JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

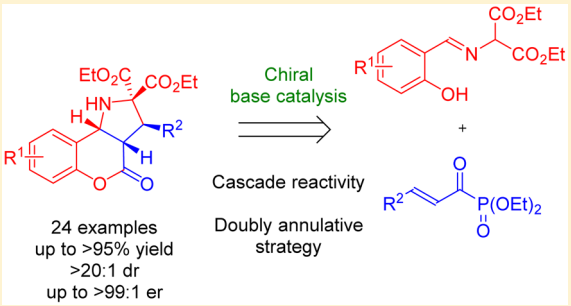
Organocatalytic Doubly Annulative Approach to 3,4-Dihydrocoumarins Bearing a Fused Pyrrolidine Scaffold

Dorota Kowalczyk and Łukasz Albrecht*

Institute of Organic Chemistry, Chemistry Department, Lodz University of Technology, Żeromskiego 116, 90-924 Łódź, Poland

Supporting Information

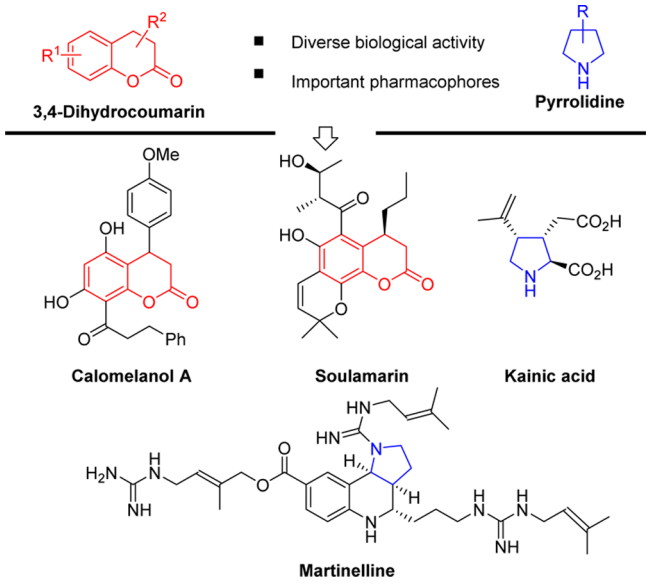
ABSTRACT: A new strategy for the highly enantio- and diastereoselective synthesis of 3,4-dihydrocoumarin derivatives bearing a fused pyrrolidine ring is reported. It is based on a Brønsted base catalyzed cascade reactivity between β,γ-unsaturated-α-ketophosphonates and imines (derived from various salicylaldehydes and diethyl aminomalonate). The approach can be described as a doubly annulative strategy where both the pyrrolidine moiety and the δ-lactone ring of the 3,4-dihydrocoumarin framework are constructed starting from acyclic precursors.



Within the realm of organic chemistry, the identification of new synthetic methodologies leading to the bioinspired targets constitutes a very important and rapidly developing field of research.[1] The asymmetric synthesis of such compounds is particularly important as their biological activity is directly correlated with the spatial arrangement of the substituents in the chiral molecule.[2]

3,4-Dihydrocoumarin[3] and pyrrolidine[4] derivatives occupy a prominent position among biologically active molecules and constitute core structures of various natural products and biologically active molecules (Scheme 1). For instance,

Scheme 1. Importance of 3,4-Dihydrocoumarin and Pyrrolidine Structural Motifs



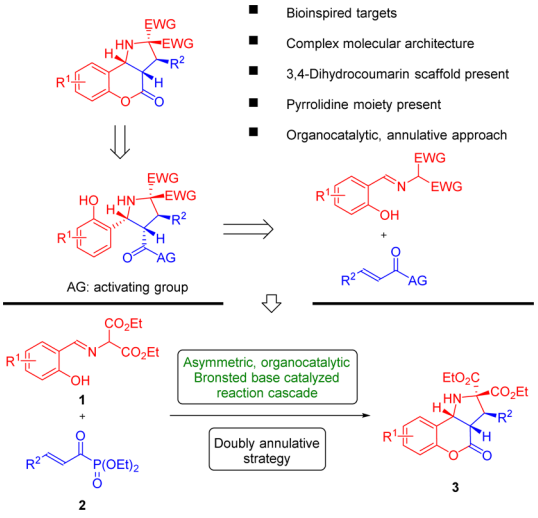
Calomelanol A was isolated from the plant *Pityrogramma calomelanos* widely employed in traditional medicine for its antihypertensive, analgesic, antihemorrhagic, and antipyretic activities.[3b] Furthermore, Soulamarin, identified in the stem bark of *Calophyllum soulattri*, exhibits various biological activities.[3c] A pyrrolidine ring is the main constituent of Kainic acid, a natural product that can be found in marine algae well-recognized for its anthelmintic activity.[4d,e] Martinelline, in which the pyrrolidine ring is merged with the tetrahydroquinoline, is a nonpeptide agonist of bradykinin receptors.[4f] Importantly, over the years, various synthetic strategies for the stereocontrolled preparation of either 3,4-dihydrocoumarin or pyrrolidine derivatives have been described with organocatalytic asymmetric strategies being increasingly important.[5]

Given the significance of both the 3,4-dihydrocoumarin and the pyrrolidine derivatives, the studies on the development of a general synthetic strategy leading to the novel group of 3,4-dihydrocoumarins bearing a fused pyrrolidine moiety were undertaken. The devised approach can be described as a doubly annulative as both the pyrrolidine ring and a δ-lactone moiety are constructed from the acyclic precursors (Scheme 2). It was anticipated that the pyrrolidine ring should be possible to ring-close under basic conditions via a [3 + 2]-cycloaddition between azomethine ylides (derived from salicylaldehydes and proper amines) and α,β-unsaturated-carbonyls bearing a suitable activating group at the carbonyl moiety. Notably, the proper choice of the activating group was crucial for the success of the strategy as it had to serve a double purpose. First, it had to activate the starting α,β-unsaturated-carbonyl, making it more prone to participate in the cycloaddition reaction. Second, it should act as a leaving group, facilitating the annulation of the δ-lactone and making the overall strategy feasible. Given the

Received: May 2, 2016
Published: June 28, 2016

DOI: 10.1021/acs.joc.6b00975
J. Org. Chem. 2016, 81, 6800−6807

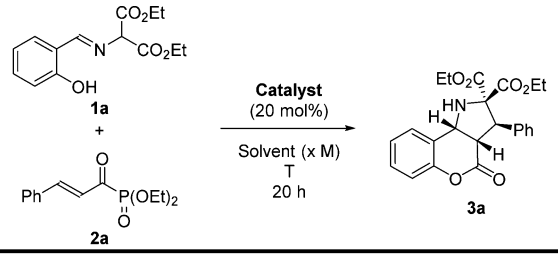
Scheme 2. Synthetic Objectives of Our Study

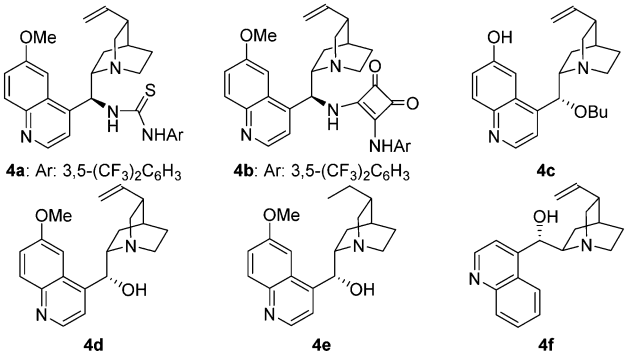


above-mentioned requirements, the diethyl phosphonate moiety was selected as the activating group. Notably, the phosphonate moiety is a strong electron-withdrawing group that enhances the electron deficiency of the double bond in the corresponding β,γ-unsaturated-α-ketophosphonates, making them more electrophilic. Furthermore, the phosphonate moiety can serve as a good leaving group with the cyclization occurring via the addition−elimination mechanism. In this context, it is worth mentioning that acylphosphonates have recently emerged as a highly useful and powerful group of the active ester surrogates.[6] However, most of the synthetic strategies rely on the displacement of the phosphonate moiety with an external nucleophile. Herein, we show one of the very first examples of methodologies where the originally formed Michael adduct is subjected to the intramolecular reaction with a nucleophile,[7] resulting in a new type of a doubly annulative strategy.[8] However, at the outset of our studies, certain challenges of the reaction had to be considered and addressed. First, due to the stereochemical complexity of the products, the control of the stereochemical reaction outcome in terms of both enantio- and diastereoselectivity was particularly important. Notably, the use of α-ketophosphonates as starting materials provides an opportunity for the activation and recognition by the catalyst via H-bonding interactions.[6] Therefore, it was anticipated that the application of such an activation strategy should be beneficial. Second, as both substrates utilized are polyfunctionalized, the control of site selectivity of the reaction was of major concern. Herein, we report our studies on the development of a Brønsted base catalyzed[9] approach to 3,4-dihydrocoumarins **3** bearing a pyrrolidine scaffold.

Initially, the optimization studies using imine **1a** and phosphonate **2a** as model reactants were performed (Table 1). To our delight, it was found that the cascade reaction was possible to realize under basic conditions using bifunctional thiourea catalyst **4a** (Table 1, entry 1). Importantly, diastereoselectivity of the process was excellent. However, both the isolated yield and the enantioselectivity required further optimization. Therefore, catalyst optimization was initiated (Table 1, entries 1−6). It indicated that simple cinchona alkaloids such as quinine **4d** and dihydroquinine **4e** (Table 1, entries 4 and 5) were better when compared to more complex catalysts **4a−c** (Table 1, entries 1−3). Interestingly,

Table 1. Organocatalytic Doubly Annulative Approach to 3,4-Dihydrocoumarins 3 Bearing a Pyrrolidine Scaffold − Optimization Studies[a]





	solvent	cat.	T [°C]	yield [%][b]	dr[c]	er[d]
1	CH_2Cl_2	**4a**	RT	42	>20:1	15:85
2	CH_2Cl_2	**4b**	RT	46	>20:1	17:83
3	CH_2Cl_2	**4c**	RT	49	>20:1	38:62
4	CH_2Cl_2	**4d**	RT	51	>20:1	85:15
5	CH_2Cl_2	**4e**	RT	69	>20:1	89:11
6	CH_2Cl_2	**4f**	RT	55	>20:1	41:59
7	$CHCl_3$	**4e**	RT	65	>20:1	80:20
8	toluene	**4e**	RT	53	>20:1	74:26
9	THF	**4e**	RT	42	>20:1	71:29
10	CH_2Cl_2	**4e**	0	65	>20:1	91:9
11	CH_2Cl_2	**4e**	−40	67	>20:1	94:6
12[e]	CH_2Cl_2	**4e**	−40	70	>20:1	97:3
13[f]	CH_2Cl_2	**4e**	−40	54	>20:1	90:10
14[g]	CH_2Cl_2	**4e**	−40	95	>20:1	98:2

[a]Reactions performed on 0.1 mmol scale using **1a** (1 equiv) and **2a** (1 equiv) in 0.2 mL of the solvent (see the Supporting Information for detailed reaction conditions screening). [b]Isolated yields are given. [c]Determined by ^{1}H NMR of a crude reaction mixture. [d]Determined by a chiral stationary phase HPLC. [e]Reaction was performed using **4e** (10 mol %). [f]Reaction was performed using **4e** (5 mol %). [g]Reaction was performed using **4e** (10 mol %) with the addition of an extra portion of **2a** (1 equiv) after 4 h.

the performance of cinchonine **4f** was much worse in the evaluated reaction (Table 1, entry 6). Subsequently, the solvent screening using **4e** as the catalyst was performed (Table 1, entries 5, 7−9). As a consequence, CH_2Cl_2 was identified as the best solvent for the optimized cascade (Table 1, entry 5). To our delight, the temperature screening (Table 1, entries 5, 10, 11) indicated that the enantioselectivity of the process can be enhanced by lowering the reaction temperature to −40 °C (Table 1, entry 11). Importantly, the catalyst loading of **4e** (Table 1, compare entries 11−13) could be decreased to 5 mol % (Table 1, entry 13) without significant effect on the reaction outcome. However, the best results were obtained using 10 mol % of **4e** (Table 1, entry 12). Finally, it was postulated that moderate to good isolated yields of the cascade are connected with a partial decomposition of **2a** under reaction conditions.

DOI: 10.1021/acs.joc.6b00975
J. Org. Chem. 2016, 81, 6800−6807

Therefore, the addition of **2a** in portions was beneficial for the overall yield of the reaction cascade, enabling establishing the final reaction conditions (Table 1, entry 14). Notably, the application of β,γ-unsaturated-α-ketophosphonates **2** as an α,β-unsaturated acid surrogate is crucial as the reaction with other derivatives (such as acid chlorides or anhydrides) did not provide any product.

With the optimization studies accomplished, the scope of the cascade with regard to both reaction partners was evaluated (Scheme 3, Table 2). Initially, various imines **1** were reacted with **2a** under optimal reaction conditions (Scheme 3). To our delight, the annulative strategy was possible to realize for a wide variety of imines **1**. It was demonstrated that various electron-withdrawing substituents could be present on the aromatic ring in **1**, affording products **3a–c** with excellent stereocontrol. In the course of further studies, it was found that the cascade reaction proceeded efficiently for the substrates containing an unsubstituted phenyl ring (Scheme 3, product **3d**) or electron-donating substituents on the aromatic ring in **1** (Scheme 3, products **3e,f**). This part of the studies also indicated that the position of the substituent on the aromatic ring in **1** had no pronounced influence on the chemical and stereochemical reaction outcome and the introduction of two substituents on the aromatic ring in **1** was also possible (Scheme 3, products **3g–i**).

Scheme 3. Organocatalytic Doubly Annulative Approach to 3,4-Dihydrocoumarins 3 – Imine 1 Scope

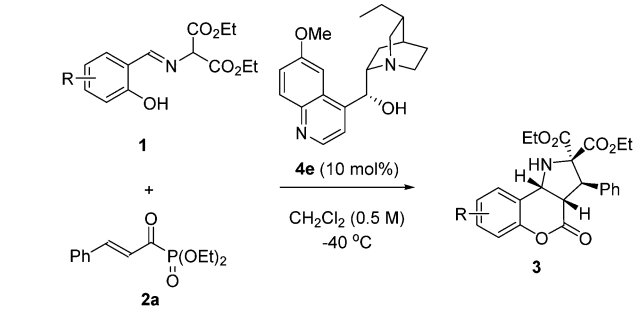
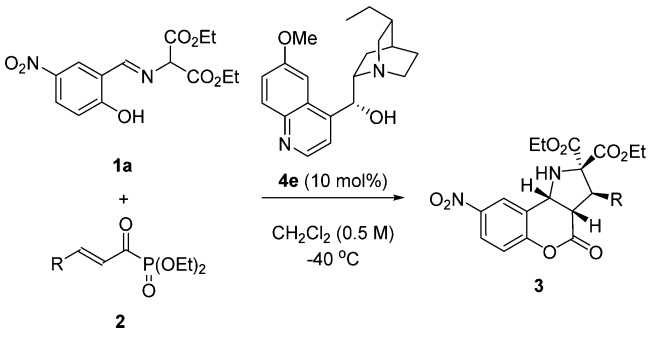


Table 2. Organocatalytic Doubly Annulative Approach to 3,4-Dihydrocoumarins 3 – β,γ-Unsaturated-α-ketophosphonates 2 Scope[a]



	R	3	yield [%]	dr[b]	er[c]
1	Ph	**3a**	95	>20:1	98:2
2	4-$CF_3C_6H_4$	**3j**	79	>20:1	98:2
3	4-CNC_6H_4	**3k**	63	>20:1	98:2
4	4-$NO_2C_6H_4$	**3l**	57	>20:1	96:4
5	4-BrC_6H_4	**3m**	89	>20:1	99:1
6	4-ClC_6H_4	**3n**	78	>20:1	96:4
7	3-ClC_6H_4	**3o**	76	>20:1	97:3
8	2-ClC_6H_4	**3p**	71	>20:1	93:7
9	4-MeC_6H_4	**3q**	72	>20:1	99.5:0.5
10	4-$MeOC_6H_4$	**3r**	65	>20:1	98:2
11	2-$MeOC_6H_4$	**3s**	76	>20:1	98.5:1.5
12	1-naphthyl	**3t**	62	>20:1	95:5
13	3,4-$OCH_2OC_6H_3$	**3u**	69	>20:1	97:3
14	1-furyl	**3v**	72	>20:1	99:1
15	C_2H_5	**3w**	95	>20:1	95:5
16	n-C_6H_{13}	**3x**	94	>20:1	96.5:3.5

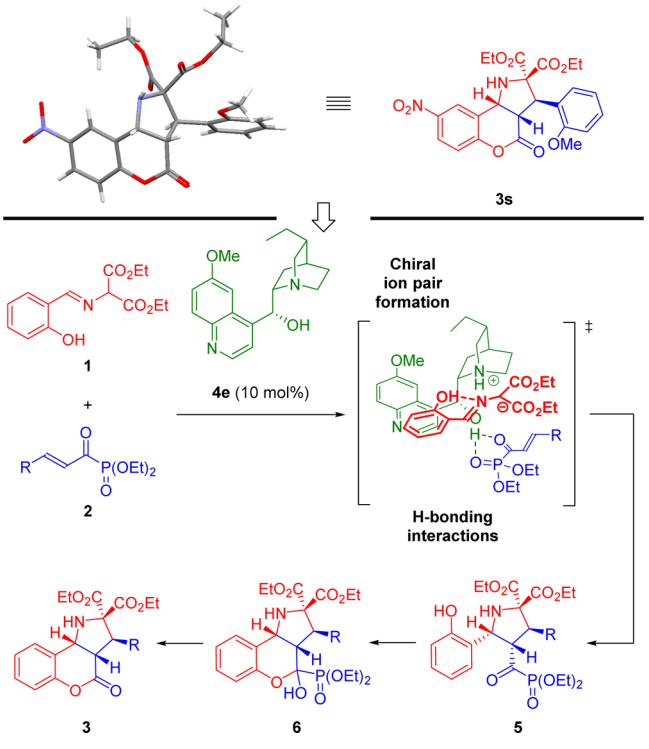
[a]Reactions performed on 0.1 mmol scale (see the Supporting Information for detailed reaction conditions). [b]Determined by ^{1}H NMR of a crude reaction mixture. [c]Determined by a chiral stationary phase HPLC.

In the second part of the scope studies, the possibility to employ various β,γ-unsaturated-α-ketophosphonates **2** in the devised strategy was tested (Table 2). To our delight, the cascade proved unbiased toward the electronic properties of substituents on the aromatic ring in **2**. Excellent enantio- and diastereoselectivities were observed for the reactions using **2** containing either electron-withdrawing (Table 2, entries 2–8) or electron-donating substituents (Table 2, entries 9–11). Furthermore, it was found that the position of the substituents had no pronounced effect on the reaction chemical and stereochemical efficiency (Table 2, compare entries 6–8 and 10–11). Disubstituted aromatic rings could also be present in **2**, affording products **3t,u** in a highly stereoselective manner (Table 2, entries 12 and 13). Importantly, the heteroaromatic moiety in **2** was also well-tolerated as demonstrated in the synthesis of **3v** containing a furan moiety (Table 2, entry 14). Finally, in order to further increase the attractiveness of the methodology, aliphatic β,γ-unsaturated-α-ketophosphonates **2** were employed with reactions proceeding efficiently and with high levels of stereocontrol (Table 2, entries 15 and 16).

The absolute configurations of the 3,4-dihydrocoumarin bearing a pyrrolidine ring **3s** was unambiguously assigned by the single-crystal X-ray analysis (Scheme 4, top).[10] The absolute configurations of the remaining polycyclic products **3a–r**, **3t–x** were assigned by analogy. Given these configurational assignments, the reaction mechanism explaining the

DOI: 10.1021/acs.joc.6b00975
J. Org. Chem. 2016, 81, 6800–6807

Scheme 4. Organocatalytic Synthesis of 3,4-Dihydrocoumarins 3 − Mechanistic Considerations



observed stereochemistry of the products was proposed (Scheme 4, bottom). The reaction was initiated through the deprotonation of **1** by the basic catalyst **4e** to give the corresponding azomethine ylide that participated in a [3 + 2] cycloaddition. Importantly, it was postulated that, in this reaction, the **4e** acted as a bifunctional catalyst. First, as a Brønsted base, it deprotonated the starting imine **1** to form the corresponding azomethine ylide. Second, it recognized the corresponding *β,γ*-unsaturated-*α*-ketophosphonate **2** through the H-bonding interactions between its hydroxyl group and the *α*-ketophosphonate moiety in **2**. Such a recognition profile forced the approach of the azomethine ylide to occur from the top face of **2**. Notably, pyrrolidines **5** have been neither observed nor isolated. With the pyrrolidine ring constructed, the annulation of the *δ*-lactone moiety occurred. Hence, the phenolic hydroxyl group in **5** attacked the carbonyl carbon atom of the *α*-ketophosphonate moiety, thus leading to the *α*-hydroxyphosphonate **6**. Subsequent elimination reaction terminated the cascade, yielding **3**.

In conclusion, we have developed a novel organocatalytic approach to 3,4-dihydrocoumarins **3** bearing a pyrrolidine ring. This doubly annulative approach is promoted by readily available and cheap dihydroquinine and benefits from high chemical and stereochemical efficiency as well as a very broad substrate scope.

EXPERIMENTAL SECTION

General Methods. NMR spectra were acquired on the instrument, running at 700 MHz for ^{1}H and 176 MHz for ^{13}C, respectively. Chemical shifts (*δ*) are reported in ppm relative to residual solvent signals ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR). Mass spectra were recorded on a spectrometer (qTOF) using electrospray (ES+) ionization. Optical rotations were measured on a polarimeter, and $[\alpha]_D$ values are given in deg·cm·g^{-1}·dm^{-1}; concentration *c* is listed in g·(100 mL)$^{-1}$. Analytical thin layer chromatography (TLC) was performed using precoated aluminum-backed plates and visualized by ultraviolet irradiation or I_2 stain. The enantiomeric ratio (er) of the products was determined by chiral stationary phase HPLC. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC), silica gel (Silica gel 60, 230−400 mesh) was used.

Asymmetric Synthesis of 3,4-Dihydrocoumarin Derivatives 3 − General Procedure. An ordinary screw-cap vial was charged with a magnetic stirring bar, the corresponding diethyl 2-hydroxy-arylideneaminomalonate **1** (0.1 mmol, 1 equiv), diethyl *β,γ*-unsaturated-*α*-ketophosphonate **2** (0.1 mmol, 1 equiv), the catalyst **4e** (0.01 mmol, 0.1 equiv), and CH_2Cl_2 (0.2 mL). The reaction mixture was stirred at −40 °C. After 4 h, the next portion of diethyl *β,γ*-unsaturated-*α*-ketophosphonate **2** (0.1 mmol, 1 equiv) was added, and the resulting mixture was stirred at −40 °C for an additional 16 h. The completion of the reaction was confirmed by ^{1}H and ^{31}P NMR spectroscopy. Subsequently, the mixture was directly purified by FC on silica gel to afford a target product **3**.

*Diethyl (3R,3aS,9bR)-8-Nitro-4-oxo-3-phenyl-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3a**).* Following the general procedure, **3a** was isolated by FC on silica (hexane/AcOEt 3:1) in 95% yield (43.2 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (250 MHz, $CDCl_3$) *δ* 8.49 (dd, *J* = 2.7, 1.0 Hz, 1H), 8.22 (ddd, *J* = 9.0, 2.8, 0.6 Hz, 1H), 7.32−7.27 (m, 5H), 7.19 (d, *J* = 9.0 Hz, 1H), 5.05 (d, *J* = 6.8 Hz, 1H), 4.71 (d, *J* = 9.7 Hz, 1H), 4.21−3.98 (m, 2H), 3.92 (s, 1H), 3.82 (dq, *J* = 10.5, 7.1 Hz, 1H), 3.67 (dd, *J* = 9.7, 6.9 Hz, 1H), 3.38 (dq, *J* = 10.6, 7.2 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.72 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) *δ* 169.8, 169.6, 165.6, 154.5, 144.7, 135.6, 128.7 (2C), 128.6 (2C), 128.4, 125.8, 125.1, 123.7, 118.2, 76.8, 62.7, 62.6, 56.9, 53.5, 49.0, 13.9, 13.4. IR (film, cm^{-1}): *ν* = 3326, 2921, 2853, 1729, 1587, 1524, 1467, 1372, 1337, 1281, 1213, 1109, 1042, 857, 752. HRMS calculated for $[C_{23}H_{22}N_2O_8 + H]^+$: 455.1449; found: 455.1457. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 14.1 min, τ_{minor} = 21.3 min (98:2 er). $[\alpha]_D^{20}$ = −44.8 (*c* = 0.7, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-8-Bromo-4-oxo-3-phenyl-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3b**).* Following the general procedure, **3b** was isolated by FC on silica (hexane/AcOEt 3:1) in 86% yield (42.0 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) *δ* 7.67 (dd, *J* = 2.5, 0.9 Hz, 1H), 7.42 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.33−7.28 (m, 4H), 7.27−7.21 (m, 1H), 6.94 (d, *J* = 8.6 Hz, 1H), 4.96 (d, *J* = 6.8 Hz, 1H), 4.73 (d, *J* = 9.3 Hz, 1H), 4.19−4.08 (m, 2H), 3.79 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.57 (dd, *J* = 9.4, 6.9 Hz, 1H), 3.37 (dq, *J* = 10.7, 7.2 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.71 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) *δ* 169.8, 169.7, 166.6, 149.3, 136.3, 133.0, 131.6, 128.8, 128.6 (2C), 128.6, 128.1, 124.1, 118.9, 117.5, 77.0, 62.5 (2C), 57.1, 53.6, 49.6, 14.1, 13.4. IR (film, cm^{-1}): *ν* = 3322, 2982, 2926, 2853, 1767, 1725, 1604, 1473, 1369, 1269, 1206, 1117, 1034, 819, 736, 699. HRMS calculated for $[C_{23}H_{22}BrNO_6 + H]^+$: 488.0703; found: 488.0713. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 10.6 min, τ_{minor} = 17.5 min (98:2 er). $[\alpha]_D^{20}$ = −73.4 (*c* = 0.8, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-8-Chloro-4-oxo-3-phenyl-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3c**).* Following the general procedure, **3c** was isolated by FC on silica (hexane/AcOEt 3:1) in 92% yield (40.8 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) *δ* 7.52 (dd, *J* = 2.5, 1.0 Hz, 1H), 7.33−7.28 (m, 5H), 7.28−7.24 (m, 1H), 7.00 (d, *J* = 8.7 Hz, 1H), 4.96 (d, *J* = 6.8 Hz, 1H), 4.73 (d, *J* = 9.3 Hz, 1H), 4.13 (m, 2H), 3.81 (s, 1H), 3.78 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.58 (dd, *J* = 9.4, 6.9 Hz, 1H), 3.37 (dq, *J* = 10.7, 7.2 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.71 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) *δ* 169.9, 169.7, 166.7, 148.8, 136.3, 130.1, 130.0, 128.8 (2C), 128.7, 128.6 (2C), 128.1, 123.7, 118.6, 77.0, 62.5, 62.4, 57.2, 53.6, 49.5, 14.0, 13.4. IR (film, cm^{-1}): *ν* = 3321, 2982, 2932, 1727, 1604, 1485, 1370, 1263, 1207, 1107, 1037, 818, 749, 699. HRMS calculated for $[C_{23}H_{22}ClNO_6 + H]^+$: 444.1208; found: 444.1200. The er was determined by HPLC using a Chiralpak IA

DOI: 10.1021/acs.joc.6b00975
J. Org. Chem. 2016, 81, 6800−6807

column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 9.8 min, τ_{minor} = 19.0 min (97:3 er). $[\alpha]_D^{20}$ = −74.4 (*c* = 0.7, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-4-Oxo-3-phenyl-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3d**).* Following the general procedure, **3d** was isolated by FC on silica (hexane/AcOEt 3:1) in 82% yield (33.6 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.52−7.48 (m, 1H), 7.35−7.32 (m, 3H), 7.32−7.28 (m, 2H), 7.26−7.23 (m, 1H), 7.16 (td, *J* = 7.5, 1.2 Hz, 1H), 7.06 (dd, *J* = 8.1, 1.1 Hz, 1H), 5.03 (d, *J* = 6.7 Hz, 1H), 4.84 (d, *J* = 7.9 Hz, 1H), 4.14 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.08 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.78 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.67 (s, 1H), 3.54 (dd, *J* = 7.9, 6.7 Hz, 1H), 3.38 (dq, *J* = 10.6, 7.2 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.72 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.2, 169.6, 167.5, 150.4, 137.2, 130.0, 128.9, 128.8 (2C), 128.6 (2C), 128.0, 124.8, 121.7, 117.1, 77.0, 62.3, 62.2, 57.5, 53.5, 49.7, 14.0, 13.4. IR (film, cm^{-1}): ν = 3331, 2930, 2858, 1724, 1619, 1487, 1368, 1270, 1202, 1106, 1032, 859, 753, 698. HRMS calculated for $[C_{23}H_{23}NO_6 + H]^+$: 410.1598; found: 410.1599. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 9.9 min, τ_{minor} = 24.0 min (85:15 er). $[\alpha]_D^{20}$ = −54.9 (*c* = 0.9, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-6-Methyl-4-oxo-3-phenyl-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3e**).* Following the general procedure, **3e** was isolated by FC on silica (hexane/AcOEt 3:1) in 59% yield (25.0 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.36−7.34 (m, 2H), 7.33−7.31 (m, 1H), 7.31−7.28 (m, 2H), 7.27−7.23 (m, 1H), 7.20−7.14 (m, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 5.02 (d, *J* = 6.6 Hz, 1H), 4.90 (d, *J* = 7.4 Hz, 1H), 4.16 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.08 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.77 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.61 (s, 1H), 3.50 (dd, *J* = 7.4, 6.6 Hz, 1H), 3.36 (dq, *J* = 10.6, 7.2 Hz, 1H), 2.31 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.72 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.4, 169.6, 167.6, 148.7, 137.5, 131.6, 128.9 (2C), 128.6 (2C), 127.9, 126.4, 126.3, 124.2, 121.3, 77.0, 62.2 (2C), 57.9, 53.3, 49.5, 16.0, 14.0, 13.4. IR (film, cm^{-1}): ν = 3319, 2981, 2926, 2854, 1727, 1597, 1468, 1369, 1264, 1204, 1108, 1038, 857, 737. HRMS calculated for $[C_{24}H_{25}NO_6 + H]^+$: 424.1755; found: 424.1743. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 8.1 min, τ_{minor} = 15.4 min (97:3 er). $[\alpha]_D^{20}$ = −26.6 (*c* = 0.8, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-8-Methoxy-4-oxo-3-phenyl-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3f**).* Following the general procedure, **3f** was isolated by FC on silica (hexane/AcOEt 3:1) in 66% yield (29.0 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.38 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.34−7.32 (m, 2H), 7.29 (t, *J* = 7.6 Hz, 2H), 7.26−7.23 (m, 1H), 6.71 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.59 (d, *J* = 2.5 Hz, 1H), 4.98 (d, *J* = 6.7 Hz, 1H), 4.84 (d, *J* = 7.8 Hz, 1H), 4.19−4.11 (m, 1H), 4.08 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.80 (s, 3H), 3.79−3.72 (m, 1H), 3.63 (s, 1H), 3.50 (dd, *J* = 7.8, 6.7 Hz, 1H), 3.37 (dq, *J* = 10.7, 7.2 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H), 0.72 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.2, 169.7, 167.7, 160.9, 151.3, 137.3, 129.5, 128.9 (2C), 128.6 (2C), 128.0, 113.6, 111.3, 102.2, 77.0, 62.3, 62.2, 57.2, 55.7, 53.5, 49.9, 14.0, 13.4. IR (film, cm^{-1}): ν = 3316, 2980, 2921, 2851, 1729, 1588, 1455, 1370, 1263, 1203, 1107, 1035, 856, 751, 701. HRMS calculated for $[C_{24}H_{25}NO_7 + H]^+$: 440.1704; found: 440.1709. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 12.1 min, τ_{minor} = 23.4 min (88.5:11.5 er). $[\alpha]_D^{20}$ = −18.9 (*c* = 0.6, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-6,8-Dichloro-4-oxo-3-phenyl-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3g**).* Following the general procedure, **3g** was isolated by FC on silica (hexane/AcOEt 3:1) in 69% yield (33.0 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 2.5, 1.0 Hz, 1H), 7.39 (d, *J* = 2.5 Hz, 1H), 7.33−7.29 (m, 4H), 7.27 (dd, *J* = 5.7, 3.1 Hz, 1H), 4.96 (dd, *J* = 6.8, 1.0 Hz, 1H), 4.74 (d, *J* = 9.3 Hz, 1H), 4.20−4.08 (m, 2H), 3.80 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.60 (dd, *J* = 9.3, 6.8 Hz, 1H), 3.37 (dq, *J* = 10.6, 7.2 Hz, 1H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.71 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.8, 169.6, 165.4, 145.0, 136.0, 130.5, 129.9, 128.8 (2C), 128.7 (2C), 128.3, 127.1, 125.1, 122.9, 76.9, 62.6, 62.5, 57.5, 53.4, 49.2, 14.1, 13.4. IR (film, cm^{-1}): ν = 3315, 2981, 2930, 1725, 1603, 1464, 1371, 1266, 1208, 1106, 1040, 860, 733, 699. HRMS calculated for $[C_{23}H_{21}Cl_2NO_6 + H]^+$: 478.0819; found: 478.0828. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 8.8 min, τ_{minor} = 17.0 min (99.5:0.5 er). $[\alpha]_D^{20}$ = −39.9 (*c* = 0.7, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-8-Fluoro-6-methyl-4-oxo-3-phenyl-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3h**).* Following the general procedure, **3h** was isolated by FC on silica (hexane/AcOEt 3:1) in 55% yield (24.3 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.35−7.32 (m, 2H), 7.30 (dd, *J* = 8.5, 6.7 Hz, 2H), 7.27−7.23 (m, 1H), 7.06 (dd, *J* = 8.3, 3.1 Hz, 1H), 6.88 (dd, *J* = 8.7, 3.0 Hz, 1H), 4.94 (d, *J* = 6.7 Hz, 1H), 4.75 (d, *J* = 9.1 Hz, 1H), 4.22−4.05 (m, 2H), 3.78 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.74 (s, 1H), 3.55 (dd, *J* = 9.1, 6.8 Hz, 1H), 3.36 (dq, *J* = 10.7, 7.2 Hz, 1H), 2.30 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.71 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.0, 169.7, 167.0, 158.9 (d, *J* = 243.3 Hz), 144.4 (d, *J* = 2.5 Hz), 136.5, 128.8 (2C), 128.7, 128.6 (2C), 128.1, 123.3 (d, *J* = 7.8 Hz), 118.1 (d, *J* = 23.2 Hz), 112.4 (d, *J* = 24.3 Hz), 77.0, 62.4, 62.3, 57.5, 53.4, 49.2, 16.1, 14.0, 13.4. IR (film, cm^{-1}): ν = 3321, 2984, 2923, 2853, 1727, 1603, 1468, 1369, 1270, 1205, 1123, 1041, 873, 750, 700. HRMS calculated for $[C_{24}H_{24}FNO_6 + H]^+$: 442.1660; found: 442.1664. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 8.3 min, τ_{minor} = 17.4 min (99:1 er). $[\alpha]_D^{20}$ = −42.4 (*c* = 1.1, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-4-Oxo-3-phenyl-1,3a,4,9b-tetrahydro-2H-benzo[g]chromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3i**).* Following the general procedure, **3i** was isolated by FC on silica (hexane/AcOEt 3:1) in 75% yield (34.5 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.34 (d, *J* = 8.4 Hz, 1H), 7.90−7.87 (m, 1H), 7.86 (d, *J* = 8.9 Hz, 1H), 7.69 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.52 (ddd, *J* = 8.0, 6.8, 1.0 Hz, 1H), 7.46−7.42 (m, 2H), 7.34 (dd, *J* = 8.3, 7.0 Hz, 2H), 7.29−7.25 (m, 3H), 5.77 (d, *J* = 6.6 Hz, 1H), 5.32 (d, *J* = 2.6 Hz, 1H), 4.21 (dq, *J* = 10.9, 7.1 Hz, 1H), 4.06 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.82 (dq, *J* = 10.6, 7.1 Hz, 1H), 3.55−3.35 (m, 2H), 1.15 (t, *J* = 7.1 Hz, 3H), 0.78 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.3, 168.8, 168.3, 149.0, 139.8, 131.9, 131.0, 130.9, 128.9, 128.8 (2C), 128.7 (2C), 128.2, 127.8, 125.5, 122.8, 117.6, 113.5, 76.8, 62.3, 62.0, 55.2, 52.5, 48.9, 14.0, 13.5. IR (film, cm^{-1}): ν = 3314, 3063, 3033, 2981, 2930, 1729, 1602, 1497, 1468, 1370, 1262, 1206, 1108, 1039, 817, 746. HRMS calculated for $[C_{27}H_{25}NO_6 + H]^+$: 460.1755; found: 460.1752. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 7.5 min, τ_{minor} = 9.1 min (87:13 er). $[\alpha]_D^{20}$ = −49.3 (*c* = 0.5, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-3-(4-Trifluoromethylphenyl)-8-nitro-4-oxo-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3j**).* Following the general procedure, **3j** was isolated by FC on silica (hexane/AcOEt 3:1) in 79% yield (41.3 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.8 Hz, 1H), 8.23 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.9 Hz, 1H), 5.13−4.98 (m, 1H), 4.74 (d, *J* = 10.1 Hz, 1H), 4.14 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.10 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.94 (s, 1H), 3.83 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.69 (dd, *J* = 10.2, 7.0 Hz, 1H), 3.43 (dd, *J* = 10.7, 7.2 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.71 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.5, 169.4, 165.3, 154.2, 144.8, 139.6, 130.8 (d, *J* = 32.8 Hz), 129.3 (2C), 125.9, 125.7, 125.6, 125.5, 125.0, 123.6, 118.3, 76.7, 62.9, 62.8, 56.8, 53.1, 48.6, 14.0, 13.2. IR (film, cm^{-1}): ν = 3330, 2919, 2851, 1731, 1587, 1523, 1466, 1374, 1327, 1279, 1213, 1123, 1040, 858, 753. HRMS calculated for $[C_{24}H_{21}F_3N_2O_8 + H]^+$: 523.1323; found: 523.1331. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 11.7 min, τ_{minor} = 17.2 min (98:2 er). $[\alpha]_D^{20}$ = −22.8 (*c* = 0.8, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-3-(4-Cyanophenyl)-8-nitro-4-oxo-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3k**).* Following the general procedure, **3k** was isolated by FC on silica (hexane/AcOEt 3:1) in 63% yield (30.2 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 2.8, 1.0 Hz, 1H), 8.23 (ddd, *J* = 9.1, 2.9, 0.7 Hz, 1H), 7.69−7.56 (m, 2H), 7.52−7.41 (m, 2H), 7.21

DOI: 10.1021/acs.joc.6b00975
J. Org. Chem. 2016, 81, 6800−6807

(d, J = 8.9 Hz, 1H), 5.06 (d, J = 6.9 Hz, 1H), 4.71 (d, J = 10.2 Hz, 1H), 4.15 (dq, J = 10.8, 7.1 Hz, 1H), 4.11 (dq, J = 10.8, 7.1 Hz, 1H), 3.93 (s, 1H), 3.88 (dq, J = 10.7, 7.2 Hz, 1H), 3.66 (dd, J = 10.2, 7.0 Hz, 1H), 3.44 (dq, J = 10.7, 7.2 Hz, 1H), 1.21 (t, J = 7.1 Hz, 3H), 0.78 (t, J = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.3, 169.3, 165.1, 154.1, 144.9, 140.9, 132.4 (2C), 129.8 (2C), 125.9, 125.0, 123.4, 118.4, 118.3, 112.4, 76.7, 63.0, 62.9, 56.8, 53.2, 48.5, 14.0, 13.5. IR (film, cm^{-1}): ν = 3328, 2922, 2852, 1732, 1589, 1522, 1464, 1376, 1338, 1262, 1209, 1102, 1022, 859, 752. HRMS calculated for $[C_{24}H_{21}N_3O_8 + H]^+$: 480.1401; found: 480.1400. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 20.7 min, τ_{minor} = 32.4 min (98:2 er). $[\alpha]_D^{20}$ = −46.0 (c = 0.6, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-3-(4-Nitrophenyl)-8-nitro-4-oxo-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3l**).* Following the general procedure, **3l** was isolated by FC on silica (hexane/AcOEt 3:1) in 57% yield (28.5 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.48 (d, J = 2.7 Hz, 1H), 8.22 (dd, J = 8.9, 2.7 Hz, 1H), 7.32−7.26 (m, 4H), 7.19 (d, J = 8.9 Hz, 1H), 5.05−5.01 (m, 1H), 4.65 (d, J = 10.2 Hz, 1H), 4.13 (dq, J = 10.8, 7.1 Hz, 1H), 4.09 (dq, J = 10.8, 7.1 Hz, 1H), 3.91 (d, J = 4.9 Hz, 1H), 3.87 (dq, J = 10.6, 7.1 Hz, 1H), 3.63 (dd, J = 10.2, 7.0 Hz, 1H), 3.48 (dq, J = 10.7, 7.2 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H), 0.79 (t, J = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.6, 169.5, 165.4, 154.3, 144.8, 134.4, 133.9, 130.1 (2C), 128.9 (2C), 125.8, 125.0, 123.7, 118.2, 76.7, 62.8, 62.7, 56.7, 52.8, 48.8, 14.0, 13.4. IR (film, cm^{-1}): ν = 3314, 2918, 2850, 1733, 1588, 1522, 1467, 1370, 1342, 1282, 1212, 1108, 1040, 853, 751. HRMS calculated for $[C_{23}H_{21}N_3O_{10} + H]^+$: 500.1300; found: 500.1291. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 23.9 min, τ_{minor} = 41.1 min (96:4 er). $[\alpha]_D^{20}$ = −59.9 (c = 0.3, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-3-(4-Bromophenyl)-8-nitro-4-oxo-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3m**).* Following the general procedure, **3m** was isolated by FC on silica (hexane/AcOEt 3:1) in 89% yield (47.4 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.48 (dd, J = 2.7, 1.0 Hz, 1H), 8.22 (dd, J = 9.0, 2.8 Hz, 1H), 7.47−7.43 (m, 2H), 7.21−7.18 (m, 3H), 5.03 (d, J = 6.9 Hz, 1H), 4.63 (d, J = 10.1 Hz, 1H), 4.13 (dq, J = 10.8, 7.1 Hz, 1H), 4.08 (dq, J = 10.8, 7.1 Hz, 1H), 3.92 (s, 1H), 3.87 (dq, J = 10.7, 7.1 Hz, 1H), 3.62 (dd, J = 10.1, 7.0 Hz, 1H), 3.49 (dq, J = 10.7, 7.2 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H), 0.79 (t, J = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.6, 169.5, 165.4, 154.3, 144.8, 134.5, 131.9 (2C), 130.5 (2C), 125.8, 125.0, 123.7, 122.5, 118.3, 76.6, 62.9, 62.7, 56.7, 52.9, 48.7, 13.9, 13.4. IR (film, cm^{-1}): ν = 3317, 2920, 2851, 1730, 1587, 1522, 1465, 1373, 1337, 1279, 1210, 1105, 1039, 857, 753. HRMS calculated for $[C_{23}H_{21}BrN_2O_8 + H]^+$: 533.0554; found: 533.0559. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 14.3 min, τ_{minor} = 21.1 min (99:1 er). $[\alpha]_D^{20}$ = −87.4 (c = 0.9, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-3-(4-Chlorophenyl)-8-nitro-4-oxo-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3n**).* Following the general procedure, **3n** was isolated by FC on silica (hexane/AcOEt 3:1) in 78% yield (38.1 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.48 (dd, J = 2.7, 1.0 Hz, 1H), 8.22 (dd, J = 8.9, 2.7 Hz, 1H), 7.32−7.28 (m, 2H), 7.28−7.25 (m, 2H), 7.19 (d, J = 8.9 Hz, 1H), 5.03 (d, J = 6.9 Hz, 1H), 4.65 (d, J = 10.2 Hz, 1H), 4.13 (dq, J = 10.8, 7.2 Hz, 1H), 4.09 (dq, J = 10.8, 7.1 Hz, 1H), 3.92 (s, 1H), 3.87 (dq, J = 10.7, 7.2 Hz, 1H), 3.63 (dd, J = 10.1, 7.0 Hz, 1H), 3.48 (dd, J = 10.7, 7.2 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H), 0.79 (t, J = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.6, 169.5, 165.4, 154.3, 144.8, 134.4, 133.9, 130.1 (2C), 128.9 (2C), 125.8, 125.0, 123.7, 118.2, 76.7, 62.8, 62.7, 56.7, 52.8, 48.8, 14.0, 13.4. IR (film, cm^{-1}): ν = 3310, 2920, 2851, 1732, 1587, 1523, 1465, 1374, 1338, 1279, 1211, 1105, 1042, 831, 752. HRMS calculated for $[C_{23}H_{21}ClN_2O_8 + H]^+$: 489.1059; found: 489.1061. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 13.7 min, τ_{minor} = 21.0 min (96:4 er). $[\alpha]_D^{20}$ = −115.3 (c = 0.7, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-3-(3-Chlorophenyl)-8-nitro-4-oxo-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3o**).* Following the general procedure, **3o** was isolated by FC on silica (hexane/AcOEt 3:1) in 76% yield (37.1 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.48 (dd, J = 2.6, 1.0 Hz, 1H), 8.22 (dd, J = 8.9, 2.8 Hz, 1H), 7.32 (d, J = 2.0 Hz, 1H), 7.29−7.24 (m, 2H), 7.22−7.18 (m, 2H), 5.04 (d, J = 6.9 Hz, 1H), 4.67 (d, J = 9.7 Hz, 1H), 4.14 (dq, J = 10.8, 7.2 Hz, 1H), 4.09 (dq, J = 10.7, 7.1 Hz, 1H), 3.91 (s, 1H), 3.87 (dq, J = 10.6, 7.1 Hz, 1H), 3.62 (dd, J = 9.7, 6.9 Hz, 1H), 3.50 (dq, J = 10.7, 7.2 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H), 0.79 (t, J = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.5, 169.4, 165.3, 154.4, 144.8, 137.8, 134.7, 130.0, 129.2, 128.6, 126.7, 125.8, 125.1, 123.5, 118.3, 76.7, 62.8, 62.7, 56.8, 53.0, 48.9, 14.0, 13.4. IR (film, cm^{-1}): ν = 3334, 2918, 2850, 1734, 1587, 1523, 1458, 1372, 1338, 1279, 1211, 1106, 1052, 846, 753. HRMS calculated for $[C_{23}H_{21}ClN_2O_8 + H]^+$: 489.1059; found: 489.1065. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 13.0 min, τ_{minor} = 21.1 min (97:3 er). $[\alpha]_D^{20}$ = −48:8 (c = 0.8, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-3-(2-Chlorophenyl)-8-nitro-4-oxo-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3p**).* Following the general procedure, **3p** was isolated by FC on silica (hexane/AcOEt 3:1) in 71% yield (34.7 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.45 (dd, J = 2.7, 0.9 Hz, 1H), 8.23 (dd, J = 8.9, 2.7 Hz, 1H), 7.46−7.37 (m, 1H), 7.28−7.24 (m, 4H), 5.55 (s, 1H), 5.09 (d, J = 7.0 Hz, 1H), 4.10 (dq, J = 10.7, 7.1 Hz, 1H), 4.03 (dq, J = 10.8, 7.1 Hz, 1H), 3.88 (dq, J = 10.7, 7.2 Hz, 2H), 3.51 (s, 1H), 1.16 (t, J = 7.1 Hz, 3H), 0.81 (t, J = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.4, 168.9, 154.8, 144.6, 135.8, 130.3 (2C), 129.4, 127.3, 125.9 (2C), 125.2, 122.7, 118.3 (2C), 77.0, 62.7, 62.6, 57.2, 57.1, 13.9, 13.4. IR (film, cm^{-1}): ν = 3314, 2923, 2853, 1732, 1594, 1523, 1464, 1372, 1338, 1273, 1211, 1111, 1019, 831, 752. HRMS calculated for $[C_{23}H_{21}ClN_2O_8 + H]^+$: 489.1059; found: 489.1070. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 17.9 min, τ_{minor} = 28.8 min (93:7 er). $[\alpha]_D^{20}$ = −21.7 (c = 0.7, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-3-(4-Methylphenyl)-8-nitro-4-oxo-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3q**).* Following the general procedure, **3q** was isolated by FC on silica (hexane/AcOEt 3:1) in 72% yield (33.8 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.48 (dd, J = 2.7, 1.0 Hz, 1H), 8.21 (dd, J = 8.9, 2.7 Hz, 1H), 7.18 (d, J = 8.6 Hz, 3H), 7.11 (d, J = 8.0 Hz, 2H), 5.02 (d, J = 6.9 Hz, 1H), 4.65 (d, J = 9.8 Hz, 1H), 4.12 (dq, J = 10.8, 7.1 Hz, 1H), 4.07 (dq, J = 10.8, 7.1 Hz, 1H), 3.92 (s, 1H), 3.83 (dq, J = 10.6, 7.1 Hz, 1H), 3.65 (dd, J = 9.9, 7.0 Hz, 1H), 3.43 (dq, J = 10.7, 7.2 Hz, 1H), 2.31 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H), 0.73 (t, J = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.8, 169.7, 165.7, 154.5, 144.7, 138.1, 132.4, 129.4 (2C), 128.6 (2C), 125.7, 125.1, 123.9, 118.2, 76.8, 62.6, 62.5, 56.8, 53.3, 49.1, 21.2, 14.0, 13.3. IR (film, cm^{-1}): ν = 3313, 2982, 2928, 2856, 1728, 1586, 1519, 1463, 1373, 1337, 1280, 1211, 1106, 1040, 832, 752. HRMS calculated for $[C_{24}H_{24}N_2O_8 + H]^+$: 469.1605; found: 469.1601. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 14.3 min, τ_{minor} = 21.2 min (99.5:0.5 er). $[\alpha]_D^{20}$ = −119.4 (c = 0.7, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-3-(4-Methoxyphenyl)-8-nitro-4-oxo-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3r**).* Following the general procedure, **3r** was isolated by FC on silica (hexane/AcOEt 3:1) in 65% yield (31.5 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.48 (dd, J = 2.8, 1.0 Hz, 1H), 8.21 (dd, J = 8.9, 2.7 Hz, 1H), 7.24−7.21 (m, 2H), 7.18 (d, J = 8.9 Hz, 1H), 6.85−6.82 (m, 2H), 5.01 (d, J = 6.9 Hz, 1H), 4.63 (d, J = 10.1 Hz, 1H), 4.12 (dq, J = 10.8, 7.1 Hz, 1H), 4.08 (dq, J = 10.8, 7.1 Hz, 1H), 3.92 (s, 1H), 3.86 (dq, J = 10.6, 7.1 Hz, 1H), 3.78 (s, 3H), 3.64 (dd, J = 10.2, 6.9 Hz, 1H), 3.46 (dq, J = 10.7, 7.2 Hz, 1H), 1.19 (t, J = 7.1 Hz, 3H), 0.78 (t, J = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.9, 169.8, 165.6, 159.6, 154.4, 144.7, 129.8 (2C), 127.3, 125.7, 125.1, 123.9, 118.2, 114.1 (2C), 76.7, 62.7, 62.5, 56.7, 55.5, 53.0, 49.1, 14.0, 13.5. IR (film, cm^{-1}): ν = 3316, 2957, 2918, 2851, 1730, 1586, 1516, 1465, 1375, 1337, 1280, 1211, 1106, 1035, 799, 752. HRMS calculated for $[C_{24}H_{24}N_2O_9 + H]^+$: 485.1555; found: 485.1563. The er was determined by HPLC using a Chiralpak IA column

DOI: 10.1021/acs.joc.6b00975
J. Org. Chem. 2016, 81, 6800−6807

[hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 19.3 min, τ_{minor} = 26.6 min (98:2 er). $[\alpha]_D^{20}$ = −105.5 (*c* = 0.6, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-3-(4-Methoxyphenyl)-8-nitro-4-oxo-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3s**).* Following the general procedure, **3s** was isolated by FC on silica (hexane/AcOEt 3:1) in 76% yield (36.9 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 2.8, 0.9 Hz, 1H), 8.20 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.29 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.28−7.25 (m, 1H), 7.18 (d, *J* = 8.9 Hz, 1H), 6.92 (td, *J* = 7.5, 1.1 Hz, 1H), 6.84 (dd, *J* = 8.3, 1.1 Hz, 1H), 5.04 (d, *J* = 7.3 Hz, 1H), 4.94 (s, 1H), 4.07 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.01 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.94−3.86 (m, 2H), 3.78 (s, 3H), 3.57−3.48 (m, 1H), 1.14 (t, *J* = 7.1 Hz, 3H), 0.78 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.5, 169.3, 166.8, 157.9, 154.8, 144.5, 129.5 (2C), 125.6, 125.5, 125.0, 123.5, 121.1, 118.1 (2C), 110.7, 100.2, 75.6, 62.4, 62.1, 56.7, 55.3, 13.9, 13.4. IR (film, cm^{-1}): ν = 3304, 2962, 2926, 2851, 1730, 1586, 1521, 1464, 1374, 1337, 1280, 1207, 1106, 1026, 799, 753. HRMS calculated for $[C_{24}H_{24}N_2O_9 + H]^+$: 485.1555; found: 485.1562. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 15.9 min, τ_{minor} = 17.9 min (98.5:1.5 er). $[\alpha]_D^{20}$ = −38.8 (*c* = 0.6, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-3-Naphthyl-8-nitro-4-oxo-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3t**).* Following the general procedure, **3t** was isolated by FC on silica (hexane/AcOEt 3:1) in 62% yield (31.3 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.54 (d, *J* = 8.6 Hz, 1H), 8.50 (d, *J* = 2.7 Hz, 1H), 8.27 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.85−7.82 (m, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.58 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H), 7.51 (ddd, *J* = 7.9, 6.9, 1.1 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 7.2 Hz, 1H), 7.25 (d, *J* = 8.9 Hz, 1H), 5.96 (d, *J* = 5.7 Hz, 1H), 5.25 (d, *J* = 6.5 Hz, 1H), 4.19−4.13 (m, 1H), 4.09 (dq, *J* = 10.7, 7.1 Hz, 1H), 3.86−3.78 (m, 1H), 3.70 (t, *J* = 6.2 Hz, 1H), 3.55 (dq, *J* = 10.6, 7.2 Hz, 1H), 3.00 (dq, *J* = 10.6, 7.2 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H), 0.22 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.7, 169.4, 166.1, 155.2, 144.5, 134.8, 133.9, 133.1, 128.9, 128.6, 126.9, 126.2, 126.0, 125.3, 125.1, 124.4 (2C), 122.7, 118.3, 76.8, 62.7, 62.1, 57.9, 51.1, 47.6, 13.9, 12.7. IR (film, cm^{-1}): ν = 3315, 2957, 2919, 2851, 1731, 1586, 1521, 1489, 1466, 1372, 1338, 1279, 1209, 1143, 1033, 798, 736. HRMS calculated for $[C_{27}H_{24}N_2O_8 + H]^+$: 505.1605; found: 505.1617. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 19.7 min, τ_{minor} = 31.8 min (95:5 er). $[\alpha]_D^{20}$ = −32.5 (*c* = 0.5, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-3-(1,3-Benzodioxol-5-yl)-8-nitro-4-oxo-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3u**).* Following the general procedure, **3u** was isolated by FC on silica (hexane/AcOEt 3:1) in 69% yield (34.4 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 2.8, 1.0 Hz, 1H), 8.21 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.18 (d, *J* = 8.9 Hz, 1H), 6.80−6.73 (m, 3H), 5.93 (d, *J* = 0.7 Hz, 2H), 5.00 (d, *J* = 7.1 Hz, 1H), 4.59 (d, *J* = 10.2 Hz, 1H), 4.12 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.08 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.92 (dq, *J* = 10.7, 7.2 Hz, 2H), 3.59 (dq, *J* = 10.7, 7.3 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.8, 169.7, 165.5, 154.3, 147.9, 147.6, 144.7, 129.0, 125.7, 125.1, 123.8, 122.2, 118.2, 109.3, 108.4, 101.4, 76.6, 62.7, 62.6, 56.6, 53.4, 49.2, 14.0, 13.6. IR (film, cm^{-1}): ν = 3316, 2982, 2924, 2852, 1727, 1586, 1521, 1490, 1446, 1371, 1337, 1278, 1212, 1104, 1038, 807, 752. HRMS calculated for $[C_{24}H_{22}N_2O_{10} + H]^+$: 499.1347; found: 499.1346. The er was determined by HPLC using a Chiralpak ID column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 18.4 min, τ_{minor} = 20.6 min (97:3 er). $[\alpha]_D^{20}$ = −77.9 (*c* = 0.5, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-3-(Furan-2-yl)-8-nitro-4-oxo-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3v**).* Following the general procedure, **3v** was isolated by FC on silica (hexane/AcOEt 3:1) in 72% yield (32.0 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 2.7, 0.8 Hz, 1H), 8.21 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.35 (t, *J* = 1.3 Hz, 1H), 7.19 (d, *J* = 8.9 Hz, 1H), 6.33 (d, *J* = 1.7 Hz, 2H), 5.06−4.95 (m, 1H), 4.94 (dd, *J* = 7.5, 1.0 Hz, 1H), 4.15 (dq, *J* = 10.9, 7.1 Hz, 1H), 4.11−4.02 (m, 2H), 3.86 (s, 1H), 3.76 (dd, *J* = 10.7, 7.2 Hz, 1H), 3.57 (dd, *J* = 7.5, 6.7 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.00 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 169.5, 168.8, 165.3, 154.7, 149.6, 144.6, 142.8, 125.8, 125.3, 123.2, 118.2, 110.9, 109.7, 74.9, 63.1, 62.7, 56.7, 48.0, 47.2, 13.9, 13.8. IR (film, cm^{-1}): ν = 3306, 2983, 2927, 2853, 1730, 1586, 1522, 1489, 1464, 1372, 1337, 1279, 1207, 1105, 1040, 858, 751. HRMS calculated for $[C_{21}H_{20}N_2O_9 + H]^+$: 445.1242; found: 445.1253. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 17.8 min, τ_{minor} = 21.9 min (99:1 er). $[\alpha]_D^{20}$ = −49.8 (*c* = 0.7, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-3-Ethyl-8-nitro-4-oxo-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3w**).* Following the general procedure, **3w** was isolated by FC on silica (hexane/AcOEt 3:1) in 95% yield (38.8 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 2.7, 0.9 Hz, 1H), 8.18 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.16 (d, *J* = 8.9 Hz, 1H), 4.79 (d, *J* = 6.8 Hz, 1H), 4.34 (dq, *J* = 10.7, 7.2 Hz, 1H), 4.25 (dq, *J* = 10.8, 7.2 Hz, 1H), 4.15 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.06 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.58 (s, 1H), 3.36 (td, *J* = 8.2, 5.9 Hz, 1H), 3.02 (dd, *J* = 7.8, 6.8 Hz, 1H), 1.68 (ddq, *J* = 13.7, 7.4, 5.9 Hz, 1H), 1.53 (ddq, *J* = 14.5, 8.7, 7.4 Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.8, 169.6, 166.9, 154.5, 144.5, 125.6, 125.2, 123.8, 118.0, 74.6, 62.8, 62.3, 55.8, 49.5, 47.7, 23.0, 14.2, 14.0, 12.5. IR (film, cm^{-1}): ν = 3300, 2967, 2930, 2854, 1724, 1584, 1519, 1485, 1457, 1370, 1336, 1281, 1203, 1092, 1025, 861, 752. HRMS calculated for $[C_{19}H_{22}N_2O_8 + H]^+$: 407.1449; found: 407.1443. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 11.1 min, τ_{minor} = 13.1 min (95:5 er). $[\alpha]_D^{20}$ = −28.9 (*c* = 0.8, $CHCl_3$).

*Diethyl (3R,3aS,9bR)-3-Hexyl-8-nitro-4-oxo-1,3a,4,9b-tetrahydrochromeno[4,3-b]pyrrole-2,2(3H)-dicarboxylate (**3x**).* Following the general procedure, **3x** was isolated by FC on silica (hexane/AcOEt 3:1) in 94% yield (43.5 mg) as a pale yellow oil (>20:1 dr). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.37 (dd, *J* = 2.6, 0.9 Hz, 1H), 8.18 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.16 (d, *J* = 8.9 Hz, 1H), 4.79 (d, *J* = 6.7 Hz, 1H), 4.34 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.25 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.14 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.06 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.57 (s, 1H), 3.42 (td, *J* = 8.1, 5.8 Hz, 1H), 3.01 (dd, *J* = 7.8, 6.8 Hz, 1H), 1.62−1.56 (m, 1H), 1.51−1.34 (m, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 1.29−1.21 (m, 6H), 1.20−1.18 (m, 3H), 0.86 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (176 MHz, $CDCl_3$) δ 170.8, 169.6, 166.9, 154.5, 144.5, 125.6, 125.2, 123.8, 118.0, 74.7, 62.7, 62.3, 55.8, 48.0, 47.9, 31.7, 30.1, 29.3, 27.8, 22.7, 14.2, 14.1, 14.0. IR (film, cm^{-1}): ν = 3340, 2956, 2928, 2858, 1726, 1590, 1528, 1481, 1466, 1368, 1342, 1268, 1201, 1094, 1028, 836, 747. HRMS calculated for $[C_{23}H_{30}N_2O_8 + H]^+$: 463.2075; found: 463.2067. The er was determined by HPLC using a Chiralpak IA column [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 10.3 min, τ_{minor} = 11.3 min (96.5:3.5 er). $[\alpha]_D^{20}$ = −27.8 (*c* = 1.0, $CHCl_3$).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00975.

Full account of screening results, X-ray structure, copies of ^{1}H and ^{13}C NMR spectra, HPLC traces (PDF)
Crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: lukasz.albrecht@p.lodz.pl.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was made possible by a financial support from the Young Scientists' Fund at the Faculty of Chemistry, Lodz University of Technology (grant W-3/FMN/18G/2015). Thanks are expressed to Dr. Jakub Wojciechowski (Faculty of

DOI: 10.1021/acs.joc.6b00975
J. Org. Chem. 2016, 81, 6800−6807

Chemistry, Lodz University of Technology) for performing X-ray analysis.

REFERENCES

(1) (a) Li, J. J., Johnson, D. S., Eds. *Modern Drug Synthesis*; John Wiley & Sons, Inc: Hoboken, NJ, 2010. (b) Schreiber, S. L. *Science* **2000**, *287*, 1964. (c) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds. *Comprehensive Asymmetric Catalysis I–III*; Springer: New York, 1999.
(2) (a) McConathy, J.; Owens, M. J. *Prim. Care Companion J. Clin. Psychiatry* **2003**, *5*, 70. (b) Hutt, A. J. *Drug Metab. Drug Interact.* **2007**, *22*, 79.
(3) (a) Kamat, D. P.; Tilve, S. G.; Kamat, V. P.; Kirtany, J. K. *Org. Prep. Proced. Int.* **2015**, *47*, 1. (b) Asai, F.; Iinuma, M.; Tanaka, T.; Mizuno, M. *Phytochemistry* **1991**, *30*, 3091. (c) Ee, G. C. L.; Mah, S. H.; Teh, S. S.; Rahmani, M.; Go, R.; Taufiq-Yap, Y. H. *Molecules* **2011**, *16*, 9721.
(4) (a) Haider, S.; Saify, Z. S.; Begum, N.; Ashrafl, S.; Zarreen, T.; Saeed, S. M. G. *World J. Pharm. Res.* **2014**, *3*, 987. (b) Bhakuni, D. S.; Rawat, D. S. *Bioactive Marine Natural Products*; Springer: New York, 1999. (c) Pinder, A. R. In *The Alkaloids*; Grundon, M. F., Ed.; Chemical Society: London, 1982; Vol. *12*. (d) McGeer, E. G.; Olney, J. W.; McGcer, P. L. *Kainic Acid as a tool in Neurobiology*; Raven Press: New York, 1983. (e) Murukami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026. (f) Witherup, K. M.; Ransom, R. W.; Graham, A. C.; Bernard, A. M.; Salvatore, M. J.; Lumma, W. C.; Anderson, P. S.; Pitzenberger, S. M.; Varga, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 6682.
(5) For selected, recent enantioselective syntheses of 3,4-dihydrocoumarins, see: (a) Engl, O. D.; Fritz, S. P.; Käslin, A.; Wennemers, H. *Org. Lett.* **2014**, *16*, 5454. (b) Hu, H.; Liu, Y.; Guo, J.; Lin, L.; Xu, Y.; Liu, X.; Feng, X. *Chem. Commun.* **2015**, *51*, 3835. (c) Hejmanowska, J.; Albrecht, A.; Pięta, J.; Albrecht, Ł. *Adv. Synth. Catal.* **2015**, *357*, 3843. (d) Wang, Y.; Pan, J.; Jiang, R.; Wang, Y.; Zhou, Z. *Adv. Synth. Catal.* **2016**, *358*, 195. (e) Nakamura, S.; Toda, A.; Sano, M.; Hatanaka, T.; Funahashi, Y. *Adv. Synth. Catal.* **2016**, *358*, 1029. For reviews on pyrrolidine derivatives synthesis, see: (f) Pandey, G.; Banerjee, P.; Gadre, S. R. *Chem. Rev.* **2006**, *106*, 4484. (g) Han, M.-Y.; Jia, J.-Y.; Wang, W. *Tetrahedron Lett.* **2014**, *55*, 784. (h) Randjelovic, J.; Simic, M.; Tasic, G.; Husinec, S.; Savic, V. *Curr. Org. Chem.* **2014**, *18*, 1073. For selected examples, see: (i) Rajkumar, V.; Babu, S. A. *Synlett* **2014**, *25*, 2629. (j) Costa, P. R. R.; Sansano, J. M.; Cossío, U.; Barcellos, J. C. F.; Dias, A. G.; Nájera, C.; Arrieta, A.; de Cózar, A.; Cossío, F. P. *Eur. J. Org. Chem.* **2015**, *2015*, 4689. (k) Qi, J.; Duan, X.-Y.; Cao, L.-L.; Wang, W.-Y. *Asian J. Org. Chem.* **2015**, *4*, 1254. (l) Zhang, L.-J.; Wang, J.; Hu, X.-Q.; Xu, P.-F. *Chem.—Asian J.* **2016**, *11*, 834.
(6) (a) Dzięgielewski, M.; Pięta, J.; Kamińska, E.; Albrecht, Ł. *Eur. J. Org. Chem.* **2015**, *2015*, 677. (b) Monge, D.; Jiang, H.; Alvarez-Casao, Y. *Chem.—Eur. J.* **2015**, *21*, 4494.
(7) Chen, L.; Wu, Z.-J.; Zhang, M.-L.; Yue, D.-F.; Zhang, X.-M.; Xu, X.-Y.; Yuan, W.-C. *J. Org. Chem.* **2015**, *80*, 12668.
(8) (a) Tian, L.; Xu, G.-Q.; Li, Y.-H.; Liang, Y.-M.; Xu, P.-F. *Chem. Commun.* **2014**, *50*, 2428.
(9) For selected reviews on the enantioselective Brønsted base catalysis, see: (a) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496. (b) Jew, S.-S.; Park, H.-G. *Chem. Commun.* **2009**, 7090. (c) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632. (d) Quigley, C.; Rodríguez-Docampo, Z.; Connon, S. J. *Chem. Commun.* **2012**, *48*, 1443. (e) Krawczyk, H.; Dzięgielewski, M.; Deredas, D.; Albrecht, A.; Albrecht, Ł. *Chem.—Eur. J.* **2015**, *21*, 10268.
(10) See the Supporting Information for details. CCDC 1474177 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

DOI: 10.1021/acs.joc.6b00975
J. Org. Chem. 2016, 81, 6800–6807