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Asymmetric synthesis of *O*-alkylated tetronic acid derivatives via an organocatalytic Mannich reaction and subsequent intramolecular cyclization

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ABSTRACT

The organocatalytic asymmetric Mannich reaction of ethyl 4-chloro-3-oxobutanoate with *N*-Boc-imines has been studied and Cinchona alkaloids and chiral thiourea-tertiary amines were evaluated as catalysts. A pyrrolidine-based thiourea-tertiary amine was identified as the best catalyst for the transformation. The Mannich adducts readily underwent a one-pot intramolecular cyclization in the presence of triethylamine. A number of *O*-ethyl tetronic acid derivatives were obtained in good yields and enantioselectivities (up to 91% ee). The products could be further converted to the heteroatomic mimics of prostaglandins via reaction with primary amines.

1. Introduction

The enantioselective Mannich reaction is a powerful tool for the preparation of chiral β-amino carbonyl compounds.[1] Among the various carbonyl compounds used in this reaction, 1,3-dicarbonyl compounds are especially attractive. Their α-methylene groups are acidic enough to allow the generation of enolate anions under mild reaction conditions. In addition, the chiral multifunctional amine products are useful intermediates for further elaborations. Metal-based chiral catalysts have been successfully developed for this transformation.[2] For example, chiral bisoxazoline-copper complexes,[2a] palladium complexes[2b], and lithium binaphtholate salts[2c] have been reported to provide good yields and enantioselectivities for the Mannich reaction of 1,3-dicarbonyl compounds with *N*-protected imines. Over the past decade, asymmetric organocatalysis has made great progress.[3] Several groups have reported organocatalytic enantioselective Mannich reactions of 1,3-dicarbonyl compounds with imines.[4] Cinchona alkaloids,[4a,b] chiral thiourea-tertiary amines,[4c–g] chiral Brønsted acids[4h,i] have been shown to be efficient catalysts. Ricci and co-workers found that chiral phase transfer catalysts derived from cinchona alkaloids also provided good yields and enantioselectivities.[4j] Recently we have developed a number of organocatalytic reactions with α-halogenated nucleophiles.[5] Chiral cyclopropanes were obtained in good yields and enantioselectivities via Michael/intramolecular alkylation pathways. We speculated that commercially available 4-chloro-3-oxobutanoate would be a useful nucleophile for asymmetric organocatalytic transformations. The reactivity of the chloro substituent allows the consequent intramolecular substitution to provide chiral cyclic compounds. In 2006, Jørgensen and co-workers reported the organocatalytic domino Michael/aldol reaction of 4-chloro-3-oxobutanoate with enals.[6] Chiral epoxycyclohexanones were prepared in excellent yields and enantioselectivities. Córdova and co-workers later found that the application of 4-bromo-3-oxobutanoate instead of 4-chloro-3-oxobutanoate led to a domino Michael/alkylation reaction. Chiral cyclopentanones were thus obtained in good yields and excellent enantioselectivities.[7] Herein, we report the asymmetric organocatalytic Mannich reaction of ethyl 4-chloro-3-oxobutanoate with *N*-Boc-imines. The consequent intramolecular cyclization provided *O*-alkylated tetronic acids in good yields and enantioselectivities.

2. Results and discussion

Encouraged by Schaus' work,[4a,b] we initially evaluated cinchonine as the catalyst for the reactions of ethyl 4-chloro-3-oxobutanoate **1** and *N*-protected imines **2a**–**2b** (Scheme 1). The reactions were carried out in dichloromethane at room temperature for 48 h. The effect of the protecting groups was found to be significant. The reaction of **1** with *N*-Boc-imine **2a** afforded β-amino ester **3a** in 78% yield. The reaction of *N*-Ts-imine **2b** afforded the Mannich adduct **3b** in only 21% yield. A couple of unidentified side products were also observed in this case. On the other hand, the reaction of *N*-PMP-imine **2c** with **1** did not occur at all.

Tetronic acid derivatives are widespread in plant and microbe metabolites. Many of them possess valuable biological activities.[8] The synthesis of chiral tetronic acid derivatives has received considerable attention.[9] When compound **3a** was treated with triethylamine, an intramolecular cyclization occurred to give 2-ethyl tetronic acid derivative **4a** in excellent yield.[10]

Compound **4a** was obtained in 15% ee as determined by chiral HPLC analysis. Although 43% ee could be achieved by running the

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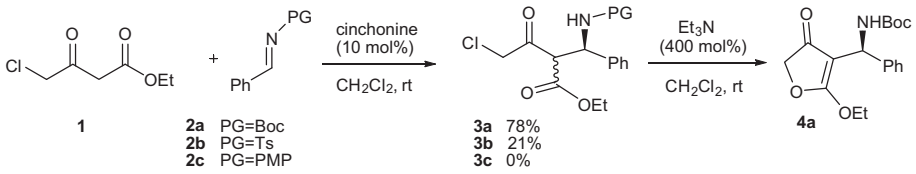


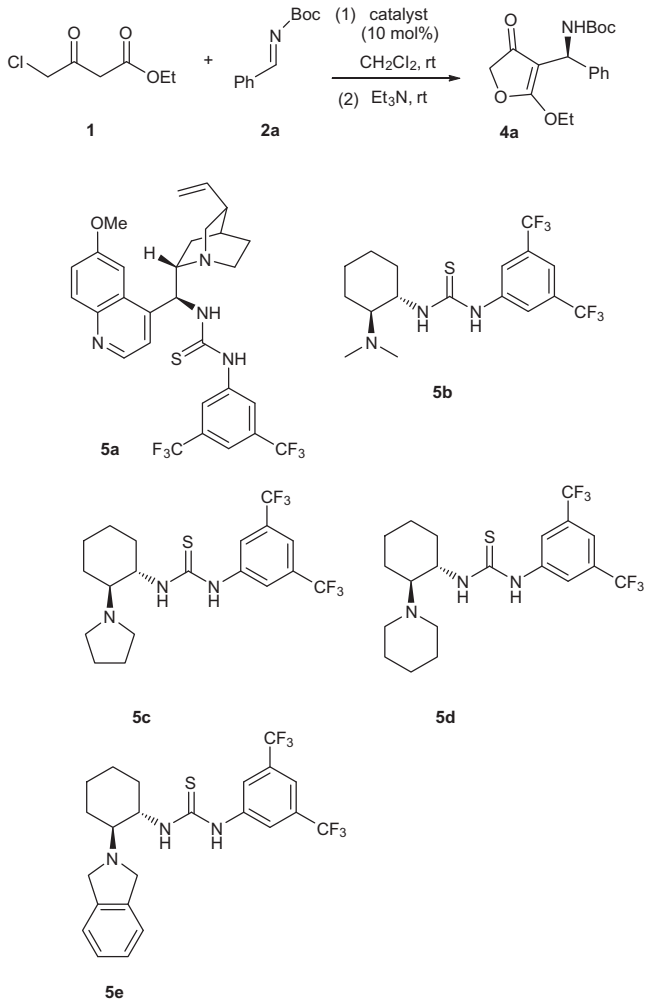
Scheme 1. Asymmetric Mannich reactions of 4-chloro-3-oxobutanoate **1** with *N*-protected-imines **2a–2c**.

reaction at −35 °C, the value was still significantly lower than the reported data from the cinchonine-catalyzed Mannich reaction of methyl acetoacetate with *N*-Boc-imines.[4a] The 4-chloro substituent resulted in a loss of enantioselectivity in the reaction. To improve the enantioselectivity, a series of organocatalysts including cinchona alkaloids and chiral thiourea-tertiary amines **5a**–**5e** were screened. The results are summarized in Table 1. Both cinchonidine and quinine provided **4a** in good yields, but with low enantioselectivities (Table 1, entries 3–4). Quinine derived thiourea **5a** also afforded **4a** in low enantioselectivity (Table 1, entry 5).[4f,g] Takemoto's catalyst **5b** provided improved enantioselectivity (Table 1, entry 6).[4e] Increasing the steric hindrance of Takemoto's catalyst led to catalyst **5c**, which provided better enantioselectivity (Table 1, entry 7).[11] However, the more sterically demanding catalysts **5d** and **5e** did not further improve the enantioselectivity (Table 1, entries 8–9).

In order to determine the optimal reaction conditions with catalyst **5c**, the effect of the reaction solvent was examined and the results are summarized in Table 2. Acetonitrile and DMF provided similar yields and enantioselectivities with dichloromethane (Table 2, entries 2–3). Methanol afforded a poor yield and enantioselectivity (Table 2, entry 4). Toluene, ether, and THF provided lower enantioselectivities than dichloromethane (Table 2, entries 5–7). Acetone provided the best results in terms of the enantioselectivity and the yield (Table 2, entry 8). Decreasing the reaction temperature significantly improved the enantioselectivity (Table 2, entries 9–11). Good enantioselectivity and yield were achieved at −78 °C (Table 2, entry 11). In order to clarify the possible kinetic resolution effect during the cyclization of **3a** to **4a** in the presence of catalyst **5c**, product **3a** was isolated before the addition of triethylamine. It was obtained as two inseparable diastereoisomers (82% yield, dr = 53/47, 83% ee and 81% ee respectively). In addition, only trace amounts of **4a** were observed in the reaction mixture by TLC analysis. The isolated **3a** was then transformed to **4a** (84% ee) via treatment with triethylamine in acetone. These results clearly indicate that catalyst **5c** has almost no catalytic activity for the cyclization of **3a**, and the kinetic resolution of **3a** did not occur in the reaction.

The scope of *N*-Boc-imines was explored and the results are summarized in Table 3. *O*-Ethyl tetronic acid derivatives were obtained in good yields, and with moderate to good enantioselectivities for a number of aryl and heteroaryl *N*-Boc-imines. The position of the substituent at the phenyl ring seemed to have a significant effect on the enantioselectivity. The *para*-substitution generally resulted in lower enantioselectivity, no matter if an electron-withdrawing or electron-donating group was introduced (Table 3, entries 2, 4, 5, 6, 7, 8). *ortho*-Chloro, and *meta*-chloro substituted imines **2b** and **2c** afforded better enantioselectivities than *para*-chloro substituted imine **2d**. Similarly, *ortho*-methoxy substituted imine **2f** gave better enantioselectivity than *para*-methoxy substituted imine **2g**. 2-Thiophenyl imine **2i** provided the product in good yield and enantioselectivity (Table 3, entry 9), however, 2-furyl imine **2j** gave a lower enantioselectivity (Table 3, entry 10). Cyclohexyl *N*-Boc-imine **2k** provided a lower yield and enantioselectivity when compared with phenyl *N*-Boc-imine **2a** (Table 3, entry 11).

Table 1
Screening of the catalysts[a]



Entry	Catalyst	Yield[b] (%)	ee[c] (%)
1	Cinchonine	78	15
2[d]	Cinchonine	78	43
3	Cinchonidine	76	14
4	Quinine	74	17
5	**5a**	78	19
6	**5b**	81	28
7	**5c**	83	45
8	**5d**	81	19
9	**5e**	80	21

[a] Reactions were carried out with **1a** (0.1 mmol), **2a** (0.1 mmol) and catalyst (0.01 mmol) in CH_2Cl_2 (1 mL) at room temperature for 48 h.
[b] Isolated yields.
[c] Determined by HPLC analysis.
[d] The reaction was carried out at −35 °C.

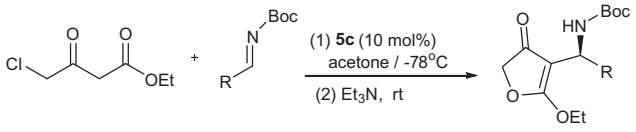
A single crystal of product **7b** was obtained. Its absolute configuration was determined as (*R*) by X-ray diffraction analysis

Table 2
Effect of the reaction solvent[a]

Entry	Solvent	T (°C)	Yield (%)	ee (%)
1	CH_2Cl_2	rt	83	45
2	Acetonitrile	rt	82	42
3	DMF	rt	80	43
4	Methanol	rt	39	5
5	Toluene	rt	78	36
6	Ether	rt	75	34
7	THF	rt	45	11
8	Acetone	rt	83	49
9	Acetone	−20	83	60
10	Acetone	−40	82	73
11	Acetone	−78	81	84

[a] Reactions were carried out with **1a** (0.1 mmol), **2a** (0.1 mmol) and **5c** (0.01 mmol) in a solvent (1 mL) for 48 h.

Table 3
Synthesis of *O*-ethyl tetronic acid derivatives from a variety of *N*-Boc-imines[a]



1 2a, 6b-6k 4a, 7b-7k

Entry	R	Yield[b] (%)	ee[c] (%)
1	Ph **2a**	**4a**, 80	84
2	2-Cl-C_6H_4 **6b**	**7b**, 82	91
3	3-Cl-C_6H_4 **6c**	**7c**, 70	89
4	4-Cl-C_6H_4 **6d**	**7d**, 80	82
5	4-F-C_6H_4 **6e**	**7e**, 80	81
6	2-MeO-C_6H_4 **6f**	**7f**, 85	83
7	4-MeO-C_6H_4 **6g**	**7g**, 88	63
8	4-CF_3-C_6H_4 **6h**	**7h**, 81	76
9	2-Thionyl **6i**	**7i**, 78	86
10	2-Furyl **6j**	**7j**, 75	60
11	cyclohexyl **6k**	**7k**, 65	68

[a] Reactions were carried out with **1** (0.1 mmol), *N*-Boc-imine (0.1 mmol), **5c** (0.01 mmol) in acetone (1 mL) at −78 °C for 48 h. Then, Et_3N (56 μL) was added at room temperature and the reaction was continued for additional 8 h.
[b] Isolated yields.
[c] Determined by chiral HPLC analysis.

(Fig. 1).[12] The absolute configurations of the other products were assigned analogously.

The reaction of ethyl 4-bromo-3-oxobutanoate with **2a** was next studied. Product **4a** was obtained in lower yield and enantioselectivity in comparison with ethyl 4-chloro-3-oxobutanoate **1** (Scheme 2, eq. 1). The bigger volume of bromine than chlorine had a detrimental effect on the enantioselectivity. The reaction of *O*-ethyl tetronic acid with **2a** was also examined, however, no substantial amount of **4a** could be obtained (Scheme 2, eq. 2). The lower reactivity of *O*-ethyl tetronic acid was proposed to account for these results.

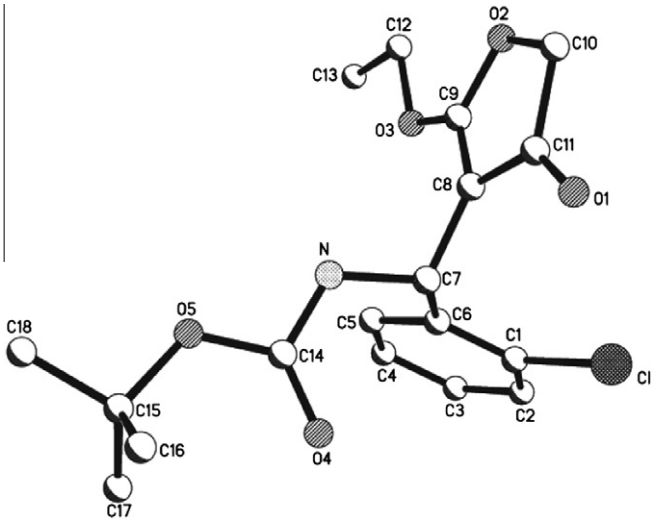


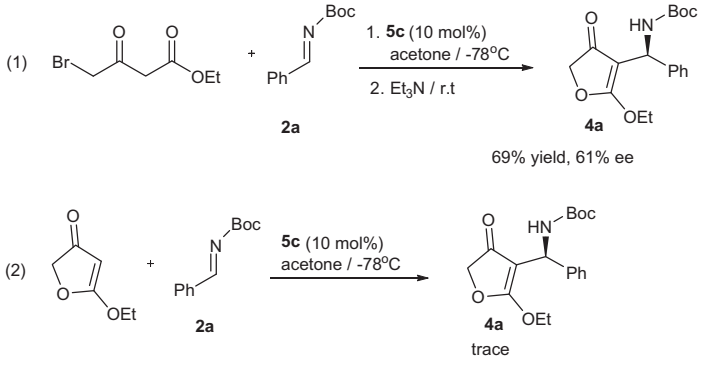
Figure 1. X-ray crystal structure of **7b**.

5c-Catalyzed Mannich reaction of ethyl 4-chloro-3-oxobutanoate **1** and *N*-Boc-imines is suggested to proceed via a bifunctional catalytic mechanism (Scheme 3).[4f] The deprotonation of **1** by catalyst **5c** gives the enolate anion. In addition to the electrostatic attraction between the enolate anion and the ammonium cation, hydrogen bonds are also expected to form. At the same time, *N*-Boc-imine **2a** is activated through double hydrogen-bonding interactions with the thiourea group of **5c**. The consequent nucleophilic attack and the proton transfer provide product **3a**, which is converted in situ to **4a** after triethylamine is added.

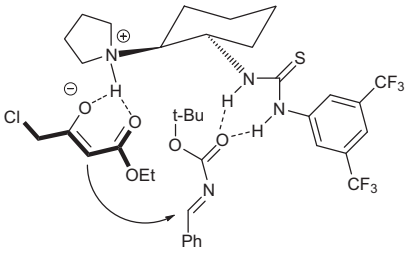
2-ethoxyl of product **4a** could be replaced readily by primary amines. The treatment of **4a** with butyl amine in methanol led to compound **8** in excellent yield and enantioselectivity (Scheme 4). The analogs of **8** were previously prepared as the heteroatomic mimics of prostaglandins, and found to show the pronounced anti-aggregatory effect.[13]

3. Conclusion

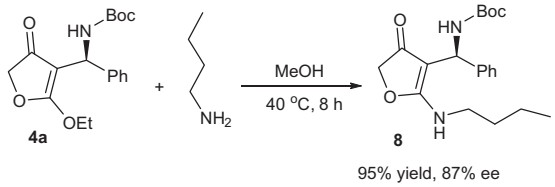
In conclusion, we have developed an efficient method for the asymmetric synthesis of *O*-alkylated tetronic acid derivatives. Enantioselective Mannich reactions of 4-chloro-3-oxobutanoate



Scheme 2. Reaction of ethyl 4-bromo-3-oxobutanoate and *O*-ethyl tetronic acid with **2a**.



Scheme 3. Proposed transition state.



Scheme 4. Transformation of **4a** to compound **8**.

with a series of *N*-Boc-imines were achieved in good yields and enantioselectivities. A pyrrolidine-based chiral thiourea-tertiary amine was identified as the best catalyst. The consequent intramolecular cyclization of the Mannich adducts in the presence of triethylamine led to *O*-alkylated tetronic acid derivatives efficiently. Furthermore, the products could be readily converted to the heteroatomic mimics of prostaglandins.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE 400 spectrometer. Chemical shifts of protons are reported in parts per million downfield from tetramethylsilane ($\delta = 0$). Chemical shifts of carbon are referenced to the central peak of the solvent ($CDCl_3$, $\delta = 77.0$). Peaks are labeled as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Optical rotations were measured on a Perkin–Elmer 341 digital polarimeter. Melting points were measured on a WRS-2A melting point apparatus and are uncorrected. The high resolution mass spectroscopic data were obtained with Shimadzu LCMS-IT-TOF spectrometer. Infrared (IR) spectra were recorded on a Bruker Tensor 37 spectrophotometer. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak). Enantiomeric excesses were determined by HPLC using a Daicel Chiralpak AS–H column (4.6 mm × 25 cm) and eluting with a hexane/2-PrOH solution. Flash chromatography was performed over Silica gel (230–400 mesh), purchased from Qingdao Haiyang Chemical Co., Ltd. Acetone was purchased from Tianjin Fuyu Chemical Co., Ltd and dried over $MgSO_4$ before use. Commercially available reagents and analytical grade solvents were used without further purification. *N*-Boc-imines were prepared according to the reported procedures.[14]

4.2. Typical procedure for asymmetric synthesis of *O*-ethyl tetronic acid derivatives

A solution of **5c** (4.2 mg, 0.01 mmol) in acetone (0.5 mL) was stirred at −78 °C for 10 min. Then, a mixture of **1** (16.4 mg, 0.1 mmol) and **2a** (20.5 mg, 0.1 mmol) in acetone (0.5 mL) was added. The reaction solution was stirred at −78 °C for 48 h and then warmed to room temperature. After triethylamine (56 μL, 0.4 mmol) was added, the reaction mixture was stirred at room temperature for 8 h. The solvent was evaporated under vacuum, and the residue was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate = 2/1) to give product **4a** as a light yellow oil.

4.3. Spectroscopic data of the products

4.3.1. (*S*)-*tert*-Butyl (2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl) (phenyl) methylcarbamate 4a

Light yellow oil, $[\alpha]_D^{20} = +17.4$ (*c* 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.40 (d, *J* = 7.2 Hz, 2H), 7.31–7.27 (m, 2H), 7.23–7.19 (m, 1H), 6.56 (d, *J* = 8.8 Hz, 1H), 5.54 (d, *J* = 9.2 Hz, 1H), 4.56 (d, *J* = 16.0 Hz, 1H), 4.51 (d, *J* = 16.0 Hz, 1H), 4.45 (qd, *J* = 7.2, 2.0 Hz, 2H), 1.43 (t, *J* = 7.2 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.9, 180.2, 155.2, 142.7, 128.5, 127.1, 126.2, 94.9, 79.3, 74.8, 66.6, 48.4, 28.4, 14.7; IR (thin film) ν/cm^{-1}: 2978 (m), 2931 (w), 1726 (m), 1618 (m), 1499 (w), 1389 (s), 1015 (m), 757 (w), 700 (m); HRMS (ESI) calcd for $C_{18}H_{23}NNaO_5$ $(M+Na)^+$: 356.1468, found: 356.1470. The enantiomeric excess was determined by HPLC with a Chiralpak AS–H column (hexane/2-PrOH = 90/10, λ = 254 nm, 1.0 mL/min); t_{major} = 19.80 min, t_{minor} = 23.28 min, 84% ee.

4.3.2. (*R*)-*tert*-Butyl (2-chlorophenyl) (2-ethoxy-4-oxo-4,5-dihydro furan-3-yl) methylcarbamate 7b

White solid, mp 125–126 °C; $[\alpha]_D^{20} = -13.3$ (*c* 0.48, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (br, 1H), 7.29–7.19 (m, 3H), 6.57 (d, *J* = 8.4 Hz, 1H), 5.51 (d, *J* = 8.8 Hz, 1H), 4.58 (d, *J* = 16.0 Hz, 1H), 4.53 (d, *J* = 16.4 Hz, 1H), 4.47 (q, *J* = 7.2 Hz, 2H), 1.46–1.42 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.7, 180.2, 155.2, 144.7, 134.2, 129.7, 127.3, 126.4, 124.4, 94.3, 79.6, 74.9, 66.8, 48.0, 28.4, 14.7; IR (thin film) ν/cm^{-1}: 2978 (m), 2929 (w), 1728 (m), 1619 (m), 1496 (w), 1388 (s), 1015 (m), 755(m); HRMS (ESI) calcd for $C_{18}H_{22}ClNNaO_5$ $(M+Na)^+$: 390.1079, found: 390.1077; The enantiomeric excess was determined by HPLC with a Chiralpak AS–H column (hexane/2-PrOH = 90/10, λ = 254 nm, 1.0 mL/min); t_{major} = 14.66 min, t_{minor} = 17.57 min, 91% ee.

4.3.3. (*S*)-*tert*-Butyl (3-chlorophenyl) (2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl) methylcarbamate 7c

Light yellow oil, $[\alpha]_D^{20} = +23.6$ (*c* 0.14, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (br, 1H), 7.29–7.27 (m, 1H), 7.24–7.17 (m, 2H), 6.55 (d, *J* = 8.0 Hz, 1H), 5.51 (d, *J* = 8.4 Hz, 1H), 4.58 (d, *J* = 16.0 Hz, 1H), 4.52 (d, *J* = 16.0 Hz, 1H), 4.47 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.7, 180.2, 155.2, 144.8, 134.3, 129.7, 127.3, 126.4, 124.4, 94.3, 79.6, 74.9, 66.8, 48.1, 28.4, 14.7; IR (thin film) ν/cm^{-1}: 2979 (m), 2930 (w), 1726 (m), 1617 (m), 1442 (w), 1388 (s), 1015 (m), 779(w), 689 (w); HRMS (ESI) calcd for $C_{18}H_{22}ClNNaO_5$ $(M+Na)^+$: 390.1079, found: 390.1079; The enantiomeric excess was determined by HPLC with a Chiralpak AS–H column (hexane/2-PrOH = 90/10, λ = 254 nm, 1.0 mL/min); t_{major} = 21.55 - min, t_{minor} =15.76 min, 89% ee.

4.3.4. (*S*)-*tert*-Butyl (4-chlorophenyl) (2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl) methylcarbamate 7d

Light yellow oil, $[\alpha]_D^{20} = +29.0$ (*c* 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33(d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 8.4 Hz, 1H), 5.49 (d, *J* = 8.8 Hz, 1H), 4.57 (d, *J* = 16.0 Hz, 1H), 4.52 (d, *J* = 16.0 Hz, 1H), 4.46 (qd, *J* = 7.2, 1.6 Hz, 2H), 1.45–1.41 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.8, 180.1, 155.2, 141.3, 132.8, 128.6, 127.7, 94.5, 79.6, 74.9, 66.8, 48.0, 28.4, 14.7; IR (thin film) ν/cm^{-1}: 2979 (m), 2925 (w), 17126 (m), 1590 (m), 1489 (w), 1388 (s), 992 (m), 861(m); HRMS (ESI) calcd for $C_{18}H_{22}ClNNaO_5$ $(M+Na)^+$: 390.1079, found: 390.1083; The enantiomeric excess was determined by HPLC with a Chiralpak AS–H column (hexane/2-PrOH = 90/10, λ = 254 nm, 1.0 mL/min); t_{major} = 17.79 min, t_{minor} = 13.99 min, 82% ee.

4.3.5. (*S*)-*tert*-Butyl (2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl) (4-fluorophenyl) methylcarbamate 7e

Light yellow oil, $[\alpha]_D^{20} = +58.0$ (*c* 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38–7.35 (m, 2H), 6.99–6.94 (m, 2H), 6.52 (d, *J* = 8.0 Hz, 1H), 5.51 (d, *J* = 8.4 Hz, 1H), 4.57 (d, *J* = 16.4 Hz, 1H), 4.52 (d, *J* = 16.0 Hz, 1H), 4.46 (qd, *J* = 7.2, 1.2 Hz, 2H), 1.45–1.41 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.8, 180.1, 163.1, 160.7, 155.2, 138.7, 127.9, 127.8, 115.3, 115.1, 94.8, 79.5, 74.8, 66.7, 47.9, 28.4, 14.7; IR (thin film) ν/cm^{-1}: 2979 (m), 2928 (w), 1719 (m), 1618 (m), 1498 (w), 1388 (s), 1054 (m), 838 (w), 700(m); HRMS (ESI) calcd for $C_{18}H_{22}FNNaO_5$ $(M+Na)^+$: 374.1374, found: .374.1377; The enantiomeric excess was determined by HPLC with a Chiralpak AS–H column (hexane/2-PrOH = 90/10, λ = 254 nm, 1.0 mL/min); t_{major} = 20.56 min, t_{minor} = 18.47 min, 81% ee.

4.3.6. (*S*)-*tert*-Butyl (2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl) (2-methoxyphenyl) methylcarbamate 7f

White solid, mp 123–124 °C; $[\alpha]_D^{20} = +27.5$ (*c* 0.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.20 (td, *J* = 8.0, 1.6 Hz, 1H), 6.91 (t, *J* = 6.4 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H,), 6.32 (d, *J* = 9.2 Hz, 1H), 5.88 (d, *J* = 8.8 Hz, 1H), 4.52–4.40 (m, 4H), 3.82 (s, 3H), 1.45–1.40 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.0, 180.1, 156.4, 155.1, 130.1, 128.1, 127.7, 120.4, 110.6, 94.5, 79.1, 74.5, 66.1, 60.3, 55.3, 28.4, 14.7; IR (thin film) ν/cm^{-1}: 2921 (m), 2851 (w), 1718 (m), 1591 (m), 1492 (w), 1385 (s), 1051 (m), 752(w), 700(m); HRMS (ESI) calcd for $C_{19}H_{25}NNaO_6$ $(M+Na)^+$: 386.1574, found: 386.1573; The enantiomeric excess was determined by HPLC with a Chiralpak AS–H column (hexane/2-PrOH = 90/10, λ = 254 nm, 1.0 mL/min); t_{major} = 12.18 min, t_{minor} = 15.88 min, 83% ee.

4.3.7. (*S*)-*tert*-Butyl (2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl) (4-methoxyphenyl) methylcarbamate 7g

Light yellow oil, $[\alpha]_D^{20} = +34.9$ (*c* 0.32, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 8.4 Hz, 1H), 5. 49 (d, *J* = 9.2 Hz, 1H), 4.56 (d, *J* = 16.0 Hz, 1H), 4.51 (d, *J* = 16.0 Hz, 1H), 4.45(qd, *J* = 7.2, 1.4 Hz, 2H), 3.77 (s, 3H), 1.45–1.41 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.0, 180.1, 158.7, 155.2, 135.1, 127.5, 113.8, 95.1, 79.3, 74.8, 66.6, 55.3, 47.9, 28.4, 14.7; IR (thin film) ν/cm^{-1}: 2978 (m), 2932 (w), 1720 (m), 1617 (m), 1441 (w), 1388 (s), 1013 (m), 860(m); HRMS (ESI) calcd for $C_{19}H_{25}NNaO_6$ $(M+Na)^+$: 386.1574, found: 386.1572; The enantiomeric excess was determined by HPLC with a Chiralpak AS–H column (hexane/2-PrOH = 90/10, λ = 254 nm, 1.0 mL/min); t_{major} = 23.87 min, t_{minor} = 26.18 min, 63% ee.

4.3.8. (*S*)-*tert*-Butyl (2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl) (4-(trifluoromethyl)phenyl) methylcarbamate 7h

Light yellow oil, $[\alpha]_D^{20} = +3.8$ (*c* 0.34, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.56–7.50 (m, 4H), 6.61 (d, *J* = 8.4 Hz, 1H), 5.57 (d, *J* = 8.4 Hz, 1H), 4.61–4.45 (m, 4H), 1.44 (t, *J* = 6.8 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.7, 180.2, 155.2, 146.7, 129.5, 129.1, 126.5, 125.5, 125.4, 122.8, 94.1, 79.7, 74.9, 66.9, 48.2, 28.4, 14.7; IR (thin film) ν/cm^{-1}: 2980 (m), 2930 (w), 1725 (m), 1618 (m), 1484 (w), 1388 (s), 1016 (m), 798(m); HRMS (ESI) calcd for $C_{19}H_{22}F_3NNaO_5$ $(M+Na)^+$: 424.1342, found: 424.1346; The enantiomeric excess was determined by HPLC with a Chiralpak AS–H column (hexane/2-PrOH = 90/10, λ = 254 nm, 1.0 mL/min); t_{major} = 12.86 min, t_{minor} = 9.15 min, 76% ee.

4.3.9. (*R*)-*tert*-Butyl (2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl) (thiophen-2-yl) methylcarbamate 7i

Light yellow oil, $[\alpha]_D^{20} = +19.2$ (*c* 0.18, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.14 (dd, *J* = 5.2, 1.2 Hz, 1H), 6.96 (d, *J* = 3.2 Hz, 1H), 6.91–6.88 (m, 1H), 6.42 (d, *J* = 8.8 Hz, 1H), 5.82 (d, *J* = 8.8 Hz, 1H), 4.58 (s, 2H), 4.48 (q, *J* = 7.2 Hz, 2H), 1.46–1.42 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.7, 180.0, 155.1, 146.4, 126.7, 124.3, 124.0, 94.6, 79.6, 74.9, 66.8, 28.4, 14.7; IR (thin film) /cm^{-1}: 2978 (m), 2928 (w), 1726 (m), 1581 (m), 1482 (w), 1387 (s), 1012 (m), 763(m), 697(w); HRMS (ESI) calcd for $C_{16}H_{21}NNaO_5S$ $(M+Na)^+$: 362.1033, found: 362.1032; The enantiomeric excess was determined by HPLC with a Chiralpak AS–H column (hexane/2-PrOH = 90/10, λ = 254 nm, 1.0 mL/min); t_{major} = 23.06 min, t_{minor} = 42.31 min, 86% ee.

4.3.10. (*R*)-*tert*-Butyl (2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl) (furan-2-yl) methylcarbamate 7j

Light yellow oil, $[\alpha]_D^{20} = +15.0$ (*c* 0.22, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.31 (br, 1H), 6.28–6.26 (m, 1H), 6.18 (br, 2H), 5.65 (d, *J* = 9.2 Hz, 1H), 4.58 (s, 2H), 4.48 (q, *J* = 7.2 Hz, 2H), 1.45–1.42 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.8, 180.4, 155.1, 153.9, 141.8, 110.2, 105.7, 92.5, 79.6, 74.9, 66.7, 42.3, 28.4, 14.7; IR (thin film) ν/cm^{-1}: 2979 (m), 2928 (w), 1727 (m), 1688 (m), 1482 (w), 1389 (s), 1007 (m), 788(m), 734(w); HRMS (ESI) calcd for $C_{16}H_{21}NNaO_6$ $(M+Na)^+$: 364.1261, found: 364.1267; The enantiomeric excess was determined by HPLC with a Chiralpak AS–H column (hexane/2-PrOH = 90/10, λ = 254 nm, 1.0 mL/min); t_{major} = 23.39 min, t_{minor} = 33.22 min, 60% ee.

4.3.11. (*S*)-*tert*-Butyl cyclohexyl (2-ethoxy-4-oxo-4,5-dihydrofuran-3-yl) methylcarbamate 7k

Light yellow oil, $[\alpha]_D^{20} = -19.2$ (*c* 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.89 (d, *J* = 9.6 Hz, 1H), 4.53–4.42 (m, 4H), 4.22 (t, *J* = 8.0 Hz, 1H), 1.79–1.60 (m, 6H), 1.44–1.41 (m, 12H), 1.21–1.11 (m, 3H), 0.99–0.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 195.8, 180.8, 155.6, 93.6, 78.8, 74.6, 66.2, 49.6, 43.0, 29.3, 28.4, 26.3, 26.0, 25.9, 14.7; IR (thin film) /cm^{-1}: 2979 (w), 2933 (m), 2922 (w) 1725 (m), 1688 (m), 1451 (w), 1388 (s), 1011 (m), 779 (w); HRMS (ESI) calcd for $C_{18}H_{28}NNaO_5$ $(M+Na)^+$: 362.1938, found: 362.1937; The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane/2-PrOH = 90/10, λ = 254 nm, 1.0 mL/min); t_{major} = 11.16 min, t_{minor} = 16.66 min, 68% ee.

4.4. Preparation of (*S*)-*tert*-butyl (2-(butylamino)-4-oxo-4,5-dihydrofuran-3-yl) (phenyl)methylcarbamate 8

A solution of **4a** (33 mg, 0.1 mmol) and butylamine (0.4 mmol) in methanol (3 mL) was stirred at 40 °C for 8 h. The solvent was evaporated under vacuum, and the residue was purified by flash column chromatography over silica gel (petroleum ether/ethyl acetate = 2/1) to give **8** as a white solid, mp 137–138 °C; $[\alpha]_D^{20} = +24.1$ (*c* 0.60, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (br, 2H), 7.22–7.18 (m, 2H), 7.14–7.11 (m, 1H), 6.67 (s, 1H), 5.47 (d, *J* = 8.0 Hz, 1H), 4.41 (d, *J* = 15.2 Hz, 1H), 4.36 (d, *J* = 15.2 Hz, 1H), 3.16 (br, 2H), 2.13 (s, 1H), 1.33 (s, 9H), 0.81–0.76 (t, *J* = 7.2 Hz, 3H), 1.19–1.11 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 191.8, 176.9, 156.4, 141.1, 128.4, 126.9, 126.4, 92.7, 79.5, 74.0, 48.2, 41.1, 31.8, 28.4, 19.7, 13.5; IR (KBr): 3553 (m), 2980 (w), 2873 (m), 1710 (m), 1689 (m), 1671 (m), 1429 (w), 1329 (m), 1076 (m), 811 (w), 752 (m), 719 (m); HRMS (ESI) calcd for $C_{20}H_{27}N_2O_4$ $(M-H)^-$: 359.1971, found: 359.1961; The enantiomeric excess was determined by HPLC with a Chiralpak AS–H column (hexane/2-PrOH = 90/10, λ = 254 nm, 1.0 mL/min); t_{major} = 8.59 min, t_{minor} = 10.93 min, 87% ee.

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