s, 1H), 6.43 (s, 1H), 4.98 (d, *J*=15.6 Hz, 1H), 4.90 (d, *J*=15.6 Hz, 1H), 3.60 (s, 3H), 3.57 (s, 1H). HPLC analysis (OD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=19.17 min (major), 11.45 min (minor).

4.2.10. Compound ***4j*** *(Table 4, entry 10).* Yield 99%, 49% ee, $[\alpha]_D$ +4.4 (*c* 0.80, CH_2Cl_2); IR (KBr, cm^{-1}): *ν* 3327, 2953, 1716, 1467, 1063, 767; ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.31 (t, *J*=8.0 Hz, 1H), 7.17 (d, *J*=7.2 Hz, 1H), 7.01 (t, *J*=7.6 Hz, 1H), 6.87 (d, *J*=8.0 Hz, 1H), 6.56 (s, 1H), 6.45 (s, 1H), 4.22 (s, 1H), 3.69 (m, 2H), 3.60 (s, 3H), 1.72 (m, 2H),1.26 (m, 18H), 0.89 (t, *J*=6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 176.3, 165.0, 144.0, 139.2, 130.1, 129.7, 127.8, 123.9, 122.7, 108.9, 76.2, 51.9, 40.4, 31.9, 29.7, 29.6, 29.4, 27.2, 27.0, 22.7, 14.1; HRMS (EI) calcd for $C_{24}H_{35}NO_4$([M]$^+$) 424.2464, obsd 424.2465. HPLC analysis (OD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 0.9 mL/min): t_R=12.04 min (major), 6.16 min (minor).

4.2.11. Compound ***4k*** *(Table 4, entry 11)*[8a]. Yield 87%, 49% ee, $[\alpha]_D$ +8.5 (*c* 0.41, CH_2Cl_2); ^1H NMR (DMSO-d_6, 400 MHz): *δ* 10.24 (s, 1H), 7.14–7.10 (m, 1H), 6.89 (d, *J*=6.8 Hz, 1H), 6.80 (t, *J*=7.2 Hz, 1H), 6.74 (d, *J*=7.6 Hz, 1H), 6.43 (s, 1H), 6.40 (s, 1H), 6.37 (s, 1H), 3.43 (s, 3H). HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=38.67 min (major), 28.17 min (minor).

4.2.12. Compound ***4l*** *(Table 4, entry 12)*[12c]. Yield 99%, 56% ee, $[\alpha]_D$ +13.5 (*c* 0.52, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.13 (d, *J*=7.6 Hz, 1H), 7.00 (s, 1H), 6.75 (d, *J*=8.0 Hz, 1H), 6.56 (s, 1H), 6.44 (s, 1H), 3.92 (s, 1H), 3.63 (s, 3H), 3.22 (s, 3H), 2.30 (s, 3H). HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=19.46 min (major), 30.18 min (minor).

4.2.13. Compound ***4m*** *(Table 4, entry 13)*[12c]. Yield 85%, 56% ee, $[\alpha]_D$ +8.3 (*c* 0.42, CH_2Cl_2); ^1H NMR (DMSO-d_6, 400 MHz): *δ* 10.15 (s, 1H), 6.93 (d, *J*=8.0 Hz, 1H), 6.72 (s, 1H), 6.64 (d, *J*=8.0 Hz, 1H), 6.40 (s, 2H), 6.36 (s, 1H), 3.45 (s, 3H), 2.14 (s, 3H). HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=49.36 min (major), 30.13 min (minor).

4.2.14. Compound ***4n*** *(Table 4, entry 14)*[8a]. Yield 99%, 8% ee, $[\alpha]_D$ +10.7 (*c* 0.56, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.30–7.28 (m, 1H), 7.13 (s, 1H), 6.78 (d, *J*=8.4 Hz, 1H), 6.58 (s, 1H), 6.49 (s, 1H), 4.50 (s, 1H), 3.62 (s, 3H), 3.21 (s, 3H). HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=16.90 min (major), 26.59 min (minor).

4.2.15. Compound ***4o*** *(Table 4, entry 15)*[8a]. Yield 82%, 16% ee, $[\alpha]_D$ +10.5 (*c* 0.43, CH_2Cl_2); ^1H NMR (DMSO-d_6, 400 MHz): *δ* 10.40 (s, 1H), 7.19–7.16 (m, 1H), *δ* 6.89(s, 1H), 6.76 (d, *J*=8.4 Hz, 1H), 6.62 (s, 1H), 6.43 (s, 1H), 6.38 (s, 1H), 3.46 (s, 3H); HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=44.06 min (major),23.19 min (minor).

4.2.16. Compound ***4p*** *(Table 4, entry 16)*[9b]. Yield 89%, 9% ee, $[\alpha]_D$ +5.8 (*c* 0.69, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.35–7.28 (m, 5H), 7.23–7.18 (m, 5H), 7.05 (d, *J*=7.6 Hz, 1H), 6.92 (s, 1H), 6.87 (d, *J*=7.2 Hz, 2H), 6.76 (s, 1H), 6.70 (d, *J*=8.0 Hz, 1H), 4.94 (d, *J*=15.6 Hz, 1H), 4.88 (d, *J*=15.6 Hz, 1H), 4.15 (s, 1H). HPLC analysis (OD-H column, λ=254 nm, eluent: hexane/2-propanol=80/20, flow rate: 1.0 mL/min): t_R=11.46 min (major), 8.93 min (minor).

4.2.17. Compound ***4q*** *(Table 4, entry 17)*[9b]. Yield 15%, 38% ee, $[\alpha]_D$ +39.3 (*c* 0.14, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz): *δ* 7.35–7.20 (m, 7H), 7.05 (t, *J*=7.6 Hz, 1H), 6.85 (s, 1H), 6.83 (s, 1H), 6.75 (d, *J*=7.2 Hz, 1H), 5.60 (s, 1H), 5.05 (d, *J*=15.6 Hz, 1H), 4.86 (d, *J*=15.6 Hz, 1H), 4.02 (s, 1H). HPLC analysis (OD-H column, λ=254 nm, eluent:

hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=17.76 min (major), 15.72 min (minor).

4.2.18. Compound ***4r*** *(Table 4, entry 18)*[9c]. Yield 99%, 35% ee, $[\alpha]_D$ +13.8 (*c* 0.80, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39–7.28 (m, 7H), 7.25 (d, *J*=7.6 Hz, 1H), 7.23–7.18 (m, 2H), 7.15–7.13 (m, 2H), 7.00 (t, *J*=7.2 Hz, 1H), 6.68 (s, 1H), 6.62 (d, *J*=7.2 Hz, 1H), 6.50 (s, 1H), 5.07 (d, *J*=12.4 Hz, 1H), 4.93 (d, *J*=12.4 Hz, 1H), 4.86 (d, *J*=15.6 Hz, 1H), 4.53 (d, *J*=15.6 Hz, 1H), 3.59 (s, 1H). HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=62.12min (major), 57.02min (minor).

4.2.19. Compound ***5*** *(Scheme 1)*[9a]. Yield 82%, 13% ee, $[\alpha]_D$ −28.6 (*c* 0.35, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz): δ 9.46 (s, 1H), 7.36–7.32 (m, 1H), 7.14 (d, *J*=7.2 Hz, 1H), 7.03(t, *J*=7.2 Hz, 1H), 6.97(s, 1H), 6.88 (d, *J*=8.0Hz, 1H), 6.37(s, 1H), 3.99(s, 1H), 3.25 (s, 3H). HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=18.23 min (major), 16.57 min (minor).

4.2.20. Compound ***6*** *(Scheme 1)*[8b]. Yield 42%, 20% ee, $[\alpha]_D$ +31.4 (*c* 0.43, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32 (t, *J*=8.0 Hz, 1H), 7.12 (d, *J*=7.2 Hz, 1H), 7.01 (t, *J*=7.6 Hz, 1H), 6.87 (d, *J*=7.6 Hz, 1H), 6.66 (s, 1H), 6.43 (s, 1H), 3.53(s, 1H), 3.26(s, 3H), 2.30(s, 3H). HPLC analysis (AD-H column, λ=254 nm, eluent: hexane/2-propanol=90/10, flow rate: 1.0 mL/min): t_R=20.02 min (major), 24.78 min (minor).

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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.2011.02.045.

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