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Stereocontrolled construction of 3*H*-furo[3,4-*b*]chromen-1(9*H*)-one scaffolds via organocatalyzed Michael addition and the following intramolecular dehydration

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An efficient approach for the stereocontrolled construction of 3*H*-furo[3,4-b]chromen-1(9*H*)-one skeleton has been successfully developed through a sequential Michael addition/intramolecular dehydration strategy. The Michael addition of tetronic acid to 2-((*E*)-2-nitrovinyl)phenols catalyzed by a bifunctional squaramide derived from L-*tert*-leucine, and the subsequent intramolecular dehydration promoted by concentrated sulfuric acid, proceed smoothly to give the corresponding pharmaceutically valuable 3*H*-Furo[3,4-b]chromen-1(9*H*)-ones in acceptable yields with 79–97% ee.

Introduction

The benzopyran scaffold ranks among the most commonly found heterocycles in known bioactive molecules. Functionalized benzopyran and fused cyclic molecular frameworks with benzopyran units have attracted much attention due to their considerable biological and pharmacological activities, such as use as antibacterial,[1] antitumor,[2] anti-anaphylactic,[3] antisecretory agents,[4] apoptosis inducers,[5] and Chk1-inhibitors.[6] Among them, 3*H*-Furo[3,4-b]chromen-1(9*H*)-ones (benzopyran lactones) represent an important class of polycyclic benzopyrans, as they are the privileged structural motif of a number of synthetic 4-oxa-podophyllotoxin derivatives displaying an extensive array of biological activities (Figure 1).[7] Despite their high relevance as biologically active compounds, however, nonracemic 3*H*-furo[3,4-*b*]chromen-1(9*H*)-ones have been entirely unknown. Since the preparation of enantiomerically pure compounds has become a stringent requirement for pharmaceutical synthesis,[8] the development of efficient synthesis of chiral benzopyran lactones in highly enantioselective manner will be of great importance and remains a challenge task. As a part of our continued interest in the stereoselective synthesis of biologically relevant heterocycles,[9] herein we describe the tertiary amine-squaramide catalyzed Michael addition of tetronic acid (4-hydroxyfuran-2-one) to 2-((*E*)-2-nitrovinyl)phenols and the subsequent acid promoted intramolecular dehydration reaction, which provide a straightforward access to a variety of functionalized chiral benzopyran lactones in a highly enantioselective manner (Scheme 1).[10]

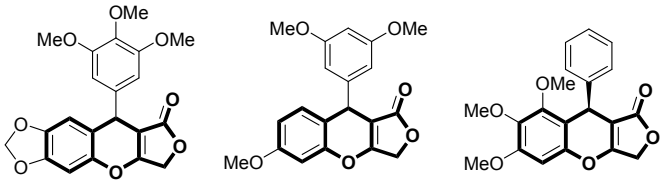
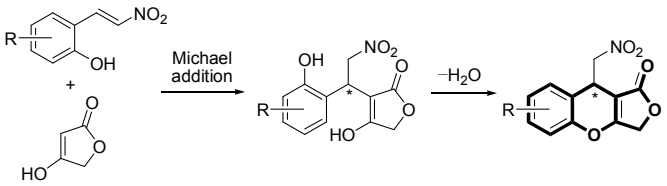


Figure 1. Examples of bioactive compounds bearing a 3*H*-furo[3,4-*b*]chromen-1(9*H*)-one motif.



Scheme 1. Construction of 3*H*-furo[3,4-*b*]chromen-1(9*H*)-one skeleton.

Results and discussion

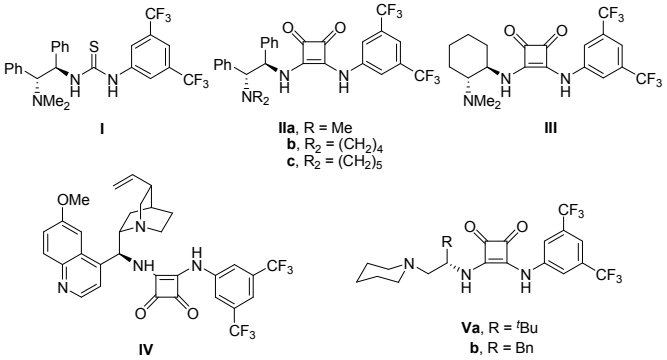
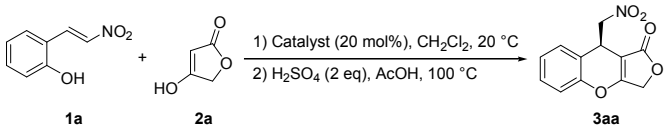


Figure 2. Screened thiourea- and squaramide-based organocatalyst.

Initially, 2-((*E*)-2-nitrovinyl)phenol (**1a**) and 4-hydroxyfuran-2-one (**2a**) were chosen as the model substrates, and the initial Michael addition reaction was investigated at 20 °C in methylene chloride, the following intramolecular dehydration was performed at 100 °C in glacial acetic acid in the presence of 2 equivalents of concentrated sulfuric acid. Various thiourea-[11] and squaramide-based[12] hydrogen-bonding catalysts **I-V** were screened for the Michael addition reaction (Table 1, entries 1–8). In the presence of (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine derived thiourea catalyst **I**, the desired polycyclic product **3aa** was obtained in 75% yield with 30% ee (Entry 1). Under the same condition, sharply increased enantioselectivity (63% ee) was observed for the squaramide catalyst **IIa** bearing the same chiral diamine scaffold (Entries 2 vs. entry 1), which indicate that the squaramide catalysts are superior to thiourea catalysts in this transformation. We then turn our attention to other chiral squaramide catalysts (Entries 3–8). The effect of the tertiary amino group on reactivity and enantioselectivity was firstly investigated in more detail (Entries 3, 4). Of the tertiary amino groups surveyed, piperidinyl group resulted in an obviously improved enantioselectivity of 79% ee (entry 4). Further changing the chiral diamine skeleton of the squaramide catalyst revealed that squaramide **Va**, derived from L-*tert*-leucine, was the optimal catalyst for this sequential process and afforded the desired product **3aa** with the highest ee value (Entry 7, 81%).

Table 1. Screening of catalyst [a]

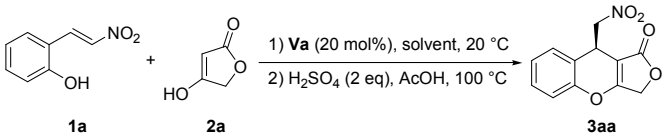


Entry	Catalyst	Time (h)	Yield (%)	Ee (%)
1	**I**	52	74	−30
2	**IIa**	28	94	−63
3	**IIb**	68	97	−67
4	**IIc**	48	87	−79
5	**III**	92	77	−38
6	**IV**	48	95	31
7	**Va**	72	87	81
8	**Vb**	92	90	57

a. Michael addition reactions were carried out with 2-((*E*)-2-nitrovinyl)phenol (**1a**, 0.24 mmol), tetronic acid (**2a**, 0.2 mmol) and catalyst (20 mol%) in methylene chloride (1 mL) at 20 °C. Intramolecular dehydration reactions were performed in glacial acetic acid (1.5 mL) at 100 °C in the presence of 2 equivalent of concentrated sulfuric acid. b. Isolated yield after two steps. c. Determined by HPLC analysis with a chiral stationary phase.

Having confirmed squaramide **Va** as the optimum catalyst for the reaction, other parameters, such as solvent, reaction temperature, and catalyst loading, influencing the reaction were further investigated employing 2-((*E*)-2-nitrovinyl)phenol (**1a**) and 4-hydroxyfuran-2-one (**2a**) as the model substrates. The results are listed in Table 2.

Table 2. Optimization of reaction conditions [a]



Entry	Solvent	Time (h)	Yield (%) [b]	Ee (%) [c]
1	CH_2Cl_2	72	87	81
2	$CHCl_3$	21	92	58
3	$ClCH_2CH_2Cl$	40	90	65
4	$PhCH_3$	40	58	47
5	CH_3CN	72	87	78
6	Et_2O	144	79	54
7	EA	72	85	80
8	THF	40	81	91

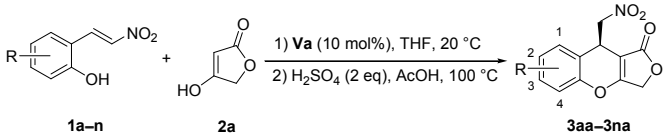
a. Unless otherwise specified, the Michael addition reactions were carried out with **1a** (0.24 mmol), **2a** (0.20 mmol) and squaramide **Va** (20 mol%) in solvent (1 mL) at 20. the intramolecular dedydration reactions were performed in glacial acetic acid (1.5 mL) at 100 °C in the presence of 2 equivalent of concentrated sulfuric acid. b. Isolated yield after two steps. c. Determined by HPLC analysis using a chiral stationary phase. d. Reaction was performed at 0 ºC. e. The catalyst loading is 10 mol%.

With 20 mol % of **Va** as the catalyst at 20 °C, various solvents have been examined for the initial Michael addition reaction (Entries 1–8). The asymmetric Michael addition could be carried out smoothly in several conventional solvents with ee values ranged from 47–91%. THF was found to be superior to any other solvents screened, delivering the tricylcic product **3aa** in 81% yield with the highest enantioselectivity of 91% ee (Entry 8). Although a slightly increased enantioselectivity was observed, conducting the reaction at 0 ºC resulted in a quite slower reaction (Entry 9 vs. entry 8). Finally, it was gratifying that the enantioselectivity could be further improved to 97% ee by adjusting the catalyst loading to 10 mol% (Entry 10). Under this condition, the Michael addition product of *ortho*-nitrovinylphenol **1a** and tetronic acid **2a** was isolated in 93% yield with a comparable enantioselectivity of 96% ee.

Having established the optimal reaction conditions (Table 2, entry 10), we next examined the scope and limitations of the above sequential process with variants of 2-((*E*)-2-nitrovinyl)phenols **1** (Table 3). Although the reactions of these

substituted 2-((*E*)-2-nitrovinyl)phenols proceeded more slowly, both the electron-withdrawing and electron-donating substituents were tolerated well in this sequential Michael addition/dehydration transformation, delivering the corresponding products in good to excellent enantioselectivities irrespective of the substitution pattern (Entries 1–13). The effect of electronic property of the substituent on the intramolecular dehydration process is obvious. Generally, the existence of electron-withdrawing group decreases the nucleophilicity of the phenolic hydroxy group and slows down the reaction. Especially for the dihalo-substituted substrate **1d** and **1f**, quite sluggish reactions were observed and provided the cyclization product **3da** and **3fa** in low yield even after a prolonged reaction time (Entries 4 and 6). In addition, 2-hydroxynaphthalene-1-carbaldehyde derived nitroolefin **1n** was also applicable, albeit the Michael addition reaction proceeded more slowly with a partial conversion of **1n** and afforded the corresponding product with decreased yield (Entry 14). Because all of the products were solids with high melting points, the optical purity of the product could be dramatically improved by a single recrystallization from methylene chlordie/hexane (v/v, 2/1) (Entry 8). Chen[13a], Sohtome and Nagasawa[13b–d] have reported the formation of dimer of that structures containing both nitro and phenol group. However, the generation of the dimer was not observed in our system, in some cases, the observed low yields may be attributed to the formation of appreciable amounts of tarry residue upon treatment with concentrated sulfuric acid.

Table 3. Substrate scope for the newly developed sequential process [a]

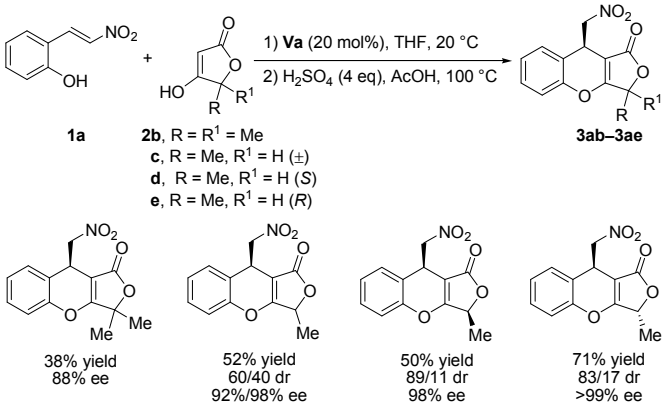


1a–n **2a** **3aa–3na**

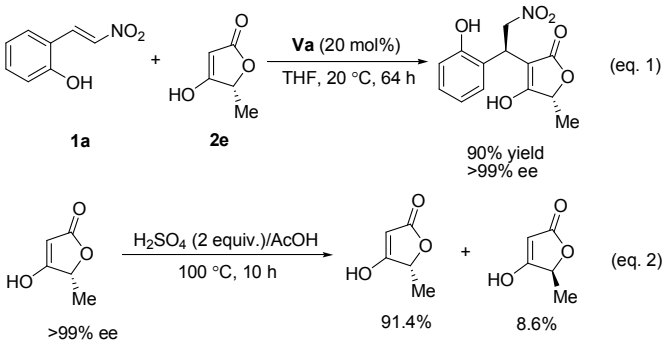
Entry	**3** (R)	Time (h, Step 1)	Time (h, Step 2)	Yield (%) [b]	Ee (%) [c]
1	**3aa** (H)	59	5	80	97
2	**3ba** (2-F)	48	10	81	87
3	**3ca** (2-Cl)	91	52	66	87
4	**3da** (2,4-Cl_2)	52	168	29	87
5	**3ea** (2-Br)	91	52	61	86
6	**3fa** (2,4-Br_2)	96	144	25	94
7	**3ga** (2-Me)	90	1.5	80	86
8	**3ha** (3-Me)	106	2.5	77 (46)	88 (98)
9	**3ia** (4-Me)	100	2.5	80	90
10	**3ja** (2-OMe)	168	3	61	88
11	**3ka** (3-OMe)	144	8	60	93
12	**3la** (4-OMe)	84	29	63	91
13	**3ma** (2,4-^{t}Bu$_2$)	168	2	40	79
14	**3na** (1,2-CH=CH-CH=CH)	240	6	27	88

a. Michael addition reactions were carried out with 2-((*E*)-2-nitrovinyl)phenol (**1a**, 0.24 mmol), tetronic acid (**2a**, 0.2 mmol) and catalyst **Va** (10 mol%) in tetrahydrofuran (1 mL) at 20 °C. Intramolecular dehydration reactions were performed in glacial acetic acid (1.5 mL) at 100 °C in the presence of 2 equivalent of concentrated sulfuric acid. [b] Isolated yield after two steps. [c] Determined by HPLC analysis with a chiral stationary phase.

In addition, tolerance to substitution on the tetronic acid derivative **2** was also preliminarily investigated (Scheme 1). The reaction of 4-hydroxy-5,5-dimethylfuran-2(5*H*)-one (**2b**) to nitrostyrene **1a** also ran smoothly to provide the desired product **3ab** in acceptable yield with high enantioselectivity. Racemic, (*R*)- and (*S*)-4-hydroxy-5-methylfuran-2(5*H*)-ones (**2c**–**e**) were also proved to be suitable reaction partners with 2-((*E*)-2-nitrovinyl)phenol (**1a**), furnishing the desired products **3ac**-**3ae** with 92%, 98% and >99% ee, respectively.



Scheme 2. Reaction of other tetronic acid derivatives.



In case of the reaction of optically pure tetronic acids **2d** and **2e**, partial racemization was observed at the C4 position of the lactone ring. To determine which step is responsible for the

racemization, two additional experiments were performed: 1) **Va**-catalyzed simple Michael addition of **2e** to **1a** (eq. 1); (2) treatment of optically active **2e** under the dehydration condition (eq. 2). These results clearly indicate that the partial recemization was occurred in the subsequent acid promoted dehydration step rather than in the first Michael addition step.

The absolute configuration and molecular structure of **3aa** was unambiguously determined by X-ray crystallography (Figure 1) and the remaining configurations are assumed by analogy.

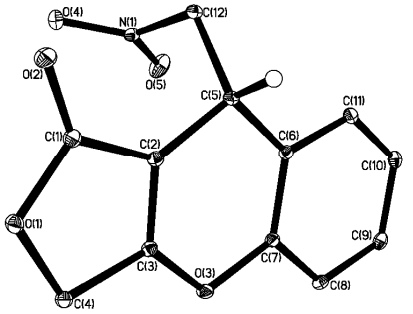


Figure 3. X-ray crystal structure of (*R*)-**3aa**. Most of the hydrogen atoms have been omitted for clarity.

To explanation of the observed stereochemistry outcome of the reaction, a plausible transition state for the initial Michael addition reaction is shown in Figure 4. *Ortho*-nitrovinylphenol **1a** is activated and fixed through double hydrogen bonding interaction with the squaramide moiety of catalyst **Va**. Meanwhile, tetronic acid is deprotonated by the basic tertiary amino group in the catalyst, and the resulting enolate is assumed to interact with the protonated amine by hydrogen bonding. Thereafter, nucleophilic addition of the enolate to the nitroolefin from the *si*-face preferentially leads to the formation of (*R*)-adduct.

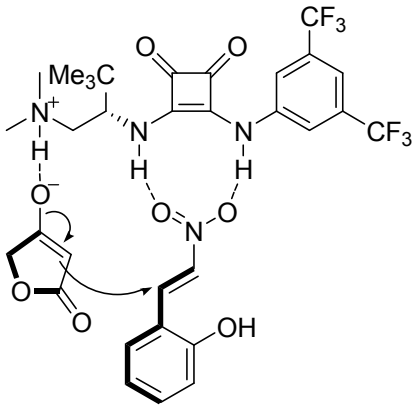


Figure 4. Proposed transition state for the Michael addition step.

Conclusions

We have developed a new methodology to access 3*H*-Furo[3,4-b]chromen-1(9*H*)-one derivatives enantioselectively through sequential Michael addition and intramolecular dehydration reactions. Bifunctional chiral squaramide **Va** derived from L-*tert*-leucine was found to be the efficient catalyst for the conjugate addition of tetronic acid to 2-((*E*)-2-nitrovinyl)phenols. The intramolecular dehydration of the Michael addition products was achieved in the presence of concentrated sulfuric acid. A number of 3*H*-Furo[3,4-b]chromen-1(9*H*)-one derivatives were synthesized in acceptable to good yields and with good to excellent enantioselectivities.

Acknowledgements

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Experimental

General Methods: All reagents and solvents were commercial grade and purified prior to use when necessary. NMR spectra were acquired on Varian 400 MHz instrumental. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ 7.26 and δ 77.0 ($CDCl_3$), 2.50 and 38.45 (DMSO-d_6). Specific rotations were measured on a Perkin-Elmer 341MC polarimeter. Enantiomeric excesses were determined on a Shimadzu LC-20A instrument (chiral column; mobile phase: Hexane/*i*-PrOH). HRMS was performed on a Varian QFT-ESI instrumental. Melting points were determined on a Taike X-4 melting point apparatus. All temperatures were uncorrected.

General procedure for sequential Michael addition-intramolecular dehydration reaction of tetronic acids and 2-((*E*)-2-nitrovinyl)phenols: A solution of squaramide catalyst **Va** (10 mol %), 2-((*E*)-2-nitrovinyl)phenols (**1**, 0.24 mmol) and tetronic acids (**2**, 0.2 mmol) in tetrahydrofuran (1 mL) was stirred at 20 °C. After the reaction was complete (monitored by TLC), the reaction mixture was concentrated under reduced pressure and the crude product was used directly in the next step without further purification. The Michael addition product of **1a** and **2a** was purified by column chromatography on silica gel (200–300 mesh, PE/EtOAc/AcOH = 80/20/1) and fully characterized by ^{1}H NMR, ^{13}C NMR, HRMS and specific rotation data.

4-hydroxy-3-((R)-1-(2-hydroxyphenyl)-2-nitroethyl)furan-2(5H)-one: Pale yellow oil, 93% yield, $[\alpha]_D^{25}$ –5.45 (*c* 1.47, ethyal acetate), 96% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.95 (br. s, 2 H), 7.13 (d, *J* = 7.6 Hz, 1 H), 7.06 (t, *J* = 7.6 Hz, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 6.73 (t, *J* = 7.6 Hz, 1 H), 5.07 (dd, J = 12.8, 10.0 Hz, 1 H), 4.80–4.89 (m, 2 H), 4.66 (s, 2 H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 175.9, 173.9, 154.6, 128.3, 128.2, 123.8, 118.9, 115.2, 96.6, 75.0, 66.5, 32.1. HRMS (ESI) *m/z* calc'd for $C_{12}H_{12}NO_6$ $[M+H]^+$: 266.0659, found 266.0660. HPLC analysis (Chiralpak OJ-H column, Hexane:2-propanol:TFA = 80:20:0.1, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 13.76 (major) and 20.31 min (minor).

To a solution of the crude Michael addition product in glacial acetic acid (1.5 mL) was added two equivalent of concentrated sulfuric acid, and the resulting mixture was heated to 100 °C and maintained this temperature for completion of the reaction

(monitored by TLC). Upon completion of the reaction, the product was directly purified by column chromatography on silica gel (200–300 mesh, PE/EtOAc = 2/1) to afford the desired 3*H*-Furo[3,4-b]chromen-1(9*H*)-ones **3**. The title compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, HRMS and specific rotation data. The enantiomeric excess of the pure products was determined by HPLC analysis using a chiral stationary phase.

(*R*)-9-Nitromethyl-3*H*-furo[3,4-b]chromen-1(9*H*)-one (3aa): White solid, m.p. 138–140 °C, 80% yield, $[\alpha]_D^{25}$ +12.96 (*c* 1.17, $CHCl_3$), 97% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.58 (d, *J* = 7.6 Hz, 1 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 7.29 (t, *J* = 7.6 Hz, 1 H), 7.24 (d, *J* = 8.0 Hz, 1 H), 5.07–5.15 (m, 3 H), 4.97 (dd, *J* = 12.8, 4.0 Hz, 1 H), 4.59 (s, 1 H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.0, 170.6, 150.3, 129.6 (2 C), 126.0, 118.8, 117.4, 98.6, 77.8, 66.1, 30.7. HRMS (ESI) *m/z* calc'd for $C_{12}H_{10}NO_5$ $[M+H]^+$: 248.0553, found 248.0552. HPLC analysis (Chiralpak OJ-H column, Hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 39.17 (major) and 44.54 min (minor).

(*R*)-7-Fluoro-9-nitromethyl-3*H*-furo[3,4-*b*]chromen-1(9*H*)-one (3ba): White solid, m.p. 189–191 °C, 81% yield, $[\alpha]_D^{25}$ +5.14 (*c* 1.40, $CHCl_3$), 87% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.54 (dd, *J* = 9.2, 2.8 Hz, 1 H), 7.32 (dd, *J* = 9.2, 4.8 Hz, 1 H), 7.26 (dt, *J* = 9.2, 2.8 Hz, 1 H), 5.19 (dd, *J* = 12.8, 4.0 Hz, 1 H), 5.03–5.15 (m, 2 H), 4.99 (dd, *J* = 12.8, 3.6 Hz, 1 H), 4.60 (s, 1 H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.1, 170.4, 159.1 (d, *J* = 242.0 Hz), 146.7 (d, *J* = 2.3 Hz), 121.0 (d, *J* = 8.2 Hz), 119.2 (d, *J* = 8.8 Hz), 116.5 (d, *J* = 23.7 Hz), 115.8 (d, *J* = 24.7 Hz), 97.9, 77.3, 66.0, 31.0. HRMS (ESI) *m/z* calc'd for $C_{12}H_9FNO_5$ $[M+H]^+$: 266.0459, found 266.0453. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 13.22 (minor) and 14.55 min (major).

(*R*)-7-Chloro-9-nitromethyl-3*H*-furo[3,4-*b*]chromen-1(9*H*)-one (3ca): White solid, m.p. 203–205 °C, 66% yield, $[\alpha]_D^{25}$ –14.83 (*c* 1.20, $CHCl_3$), 87% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.75 (d, *J* = 2.0 Hz, 1 H), 7.45 (dd, *J* = 8.8, 2.4 Hz, 1 H), 7.30 (d, *J* = 8.8 Hz, 1 H), 5.20 (dd, *J* = 12.8, 4.0 Hz, 1 H), 5.04–5.16 (m, 2 H), 4.98 (dd, *J* = 12.8, 3.6 Hz, 1 H), 4.60 (s, 1 H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 170.9, 170.3, 149.2, 129.64, 129.5, 129.2, 121.1, 119.2, 98.4, 77.4, 66.0, 30.7. HRMS (ESI) *m/z* calc'd for $C_{12}H_9ClNO_6$ $[M+H]^+$: 282.0162, found 282.0160. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 27.36 (minor), and 29.23 min (major).

(*R*)-5,7-Dichloro-9-nitromethyl-3*H*-furo[3,4-*b*]chromen-1(9*H*)-one (3da): Red solid, m.p. 218–220 °C, 29% yield, $[\alpha]_D^{25}$ +37.73 (*c* 0.32, $CHCl_3$), 87% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 2.4 Hz, 1 H), 7.20 (d, *J* = 2.0 Hz, 1 H), 4.91–5.03 (m, 3 H), 4.82 (dd, *J* = 13.2, 3.6 Hz, 1 H), 4.48 (s, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.2, 169.8, 145.7, 131.4, 130.7, 126.9, 124.5, 121.5, 99.5, 76.3, 66.2, 31.6. HRMS (ESI) *m/z* calc'd for $C_{12}H_{11}Cl_2N_2O_5$ $[M+NH_4]^+$: 333.0040, found 333.0040. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 20.42 (minor) and 23.33 min (major).

(*R*)-7-Bromo-9-nitromethyl-3*H*-furo[3,4-*b*]chromen-1(9*H*)-one (3ea): Pale red solid, m.p. 215–217 °C, 61% yield, $[\alpha]_D^{25}$ +56.80 (*c* 1.00, $CHCl_3$), 86% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.80 (s, 1 H), 7.58 (d, *J* = 8.8 Hz, 1 H), 7.23 (d, *J* = 8.8 Hz, 1 H), 5.20 (dd, *J* = 12.8, 3.6 Hz, 1 H), 5.04–5.15 (m, 2 H), 4.97 (dd, *J* = 12.8, 3.6 Hz, 1 H), 4.60 (s, 1 H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 170.8, 170.2, 149.7, 132.4, 132.1, 121.5, 119.5, 117.6, 98.5, 77.4, 66.1, 30.6. HRMS (ESI) *m/z* calc'd for $C_{12}H_9BrNO_6$ $[M+H]^+$: 325.9659, found 325.9666. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 57.42 (minor) and 60.13 min (major).

(*R*)-5,7-Dibromo-9-nitromethyl-3*H*-furo[3,4-*b*]chromen-1(9*H*)-one (3fa): Red solid, m.p. 254–256 °C, 25% yield, $[\alpha]_D^{25}$ +43.50 (*c* 0.27, $CHCl_3$), 94% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 2.0 Hz, 1 H), 7.39 (d, *J* = 2.0 Hz, 1 H), 4.91–5.03 (m, 3 H), 4.82 (dd, *J* = 13.2, 3.6 Hz, 1 H), 4.48 (s, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.4, 169.8, 147.1, 136.4, 130.6, 121.8, 118.9, 113.3, 99.7, 76.4, 66.2, 31.6. HRMS (ESI) *m/z* calc'd for $C_{12}H_{11}Br_2N_2O_5$ $[M+NH_4]^+$: 420.9029, found 420.9013. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 20.15 (minor) and 23.63 min (major).

(*R*)-7-Methyl-9-nitromethyl-3*H*-furo[3,4-*b*]chromen-1(9*H*)-one (3ga): White solid, m.p. 212–214 °C, 80% yield, $[\alpha]_D^{25}$ +29.00 (*c* 1.40, $CHCl_3$), 86% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38 (s, 1 H), 7.19 (d, *J* = 8.4 Hz, 1 H), 7.13 (d, *J* = 8.4 Hz, 1 H), 5.02–5.12 (m, 3 H), 4.95 (dd, *J* = 12.8, 3.6 Hz, 1 H), 4.53 (s, 1 H), 2.30 (s, 3 H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.1, 170.6, 148.4, 135.2, 130.1, 129.6, 118.4, 117.1, 98.4, 77.7, 66.0, 30.7, 20.3. HRMS (ESI) *m/z* calc'd for $C_{13}H_{12}NO_5$ $[M+H]^+$: 262.0710, found 262.0714. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 85:15, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 12.97 (minor) and 14.18 min (major).

(*R*)-6-Methyl-9-nitromethyl-3H-furo[3,4-*b*]chromen-1(9*H*)-one (3ha): White solid, m.p. 144–146 °C, 77% yield (46% yield after a single recrystallizaition), $[\alpha]_D^{25}$ +131.23 (*c* 1.30, $CHCl_3$), 88% ee (98% ee after a single recrystallization). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44 (d, *J* = 8.0 Hz, 1 H), 7.11 (d, *J* = 8.0 Hz, 1 H), 7.06 (s, 1 H), 5.02–5.13 (m, 3 H), 4.93 (dd, *J* = 12.4, 3.6 Hz, 1 H), 4.52 (s, 1 H), 2.31 (s, 3 H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.1, 170.6, 150.1, 139.6, 129.2, 126.8, 117.5, 115.6, 98.6, 77.7, 66.0, 30.5, 20.4. HRMS (ESI) *m/z* calc'd for $C_{13}H_{12}NO_5$ $[M+H]^+$: 262.0710, found 262.0712. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 21.87 (major) and 23.62 min (minor).

(*R*)-5-Methyl-9-nitromethyl-3*H*-furo[3,4-*b*]chromen-1(9*H*)-one (3ia): Pale yellow solid, m.p. 201–203 °C, 80% yield, $[\alpha]_D^{25}$ +12.60 (*c* 1.00, $CHCl_3$), 90% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38 (d, *J* = 7.6 Hz, 1 H), 7.26 (d, *J* = 7.2 Hz, 1 H), 7.18 (t, *J* = 7.6 Hz, 1 H), 5.05–5.16 (m, 3 H), 4.95 (dd, *J* = 12.8, 4.0 Hz, 1 H), 4.58 (s, 1 H), 2.28 (s, 3 H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 170.9, 170.6, 148.6, 130.9, 127.1, 126.2, 125.3, 118.4, 98.5, 77.9, 66.2, 30.9, 15.5. HRMS (ESI) *m/z* calc'd for $C_{13}H_{12}NO_5$ $[M+H]^+$: 262.0710, found 262.0715. HPLC analysis (Chiralpak OJ-H column, Hexane:2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 50.05 (major) and 57.38 min (minor).

(*R*)-7-Methoxy-9-nitromethyl-3*H*-furo[3,4-*b*]chromen-1(9*H*)-one (3ja): White solid, m.p. 168–170 °C, 61% yield, $[\alpha]_D^{25}$ +47.23 (*c* 1.03, $CHCl_3$), 88% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (d, *J* = 8.8 Hz, 1 H), 6.87 (dd, *J* = 9.2, 2.8 Hz, 1 H), 6.76 (d, *J* = 2.8 Hz, 1 H), 4.81–4.92 (m, 4 H), 4.50 (br. s, 1 H), 3.80 (s, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 171.1, 170.8, 157.5, 144.6, 119.0, 118.8, 115.4, 113.0, 98.1, 76.9, 66.1, 55.7, 31.6. HRMS (ESI) *m/z* calc'd for $C_{13}H_{12}NO_6$ $[M+H]^+$: 278.0659, found 278.0664. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 9.57 (minor) and 10.78 min (major).

(*R*)-6-Methoxy-9-nitromethyl-3*H*-furo[3,4-*b*]chromen-1(9*H*)-one (3ka): White solid, m.p. 158–160 °C, 60% yield, $[\alpha]_D^{25}$ –12.46 (*c* 0.87, $CHCl_3$), 94% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.47 (d, *J* = 8.8 Hz, 1 H), 6.89 (dd, *J* = 8.8, 2.4 Hz, 1 H), 6.81 (d, *J* = 2.4 Hz, 1 H), 5.03–5.13 (m, 3 H), 4.92 (dd, *J* = 12.4, 3.6 Hz, 1 H), 4.50 (s, 1 H), 3.78 (s, 3 H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 171.0, 170.5,

159.9, 151.1, 130.2, 112.4, 110.2, 102.5, 99.0, 77.8, 66.0, 55.6, 30.3. HRMS (ESI) *m/z* calc'd for $C_{13}H_{12}NO_6$ $[M+H]^+$: 278.0659, found 278.0660. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 11.13 (major) and 12.31 min (minor).

(*R*)-5-Methoxy-9-nitromethyl-3*H*-furo[3,4-b]chromen-1(9*H*)-one (3la): White solid, m.p. 182–184 °C, 63% yield, $[\alpha]_D^{25}$ +56.8 (*c* 1.10, $CHCl_3$), 91% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.22 (t, *J* = 8.0 Hz, 1 H), 7.10 (d, *J* = 6.4 Hz, 1 H), 7.08 (d, *J* = 6.4 Hz, 1 H), 5.03–5.15 (m, 3 H), 4.94 (dd, *J* = 12.8, 3.6 Hz, 1 H), 4.56 (s, 1 H), 3.84 (s, 3 H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 170.7, 170.5, 147.9, 139.9, 125.8, 120.2, 119.6, 112.3, 98.5, 77.8, 66.2, 55.8, 30.8. HRMS (ESI) *m/z* calc'd for $C_{13}H_{12}NO_6$ $[M+H]^+$: 278.0659, found 278.0665. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 11.77 (minor) and 13.52 min (major).

(*R*)-5,7-Di-tert-butyl-9-nitromethyl-3*H*-furo[3,4-*b*]chromen-1(9*H*)-one (3ma): White solid, m.p. 213–215 °C, 40% yield, $[\alpha]_D^{25}$ +35.14 (*c* 0.70, $CHCl_3$), 79% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (dd, *J* = 2.4 Hz, 1 H), 7.08 (d, *J* = 2.4 Hz, 1 H), 4.96 (d, *J* = 16.0 Hz, 1 H), 4.86 (dd, *J* = 16.4, 1.6 Hz, 1 H), 4.83 (d, *J* = 4.8 Hz, 2 H), 4.54 (t, *J* = 4.4 Hz, 1 H), 1.40 (s, 9 H), 1.30 (s, 9 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.8, 170.36, 148.5, 147.3, 138.1, 124.7, 123.5, 117.6, 98.6, 77.8, 66.1, 35.4, 34.7, 32.0, 31.2, 30.2. HRMS (ESI) *m/z* calc'd for $C_{20}H_{26}NO_5$ $[M+H]^+$: 360.1805, found 360.1808. HPLC analysis (Chiralpak AS-H column, Hexane:2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 5.58 (minor) and 8.75 min (minor).

(*R*)-11-Nitromethyl-8*H*-benzo[*f*]furo[3,4-*b*]chromene-10(11*H*)-one (3na): Yellow solid, m.p. 246–248 °C, 27% yield, $[\alpha]_D^{25}$ +70.80 (*c* 0.57, $CHCl_3$), 88% ee. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (dd, *J* = 2.4 Hz, 1 H), 7.08 (d, *J* = 2.4 Hz, 1 H), 4.96 (d, *J* = 16.0 Hz, 1 H), 4.86 (dd, *J* = 16.4, 1.6 Hz, 1 H), 4.83 (d, *J* = 4.8 Hz, 2 H), 4.54 (t, *J* = 4.4 Hz, 1 H), 1.40 (s, 9 H), 1.30 (s, 9 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 171.2, 170.4, 149.1, 131.4, 130.8, 130.4, 129.0, 127.9, 125.8, 123.0, 117.4, 111.5, 99.5, 78.0, 66.1, 29.1. HRMS (ESI) *m/z* calc'd for $C_{16}H_{12}NO_5$ $[M+H]^+$: 298.0710, found 298.0713. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 92:8, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 33.85 (minor) and 36.57 min (major).

(*R*)-3,3-Dimethyl-9-nitromethyl-3*H*-furo[3,4-*b*]chromen-1(9*H*)-one (3ab): White solid, m.p. 150–152 °C, 38% yield, $[\alpha]_D^{25}$ +12.24 (*c* 0.83, $CHCl_3$), 88% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.59 (d, *J* = 7.2 Hz, 1 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 7.30 (t, *J* = 7.6 Hz, 1 H), 7.25 (d, *J* = 8.0 Hz, 1 H), 5.10 (dd, *J* = 12.8, 3.6 Hz, 1 H), 4.96 (dd, *J* = 12.8, 3.6 Hz, 1 H), 4.58 (t, *J* = 3.6 Hz, 1 H), 1.54 (s, 3 H), 1.53 (s, 3 H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 175.3, 168.5, 150.5, 129.6 (2 C), 126.0, 118.6, 117.5, 97.2, 80.8, 78.0, 30.7, 23.8, 23.3. HRMS (ESI) *m/z* calc'd for $C_{14}H_{14}NO_5$ $[M+H]^+$: 276.0866, found 276.0869. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 11.81 (minor) and 13.37 min (major).

(9*R*)-3-Methyl-9-nitromethyl-3*H*-furo[3,4-*b*]chromen-1(9*H*)-one (3ac): White solid, m.p. 140–142 °C, 52% yield, $[\alpha]_D^{25}$ +14.10 (*c* 0.67, $CHCl_3$), 60/40 dr, 92% ee for the major isomer, 98% ee for the minor isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.37 (m, 2 H), 7.22–7.26 (m, 1 H), 7.14–7.17 (m, 1 H), 5.04–5.15 (m, 1 H), 4.90–4.98 (m, 1 H), 4.83–4.88 (m, 1 H), 4.49–4.54 (m, 1 H), 1.62 (d, *J* = 6.8 Hz, 1.80 H), 1.59 (d, *J* = 6.8 Hz, 1.20 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ major isomer: 174.1, 170.0, 150.8, 129.9, 128.8, 126.3, 118.0, 117.9, 98.3, 77.2, 74.1, 31.4, 17.4. minor isomer: 173.9, 169.9, 150.7, 129.9, 128.7, 126.4, 118.1, 118.0, 98.2, 77.1, 74.0, 31.3, 17.3. HRMS (ESI) *m/z* calc'd for $C_{13}H_{12}NO_5$ $[M+H]^+$: 262.0710, found 262.0713. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 98:2, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 56.55 (minor for the major diastereomer), 61.70 (minor for the minor diastereomer), 65.10 (major for the minor diastereomer) and 69.38 min (major for the major diastereomer).

(3*S*,9*R*)-3-Methyl-9-nitromethyl-3*H*-furo[3,4-*b*]chromen-1(9*H*)-one (3ad): White solid, m.p. 140–142 °C, 52% yield, $[\alpha]_D^{25}$ +3.50 (*c* 0.80, $CHCl_3$), 89/11 dr, 98% ee for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (t, *J* = 7.6 Hz, 1 H), 7.31 (d, *J* = 7.2 Hz, 1 H), 7.24 (t, *J* = 7.6 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 1 H), 5.12 (q, *J* = 6.8 Hz, 0.11 H), 5.06 (q, *J* = 6.8 Hz, 0.89 H), 4.96 (dd, *J* = 12.4, 4.4 Hz, 0.89 H), 4.92 (dd, *J* = 12.4, 4.8 Hz, 0.11 H), 4.85 (dd, *J* = 12.4, 3.6 Hz, 1 H), 4.50 (s, 1 H), 1.62 (d, *J* = 6.8 Hz, 2.67 H), 1.58 (d, *J* = 6.8 Hz, 0.33 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ major isomer: 174.1, 170.0, 150.8, 129.9, 128.8, 126.3, 118.0, 117.9, 98.3, 77.2, 74.1, 31.4, 17.4. minor isomer: 173.9, 169.9, 150.7, 129.9, 128.7, 126.4, 118.1, 118.0, 98.2, 77.1, 74.0, 31.3, 17.3. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 98:2, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 55.32 (minor for the major diastereomer), 60.09 (major for the minor diastereomer), 63.49 (minor for the minor diastereomer) and 68.07 min (major for the major diastereomer).

(3*R*,9*R*)-3-Methyl-9-nitromethyl-3*H*-furo[3,4-*b*]chromen-1(9*H*)-one (3ae): White solid, m.p. 140–142 °C, 52% yield, $[\alpha]_D^{25}$ +28.11 (*c* 1.17, $CHCl_3$), 83/17 dr, >99% ee for the major isomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (t, *J* = 8.0 Hz, 1 H), 7.30 (d, *J* = 7.2 Hz, 1 H), 7.24 (t, *J* = 7.6 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 1 H), 5.12 (q, *J* = 6.8 Hz, 0.83 H), 5.06 (q, *J* = 6.8 Hz, 0.17 H), 4.96 (dd, *J* = 12.4, 4.4 Hz, 0.17 H), 4.92 (dd, *J* = 12.4, 4.8 Hz, 0.83 H), 4.86 (dd, *J* = 12.4, 3.6 Hz, 1 H), 4.53 (t, *J* = 4.4 Hz, 1 H), 1.62 (d, *J* = 6.8 Hz, 0.51 H), 1.58 (d, *J* = 6.8 Hz, 2.49 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ minor isomer: 174.1, 170.0, 150.8, 129.9, 128.8, 126.3, 118.0, 117.9, 98.3, 77.2, 74.1, 31.4, 17.4. minor isomer: 173.9, 169.9, 150.7, 129.9, 128.7, 126.4, 118.1, 118.0, 98.2, 77.1, 74.0, 31.3, 17.3. HPLC analysis (Chiralpak AD-H column, Hexane:2-propanol = 98:2, flow rate = 1.0 mL/min, wavelength = 220 nm): *R*t = 57.13 (minor for the minor diastereomer), 65.83 (major for the major diastereomer) and 69.38 min (major for the minor diastereomer).

Notes and references

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