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Highly enantioselective synthesis of biologically important 2,5-dihydropyrroles via phosphoric acid-catalyzed three-component reactions and evaluation of their cytotoxicity

Feng Shi [a,c,*], Zhong-Lin Tao [b], Jie Yu [b], Shu-Jiang Tu [a,c,*]

[a] College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215000, China
[b] Department of Chemistry, University of Science and Technology of China, Hefei 230026, China
[c] School of Chemistry and Chemical Engineering, Xuzhou Normal University, Xuzhou 221116, PR China

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ABSTRACT

A series of new chiral 2,5-dihydropyrrole derivatives were synthesized with high enantioselectivity via phosphoric acid-catalyzed three-component reactions of aldehydes, amino-esters, and alkyl ynones. This approach has the prominent features of high enantioselectivity (up to 98% ee), atom economy, a broad scope of substrate tolerance as well as operational simplicity, leading to a facile and straightforward access to biologically important chiral 2,5-dihydropyrroles. Moreover, the preliminary evaluation on the cytotoxic activity of this type of chiral 2,5-dihydropyrrole derivatives has resulted in the finding of several compounds with effective cytotoxicity to the carcinoma cell line MCF7.

1. Introduction

The 2,5-dihydropyrrole skeleton not only exists in a number of natural alkaloids, constituting the core structural element of these natural products (Fig. 1),[1] but also serves as important building block for a variety of natural products since the double bond of 2,5-dihydropyrroles would allow the introduction of other functional groups.[2a–d]

More significantly, many 2,5-dihydropyrrole derivatives exhibit important and versatile bioactivity including antioxidant activity,[3] inhibition of the quinone-dependent amine oxidases,[4] antimicrobial,[5] anti-tumor,[1c] anti-inflammatory,[6] and antibiotic[7] activities. As exemplified by those shown in Figure 2, compound **I** linked with an acetyl group and its analogues are antioxidants capable of providing cytoprotection in mammalian cells against oxidative insult and identifying the structural determinants that are optimal for protection against individual types of damage.[3] Compound **II** serves as a tumor inhibitor, which is very active against P388 lymphocytic leukemia in vivo.[1c] Compounds **III** and **IV** have anti-inflammatory[6] and antibiotic[7] activities, respectively, which are crucial in the treatment of related diseases.

The importance of the 2,5-dihydropyrrole skeleton with regards to synthetic and medicinal applications has resulted in a demand for efficient and straightforward syntheses of these compounds, especially chiral 2,5-dihydropyrrole derivatives. In spite of the demand, only a few asymmetric transformations have been developed for the construction of these structural skeletons.[2c–h] One such method is the aminolysis of optically active vinyl epoxides

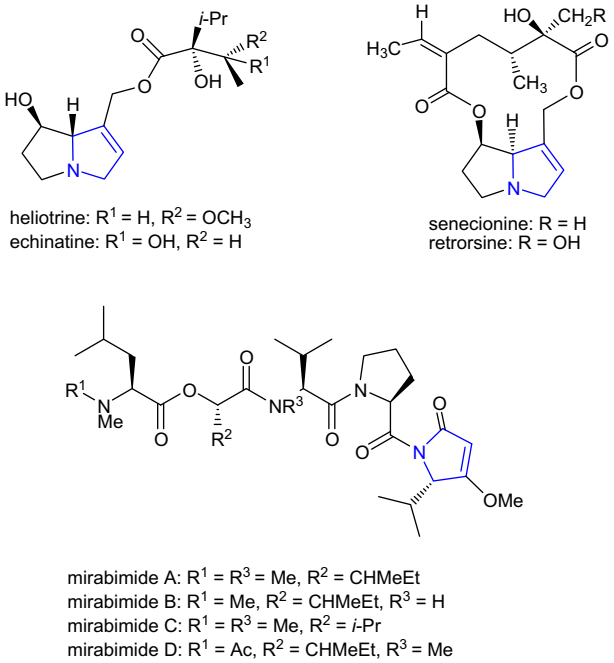

Figure 1. Natural products containing the 2,5-dihydropyrrole skeleton.

* Corresponding authors. Tel./fax: +86 516 83500065.
E-mail address: fshi@xznu.edu.cn (F. Shi).

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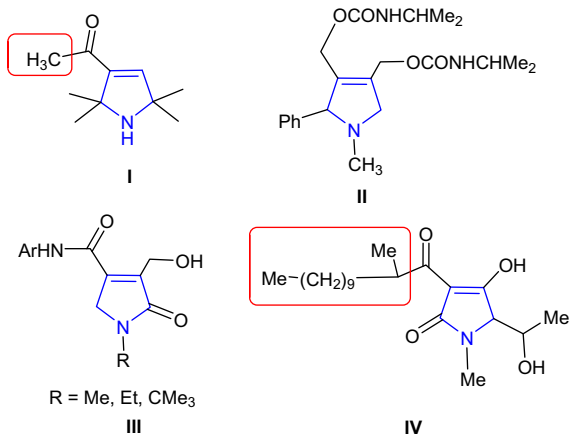


Figure 2. Some 2,5-dihydropyrroles exhibiting important bioactivities.

with allyl amine followed by ring-closing metathesis,[2c] another method is the tandem Wittig–Horner/intramolecular Michael reaction of optically active hydroxy amide or hydroxy carbamates, followed by a retro Diels–Alder cleavage.[2d] Although these early approaches accomplished the synthesis of chiral 2,5-dihydropyrrole derivatives, they employed enantiopure starting materials and multi-step reactions to construct the optically active 2,5-dihydropyrrole skeletons. Consequently, an enantioselective catalytic method for the direct construction of the chiral 2,5-dihydropyrrole skeleton in a one-pot manner is highly desirable with respect to synthetic efficiency and atom economy.

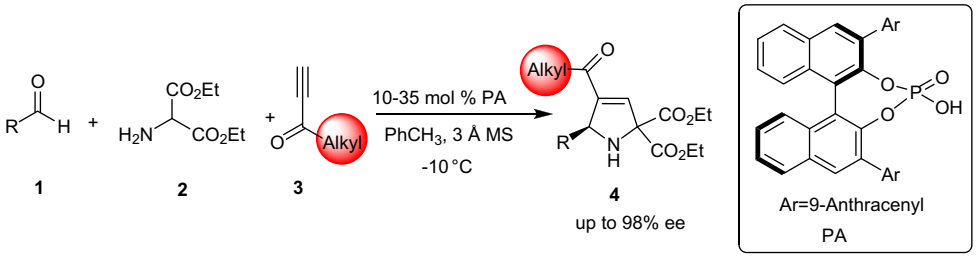
Recently, phosphoric acid-catalyzed asymmetric multicomponent reactions (MCRs) have emerged as robust tools for the facile synthesis of highly enantioenriched nitrogenous heterocycles with structural diversity.[8] The strategy of utilizing catalytic asymmetric 1,3-dipolar cycloadditions between azomethine ylides and electron-deficient alkynes to construct chiral 2,5-dihydropyrrole skeletons was not established until we reported the first catalytic asymmetric versions between azomethine ylides and ynones.[9] However, that work mainly concentrated on 1,3-dipolar cycloadditions involving aryl ynones and reported just one alkyl ynone-involved example. Detailed studies for alkyl ynones have not been fully described. Furthermore, as shown in Figure 2 and 2,5-dihydropyrroles **I** and **IV** linked with aliphatic acyl groups such as an acetyl group exhibited significant pharmaceutical activities. In this regard, the three-component reactions of alkyl ynones as dipolarophiles with azomethine ylides produced in situ will be more valuable, since it can lead to the formation of the privileged 2,5-dihydropyrrole skeleton bearing an aliphatic acyl group more suitable for bioassay. Therefore, based on this anticipation and as a continuation of our efforts on synthesizing pharmaceutically relevant heterocycles via MCRs,[10] we herein report the highly enantioselective synthesis of bioactive 2,5-dihydropyrrole derivatives **4** linked with an acetyl group via a chiral phosphoric acid (PA)-catalyzed three-component 1,3-dipolar cycloadditions of aldehydes **1**, amino-ester **2,** and alkyl ynones **3** (Scheme 1).

2. Results and discussion

Initially, the three-component reaction of 4-nitrobenzaldehyde **1a**, diethyl 2-aminomalonate **2,** and 2-butyn-3-one **3a** in toluene at room temperature in the presence of 10 mol % of chiral phosphoric acid **5** or **6** was employed to screen the most suitable catalyst (Table 1, entries 1–8). The results indicated that catalysts **5d** and **5e** with bulky substituents at the 3,3′-positions of BINOL-derived phosphoric acids were much more efficient in obtaining the 2,5-dihydropyrrole derivative **4a** with high yields and good enantioselectivities (entries 4 and 5). Although the bisphosphoric acid **6** gave the reaction with the highest yield, the enantioselectivity was unsatisfactory (entry 8). Using phosphoric acid **5e** as the best catalyst, the reaction conditions were further optimized by changing the solvents (entries 9–12) and molecular sieves (MS) (entries 13 and 14). However, these changes did not improve either the yield or enantioselectivity in comparison to the results obtained in toluene with 3 Å MS in the presence of **5e** (entry 5). Hence these reaction conditions, as illustrated by entry 5, were preliminarily regarded as the most suitable for other substrates.

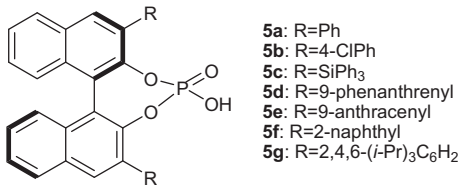
Next, aldehyde **1m** with an electron-donating group on the aromatic ring used in this reaction under the aforementioned reaction conditions. However the results were disappointing because of their low yields and moderate ee values (Table 2, entry 1). It is obvious that the electronic nature of the aldehyde has a significant influence on this reaction and the reaction conditions should be further optimized to tolerate various aldehydes with different electronic properties. As shown in Table 2, the yield and enantioselectivity were considerably improved when increasing the amount of **3a** (entry 2) and lowering the reaction temperature from rt to −10 °C (entry 3). However, lowering the reaction temperature further to −20 °C caused the ee value to decrease (entry 4). To further increase the enantioselectivity of this reaction, the loading of catalyst **5e** was investigated under −10 °C and the results revealed that the ee value of the product **4m** had a positive relationship with the amount of catalyst **5e** (entries 3 and 5–8). It is noteworthy that high enantioselectivity of 84% ee was obtained in the presence of 30 mol % of **5e** (entry 8). However at the same time, the yield was decreased to a moderate level of 50% due to the formation of a by-product, which was generated by the self-cycloaddition of two molecules of azomethine ylide produced in situ.[11] Nevertheless, utilizing different loadings of catalyst according to the electronic nature of substituents on aldehydes **1** was employed as an efficient strategy to improve the enantioselectivity under the optimized reaction conditions.

The synthesis of bioactive 2,5-dihydropyrrole derivatives **4** linked with an acetyl group was then carried out by the three-component reactions of different aldehydes **1** with diethyl

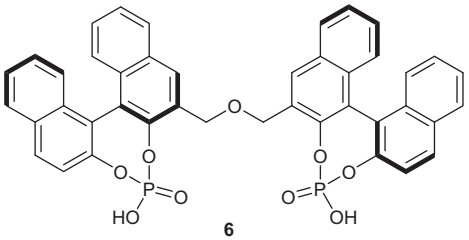


Scheme 1. Enantioselective synthesis of 2,5-dihydropyrroles **4**.

Table 1
Screening of catalysts, solvents, and molecular sieves[a]



5a: R=Ph
5b: R=4-ClPh
5c: R=$SiPh_3$
5d: R=9-phenanthrenyl
5e: R=9-anthracenyl
5f: R=2-naphthyl
5g: R=2,4,6-(*i*-Pr)$_3$C$_6$H$_2$



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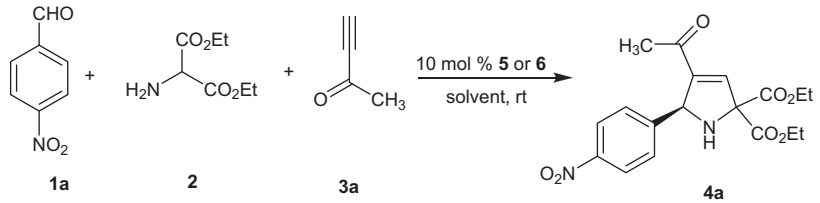
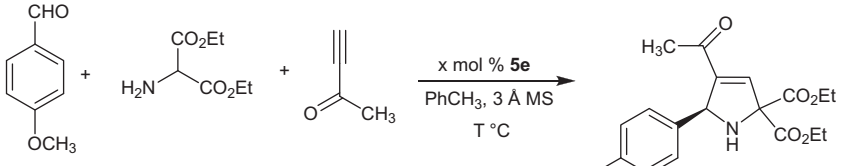


1a **2** **3a** **4a**

Entry	Catalyst	Solvent	Yield[b] (%)	ee[c] (%)
1	**5a**	Toluene	59	2
2	**5b**	Toluene	39	3
3	**5c**	Toluene	22	0
4	**5d**	Toluene	72	80
5	**5e**	Toluene	74	94
6	**5f**	Toluene	43	11
7	**5g**	Toluene	36	−11
8	**6**	Toluene	76	−20
9	**5e**	CH_2Cl_2	79	13
10	**5e**	$CHCl_3$	76	26
11	**5e**	$Cl(CH_2)_2Cl$	62	50
12	**5e**	THF	82	5
13	**5e**	Toluene	71	86[d]
14	**5e**	Toluene	65	94[e]

[a] Unless indicated otherwise, the reaction was carried out on a 0.1 mmol scale in a solvent (1 mL) with 3 Å MS (100 mg) for 12 h at rt; the ratio of **1a**/**2**/**3a** was 1.2:1:2.5.
[b] Isolated yield.
[c] Determined by HPLC.
[d] 4 Å MS were used.
[e] 5 Å MS were used.

Table 2
Further optimization of the reaction conditions[a]

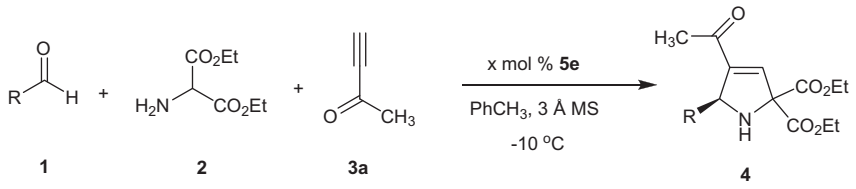


1m **2** **3a** **4m**

Entry	*T* (°C)	*x* (mol %)	Yield[b] (%)	ee[c] (%)
1	rt	10	32	50[d]
2	rt	10	71	57[e]
3	−10	10	70	61
4	−20	10	80	54
5	−10	15	88	70
6	−10	20	82	74
7	−10	25	56	79
8	−10	30	50	84

[a] Unless indicated otherwise, the reaction was carried out on a 0.1 mmol scale in toluene (1 mL) with 3 Å MS (100 mg) for 30 h; the ratio of **1m**/**2**/**3a** was 1.2:1:5.
[b] Isolated yield.
[c] Determined by HPLC.
[d] The ratio of **1m**/**2**/**3a** was 1.2:1:2.5, and the reaction time was 12 h.
[e] The ratio of **1m**/**2**/**3a** was 1.2:1:5, and the reaction time was 12 h.

Table 3
The synthesis of bioactive 2,5-dihydropyrrole derivatives **4**[a]



1 2 3a 4

Entry	4	R	x (mol %)	Yield[b] (%)	ee[c] (%)
1	**4a**	4-$NO_2C_6H_4$	10	73	98
2	**4b**	3-$NO_2C_6H_4$	10	88	92
3	**4c**	2-$NO_2C_6H_4$	10	87	90
4	**4d**	4-FC_6H_4	10	97	78
5	**4e**	4-BrC_6H_4	10	74	82
6	**4f**	4-CNC_6H_4	10	71	94
7	**4g**	2-BrC_6H_4	20	62	86
8	**4h**	4-MsC_6H_4	20	54	97
9	**4i**	Ph	20	81	79
10	**4j**	2-Naphthyl	20	64	84
11	**4k**	3,4-$Cl_2C_6H_3$	20	68	93
12	**4l**	4-MeC_6H_4	35	47	83
13	**4m**	4-$MeOC_6H_4$	30	50	84
14	**4n**	3-$MeOC_6H_4$	35	36	85
15	**4o**	2-Thiophenyl	35	62	74
16	**4p**	2-Furanyl	35	50	61
17	**4q**	4-$MeOC_6H_4CH{=}CH$	30	24	86[d]
18	**4r**	Cyclohexanyl	30	31	66[e]

[a] Unless indicated otherwise, the reaction was carried on a 0.1 mmol scale in toluene (1 mL) with 3 Å MS (100 mg) at −10 °C for 30 h; the ratio of **1**/**2**/**3a** was 1.2:1:5.
[b] Isolated yield.
[c] Determined by HPLC.
[d] The reaction time was 48 h.
[e] The reaction time was 72 h.

2-aminomalonate **2** and 2-butyn-3-one **3a** under the optimal reaction conditions, combined with the strategy of employing different loadings of the catalyst on the basis of the electronic nature of aldehydes **1**. Only 10 mol % of catalyst **5e** was needed for aromatic aldehydes with strong electron-withdrawing groups (Table 3, entries 1–6), while 20 mol % of **5e** was loaded for those with electronically neutral groups (entries 9 and 10) as well as some aldehydes bearing electron-withdrawing groups (entries 7, 8, and 11). For aromatic aldehydes with electron-donating groups (entries 12–14), hetero-aromatic aldehydes (entries 15 and 16) and aliphatic aldehydes (entries 17 and 18), 30–35 mol % of **5e** was utilized to enhance the enantioselectivity of the reaction. It is obvious that this approach can be applied to various aromatic, hetero-aromatic, and aliphatic aldehydes, leading to the efficient synthesis of bioactive 2,5-dihydropyrrole derivatives **4** linked with an acetyl group in high to excellent enantioselectivity (up to 98% ee).

Furthermore, the substrate scope with respect to alkyl ynones **3** was also explored by the reactions of 4-nitrobenzaldehyde **1a**, and 2-aminomalonate **2** with a variety of aliphatic ynones **3** bearing linear, branched, cyclic alkyl groups or benzyl group in the presence of 10 mol % of catalyst **5e** under the optimized reaction conditions (Table 4). Linear alkyl ynones or benzyl ynones gave higher stereoselectivities than branched and cyclic alkyl ynones (entries 1–3, 6 vs 4, and 5). In general, this protocol is amenable to a wide scope of aliphatic ynones with different types of alkyl and benzyl groups in good enantioselectivities (87–98% ee).

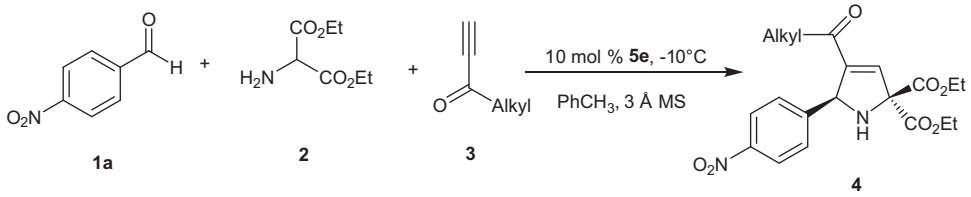
The structures of the synthesized 2,5-dihydropyrroles derivatives **4** were unambiguously characterized by IR, ^1H, ^{13}C NMR, and HRMS (ESI). The absolute configuration of compound **4a** was determined to be (5*S*) by comparing its specific rotation $[\alpha]_D^{20} = +178.4$ (*c* 0.5, $CHCl_3$) to the literature value $[\alpha]_D^{20} = +173.4$ (*c* 0.5, $CHCl_3$).[9] The configurations of the other new 2,5-dihydropyrroles **4** were assigned by analogy.

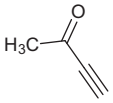
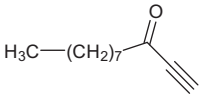
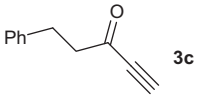
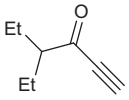
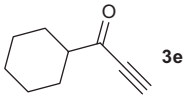
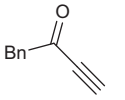
In order to evaluate the possible cytotoxicity of these chiral heterocyclic compounds, the IC_{50} values of some selected 2,5-dihydropyrroles **4** to mammary carcinoma cell line MCF7 were tested (Table 5). All of the compounds tested exhibited moderate cytotoxicity to MCF7 cells. Compounds **4a**, **4c**, and **4l** (entries 1, 2, 4, and 6) showed much stronger cytotoxicity than the other compounds. It is noteworthy that the IC_{50} value of compounds **4a** with 94% ee is lower than that of **4a** with 86% ee (entry 1 vs 2), which indicates that the cytotoxicity of the (*S*)-enantiomer of **4a** should be stronger than its racemic counterpart and the (*R*)-enantiomer. Although the cytotoxicity to MCF7 cells of the tested compounds **4** was moderate, it should be noted that high cytotoxicity is not a prerequisite for the further development of a compound as an anticancer drug candidate.[12] Therefore, those 2,5-dihydropyrroles **4** with a moderate cytotoxicity could still be promising antitumor drug candidates after further structural modification and biological investigations.

3. Conclusions

In conclusion, we have achieved the highly enantioselective synthesis of new bioactive 2,5-dihydropyrrole derivatives linked with an aliphatic acyl group via chiral phosphoric acid-catalyzed three-component 1,3-dipolar cycloadditions of aldehydes, amino-esters, and alkyl ynones. This approach has the prominent features of high enantioselectivity (up to 98% ee), atom economy, and a broad scope of substrate tolerance as well as operational simplicity, leading to a facile and straightforward access to biologically important chiral 2,5-dihydropyrrole derivatives. Moreover, the preliminary evaluation of the cytotoxic activity of this type of 2,5-dihydropyrrole derivative has resulted in us finding several compounds with promising antitumor activity. Therefore, this

Table 4
The scope of the alkyl ynones[a]

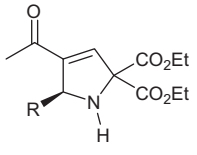


Entry	4	3	Yield[b] (%)	ee[c] (%)
1	**4a**	 **3a**	73	98
2	**4s**	 **3b**	67	97
3	**4t**	 **3c**	74	95
4	**4u**	 **3d**	50	87
5	**4v**	 **3e**	69	94
6	**4w**	 **3f**	51	97

[a] Unless indicated otherwise, the reaction was carried on a 0.1 mmol scale in toluene (1 mL) with 3 Å MS (100 mg) at −10 °C for 30 h; the ratio of **1a**/**2**/**3** was 1.2:1:5.
[b] Isolated yield.
[c] Determined by HPLC.

protocol not only allows the rapid construction of the chiral 2,5-dihydropyrrole architecture, which has potential application in synthetic and medicinal chemistry, but also provides enantioenriched 2,5-dihydropyrrole derivatives linked with an aliphatic acyl group for further structural modification and bioassay.

Table 5
The cytotoxicity of 2,5-dihydropyrroles **4** to MCF7 cells[a]



4

Entry	4	R	IC_{50}[a] (μg/mL)
1	**4a** (94% ee)	4-$NO_2C_6H_4$	166.92
2	**4a** (86% ee)	4-$NO_2C_6H_4$	201.40
3	**4b**	3-$NO_2C_6H_4$	2161.89
4	**4c**	2-$NO_2C_6H_4$	810.93
5	**4f**	4-CNC_6H_4	1378.78
6	**4l**	4-MeC_6H_4	617.45
7	**4o**	2-Thiophenyl	1360.20
8	**4q**	4-$MeOC_6H_4CH{=}CH$	1698.66

[a] The IC_{50} value corresponded to the compound concentration causing 50% mortality in MCF7 cells.

4. Experimental

4.1. General information

NMR spectra were recorded on a Brucker-400 MHz spectrometer. HRMS (Bio TOF Q) spectra were recorded on P-SIMS-Gly of Bruker Daltonics Inc. Infrared spectra were recorded on a Nicolet MX-1E FT-IR spectrometer. HPLC analysis was performed on Waters-Breeze (2487 Dual Absorbance Detector and 1525 Binary HPLC Pump) and Agilent 1200. Chiralpak OD, IC, IA columns were purchased from Daicel Chemical Industries, LTD.

Analytical grade solvents for column chromatography and commercially available reagents were used as received. Toluene was dried over Na and distilled prior to use. All starting materials were commercially available and used directly. Substrates **3b**–**3f** were obtained according to the literature methods.[9,13] Catalysts **5a**–**5g** and **6** were prepared according to the previously described procedures[14] and **5e** was acidified with 4 M HCl before use.

4-Ethylhex-1-yn-3-one **3d**: colorless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.20 (s, 1H, CH), 2.39–2.35 (m, 1H, CH), 1.80–1.70 (m, 2H, CH_2), 1.64–1.53 (m, 2H, CH_2), 0.91 (t, J = 7.2 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.5, 78.6, 77.3, 77.0, 16.7, 57.5, 23.7, 11.5.

4.2. General procedure for the asymmetric synthesis of 2,5-dihydropyrroles 4a–4w

Unless indicated otherwise, a solution of aldehyde **1** (0.12 mmol), amino-ester **2** (0.1 mmol), catalyst **5e** (0.01–0.035 mmol), and 3 Å molecular sieves (100 mg) in toluene (1 mL) was stirred and cooled to −10 °C. Then, ynone **3** (0.5 mmol) was added to the solution. After the reaction mixture was stirred at −10 °C for 30 h, it was filtered to remove the molecular sieves and the solid powder was washed with ethyl acetate. The resulting solution was quenched with saturated aqueous $NaHCO_3$ and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4. After evaporation under the reduced pressure, the residue was purified by flash column chromatography on silica gel to yield pure products **4a**–**4w**.

4.3. Characterization of compounds 4

4.3.1. (5*S*)-Diethyl 4-acetyl-5-(4-nitrophenyl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4a

Flash column chromatography eluent, petroleum ether–ethyl acetate = 8:1; yield: 73%; yellow solid; mp 125–126 °C; $[\alpha]_D^{20} = +178.4$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.14 (d, *J* = 8.8 Hz, 2H, ArH), 7.51 (d, *J* = 8.8 Hz, 2H, ArH), 6.81 (d, *J* = 2.0 Hz, 1H, =CH), 5.51 (s, 1H, CH), 4.37–4.25 (m, 4H, $2CH_2$), 3.61 (s, 1H, NH), 2.31 (s, 1H, CH_3), 1.33 (t, *J* = 7.2 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 193.9, 169.1, 169.0, 149.3, 147.4, 147.3, 136.1, 128.8, 123.6, 79.3, 67.2, 63.0, 62.7, 27.6, 14.1; IR (KBr): *v* 3355, 3081, 2963, 2924, 1732, 1682, 1518, 1348, 1283, 1228, 1110, 1039, 854, 704, 593; ESI FTMS exact mass calcd for $(C_{18}H_{20}N_2O_7+H)^+$ requires *m*/*z* 377.1349, found *m*/*z* 377.1365; enantiomeric excess: 98%, determined by HPLC (Daicel Chirapak OD-H, hexane–2-propanol = 70:30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 5.80 min (major), t_R = 7.69 min (minor).

4.3.2. (5*S*)-Diethyl 4-acetyl-5-(3-nitrophenyl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4b

Flash column chromatography eluent, petroleum ether–ethyl acetate = 6:1); yield: 88%; colorless oil; $[\alpha]_D^{20} = +249.2$ (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.21 (t, *J* = 8.0 Hz, 1H, ArH), 8.10–8.07 (m, 1H, ArH), 7.69 (d, *J* = 7.6 Hz, 1H, ArH), 7.45 (t, *J* = 8.0 Hz, 1H, ArH), 6.82 (d, *J* = 2.0 Hz, 1H, =CH), 5.52 (d, *J* = 1.6 Hz, 1H, CH), 4.38–4.26 (m, 4H, $2CH_2$), 3.64 (s, 1H, NH), 2.32 (s, 3H, CH_3), 1.34 (q, *J* = 7.2 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 194.0, 169.1, 169.0, 148.4, 147.2, 144.4, 136.3, 134.3, 129.1, 122.8, 122.7, 79.2, 67.1, 63.0, 62.8, 27.6, 14.1, 14.0; IR (KBr): *v* 3360, 3089, 2923, 2851, 1731, 1680, 1530, 1460, 1348, 1224, 1111, 1040, 856, 738, 699, 602; ESI FTMS exact mass calcd for $(C_{18}H_{20}N_2O_7+H)^+$ requires *m*/*z* 377.1349, found *m*/*z* 377.1356; enantiomeric excess: 92%, determined by HPLC (Daicel Chirapak OD-H, hexane–2-propanol = 70:30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 5.64 min (major), t_R = 6.56 min (minor).

4.3.3. (5*S*)-Diethyl 4-acetyl-5-(2-nitrophenyl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4c

Flash column chromatography eluent, petroleum ether–ethyl acetate = 6:1; yield: 87%; yellow oil; $[\alpha]_D^{20} = +364.4$ (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.83 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.50 (dt, J_1 = 8.2 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.39–7.33 (m, 2H, ArH), 6.85 (d, *J* = 2.0 Hz, 1H, =CH), 6.08 (dd, J_1 = 6.4 Hz, J_2 = 2.0 Hz, 1H, CH), 4.38–4.20 (m, 4H, $2CH_2$), 3.91 (d, *J* = 6.4 Hz, 1H, NH), 2.31 (s, 3H, CH_3), 1.33 (t, *J* = 7.2 Hz, 3H, CH_3), 1.29 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 193.8, 169.0, 168.9, 149.4, 146.9, 136.8, 136.7, 132.9, 129.4, 128.2, 124.2, 79.0, 63.0, 62.4, 62.0, 27.3, 14.1, 14.0; IR (KBr): *v* 3362, 3082, 2961, 2927, 1732, 1682, 1529, 1465, 1355, 1282, 1229, 1119, 1074, 1040, 852, 743, 602; ESI FTMS exact mass calcd for $(C_{18}H_{20}N_2O_7+H)^+$ requires *m*/*z* 377.1349, found *m*/*z* 377.1329; enantiomeric excess: 90%, determined by HPLC (Daicel Chirapak OD-H, hexane–2-propanol = 70:30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 5.97 min (minor), t_R = 9.25 min (major).

4.3.4. (5*S*)-Diethyl 4-acetyl-5-(4-fluorophenyl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4d

Flash column chromatography eluent, petroleum ether–ethyl acetate = 8:1; yield: 97%; colorless oil; $[\alpha]_D^{20} = +170.4$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.27–7.24 (m, 2H, ArH), 6.97 (dt, J_1 = 8.8 Hz, J_2 = 2.0 Hz, 2H, ArH), 6.76 (d, *J* = 2.0 Hz, 1H, =CH), 5.39 (d, *J* = 2.0 Hz, 1H, CH), 4.33–4.26 (m, 4H, $2CH_2$), 3.43 (s, 1H, NH), 2.27 (s, 3H, CH_3), 1.31 (dt, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 194.2, 169.4, 169.2, 163.5, 161.1, 147.9, 137.6, 137.6, 135.3, 129.3, 129.3, 115.4, 115.2, 79.0, 67.4, 62.7, 62.6, 27.8, 14.0, 14.0; IR (KBr): *v* 3358, 3074, 2961, 2931, 1732, 1628, 1605, 1510, 1367, 1281, 1224, 1119, 1038, 838, 747; ESI FTMS exact mass calcd for $(C_{18}H_{20}FNO_5+H)^+$ requires *m*/*z* 350.1404, found *m*/*z* 350.1411; enantiomeric excess: 78%, determined by HPLC (Daicel Chirapak OD-H, hexane–2-propanol = 90:10, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 6.01 min (major), t_R = 7.08 min (minor).

4.3.5. (5*S*)-Diethyl 4-acetyl-5-(4-bromophenyl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4e

Flash column chromatography eluent, petroleum ether–ethyl acetate = 8:1; yield: 74%; colorless oil; $[\alpha]_D^{20} = +158.1$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.41 (d, *J* = 8.4 Hz, 2H, ArH), 7.17 (d, *J* = 8.4 Hz, 2H, ArH), 6.76 (d, *J* = 2.0 Hz, 1H, =CH), 5.36 (s, 1H, CH), 4.33–4.26 (m, 4H, $2CH_2$), 3.45 (s, 1H, NH), 2.27 (s, 3H, CH_3), 1.31(dt, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 194.1, 169.3, 169.1, 147.7, 140.9, 135.5, 131.5, 129.4, 121.7, 79.1, 67.5, 62.7, 62.6, 27.8, 14.0, 14.0; IR (KBr): *v* 3357, 3088, 2981, 2922, 1735, 1683, 1366, 1274, 1231, 1109, 1011, 857; ESI FTMS exact mass calcd for $(C_{18}H_{20}BrNO_5+H)^+$ requires *m*/*z* 410.0603, found *m*/*z* 410.0611; enantiomeric excess: 82%, determined by HPLC (Daicel Chirapak OD-H, hexane–2-propanol = 90:10, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 6.34 min (major), t_R = 7.97 min (minor).

4.3.6. (5*S*)-Diethyl 4-acetyl-5-(4-cyanophenyl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4f

Flash column chromatography eluent, petroleum ether–ethyl acetate = 6:1; yield: 71%; pale yellow solid; $[\alpha]_D^{20} = +215.0$ (*c* 0.3, $CHCl_3$); mp 90–92 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.57 (d, *J* = 8.4 Hz, 2H, ArH), 7.44 (d, *J* = 8.4 Hz, 2H, ArH), 6.79 (d, *J* = 2.0 Hz, 1H, =CH), 5.45 (d, *J* = 2.0 Hz, 1H, CH), 4.36–4.24 (m, 4H, $2CH_2$), 3.58 (s, 1H, NH), 2.30 (s, 3H, CH_3), 1.32 (t, *J* = 7.2 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 194.0, 169.1, 169.0, 147.3, 147.3, 136.0, 132.2, 128.6, 118.9, 111.5, 79.2, 67.5, 62.9, 62.6, 27.6, 14.1, 14.0; IR (KBr): *v* 3356, 3090, 2982, 2922, 2227, 1735, 1681, 1368, 1278, 1232, 1111, 1038, 855, 565; ESI FTMS exact mass calcd for $(C_{19}H_{20}N_2O_5+H)^+$ requires *m*/*z* 357.1451, found *m*/*z* 357.1458; enantiomeric excess: 94%, determined by HPLC (Daicel Chirapak OD-H, hexane–2-propanol = 90:10, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 11.36 min (major), t_R = 16.13 min (minor).

4.3.7. (5*S*)-Diethyl 4-acetyl-5-(2-bromophenyl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4g

Flash column chromatography eluent, petroleum ether–ethyl acetate = 8:1; yield: 62%; colorless oil; $[\alpha]_D^{20} = +117.4$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.48–7.45 (m, 1H, ArH), 7.15 (dt, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.03–6.99 (m, 2H,

ArH), 6.80 (d, J = 2.0 Hz, 1H, =CH), 5.84 (d, J = 2.0 Hz, 1H, CH), 4.25–4.15 (m, 4H, $2CH_2$), 3.53 (s, 1H, NH), 2.22 (s, 3H, CH_3), 1.25 (t, J = 7.2 Hz, 3H, CH_3), 1.19 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 192.8, 168.2, 146.4, 139.9, 135.4, 131.9, 129.9, 128.1, 126.8, 123.2, 77.9, 65.5, 61.8, 61.4, 28.7, 13.0, 12.9; IR (KBr): ν 3352, 3062, 2983, 2928, 1735, 1628, 1470, 1367, 1278, 1231, 1108, 1026, 856, 751; ESI FTMS exact mass calcd for $(C_{18}H_{20}BrNO_5+H)^+$ requires m/z 410.0603, found m/z 410.0593; enantiomeric excess: 86%, determined by HPLC (Daicel Chirapak OD-H, hexane–2-propanol = 95:5, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 10.45 min (minor), t_R = 11.23 min (major).

4.3.8. (5*S*)-Diethyl 4-acetyl-5-(4-(methylsulfonyl)phenyl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4h

Flash column chromatography eluent, petroleum ether–ethyl acetate = 3:1; yield: 54%; colorless oil; $[\alpha]_D^{20} = +181.4$ (c 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.86 (d, J = 8.4 Hz, 2H, ArH), 7.53 (d, J = 8.4 Hz, 2H, ArH), 6.80 (d, J = 2.0 Hz, 1H, =CH), 5.49 (s, 1H, CH), 4.38–4.25 (m, 4H, $2CH_2$), 3.60 (s, 1H, NH), 3.02 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 1.32 (t, J = 7.2 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 194.0, 169.1, 168.9, 148.3, 147.4, 139.6, 136.1, 128.9, 127.5, 79.3, 67.3, 63.0, 62.6, 44.5, 27.6, 14.0; IR (KBr): ν 3354, 3088, 2983, 2929, 1732, 1679, 1410, 1370, 1305, 1228, 1148, 1038, 957, 855, 769, 545; ESI FTMS exact mass calcd for $(C_{19}H_{23}NO_7S+H)^+$ requires m/z 410.1273, found m/z 410.1248; enantiomeric excess: 97%, determined by HPLC (Daicel Chirapak OD-H, hexane–2-propanol = 70:30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 10.83 min (major), t_R = 12.38 min (minor).

4.3.9. (5*S*)-Diethyl 4-acetyl-5-phenyl-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4i

Flash column chromatography eluent, petroleum ether–ethyl acetate = 8:1; yield: 81%; colorless oil; $[\alpha]_D^{20} = +122.2$ (c 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.31–7.23 (m, 5H, ArH), 6.78 (d, J = 2.0 Hz, 1H, =CH), 5.39 (d, J = 1.6 Hz, 1H, CH), 4.33–4.24 (m, 4H, $2CH_2$), 3.41 (s, 1H, NH), 2.26 (s, 3H, CH_3), 1.31 (dt, J_1 = 7.2 Hz, J_2 = 0.4 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 194.3, 169.5, 169.2, 148.0, 141.7, 135.3, 128.5, 127.8, 127.6, 79.2, 68.3, 62.6, 62.5, 27.9, 14.0, 14.0; IR (KBr): ν 3356, 3062, 2981, 2928, 1731, 1682, 1456, 1367, 1229, 1111, 1030, 857, 700; ESI FTMS exact mass calcd for $(C_{18}H_{21}NO_5+H)^+$ requires m/z 332.1498, found m/z 332.1485; enantiomeric excess: 79%, determined by HPLC (Daicel Chirapak OD-H, hexane–2-propanol = 95:5, flow rate 0.5 mL/min, T = 30 °C, 254 nm): t_R = 17.80 min (major), t_R = 19.56 min (minor).

4.3.10. (5*S*)-Diethyl 4-acetyl-5-(naphthalen-2-yl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4j

Flash column chromatography eluent, petroleum ether–ethyl acetate = 9:1; yield: 64%; colorless oil; $[\alpha]_D^{20} = +150.0$ (c 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.81–7.76 (m, 4H, ArH), 7.47–7.41 (m, 2H, ArH), 7.36 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H, ArH), 6.83 (d, J = 2.0 Hz, 1H, =CH), 5.57 (d, J = 2.0 Hz, 1H, CH), 4.36–4.26 (m, 4H, $2CH_2$), 3.51 (s, 1H, NH), 2.26 (s, 3H, CH_3), 1.32 (dt, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 194.3, 169.5, 169.2, 147.9, 138.9, 135.4, 133.3, 133.1, 128.4, 128.1, 127.6, 127.0, 126.0, 125.9, 125.2, 79.2, 68.3, 62.7, 62.6, 27.9, 14.1; IR (KBr): ν 3361, 3055, 2981, 2927, 1734, 1681, 1367, 1273, 1230, 1190, 1036, 856, 820, 755, 479; ESI FTMS exact mass calcd for $(C_{22}H_{23}NO_5+H)^+$ requires m/z 382.1655, found m/z 382.1640; enantiomeric excess: 84%, determined by HPLC (Daicel Chirapak IC-H, hexane–2-propanol = 90:10, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 28.36 min (minor), t_R = 30.34 min (major).

4.3.11. (5*S*)-Diethyl 4-acetyl-5-(3,4-dichlorophenyl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4k

Flash column chromatography eluent, petroleum ether–ethyl acetate = 8:1; yield: 68%; colorless oil; $[\alpha]_D^{20} = +126.1$ (c 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.41 (d, J = 2.0 Hz, 1H, ArH), 7.34 (d, J = 8.4 Hz, 1H, ArH), 7.16 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H, ArH), 6.77 (d, J = 1.6 Hz, 1H, =CH), 5.36 (d, J = 1.6 Hz, 1H, CH), 4.35–4.24 (m, 4H, $2CH_2$), 3.52 (s, 1H, NH), 2.30 (s, 3H, CH_3), 1.32 (q, J = 6.8 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 194.0, 169.2, 169.0, 147.4, 142.3, 135.8, 132.4, 131.6, 130.2, 129.7, 127.3, 79.1, 66.9, 62.9, 62.7, 27.7, 14.0; IR (KBr): ν 3357, 3090, 2983, 2937, 1737, 1682, 1466, 1367, 1277, 1235, 1111, 1032, 858, 674, 852; ESI FTMS exact mass calcd for $(C_{18}H_{19}C_{l2}NO_5+H)^+$ requires m/z 399.0640, found m/z 399.0640; enantiomeric excess: 93%, determined by HPLC (Daicel Chirapak OD-H, hexane–2-propanol = 90:10, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 6.29 min (major), t_R = 8.18 min (minor).

4.3.12. (5*S*)-Diethyl 4-acetyl-5-p-tolyl-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4l

Flash column chromatography eluent, petroleum ether–ethyl acetate = 8:1; yield: 47%; colorless oil; $[\alpha]_D^{20} = +135.1$ (c 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.15 (d, J = 8.0 Hz, 2H, ArH), 7.10 (d, J = 8.0 Hz, 2H, ArH), 6.77 (d, J = 2.0 Hz, 1H, =CH), 5.35 (d, J = 2.0 Hz, 1H, CH), 4.33–4.24 (m, 4H, $2CH_2$), 3.37 (s, 1H, NH), 2.30 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 1.30 (dt, J_1 = 7.2 Hz, J_2 = 2.0 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 194.4, 169.5, 169.2, 148.0, 138.7, 137.5, 135.2, 129.2, 127.5, 79.1, 68.0, 62.6, 62.5, 28.0, 21.1, 14.0; IR (KBr): ν 3356, 3091, 2981, 2924, 1735, 1683, 1367, 1271, 1230, 1110, 1033, 856, 820, 599, 544; ESI FTMS exact mass calcd for $(C_{19}H_{23}NO_5+H)^+$ requires m/z 346.1654, found m/z 346.1649; enantiomeric excess: 83%, determined by HPLC (Daicel Chirapak OD-H, hexane–2-propanol = 95:5, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 7.99 min (major), t_R = 9.17 min (minor).

4.3.13. (5*S*)-Diethyl 4-acetyl-5-(4-methoxyphenyl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4m

Flash column chromatography eluent, petroleum ether–ethyl acetate = 6:1; yield: 50%; colorless oil; $[\alpha]_D^{20} = +147.8$ (c 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.18 (d, J = 8.8 Hz, 2H, ArH), 6.82 (d, J = 8.8 Hz, 2H, ArH), 6.75 (d, J = 2.0 Hz, 1H, =CH), 5.35 (d, J = 2.0 Hz, 1H, CH), 4.33–4.24 (m, 4H, $2CH_2$), 3.77 (s, 3H, OCH_3), 3.35 (s, 1H, NH), 2.25 (s, 3H, CH_3), 1.30 (dt, J_1 = 7.2 Hz, J_2 = 3.2 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 194.4, 169.5, 169.2, 159.2, 148.0, 135.0, 133.8, 128.7, 113.9, 79.0, 67.7, 62.6, 62.5, 55.2, 28.0, 14.0; IR (KBr): ν 3355, 3078, 2963, 2924, 2852, 1735, 1679, 1609, 1513, 1463, 1366, 1231, 1174, 1109, 1031, 834; ESI FTMS exact mass calcd for $(C_{19}H_{23}NO_6)^+$ requires m/z 361.1525, found m/z 361.1503; enantiomeric excess: 84%, determined by HPLC (Daicel Chirapak OD-H, hexane–2-propanol = 95:5, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 13.12 min (major), t_R = 15.20 min (minor).

4.3.14. (5*S*)-Diethyl 4-acetyl-5-(3-methoxyphenyl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4n

Flash column chromatography eluent, petroleum ether–ethyl acetate = 7:1; yield: 36%; colorless oil; $[\alpha]_D^{20} = +189.8$ (c 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.20 (t, J = 8.0 Hz, 1H, ArH), 6.87–6.82 (m, 2H, ArH), 6.80–6.75 (m, 2H, ArH, and =CH), 5.36 (d, J = 1.6 Hz, 1H, CH), 4.33–4.24 (m, 4H, $2CH_2$), 3.77 (s, 3H, OCH_3), 3.40 (s, 1H, NH), 2.26 (s, 3H, CH_3), 1.30 (t, J = 7.2 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 194.3, 169.5, 169.1, 159.8, 147.9, 143.2, 135.3, 129.5, 120.0, 113.4, 113.2, 79.2, 68.2, 62.6, 62.5, 55.2, 27.9, 14.0, 14.0; IR (KBr): ν 3355, 3085, 2961, 2921, 1737, 1682, 1601, 1466, 1367, 1277, 1231, 1159, 1041,

858, 765, 701, 596; ESI FTMS exact mass calcd for $(C_{19}H_{23}NO_6)^+$ requires *m*/*z* 361.1525, found *m*/*z* 361.1492; enantiomeric excess: 85%, determined by HPLC (Daicel Chirapak OD-H, hexane–2-propanol = 95:5, flow rate 0.5 mL/min, *T* = 30 °C, 254 nm): t_R = 24.92 min (major), t_R = 26.93 min (minor).

4.3.15. (5*S*)-Diethyl 4-acetyl-5-(thiophen-2-yl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4o

Flash column chromatography eluent, petroleum ether–ethyl acetate = 8:1; yield: 62%; colorless oil; $[\alpha]_D^{20} = +192.3$ (*c* 0.03, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.17 (dd, J_1 = 4.8 Hz, J_2 = 1.2 Hz, 1H, Thiophene-H), 7.01 (dt, J_1 = 3.6 Hz, J_2 = 0.4 Hz, 1H, Thiophene-H), 6.91 (dd, J_1 = 4.8 Hz, J_2 = 3.6 Hz, 1H, Thiophene-H), 6.74 (d, *J* = 2.0 Hz, 1H, =CH), 5.72 (s, 1H, CH), 4.33–4.24 (m, 4H, $2CH_2$), 3.53 (s, 1H, NH), 2.32 (s, 3H, CH_3), 1.31 (dt, J_1 = 7.2 Hz, J_2 = 2.8 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 194.2, 169.2, 168.7, 147.2, 146.1, 135.1, 126.9, 125.5, 125.0, 78.8, 63.0, 62.7, 62.6, 27.8, 14.1, 14.0; IR (KBr): *v* 3361, 3091, 2982, 2934, 1735, 1682, 1272, 1230, 1109, 1040, 855, 706; ESI FTMS exact mass calcd for $(C_{16}H_{19}NO_5S+H)^+$ requires *m*/*z* 338.1062, found *m*/*z* 338.1077; enantiomeric excess: 74%, determined by HPLC (Daicel Chirapak OD-H, hexane–2-propanol = 95:5, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 10.14 min (major), t_R = 11.62 min (minor).

4.3.16. (5*S*)-Diethyl 4-acetyl-5-(furan-2-yl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4p

Flash column chromatography eluent, petroleum ether–ethyl acetate = 7:1; yield: 50%; colorless oil; $[\alpha]_D^{20} = +63.2$ (*c* 0.2, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.28 (dd, J_1 = 2.0 Hz, J_2 = 0.8 Hz, 1H, Furan-H), 6.83 (d, *J* = 2.0 Hz, 1H, Furan-H), 6.28 (dd, J_1 = 3.2 Hz, J_2 = 1.6 Hz, 1H, Furan-H), 6.19 (d, *J* = 2.8 Hz, 1H, =CH), 5.44 (s, 1H, CH), 4.32–4.23 (m, 4H, $2CH_2$), 3.37 (s, 1H, NH), 2.34 (s, 3H, CH_3), 1.29 (dt, J_1 = 7.2 Hz, J_2 = 4.0 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 194.0, 169.1, 168.7, 153.6, 145.0, 142.1, 136.5, 110.5, 107.3, 79.0, 62.6, 62.6, 61.1, 27.6, 14.0, 14.0; IR (KBr): *v* 3352, 3093, 2961, 2926, 1735, 1683, 1367, 1277, 1231, 1112, 1032, 856, 744, 599; ESI FTMS exact mass calcd for $(C_{16}H_{19}NO_6)^+$ requires *m*/*z* 321.1212, found *m*/*z* 321.1198; enantiomeric excess: 61%, determined by HPLC (Daicel Chirapak OD-H, hexane–2-propanol = 95:5, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 11.72 min (major), t_R = 13.48 min (minor).

4.3.17. (5*S*)-Diethyl 4-acetyl-5-(4-methoxystyryl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4q

Flash column chromatography eluent, petroleum ether–ethyl acetate = 6:1; yield: 24%; yellow oil; $[\alpha]_D^{20} = +15.3$ (*c* 0.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.28 (d, *J* = 8.8 Hz, 2H, ArH), 6.81 (d, *J* = 8.8 Hz, 2H, ArH), 6.67 (d, *J* = 2.0 Hz, 1H, =CH), 6.61 (d, *J* = 16.0 Hz, 1H, =CH), 5.98 (dd, J_1 = 16.0 Hz, J_2 = 7.6 Hz, 1H, =CH), 4.98 (d, *J* = 7.6 Hz, 1H, CH), 4.35–4.23 (m, 4H, $2CH_2$), 3.79 (s, 3H, OCH_3), 3.19 (s, 1H, NH), 2.36 (s, 3H, CH_3), 1.30 (q, *J* = 7.2 Hz, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 194.5, 169.6, 169.3, 159.3, 147.3, 135.1, 131.4, 129.5, 127.8, 126.8, 113.9, 78.9, 66.4, 62.6, 62.5, 55.3, 27.8, 14.1, 14.0; IR (KBr): *v* 3349, 2959, 2925, 1736, 1680, 1605, 1512, 1366, 1251, 1174, 1030, 853; ESI FTMS exact mass calcd for $(C_{21}H_{25}NO_{6-}2H)^+$ requires *m*/*z* 385.1525, found *m*/*z* 385.1500; enantiomeric excess: 86%, determined by HPLC (Daicel Chirapak OD-H, hexane–2-propanol = 90:10, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 8.82 min (major), t_R = 10.33 min (minor).

4.3.18. (5*S*)-Diethyl 4-acetyl-5-cyclohexyl-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4r

Flash column chromatography eluent, petroleum ether–ethyl acetate = 10:1; yield: 31%; colorless oil; $[\alpha]_D^{20} = +105.0$ (*c* 0.04, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 6.61 (d, *J* = 2.0 Hz, 1H, =CH), 4.35 (s, 1H, CH), 4.30–4.21 (m, 4H, $2CH_2$), 3.09 (s, 1H, NH), 2.38 (s, 3H, CH_3), 1.87–1.62 (m, 4H, $2CH_2$), 1.29 (dt, J_1 = 7.2 Hz, J_2 = 3.2 Hz, 6H, $2CH_3$), 1.26–1.01 (m, 7H, CH, and $3CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 195.4, 169.8, 169.4, 147.3, 135.9, 78.8, 69.0, 62.6, 62.0, 40.0, 30.6, 27.8, 26.6, 26.3, 26.0, 25.7, 14.0; IR (KBr): *v* 3366, 3093, 2982, 2926, 1736, 1679, 1449, 1367, 1228, 1111, 1035, 856, 604; ESI FTMS exact mass calcd for $(C_{18}H_{27}NO_5+H)^+$ requires *m*/*z* 338.1968, found *m*/*z* 338.1983; enantiomeric excess: 66%, determined by HPLC (Daicel Chirapak IC-H, hexane–2-propanol = 70:30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 4.77 min (minor), t_R = 5.49 min (major).

4.3.19. (5*S*)-Diethyl 5-(4-nitrophenyl)-4-nonanoyl-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4s

Flash column chromatography eluent, petroleum ether–ethyl acetate = 12:1; yield: 67%; colorless oil; $[\alpha]_D^{20} = +167.2$ (*c* 0.634, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.14 (d, *J* = 8.8 Hz, 2H, ArH), 7.50 (d, *J* = 8.8 Hz, 2H, ArH), 6.77 (d, *J* = 2.0 Hz, 1H, =CH), 5.52 (s, 1H, CH), 4.37–4.25 (m, 4H, $2CH_2$), 3.60 (s, 1H, NH), 2.67–2.56 (m, 2H, CH_2), 1.50–1.44 (m, 2H, CH_2), 1.33 (t, *J* = 6.8 Hz, 3H, CH_3), 1.32 (t, *J* = 7.2 Hz, 3H, CH_3), 1.24–1.16 (m, 10H, $5CH_2$), 0.86 (t, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):196.9, 169.2, 169.1, 149.4, 147.4, 147.1, 134.8, 128.7, 123.6, 79.3, 67.3, 63.0, 62.6, 40.0, 31.8, 29.7, 29.1, 29.0, 23.8, 22.6, 14.1; enantiomeric excess: 97%, determined by HPLC (Daicel Chirapak AD-H, hexane–2-propanol = 80:20, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 6.917 min (major), t_R = 18.660 min (minor).

4.3.20. (5*S*)-Diethyl 5-(4-nitrophenyl)-4-(3-phenylpropanoyl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4t

Flash column chromatography eluent, petroleum ether–ethyl acetate = 8:1; yield: 74%; colorless oil; $[\alpha]_D^{20} = +174.1$ (*c* 0.692, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.13 (d, *J* = 8.8 Hz, 2H, ArH), 7.47 (d, *J* = 8.8 Hz, 2H, ArH), 7.25–7.21 (m, 2H, ArH), 7.19–7.16 (m, 1H, ArH), 7.09–7.06 (m, 2H, ArH), 6.76 (d, *J* = 2.0 Hz, 1H, =CH), 5.52 (dd, *J* = 5.6, 2.0 Hz, 1H, CH), 4.37–4.17 (m, 4H, $2CH_2$), 3.59 (d, *J* = 5.6 Hz, 1H, NH), 3.06–2.88 (m, 2H, CH_2), 2.93–2.75 (m, 2H, CH_2), 1.32 (t, *J* = 7.2 Hz, 3H, CH_3), 1.31 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 195.6, 169.0, 168.9, 149.3, 147.4, 146.9, 140.4, 135.4, 128.8, 128.5, 128.3, 126.3, 123.6, 79.3, 67.3, 63.0, 62.6, 41.6, 14.1; enantiomeric excess: 95%, determined by HPLC (Daicel Chirapak OD-H, hexane–2-propanol = 85:15, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 10.957 min (major), t_R = 12.006 min (minor).

4.3.21. (5*S*)-Diethyl 4-(2-ethylbutanoyl)-5-(4-nitrophenyl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4u

Flash column chromatography eluent, petroleum ether–ethyl acetate = 12:1; yield: 50%; colorless oil; $[\alpha]_D^{20} = +183.0$ (*c* 0.436, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.13 (d, *J* = 8.8 Hz, 2H, ArH), 7.51 (d, *J* = 8.8 Hz, 2H, ArH), 6.76 (d, *J* = 2.0 Hz, 1H, =CH), 5.55 (dd, *J* = 6.0, 2.0 Hz, 1H, CH), 4.38–4.26 (m, 4H, $2CH_2$), 3.62 (d, *J* = 6.0 Hz, 1H, NH), 2.86–2.81 (m, 1H, CH), 1.65–1.53 (m, 2H, CH_2), 1.46–1.37 (m, 2H, CH_2), 1.34 (t, *J* = 6.8 Hz, 3H, CH_3), 1.32 (t, *J* = 7.2 Hz, 3H, CH_3), 0.81 (t, *J* = 7.2 Hz, 3H, CH_3), 0.51 (t, *J* = 7.6 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 201.0, 169.2, 169.1, 149.5, 148.0, 147.4, 134.6, 128.8, 123.5, 79.4, 67.4, 62.9, 62.6, 51.3, 25.1, 23.8, 14.1, 14.0, 11.9, 11.0; enantiomeric excess: 87%, determined by HPLC (Daicel Chirapak AD-H, hexane–2-propanol = 80:20, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm): t_R = 5.777 min (major), t_R = 21.000 min (minor).

4.3.22. (5*S*)-Diethyl 4-(cyclohexanecarbonyl)-5-(4-nitrophenyl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4v

Flash column chromatography eluent, petroleum ether–ethyl acetate = 12:1; yield: 69%; colorless oil; $[\alpha]_D^{20} = +191.8$ (*c* 0.61,

$CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.13 (d, J = 8.8 Hz, 2H, ArH), 7.49 (d, J = 8.8 Hz, 2H, ArH), 6.73 (d, J = 2.0 Hz, 1H, =CH), 5.53 (s, 1H, CH), 4.35–4.28 (m, 4H, $2CH_2$), 3.61 (d, J = 4.4 Hz, 1H, NH), 2.86–2.78 (m, 1H, CH), 1.78–1.62 (m, 6H, $3CH_2$), 1.33 (t, J = 7.2 Hz, 3H, CH_3), 1.32 (t, J = 7.2 Hz, 3H, CH_3), 1.18–1.06 (m, 2H, CH_2), 0.98–0.86 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 200.3, 169.2, 169.1, 149.5, 147.4, 146.4, 135.2, 133.9, 129.4, 128.7, 124.8, 123.6, 79.4, 67.4, 62.9, 62.6, 47.5, 29.5, 27.9, 25.8, 25.6, 25.2, 14.1, 14.0; enantiomeric excess: 94%, determined by HPLC (Daicel Chirapak AD-H, hexane–2-propanol = 70:30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 7.111 min (major), t_R = 22.524 min (minor).

4.3.23. (5*S*)-Diethyl 5-(4-nitrophenyl)-4-(2-phenylacetyl)-1*H*-pyrrole-2,2(5*H*)-dicarboxylate 4w

Flash column chromatography eluent, petroleum ether–ethyl acetate = 8:1; yield: 51%; colorless oil; $[\alpha]_D^{20} = +170.8$ (c 0.462, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.04 (d, J = 8.8 Hz, 2H, ArH), 7.35 (d, J = 8.8 Hz, 2H, ArH), 7.25–7.21 (m, 3H, ArH), 7.04–7.01 (m, 2H, ArH), 6.34 (d, J = 2.0 Hz, 1H, =CH), 5.51 (s, 1H, CH), 4.35–4.25 (m, 4H, $2CH_2$), 3.96–3.87 (m, 2H, CH_2), 3.58 (d, J = 4.8 Hz, 1H, NH), 1.32 (t, J = 7.2 Hz, 3H, CH_3), 1.31 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm):193.8, 169.0, 168.9, 148.9, 147.3, 146.5, 135.7, 132.9, 129.3, 128.7, 127.2, 123.5, 79.4, 67.4, 63.0, 62.6, 47.2, 14.1; enantiomeric excess: 97%, determined by HPLC (Daicel Chirapak AD-H, hexane–2-propanol = 70:30, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 10.231 min (major), t_R = 35.614 min (minor).

4.4. Cytotoxic evaluation of selected 2,5-dihydropyrroles 4 to mammary carcinoma cell line MCF7

The cytotoxicity of the tested compounds to MCF7 cells was assayed using the MTT method. Cells were collected and seeded in 96-well plates at a density of 10^5 cells/cm^2. After incubation for 24 h, the cells were exposed to a fresh medium containing various concentrations of compounds (0.01, 0.1, 1, 10, and 100 μg/mL) at 37 °C. After incubation for up to 24 h, 20 μL of MTT tetrazolium salt dissolved in Hank's balanced salt solution at a final concentration of 5 mg/mL were added to each well and incubated in the CO_2 incubator for 4 h. Finally, the medium was aspirated from each well and 150 μL of DMSO was added to dissolve the formazan crystals; the absorbance of each well was obtained using a Model 680 microplate reader (Bio Rad., USA) counter at test and reference wavelengths of 570 nm. The inhibition rate was calculated according to the following formula: Inhibition rate = $(OD_{570\ control} - OD_{570\ sample})/OD_{570\ control} \times 100\%$, where OD stands for optical density at 570 nm. Then the inhibition rates of the tested compounds in various concentrations were processed by SPSS 13.0 software to calculate the IC_{50} values. The IC_{50} value to MCF7 cells corresponded to the compound concentration causing 50% mortality in MCF7 cells.

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