JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis of Thiophene-Based TAK-779 Analogues by C−H Arylation

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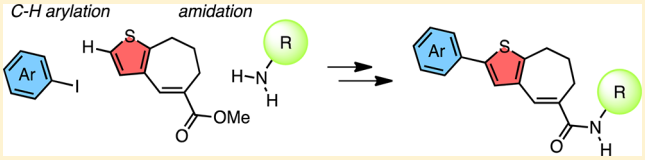
Supporting Information

ABSTRACT: A rapid synthesis of thiophene-based TAK-779 analogues **1** is reported using a late-stage diversification strategy. At the end of the synthesis, the key building block **2**, which was prepared in six steps from thiophene, was arylated regioselectively at the α-position directly with iodoarenes. Since **2** offers several reactive positions, various established catalyst systems were tested. It was found that Crabtree catalyst (an Ir catalyst) converted efficiently and selectively the thiophene system **2** into 2-aryl-substituted compounds **9**. The direct C−H arylation of **2** with electron-rich iodoarenes led to high yields, whereas electron-deficient iodoarenes required longer reaction times for complete conversion. A small set of diverse amides **1** was synthesized by hydrolysis of **9** and subsequent HATU coupling with primary amines **4**.



INTRODUCTION

Chemokine receptor 5 (CCR5) antagonists represent a novel class of HIV entry inhibitors. The highly potent CCR5 receptor antagonist TAK-779 is among the most potent CCR5 receptor antagonists reported thus far and can serve as a lead compound for the development of novel antagonists (Figure 1).[1,2] In this research program, the benzene ring in the core benzo[7]-annulene of TAK-779 is replaced bioisosterically by a thiophene moiety (**1**). Although thiophene and benzene rings are very similar in size, they differ in electronic and geometric properties, which leads to the modification of pharmacological properties.

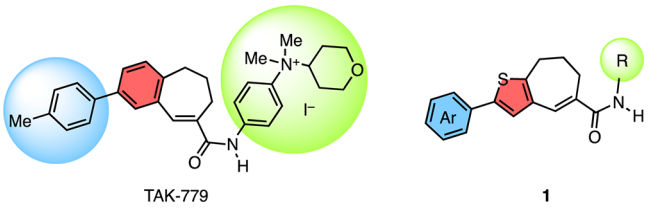


Figure 1. Design of thiophene bioisosteric CCR5 receptor antagonists **1** derived from TAK-779.

Furthermore, the bioisosteric introduction of the thiophene moiety will allow the rapid modification at a late stage of the synthesis by C−H arylation. A large and diverse set of novel ligands **1** will give new information about the complementary binding pocket of the CCR5 receptor protein. In order to obtain a large set of diverse ligands **1**, recently emerging C−H arylation technology and subsequent amidation of the key building block **2** are envisaged (Figure 2). This straightforward late-stage diversification strategy would allow us to rapidly generate molecular diversity for CCR5 antagonists **1** by using different iodoarenes **3** and primary amines **4**.

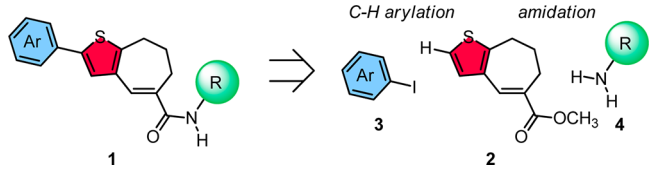


Figure 2. Late-stage diversification strategy for the rapid synthesis of a large set of CCR5 receptor antagonists via sequential C−H functionalization and amidation of key building block **2**.

RESULTS AND DISCUSSION

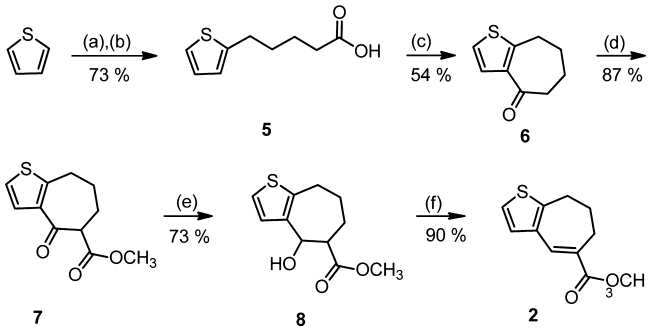
The synthesis of ester **2** commenced with a Friedel-Crafts acylation of thiophene with glutaric anhydride and subsequent Wolff−Kishner reduction to afford pentanoic acid **5** in 72% yield.[3] Intramolecular Friedel−Crafts acylation of **5** with P_2O_5 required careful optimization of reaction conditions.[3] Addition of Celite (5 g/mol) to the reaction mixture to remove water led to a considerable increase of the yield of ketone **6**. Claisen condensation of ketone **6** with dimethyl carbonate provided β-ketoester **7**, which was reduced with $NaBH_4$ (to give **8**) and dehydrated by CH_3SO_2Cl and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to yield the α,β-unsaturated ester **2** (Scheme 1).

The transition-metal-catalyzed direct transformation of C−H bonds of heteroarenes with haloarenes has been a topic of immense importance during the past decade. In contrast to standard cross-coupling methods such as the Pd-catalyzed Suzuki−Miyaura reaction, the direct C−H bond functionalization can streamline the synthetic process by skipping the premetalation step.[4] The most common catalysts applied in the synthesis of heterobiaryls by C−H arylation are Pd,[5−7] Rh,[8−10]

Received: April 4, 2013
Published: May 3, 2013

   dx.doi.org/10.1021/jo400692p | J. Org. Chem. 2013, 78, 5579−5586

Scheme 1. Synthesis of Key Building Block 2[a]



[a]Reagents and reaction conditions: (a) glutaric anhydride, $AlCl_3$ (2.2 equiv), CH_2Cl_2, rt, 1 h, 83%; (b) hydrazine monohydrate (5.5 equiv), KOH (4.4 equiv), tri(ethylene glycol), 200 °C, 15 h, 87% (c) P_2O_5 (2 equiv), Celite, toluene, reflux, 3 h, 64%; (d) NaOMe (10 equiv), dimethyl carbonate, 80 °C, 10 h, 87%; (e) $NaBH_4$ (3 equiv), MeOH, CH_2Cl_2, −10 °C, 3 h, 73%; (f) methanesulfonyl chloride (1.5 equiv), Et_3N (3.0 equiv), CH_2Cl_2, rt, overnight, then DBU (4 equiv), CH_2Cl_2, rt, 1 h, 90%.

Cu,[11] and Ni[12−15] complexes. However, it was not easy to identify the right catalyst for the C−H arylation of the thiophene system **2** containing an α,β-unsaturated ester moiety.[16−19]

The $PdCl_2$/bipy system[20,21] failed to produce selectively the α-arylated thiophene **9a** with 4-iodobenzene (**3a**), since a mixture of monoarylated products was formed. Variation of the Pd source to $PdBr_2$[21] and of the aryl halide to 4-bromotoluene did not improve the selectivity of the transformation. The $Pd(OAc)_2$/1,10-phenanthroline/Cs_2CO_3 system[5] led predominantly to diarylated products. The Rh-based catalyst $[RhCl(CO)(P\{OCH(CF_3)_2\}_3)_2]/Ag_2CO_3$[9] was the least efficient system, leading to several products but only traces of the desired compound **9a**. In addition to the thiophene moiety, the double bond (position 4) and the benzylic position (position 8) of the α,β-unsaturated ester **2** can be attacked by 4-iodotoluene (**3a**) and are therefore responsible for side product formation.

Finally, we identified that cationic iridium(I) complex $[Ir(cod)(py)PCy_3]PF_6$,[22] known as the Crabtree catalyst,[23,24] can catalyze the regioselective C−H arylation of **2** with 4-iodotoluene (**3a**) (Scheme 2).

Next the reaction conditions for the selective α-arylation using the $[Ir(cod)(py)PCy_3]PF_6/Ag_2CO_3$ system were carefully optimized (Table 1). A mixture of thiophene **2**, 4-iodotoluene (**3a**), and $[Ir(cod)(py)PCy_3]PF_6/Ag_2CO_3$ in 1,4-dioxane was stirred at 170 °C for 12 h. One equivalent of 4-iodotoluene and 5 mol % of the catalyst led to an yield of 23% of **9a** (entry 1). Increasing of the amount of 4-iodotoluene up to 1.4 equiv resulted in complete conversion and afforded the monoarylated compound **9a** regioselectively in 93% yield (entry 3). Next the amount of catalyst was investigated; 5.0 mol % as well as 2.5 mol % of the catalyst provided the product in excellent yields (entries 3 and 5). A further reduction of the catalyst amount to 1.0 and 0.5 mol % resulted in significantly lower conversion and yields (entries 7 and 8). Surprisingly, increasing of the reaction scale from 0.48 to 4.8 or even 7.2 mmol of **2** led to dramatically decreased yields of **9a** (entry 4 and 6).

Table 1. Optimization of Reaction Conditions for C−H Bond Arylation of 1 with 4-Iodotoluene and Crabtree Catalyst[b]

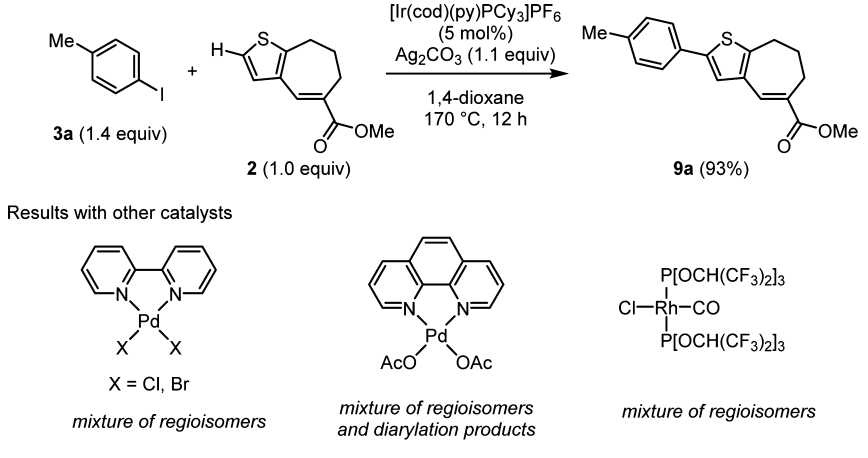
entry	mol % of catalyst	equiv of 4-iodotoluene	scale (mmol)	yield of **9a** (%)
1	5.0	1.0	0.48	23
2	5.0	1.1	0.48	50
3	5.0	1.4	0.48	93
4	5.0	1.4	4.8	43
5	2.5	1.4	0.48	90
6	2.5	1.4	7.2	27
7[a]	1.0	1.4	0.48	12
8	0.5	1.4	0.48	5

[a]50% starting material recovered. [b]Reagents and reaction conditions: **2** (1 equiv), catalyst, 4-iodotoluene **3a**, and base (1.1 equiv) were dissolved in 1,4-dioxane (0.1 M) and heated to 170 °C for 12 h in a sealed tube.

In order to prove the position of the aryl moiety unequivocally, **9a** was recrystallized from acetonitrile to afford crystals suitable for X-ray crystal structure analysis. The X-ray crystal structure reveals clearly that the *p*-tolyl moiety is attached to position 2 of the bicyclic system, indicating that the arylation had taken place selectively at the α-position of the thiophene.

The optimized reaction conditions (1.4 equiv of iodobenzene derivative, 5 mol % of $[Ir(cod)(py)PCy_3]PF_6$, 1.1 equiv of Ag_2CO_3 in 1,4-dioxane at 170 °C for 12 h) were used to

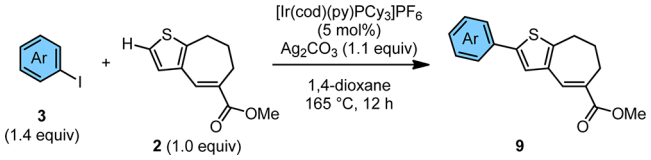
Scheme 2. α-Arylation of Key Thiophene 2 with 4-Iodotoluene (3a) in the Presence of Different Catalysts



dx.doi.org/10.1021/jo400692p | J. Org. Chem. 2013, 78, 5579−5586

introduce other aryl moieties into the bicyclic thiophene derivative **2** (Table 2). Excellent yields (87–97%) were

Table 2. Iridium-Catalyzed C–H Arylation of Bicyclic Thiophene 2 with Different Iodoarenes 3[a]



entry	3 (Ar)	9 (yield)
1	**3a** (4-$CH_3C_6H_4$)	**9a** (93%)
2	**3b** (3-$CH_3C_6H_4$)	**9b** (87%)
3	**3c** (4-^{n}BuC_6H_4)	**9c** (97%)
4	**3d** (4-PhC_6H_4)	**9d** (78%)
5	**3e** (4-^{t}BuC_6H_4)	**9e** (55%)
6	**3f** (4-$CF_3C_6H_4$)	**9f** (55%)[b]
7	**3g** (4-$NO_2C_6H_4$)	**9g** (56%)

[a]Standard conditions for the arylation of **2**: (a) **2** (1.0 equiv), iodobenzene derivative **3** (1.4 equiv), [Ir(cod)(py)PCy_3]PF_6 (5 mol %), Ag_2CO_3 (1.1 equiv), 1,4-dioxane, 170 °C, 12 h. [b]Reaction time 72 h.

obtained with electron-rich alkyl iodoarenes (compounds **9a–c**). A slightly reduced yield of 78% was obtained in the arylation of **2** with biphenylyl iodide (**9d**). Despite its high electron density, *tert*-butyl iodobenzene led to only 55% of arylated product **9e**. In contrast to electron-rich iodobenzenes, electron-deficient analogues such as 4-trifluoromethyl- and 4-nitro-substituted iodobenzenes gave reduced yields of arylated products **9f** and **9g**. However, lengthening the reaction time from 12 to 48 and 72 h increased the yield of **9f** from 21% to 41% and finally to 55%. The surprising reduced reactivity of electron-deficient iodoarenes can be compensated at least partially by lengthening of the reaction time.

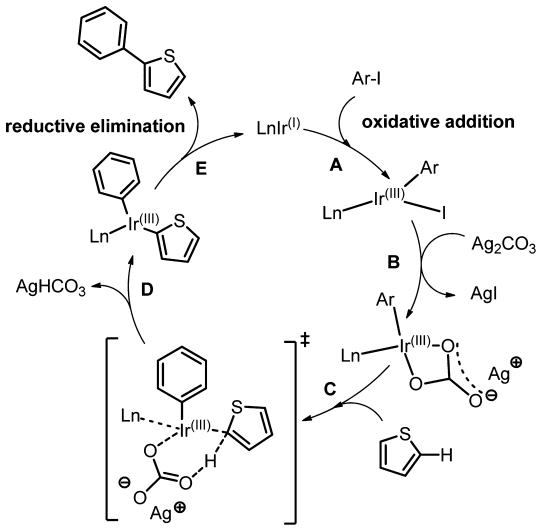
Although the mechanism of this transformation remains unclear, we assume a concerted metalation deprotonation (CMD) mechanism[25−27] (Scheme 3). At first an Ir(III) complex is formed by oxidative addition of the aryl iodide to the Ir(I) complex of Crabtree catalyst (step **A**). Next, Ag_2CO_3 removes iodide and releases the base CO_3^{2-}, which is able to coordinate with the Ir center to generate the Ir(III)-carbonate complex (step **B**). After coordination of the thiophene to Ir(III) of the metal complex (step **C**), a simultaneous metalation and deprotonation in α-position of the thiophene ring by carbonate occurs (step **D**). Reductive elimination of Ir(I)-complex regenerates the catalyst and provides the biaryl product (step **E**).

In order to prepare the final amides **1**, selected esters **9** were hydrolyzed with NaOH, and the resulting acids **10** were subsequently coupled with various amines. Scheme 4 shows that various esters **9** can be combined with various amines **4** to give a diverse set of amides **1aA–1cC**.

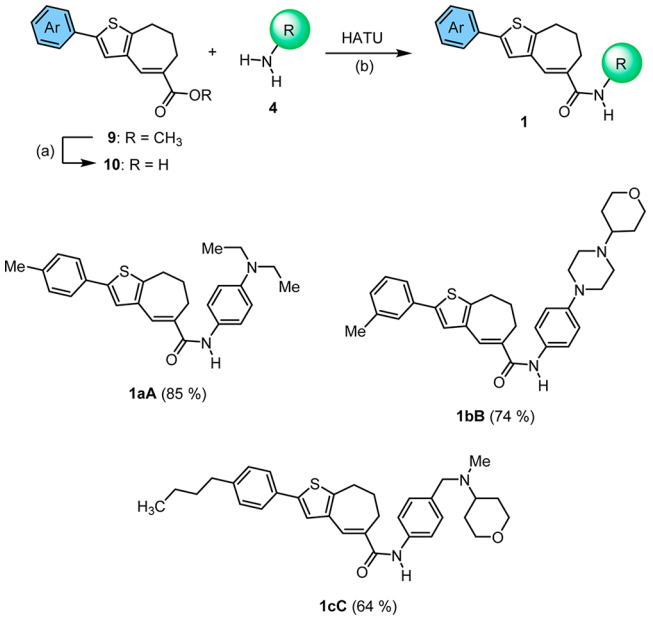
CONCLUSION

A strategy to introduce diversity at the end of the synthesis to generate thiophene-based TAK-779 analogs **1** has been realized. The central building block **2** containing an α,β-unsaturated ester was structurally diversified by two transformations: thiophene C–H arylation and amide formation. First, the arylation of annulated thiophene **2** was achieved by

Scheme 3. Proposed Concerted Metalation Deprotonation (CMD) Mechanism of the Direct C–H Bond Arylation with the Ir-Based Crabtree Catalyst; Step D Represents the Crucial Concerted Metalation Deprotonation Step



Scheme 4. Synthesis of Diverse Amides 1[a]



[a]Reagents and reaction conditions: (a) NaOH, CH_3OH, reflux, 3 h, 89 – 97%; (b) RNH_2 **4A–C** (1.0 equiv), HATU (1.1 equiv), Et_3N (2.0 equiv), THF (acetonitrile for **1cC**), rt, overnight, 64–85%.

the Ir-based Crabtree catalyst, which was superior to established Pd catalysts with respect to regioselectivity and yield. It was shown that electron-rich iodoarenes give high yields of α-arylated compounds **9**, whereas the coupling of electron-deficient iodoarenes required longer reaction times. Second, the resulting esters **9** were transformed into diverse amides **1**, showing the potential of the late-stage diversification strategy.

EXPERIMENTAL SECTION

General. Unless otherwise noted, moisture-sensitive reactions were conducted under dry nitrogen. THF and 1,4-dioxane were dried with sodium/benzophenone and was freshly distilled before use. Flash

dx.doi.org/10.1021/jo400692p | J. Org. Chem. 2013, 78, 5579–5586

chromatography (fc): silica gel 60, 40−64 μm; parentheses include diameter of the column, length of column, fraction size, eluent, R_f value. Melting point: melting point apparatus, uncorrected. IR: IR spectrophotometer FT-ATR-IR. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz): 400 MHz spectrometer; δ in ppm relative to tetramethylsilane; coupling constants are given with 0.5 Hz resolution. MS: APCI = atmospheric pressure chemical ionization, EI = electron impact, ESI = electro spray ionization; calibration with lithium formate clusters before measurement. HPLC method for determination of the product purity: UV detector; autosampler; pump; degasser. Method A: column, 60 RP-select B (5 μm), 250−4 mm cartridge; flow rate, 1.00 mL/min; injection volume, 5.0 μL; detection at λ = 210 nm; solvents: A, water with 0.05% (v/v) trifluoroacetic acid; B, acetonitrile with 0.05% (v/v) trifluoroacetic acid; gradient elution: (A %) 0−4 min, 90%; 4−29 min, gradient from 90% to 0%; 29−31 min, 0%; 31−31.5 min, gradient from 0% to 90%; 31.5−40 min, 90%. X-ray crystal structure analysis: suitable crystals were mounted with mineral oil on a glass fiber and transferred to the goniometer of a CCD diffractometer. Graphite-monochromated Mo Kα irradiation (λ = 0.71070 Å) was used. The structures were solved by direct methods with (SIR-97) and refined by full-matrix least-squares techniques against F^2 (SHELXL-97). The intensities were corrected for Lorentz and polarization effects. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using AFIX instructions.

5-Oxo-5-(thiophen-2-yl)pentanoic Acid.[3] Anhydrous $AlCl_3$ (68 g, 0.5 mol) was added portionwise to a vigorously stirred solution of glutaric anhydride (20 g, 0.175 mol) in CH_2Cl_2 (350 mL) at 0 °C. After stirring for 30 min, a solution of thiophene (14.9 g, 0.175 mol) in CH_2Cl_2 (100 mL) was added over a period of 30 min followed by stirring for an additional 1 h. Next, crushed ice (150 g) and conc HCl (150 mL) were added, and the mixture was warmed until the suspended material was dissolved. The layers were separated, the aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed thoroughly with water (200 mL) and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to give an orange solid, which was finally recrystallized from EtOAc to give 5-oxo-5-(thiophen-2-yl)pentanoic acid as a slightly yellow solid, R_f = 0.22 (EtOAc/cyclohexane = 1:1), mp 93−94 °C, yield 29 g (83%). $C_9H_{10}O_3S$ (198.2 g/mol). Purity (HPLC): 96.4%, t_R = 12.75 min. Exact MS (APCI): m/z = calcd for $C_9H_{11}O_3S$ [M^+] 199.0423, found 199.0433. ^{1}H NMR ($CDCl_3$): δ (ppm) 2.09 (quint., J = 7.2 Hz, 2H, CH_2-CH_2-CH_2), 2.51 (t, J = 7.2 Hz, 2H, CH_2-COOH), 3.02 (t, J = 7.2 Hz, 2H, O=C-CH_2-CH_2), 7.13 (dd, J = 5.0, 3.8 Hz, 1H, 4-*H*-thiophene), 7.64 (dd, J = 5.0, 1.1 Hz, 1H, 5-*H*-thiophene), 7.73 (dd, J = 3.8/1.1 Hz, 1H, 3-*H*-thiophene). FT-IR (neat): ν (cm^{-1}) = 2916 (C−H_{aryl}), 2360 (COOH), 1690 (C=O), 1651 (C=C), 735, 694 (C−H).

5-(Thiophene-2-yl)pentanoic Acid (5).[3] A solution of the 5-oxo-5-(thiophen-2-yl)pentanoic acid (65.51 g, 0.33 mol), KOH (82 g, 1.45 mol, 4.4 equiv), and hydrazine monohydrate (102.1 g, 1.82 mol, 5.5 equiv) in tri(ethylene glycol) was heated to reflux (200 °C) in a Dean−Stark apparatus for 15 h. The mixture was poured into cold water and washed with Et_2O. The aqueous layer was acidified using 6 M HCl and extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were successively washed with water (2 × 150 mL) and brine (200 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product as brown solid, which was purified by recondensation to give the acid **5** as a colorless solid, R_f = 0.51(EtOAc/cyclohexane = 1:1), mp 38 °C, yield 53 g (87%). $C_9H_{12}O_2S$ (184.3 g/mol). Purity (HPLC): 99.2%, t_R = 17.42 min. Exact MS (APCI): m/z = calcd for $C_9H_{13}O_2S$ [M^+] 185.0631, found 185.0630. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.73 (m, 4H, CH_2-CH_2-CH_2-CH_2), 2.39 (t, J = 7.0 Hz, 2H, CH_2-COOH), 2.86 (t, J = 6.9 Hz, 2H, thiophene-CH_2-CH_2), 6.79 (dd, J = 3.4/1.1 Hz, 1H, 3-*H*-thiophene), 6.91 (dd, J = 5.1/3.4 Hz, 1H, 4-*H*-thiophene), 7.11 (dd, J = 5.1/1.2 Hz, 1H, 5-*H*-thiophene). FT-IR (neat): ν (cm^{-1}) = 2928 (C−H_{aryl}), 2359 (COOH), 1698 (C=C), 720, 691 (C−H).

5,6,7,8-Tetrahydro[7]annuleno[*b*]thiophen-4-one (6).[3] A solution of acid **5** (16.5 g, 90 mmol), P_2O_5 (25.5 g, 179 mmol, 2 equiv), and Celite (45 g) in toluene was heated to reflux for 3 h. The Celite was filtered off, and the filtrate was concentrated in vacuo to give a deep brown oil. The filter cake was washed with EtOAc (500 mL). The combined organic layers were washed with 5% $NaHCO_3$ solution (300 mL), water (200 mL), and brine (150 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product as brown oil, which was purified by distillation to yield the keton **6** as a colorless oil, R_f = 0.73 (EtOAc/cyclohexane = 1:1), R_f = 0.43, (EtOAc/cyclohexane = 1:4), bp 180 °C (2.1 × 10^{-2} mbar), yield 8 g (54%). $C_9H_{10}OS$ (166.2 g/mol). Purity (HPLC): 99.26%, t_R = 16.97 min. Exact MS (APCI): m/z = calcd for $C_9H_{11}OS$ [M^+] 167.0525, found 167.0548. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.80−2.11 (m, 4H, CH_2-C_2H_4-CH_2), 2.62−2.81 (m, 2H, CH_2-C=O), 3.08 (t, J = 6.1 Hz, 2H, thiophene-CH_2-CH_2), 6.93 (d, J = 5.4 Hz, 1H, 3-*H*-thiophene), 7.35 (d, J = 5.5 Hz, 1H, 2-*H*-thiophene). FT-IR (neat): ν (cm^{-1}) = 2938 (C-H_{aryl}), 1659 (C=O), 684, 647 (C−H).

Methyl 7,8-Dihydro-6*H*-[7]annuleno[*b*]thiophene-5-carboxylate (2). A solution of ketone **6** (7.2 g, 43 mmol) and $NaOCH_3$ (23 g, 432 mmol, 10 equiv) in dimethyl carbonate (350 mL) was heated to reflux for 10 h. Then the reaction mixture was diluted with water (200 mL), and 6 M HCl (100 mL) was added under ice cooling. The aqueous mixture was extracted with EtOAc (3 × 200 mL). The combined organic layers were washed successively with water (150 mL) and brine (150 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product as an orange oil, which was purified by flash column chromatography (EtOAc/cyclohexane = 2:8, d = 8 cm, l = 12 cm, V = 65 mL) to give the β-ketoester **7** as a pale yellow oil, yield 8.5 g (87%). A solution of the β-ketoester **7** (8.5 g, 37.8 mmol) in CH_2Cl_2 (100 mL) was cooled down to −20 °C, and then $NaBH_4$ (4.3 g, 113 mmol, 3.0 equiv) and abs MeOH (2 mL) were added. The mixture was stirred at −10 °C for 3 h. Then the reaction mixture was poured into water (100 mL) and acidified with 2 M HCl. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed successively with water (100 mL) and brine (150 mL), dried (Na_2SO_4), and concentrated in vacuo to give the crude product as a yellow oil, which was purified by flash column chromatography (EtOAc/cyclohexane = 2:8, d = 6 cm, l = 14 cm, V = 65 mL) to give β-hydroxyester **8** as a colorless oil, yield 6.2 g (73%). A mixture of the β-hydroxyester **8** (6.2 g, 27.5 mmol) and triethylamine (8.4 g, 83 mmol, 3 equiv) in abs CH_2Cl_2 (100 mL) was sirred under ice cooling for 0.5 h. Methanesulfonyl chloride (4.8 g, 42 mmol, 1.5 equiv) was added dropwise under ice cooling. The mixture was stirred overnight at room temperature; then DBU (16.8 g, 110 mmol, 4.0 equiv) was added dropwise under ice cooling. The reaction mixture was stirred for 1 h at room temperature, then poured into water (100 mL), acidified with 6 M HCl, and extracted with CH_2Cl_2 (4 × 100 mL). The combined organic layers were washed successively with water and brine, dried (Na_2SO_4), and concentrated in vacuo to give the crude product as an orange oil, which was purified by flash column chromatography (EtOAc/cyclohexane = 2:8, d = 6 cm, l = 13 cm, V = 65 mL) to give the ester **2** as a colorless oil. (R_f = 0.83, EtOAc/cyclohexane = 1:1; R_f = 0.25, EtOAc/cyclohexane = 1:9), bp 187 °C at 9.1 × 10^{-2} mbar, yield 5.2 g (90%). $C_{11}H_{12}O_2S$ (208.3 g/mol). Purity (HPLC): 95%, t_R = 20.70 min. Exact MS (APCI): m/z = calcd for $C_{11}H_{13}O_2S$ [MH^+] 209.0631, found 209.0644. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.94−2.09 (m, 2H, 7-CH_2), 2.78 (t, J = 5.7 Hz, 2H, 6-CH_2), 3.09 (t, J = 5.7 Hz, 2H, 8-CH_2),3.78 (s, 3H, CO_2CH_3), 6.92 (d, J = 5.2 Hz, 1H, 3-*H*), 7.01 (d, J = 5.5 Hz, 1H, 2-*H*), 7.61 (s, 1H, 4-C*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) 23.4 (1C, C-7), 29.7 (1C, *C*-6), 30.3 (1C, *C*-8), 51.6 (1C, CO_2CH_3), 121.3 (1C, *C*-3), 129.6 (1C, *C*-8a), 131.7 (1C, *C*-2), 132.1 (1C, *C*-4), 132.4 (1C, *C*-5),145.1 (1C, *C*-3a), 168.8 (1C, C=O). FT-IR (neat): ν (cm^{-1}) = 2943, 2924 (C-H_{allyl}), 1697 (C=O).

Methyl 2-(4-Methylphenyl)-7,8-dihydro-6*H*-[7]annuleno[b]-thiophene-5-carboxylate (9a). A 20 mL glass vessel was equipped with a magnetic stirring bar and closed by a J. Young O-ring tap. The flask was flame-dried under vacuo and filled with N_2. Under a permanent flow of N_2, ester **2** (100 mg, 0.48 mmol), Crabtree catalyst (20 mg, 0.024 mmol, 5 mol %), Ag_2CO_3 (150 mg, 0.54 mmol, 1.1 equiv), and 4-iodotoluene (**3a**, 150 mg, 0.69 mmol, 1.4 equiv) were suspended in dry 1,4-dioxane (5 mL). The vessel was sealed with the

dx.doi.org/10.1021/jo400692p | J. Org. Chem. 2013, 78, 5579−5586

O-ring tap and heated to 170 °C for 12 h in a 8-well reaction block. After the vessel cooled to rt the mixture was filtered through a short silica pad (EtOAc). The filtrate was concentrated in vacuo to give the crude product as a brown oil, which was purified by flash column chromatography (EtOAc/cyclohexane = 2:8, d = 4 cm, l = 8 cm, V = 30 mL) to give a yellow oil, which crystallized slowly. Recrystallization from acetonitrile afforded the ester **9a** as a yellow solid. (R_f = 0.25, EtOAc/cyclohexane = 1:9), mp 95−96 °C, yield 132 mg (93%). $C_{18}H_{18}O_2S$ (298.4 g/mol). Purity (HPLC): 99%, t_R = 23.89 min. Exact MS (APCI): m/z = calcd for $C_{18}H_{19}O_2S$ [MH^+] 299.1100, found 299.1106.^{1}H NMR ($CDCl_3$): δ (ppm) 2.06 (tt, J = 7.4/4.7 Hz, 2H, 7-CH_2), 2.36 (s, 3H, Ph-CH_3), 2.79 (t, J = 5.4 Hz, 2H, 6-CH_2), 3.09 (t, J = 7.4 Hz, 2H, 8-CH_2), 3.79 (s, 3H, CO_2CH_3), 7.08 (s, 1H, 3-CH), 7.17 (d, J = 7.7 Hz, 2H, 3-CH_{phenyl}, 5-CH_{phenyl}), 7.41 (d, J = 8.1 Hz, 2H, 2-CH_{phenyl}, 6-CH_{phenyl}), 7.60 (s, 1H, 4-CH). ^{13}C NMR ($CDCl_3$): δ (ppm) 21.4 (1C, Ph-CH_3), 24.1 (1C, C-7), 30.2 (1C, C-6), 31.1 (1C, C-8), 52.2 (1C, CO_2CH_3), 125.6 (2C, C-2_{phenyl}, C-6_{phenyl}), 127.3 (1C, C-3), 129.8 (2C, C-3_{phenyl}, C-5_{phenyl}), 130.5 (1C, C-8a), 132.8 (1C, C-4), 133.8 (1C, C-5), 137.6 (1C, C-1_{phenyl}), 140.4 (1C, C-4_{phenyl}), 144.9 (1C, C-3a). Signals for carbon the atoms (C-2) and (C═O) are not visible. FT-IR (neat): ν (cm^{-1}) = 2727 (C-H_{allyl}), 1697 (C═O). X-ray crystal structure data: Intensity data were collected at 103 K. Total 15111 reflections were corrected, of which 5638 were independent reflections (R_{int} = 0.1087). The crystal data are as follows: $C_{18}H_{18}O_2S$, FW = 298.38, crystal size 0.05 × 0.03 × 0.02 mm^3, monoclinic, space group P-1. a = 9.917(18) Å, b = 10.332(18) Å, c = 17.37(4) Å, α = 89.13(7)°, β = 88.64(7)°, γ = 67.30(5)°, V = 1642(5) $Å^3$, Z = 4, D_{calc} = 1.207 g/cm^3. The refinement converged to R_1 = 0.1153, wR_2 = 0.2623 ($I > 2\sigma(I)$), R_1 = 0.1788, wR_2 = 0.3115 (for all data), GOF = 1.115. CCDC 927164 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; Fax: +44(1223)336−033, E-mail: deposit@ccdc.cam.ac.uk].

Methyl 2-(3-Methylphenyl)-7,8-dihydro-6*H*-[7]annuleno[*b*]-thiophene-5-carboxylate (9b). A 20 mL glass vessel was equipped with a magnetic stirring bar and closed by a J. Young O-ring tap. The flask was flame-dried under vacuo and filled with N_2. Under a permanent flow of N_2, ester **2** (300 mg, 1.44 mmol), Crabtree catalyst (58 mg, 0.072 mmol, 5 mol %), Ag_2CO_3 (442 mg, 1.6 mmol, 1.1 equiv), and 3-iodotoluene (**3b**, 440 mg, 2.01 mmol, 1.4 equiv) were suspended in dry 1,4-dioxane (14 mL). The vessel was sealed with the O-ring tap and heated to 170 °C for 12 h in a 8-well reaction block. After the vessel cooled to rt, the mixture was filtered through a short silica pad (EtOAc). The filtrate was concentrated in vacuo to give the crude product as a brown oil, which was purified by flash column chromatography (EtOAc/cyclohexane = 2:8, d = 4 cm, l = 6 cm, V = 30 mL) to give a yellow oil, which was recrystallized from acetonitrile to give the ester **9b** as a pale yellow solid. (R_f = 0.88, MeOH/CH_2Cl_2 = 5:95), mp 90−91 °C, yield 373 mg (87%). $C_{18}H_{18}O_2S$ (298.4 g/mol). Purity (HPLC): 99%, t_R = 23.89 min. Exact MS (APCI): m/z = calcd for $C_{18}H_{19}O_2S$ [MH^+] 299.1100, found 299.1106. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.94−2.13 (m, 2H, 7-CH_2), 2.38 (s, 3H, Ph-CH_3), 2.80 (t, J = 5.2 Hz, 2H, 6-CH_2), 3.10 (t, J = 5.8 Hz, 2H, 8-CH_2), 3.80 (s, 3H, CO_2CH_3), 7.10 (d, J = 7.7 Hz, 1H, 4-H_{phenyl}), 7.12 (s, 1H, 3-CH), 7.25 (td, J = 7.4/1.0 Hz, 1H, 5-H_{phenyl}), 7.28−7.38 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.61 (s, 1H, 4-CH). ^{13}C NMR ($CDCl_3$): δ (ppm) 21.8 (1C, Ph-CH_3), 24.1 (1C, C-7), 30.3 (1C, C-6), 31.2 (1C, C-8), 52.3 (1C, CO_2CH_3), 122.9 (1C, C-2_{phenyl}), 126.5 (1C, C-6_{phenyl}), 127.7 (1C, C-3), 128.5 (1C, C-4_{phenyl}), 129.0 (1C, C-3_{phenyl}), 130.6 (1C, C-2), 132.8 (1C, C-4), 133.9 (1C, C-5), 137.6 (1C, C-1_{phenyl}), 138.8 (1C, C-3a), 140.4 (1C, C-5_{phenyl}), 145.3 (1C, C-8a), 169.4 (1C, C═O). FT-IR (neat): ν (cm^{-1}) = 2715 (C-H_{allyl}), 1689 (C═O), 1627 (C═C).

Methyl 2-(4-Butylphenyl)-7,8-dihydro-6*H*-[7]annuleno[*b*]-thiophene-5-carboxylate (9c). A 50 mL Rettberg Schlenk flask was equipped with a magnetic stirring bar and closed. The flask was flame-dried under vacuo and filled with N_2. Under a permanent flow of N_2, ester **2** (300 mg, 1.44 mmol), Crabtree catalyst (58 mg, 0.07 mmol, 5 mol %), Ag_2CO_3 (442 mg, 1.6 mmol, 1.1 equiv), and 1-butyl-4-iodobenzene (**3c**, 523 mg, 2.0 mmol, 1.4 equiv) were suspended in dry 1,4-dioxane (15 mL). The vessel was sealed and heated to 170 °C for 48 h. After the vessel cooled to rt, the mixture was filtered through a short silica pad (EtOAc). The filtrate was concentrated in vacuo to give the crude product as a brown oil, which was purified by column chromatography (EtOAc/cyclohexane = 5:95, d = 6 cm, l = 9 cm, V = 30 mL) to give an orange oil, which was recrystallized from acetonitrile to give the ester **9c** as a yellow solid. (R_f = 0.27, EtOAc/cyclohexane = 1:9; R_f = 0.95, MeOH/CH_2Cl_2 = 5:95), mp 57−58 °C, yield 477 mg (97%). $C_{21}H_{24}O_2S$ (340.5 g/mol). Purity (HPLC): 97%, t_R = 26.57 min. Exact MS (ESI): m/z = calcd for $C_{21}H_{25}O_2S$ [MH^+] 341.1570, found 341.1578. ^{1}H NMR ($CDCl_3$): δ (ppm) 0.94 (t, J = 7.3 Hz, 3H, 4-$CH_{3n\text{-}butyl}$), 1.38 (hept, J = 7.3 Hz, 2H, 3-$CH_{2n\text{-}butyl}$), 1.50−1.68 (m, 2H, 2-$CH_{2n\text{-}butyl}$), 1.97−2.13 (m, 2H, 7-CH_2), 2.62 (t, J = 7.7 Hz, 2H, 1-$CH_{2n\text{-}butyl}$), 2.80 (t, J = 5.9 Hz, 2H, 6-CH_2), 3.10 (t, J = 5.6 Hz, 2H, 8-CH_2), 3.80 (s, 3H, CO_2CH_3), 7.09 (s, 1H, 4-CH), 7.18 (d, J = 8.2 Hz, 2H, 3-CH_{phenyl}, 5-CH_{phenyl}), 7.44 (d, J = 8.2 Hz, 2H, 2-CH_{phenyl}, 6-CH_{phenyl}), 7.61 (s, 1H, 3-CH). ^{13}C NMR ($CDCl_3$): δ (ppm) 14.4 (1C, C-$4_{n\text{-}butyl}$), 22.8 (1C, C-$3_{n\text{-}butyl}$), 24.3 (1C, C-7), 30.5 (1C, C-6), 31.3 (1C, C-8), 34.0 (1C, C-$2_{n\text{-}butyl}$), 35.8 (C-$1_{n\text{-}butyl}$), 52.5 (1C, CO_2CH_3), 125.9 (2C, C-2_{phenyl}, C-6_{phenyl}), 127.5 (1C, C-4), 129.4 (2C, C-3_{phenyl}, C-5_{phenyl}), 130.7 (1C, C-4), 131.7 (1C, C-2), 133.1 (1C, C-5), 134.1 (1C, C-1_{phenyl}), 140.7 (1C, C-3a), 142.8 (1C, C-3_{phenyl}), 145.2 (1C, C-8a), 169.5 (1C, C═O). FT-IR (neat): ν (cm^{-1}) = 2920, 2854 (C-H_{allyl}), 1693 (C═O), 1631 (C═C).

Methyl 2-([1,1′-Biphenyl]-4-yl)-7,8-dihydro-6*H*-[7]annulene-[*b*]thiophene-5-carboxylate (9d). A 50 mL Rettberg Schlenk flask was equipped with a magnetic stirring bar and closed. The flask was flame-dried under vacuo and filled with N_2. Under a permanent flow of N_2 ester **2** (300 mg, 1.44 mmol), Crabtree catalyst (58 mg, 0.07 mmol, 5 mol %), Ag_2CO_3 (442 mg, 1.6 mmol, 1.1 equiv), and 4-iodobiphenyl (**3d**, 565 mg, 2.0 mmol, 1.4 equiv) were suspended in dry 1,4-dioxane (15 mL). The vessel was sealed and heated to 170 °C for 48 h. After the vessel cooled to rt, the mixture was filtered through a short silica pad (EtOAc). The filtrate was concentrated in vacuo to give the crude product as a brown oil, which was purified by column chromatography (EtOAc/cyclohexane = 5:95, d = 4 cm, l = 8 cm, V = 30 mL) to give a yellow solid, which was recrystallized from acetonitrile to give the ester **9d** as a yellow solid. (R_f = 0.93, MeOH/CH_2Cl_2 = 5:95), mp 179−180 °C, yield 406 mg (78%). $C_{23}H_{20}O_2S$ (360.5 g/mol). Purity (HPLC): 94%, t_R = 25.41 min. Exact MS (ESI): m/z = calcd for $C_{23}H_{21}O_2S$ [MH^+] 361.1257, found 361.1260.^{1}H NMR ($CDCl_3$): δ (ppm) 2.08 (quint, J = 5.7 Hz, 2H, 7-CH_2), 2.81 (t, J = 5.7 Hz, 2H, 6-CH_2), 3.12 (t, J = 5.6 Hz, 2H, 8-CH_2), 3.80 (s, 3H, CH_3), 7.18 (s, 1H, 4-CH), 7.29−7.43 (m, 1H, 4′-CH_{phenyl}), 7.45 (t, J = 7.5 Hz, 2H, 3′-CH_{phenyl}, 5′-CH_{phenyl}), 7.53−7.71 (m, 7H, 2-CH_{phenyl}, 3-CH_{phenyl}, 5-CH_{phenyl}, 6-CH_{phenyl}, 2′-CH_{phenyl}, 6′-CH_{phenyl}, 3-CH).^{13}C NMR ($CDCl_3$): δ (ppm) 24.1 (1C, C-7), 30.3 (1C, C-6), 31.1 (1C, C-8), 52.27 (1C, CH_3), 126.0 (2C, C-3_{phenyl}, C-5_{phenyl}), 127.11 (2C, C-2_{phenyl}, C-6_{phenyl}), 127.65 (1C, C-$4'_{phenyl}$), 127.8 (1C, C-4), 127.8 (2C, 2′-C_{phenyl}, 6′-C_{phenyl}), 129.06 (2C, C-$3'_{phenyl}$, C-$5'_{phenyl}$), 130.7 (1C, C-2), 132.7 (1C, C-3), 134.0 (1C, C-5), 139.9 (1C, C-3a), 140.4 (1C, C-$1'_{phenyl}$), 140.6 (1C, C-1_{phenyl}), 145.5 (1C, C-8a), 169.3(1C, C═O). FT-IR (neat): ν (cm^{-1}) = 3028 (C-H_{aryl}), 2920, 2843 (C-H_{allyl}), 1701 (C═O), 1627 (C═C).

Methyl 2-(4-*tert*-Butylphenyl)-7,8-dihydro-6*H*-[7]annuleno-[*b*]thiophene-5-carboxylate (9e). A 50 mL Rettberg Schlenk flask was equipped with a magnetic stirring bar and closed. The flask was flame-dried under vacuo and filled with N_2. Under a permanent flow of N_2, ester **2** (300 mg, 1.44 mmol), Crabtree catalyst (58 mg, 0.07 mmol, 5 mol %), Ag_2CO_3 (442 mg, 1.6 mmol, 1.1 equiv), and 1-*tert*-butyl-4-iodobenzene (**3e**, 523 mg, 2.0 mmol, 1.4 equiv) were suspended in dry 1,4-dioxane (14 mL). The vessel was sealed and heated to 170 °C for 12 h. After the vessel cooled to rt, the mixture was filtered through a short silica pad (EtOAc). The filtrate was concentrated in vacuo to give the crude product as a brown oil, which was purified by column chromatography (EtOAc/cyclohexane = 5:95, d = 4 cm, l = 8 cm, V = 30 mL) to give an orange oil which was crystallized from acetonitrile to give the ester **9e** as an orange solid. (R_f = 0.90, EtOAc/CH_2Cl_2 = 1:2 + 5% MeOH), mp 109−110 °C, yield

dx.doi.org/10.1021/jo400692p | J. Org. Chem. 2013, 78, 5579−5586

269 mg (55%). $C_{21}H_{24}O_2S$ (340.5 g/mol). Purity (HPLC): 99%, t_R = 25.69 min. Exact MS (ESI): m/z = calcd for $C_{21}H_{25}O_2S$ [M^+] 341.1570, found 341.1578. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.34 (s, 9H, $C(CH_3)_3$), 2.06 (tt, J = 7.4/4.8 Hz, 2H, 7-CH_2), 2.79 (t, J = 5.8 Hz, 2H, 6-CH_2), 3.09 (t, J = 5.6 Hz, 2H, 8-CH_2), 3.80 (s, 3H, CO_2CH_3), 7.09 (s, 1H, 4-CH), 7.39 (d, J = 8.4, 2H, 3-H_{phenyl}, 5-H_{phenyl}), 7.46 (d, J = 8.4 Hz, 2H, 2-H_{phenyl}, 6-H_{phenyl}) 7.60 (s, 1H, 3-H). ^{13}C NMR ($CDCl_3$): δ (ppm) 24.2 (1C, C-7), 30.5 (1C, C-6), 31.3 (1C, C-8), 31.7 (3C, $C(CH_3)_3$), 35.1 (1C, $C(CH_3)_3$), 52.5 (1C, $COOCH_3$), 125.7 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 126.3 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 127.6 (1C, C-3), 130.7 (1C, C-1$_{phenyl}$), 131.5 (1C, C-8a), 133.1 (1C, C-4), 134.1 (1C, C-5), 140.5 (1C, C-2), 145.2 (1C, C-3a), 151.0 (1C, C-4$_{phenyl}$), 169.5 (1C, C=O). FT-IR (neat): ν (cm^{-1}) = 2715 (C-H_{allyl}), 1693 (C=O), 1631 (C=C).

Methyl-2-(4-(trifluoromethyl)phenyl)-7,8-dihydro-6*H*-[7]annuleno[*b*]thiophene-5-carboxylate (9f). A 50 mL Rettberg Schlenk flask was equipped with a magnetic stirring bar and closed. The flask was flame-dried under vacuo and filled with N_2. Under a permanent flow of N_2, ester **2** (300 mg, 1.44 mmol), Crabtree catalyst (58 mg, 0.07 mmol, 5 mol %), Ag_2CO_3 (442 mg, 1.6 mmol, 1.1 equiv), and 1-iodo-4-(trifluoromethyl)benzene (**3f**, 550 mg, 2.0 mmol, 1.4 equiv) were suspended in dry 1,4-dioxane (15 mL). The vessel was sealed and heated to 170 °C for 72 h. After the vessel cooled to rt, the mixture was filtered through a short silica pad (EtOAc). The filtrate was concentrated in vacuo to give the crude product as a brown oil, which was purified by column chromatography (EtOAc/cyclohexane = 1:9, d = 2 cm, l = 11 cm, V = 30 mL) to give a yellow solid, which was recrystallized from acetonitrile to give the ester **9f** as a yellow solid. (R_f = 0.23, EtOAc/cyclohexane = 1:9; R_f = 0.88, EtOAc/CH_2Cl_2 + 5% MeOH = 1:2), mp 97−98 °C, yield 280 mg (55%). $C_{18}H_{15}F_3O_2S$ (352.4 g/mol). Purity (HPLC): 99%, t_R = 24.55 min. Exact MS (ESI): m/z = calcd for $C_{21}H_{25}O_2S$ [M^+] 341.1570, found 341.1578. ^{1}H NMR ($CDCl_3$): δ (ppm) 2.07 (quint, J = 5.7 Hz, 2H, 7-CH_2), 2.80 (t, J = 5.9 Hz, 2H, 6-CH_2), 3.11 (t, J = 5.6 Hz, 2H, 8-CH_2), 7.22 (s, 1H, 3-H), 7.61 (m, 5H, 3-H_{phenyl}, 5-H_{phenyl}, 2-H_{phenyl}, 6-H_{phenyl}, 4-CH). ^{13}C NMR ($CDCl_3$): δ (ppm) 24.2 (1C, C-7), 30.5 (1C, C-6), 31.3 (1C, C-8), 52.5 (1C, $COOCH_3$), 125.9 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 126.2 (q, J = 3.8 Hz, 2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 126.3 (m, 1C, CF_3), 129.4 (1C, C-3), 131.4 (1C, C-8a), 132.5 (1C, C-4), 134.5 (1C, C-5), 137.6 (1C, C-2), 138.6 (1C, C-3a), 146.8 (1C, C-4$_{phenyl}$), 169.4 (1C, C=O). The signal for (C-1$_{phenyl}$) is not visible. FT-IR (neat): ν (cm^{-1}) = 2711 (C-H_{allyl}), 1689 (C=O), 1612 (C=C).

Methyl 2-(4-Nitrophenyl)-7,8-dihydro-6*H*-[7]annulene[*b*]-thiophene-5-carboxylate (9g). A 50 mL Rettberg Schlenk flask was equipped with a magnetic stirring bar and closed. The flask was flame-dried under vacuo and filled with N_2. Under a permanent flow of N_2, ester **2** (300 mg, 1.44 mmol), Crabtree catalyst (58 mg, 0.07 mmol, 5 mol %), Ag_2CO_3 (442 mg, 1.6 mmol, 1.1 equiv), and 1-iodo-4-nitrobenzene (500 mg, 2.0 mmol, 1.4 equiv) were suspended in dry 1,4-dioxane (14 mL). The vessel was sealed and heated at 170 °C for 72 h. After the vessel cooled to rt, the mixture was filtered through a short silica pad (EtOAc). The filtrate was concentrated in vacuo to give the crude product as a brown oil, which was purified by column chromatography (EtOAc/cyclohexane = 1:9, d = 4 cm, l = 8 cm, V = 30 mL) to give a yellow solid, which was recrystallized from acetonitrile to give the ester **9g** as a yellow solid. (R_f = 0.93, EtOAc/CH_2Cl_2 + 5% MeOH = 1:2), mp 175 °C, yield 265 mg (56%). $C_{17}H_{15}NO_4S$ (329.4 g/mol). Purity (HPLC): 96%, t_R = 22.99 min. Exact MS (ESI): m/z = calcd for $C_{17}H_{16}NO_4S$ [MH^+] 330.0801, found 330.0795. ^{1}H NMR ($CDCl_3$): δ (ppm) 2.02−2.13 (m, 2H, 7-CH_2), 2.81 (t, J = 6.4 Hz, 2H, 6-CH_2), 3.12 (t, J = 5.6 Hz, 2H, 8-CH_2), 3.80 (s, 3H, CO_2CH_3), 7.20 (s, 1H, 4-CH), 7.60 (s, 1H, 3-CH), 7.64 (d, J = 8.9 Hz, 2H, 2-CH_{phenyl}, 6-CH_{phenyl}), 8.22 (d, J = 8.9 Hz, 2H, 3-CH_{phenyl}, 5-CH_{phenyl}). ^{13}C NMR ($CDCl_3$): δ (ppm) 24.1 (1C, C-7), 30.6 (1C, C-6), 31.8 (1C, C-8), 52.6 (1C, $COOCH_3$), 124.9 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 125.9 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 130.6 (1C, C-3), 131.8 (1C, C-8a), 132.2 (1C, C-4), 134.9 (1C, C-5), 137.6 (1C, C-2), 140.4 (1C, C-4$_{phenyl}$), 149.9 (1C, C-3a), 148.3 (1C, C-1$_{phenyl}$), 169.3 (1C, C=O). FT-IR (neat): ν (cm^{-1}) = 2927 (C-H_{allyl}), 1697 (C=O), 1624 (C=C), 1500, 1327 (NO_2).

2-(4-Methylphenyl)-7,8-dihydro-6*H*-[7]annuleno[*b*]-thiophene-5-carboxylic Acid (10a). A solution of ester **9a** (620 mg, 2.07 mmol) and 5 M NaOH (30 mL) in MeOH (30 mL) was heated to reflux for 3 h. After cooling to rt, the mixture was concentrated in vacuo and acidified with conc HCl to give a precipitate. The mixture was cooled in an ice bath to complete the precipitation, and the solid was filtered off, washed with 1 M HCl and water, and dried overnight to give the acid **10a** as a colorless solid. (R_f = 0.50, MeOH/CH_2Cl_2 = 5:95), mp 216 °C (dec), yield 570 mg (97%). $C_{17}H_{16}O_2S$ (284.4 g/mol). Purity (HPLC): 98%, t_R = 21.55 min. Exact MS (APCI): m/z = calcd for $C_{17}H_{17}O_2S$ [MH^+] 285.0944, found 285.0947. ^{1}H NMR ($CDCl_3$): δ (ppm) 2.08 (quint, J = 5.9 Hz, 2H, 7-CH_2), 2.36 (s, 3H, CH_3), 2.81 (t, J = 5.8 Hz, 2H, 6-CH_2), 3.11 (t, J = 5.7 Hz, 2H, 8-CH_2), 7.10 (s, 1H, 3-H), 7.18 (d, J = 7.8 Hz, 2H, 3-CH_{phenyl}, 5-CH_{phenyl}), 7.42 (d, J = 7.9 Hz, 2H, 2-CH_{phenyl}, 6-CH_{phenyl}), 7.73 (s, 1H, 4-CH). ^{13}C NMR ($CDCl_3$): δ (ppm) 21.5 (1C, Ph-CH_3), 24.0 (1C, C-7), 30.0 (1C, C-6), 31.2 (1C, C-8), 125.7 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 127.4 (1C, C-3), 129.9 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 130.0 (1C, C-8a), 133.7 (1C, C-4), 134.9 (1C, C-5), 137.7 (1C, C-1$_{phenyl}$), 146.0 (1C, C-3a), 179.0 (1C, CO_2H). Signals for the carbon atoms C-2 and C-4$_{phenyl}$ are not seen. FT-IR (neat): ν (cm^{-1}) = 2500 (CO_2H), 1666 (C=O).

2-(3-Methylphenyl)-7,8-dihydro-6*H*-[7]annuleno[*b*]-thiophene-5-carboxylic Acid (10b). A solution of ester **9b** (200 mg, 0.67 mmol) and 5 M NaOH (30 mL) in MeOH (30 mL) was heated to reflux for 3 h. After cooling to rt, the mixture was concentrated in vacuo and acidified with conc HCl to give a precipitate. The mixture was cooled in an ice bath to complete the precipitation, and the solid was filtered off, washed with 1 M HCl and water, and dried overnight to give the acid **10b** as a colorless solid. (R_f = 0.34, MeOH/CH_2Cl_2 = 5:95; R_f =0.54, EtOAc/CH_2Cl_2 + 5% MeOH = 1:2), mp 201 °C, yield 177 mg (93%). $C_{17}H_{16}O_2S$ (284.4 g/mol). Purity (HPLC): 98%, t_R = 21.87 min. Exact MS (APCI): m/z = calcd for $C_{17}H_{17}O_2S$ [MH^+] 285.0944, found 285.0949. ^{1}H NMR (MeOD-d_4): δ (ppm) 2.03 (quint, J = 5.4 Hz, 2H, 7-CH_2), 2.35 (s, 3H, Ph-CH_3), 2.77 (t, J = 5.9 Hz, 2H, 6-CH_2), 3.06 (t, J = 5.5 Hz, 2H, 8-CH_2), 7.06 (d, J = 7.7 Hz, 1H, 4-H_{phenyl}), 7.17 (s, 1H, 3-CH), 7.22 (t, J = 7.7 Hz, 1H, 5-H_{phenyl}), 7.29−7.38 (m, 2H, 2-H_{phenyl}, 6-H_{phenyl}), 7.44 (s, 1H, 4-CH). ^{13}C NMR (DMSO-d_6): δ (ppm) 21.1 (1C, Ph-CH_3), 23.5 (1C, C-7), 29.7 (1C, C-6), 30.3 (1C, C-8), 122.3 (1C, C-6$_{phenyl}$), 125.7 (1C, C-2$_{phenyl}$), 128.3 (1C, C-3), 128.4 (1C, C-4$_{phenyl}$), 129.2 (1C, C-5$_{phenyl}$), 131.4 (1C, C-2), 131.5 (1C, C-4), 133.3 (1C, C-5), 133.8 (1C, C-1$_{phenyl}$), 138.5 (1C, C-3a), 139.2 (1C, C-3$_{phenyl}$), 144.6 (1C, C-8a), 169.4 (1C, C=O). FT-IR (neat): ν (cm^{-1}) = 3267 (CO_2H), 1666 (C=O), 1604 (C=C).

2-(4-*n*-Butylphenyl)-7,8-dihydro-6*H*-[7]annulene[*b*]-thiophene-5-carboxylic Acid (10c). A solution of ester **9c** (477 mg, 1.4 mmol) and 5 M NaOH (20 mL) in MeOH (20 mL) was heated to reflux for 3 h. After cooling to rt, the mixture was concentrated in vacuo and acidified with conc HCl to give a precipitate. The mixture was cooled in an ice bath to complete the precipitation, and the solid was filtered off, washed with 1 M HCl and water, and dried overnight to give the acid **10c** as a colorless solid. (R_f = 0.41, MeOH/CH_2Cl_2 = 5:95), mp 190 °C, yield 420 mg (89%). $C_{20}H_{22}O_2S$ (326.4 g/mol). Purity (HPLC): 98%, t_R = 24.21 min. Exact MS (APCI): m/z = calcd for $C_{20}H_{23}O_2S$ [MH^+] 327.1413, found 327.1415. ^{1}H NMR ($CDCl_3$): δ (ppm) 0.94 (t, J = 7.3 Hz, 3H, 4-$CH_{3n\text{-}butyl}$), 1.37 (sept, J = 7.3 Hz, 2H, 3-$CH_{2n\text{-}butyl}$), 1.48−1.75 (m, 2H, 2-$CH_{2n\text{-}butyl}$), 2.08 (quint, J = 5.5 Hz, 2H, 7-CH_2), 2.62 (t, J = 7.7 Hz, 2H, 1-$CH_{2n\text{-}butyl}$), 2.81 (t, J = 5.9 Hz, 2H, 6-CH_2), 3.12 (t, J = 5.6 Hz, 2H, 8-CH_2), 7.11 (s, 1H, 4-CH), 7.18 (d, J = 8.2 Hz, 2H, 3-CH_{phenyl}, 5-CH_{phenyl}), 7.44 (d, J = 8.1 Hz, 2H, 2-CH_{phenyl}, 6-CH_{phenyl}), 7.74 (s, 1H, 3-CH). ^{13}C NMR ($CDCl_3$): δ (ppm) 14.4 (1C, C-4$_{n\text{-}butyl}$), 22.8 (1C, C-3$_{n\text{-}butyl}$), 24.2 (1C, C-7), 30.1 (1C, C-6), 31.4 (1C, C-8), 34.0 (1C, C-2$_{n\text{-}butyl}$), 35.8 (C-1$_{n\text{-}butyl}$), 125.9 (2C, C-2$_{phenyl}$, C-6$_{phenyl}$), 127.6 (1C, C-4), 129.4 (2C, C-3$_{phenyl}$, C-5$_{phenyl}$), 129.7 (1C, C-4), 131.6 (1C, C-2), 133.9 (1C, C-5), 135.1 (1C, C-1$_{phenyl}$), 140.8 (1C, C-3a), 142.9 (1C, C-3$_{phenyl}$), 146.2 (1C, C-8a), 174.1 (1C, C=O). FT-IR (neat): ν (cm^{-1}) = 2619 (CO_2H), 1624 (C=O), 1612 (C=C).

dx.doi.org/10.1021/jo400692p | J. Org. Chem. 2013, 78, 5579−5586

***N*-[4-(Diethylamino)phenyl]-2-(4-methylphenyl)-7,8-dihydro-6*H*-[7]annuleno[*b*]thiophene-5-carboxamide (1aA).** *N*,*N*-Diethylbenzene-1,4-diamine (**4A**, 58 mg, 0.35 mmol, 1.0 equiv) was added to a vigorously stirred mixture of acid **9a** (100 mg, 0.35 mmol), triethylamine (71 mg, 0.70 mmol, 2.0 equiv), and HATU (150 mg, 0.38 mmol. 1.1 equiv) in THF (5 mL). The mixture was stirred overnight at rt. The mixture was concentrated in vacuo, and the residue was purified by flash column chromatography (EtOAc/CH_2Cl_2 = 1:2 + 5% MeOH, d = 3 cm, l = 8 cm, V = 30 mL) to give a colorless solid. Recrystallization from acetonitrile afforded the amide **1aA** as a colorless solid. (R_f = 0.84, MeOH/CH_2Cl_2 = 5:95), mp 169 °C, yield 128 mg (85%). $C_{27}H_{30}N_2OS$ (430.6 g/mol). Purity (HPLC): 96%, t_R = 21.27 min. Exact MS (APCI): m/z = calcd for $C_{27}H_{31}N_2OS$ [MH^+] 431.2152, found 431.2124. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.15 (t, J = 7.0 Hz, 6H, N(CH_2CH_3)$_2$), 2.06−2.19 (m, 2H, 7-CH_2), 2.36 (s, 3H, CH_{3tolyl}), 2.83 (t, J = 5.8 Hz, 2H, 6-CH_2), 3.10 (t, J = 5.6 Hz, 2H, 8-CH_2), 3.34 (q, J = 7.0 Hz, 4H, N(CH_2CH_3)$_2$), 6.67 (d, J = 9.0 Hz, 2H, 3-CH_{phenyl}, 5-$CH_{phenyl.}$), 7.06 (s, 1H, 3-C*H*), 7.13−7.20 (m, 3H, 3-CH_{tolyl}, 5-CH_{tolyl}, 4-C*H*), 7.35−7.40 (m, 3H, 2-CH_{phenyl}, 6-CH_{phenyl}, N*H*), 7.42 (d, J = 8.1 Hz, 2H, 2-CH_{tolyl}, 6-CH_{tolyl}). ^{13}C NMR ($CDCl_3$): δ (ppm) 13.0 (2C, N(CH_2CH_3)$_2$), 21.6 (1C, CH_{3tolyl}), 24.7 (1C, *C*-7), 31.1 (1C, *C*-8), 31.2 (1C, *C*-6), 45.0 (2C, N(CH_2CH_3)$_2$), 112.9 (2C, *C*-3$_{phenyl}$, *C*-5$_{phenyl}$), 122.7 (2C, *C*-2$_{phenyl}$, *C*-6$_{phenyl}$), 125.8 (2C, *C*-2$_{tolyl}$, *C*-6$_{tolyl}$), 127.1 (1C, *C*-3), 127.2 (1C, *C*-1$_{phenyl}$), 127.3 (1C, *C*-4), 130.0 (2C, *C*-3$_{tolyl}$, *C*-5$_{tolyl}$), 131.6 (1C, C-4$_{phenyl}$), 134.1 (1C, *C*-1$_{tolyl}$), 136.7 (1C, *C*-2), 137.7 (1C, *C*-3a), 140.6 (1C, *C*-5), 143.3 (1C, *C*-8a), 145.7 (1C, *C*-4$_{tolyl}$), 168.6 (1C, O=*C*-NH). FT-IR (neat): ν (cm^{-1}) = 3275 (N-H), 2966 (C-H$_{alkyl}$), 1620 (C=O).

2-(3-Methylphenyl)-*N*-{4-[4-(tetrahydro-2*H*-pyran-4-yl)-piperazin-1-yl]phenyl}-7,8-dihydro-6*H*-[7]annuleno[*b*]-thiophene-5-carboxamide (1bB). Primary amine **4B** (92 mg, 0.35 mmol, 1.0 equiv) was added to a vigorously stirred mixture of acid **9b** (100 mg, 0.35 mmol), triethylamine (71 mg, 0.70 mmol, 2.0 equiv), and HATU (150 mg, 0.38 mmol. 1.1 equiv) in THF (5 mL). The mixture was stirred overnight at rt during which a precipitate was formed. The solid was filtered off, washed with acetonitrile, and recrystallized from acetonitrile/$CHCl_3$ to give the amide **1bB** as a yellow solid. (R_f = 0.26, EtOAc/CH_2Cl_2 + 5% MeOH = 1:2), mp 269 °C, yield 138 mg (74%). $C_{32}H_{37}N_3O_2S$ (527.7 g/mol). Purity (HPLC): >99%, t_R = 21.09 min. Exact MS (APCI): m/z = calcd for $C_{32}H_{38}N_3O_2S$ [MH^+] 528.2679, found 528.2688. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.58−1.89 (m, 4H, 3-CH_{2pyran}, 5-CH_{2pyran}), 2.03−2.19 (m, 2H, 7-CH_2), 2.38 (s, 3H, CH_{3tolyl}), 2.47 (tt, J = 10.9/3.6 Hz, 1H, 4-H_{pyran}), 2.73 (t, J = 5.0 Hz, 4H, 2-CH_{2piper}, 6-CH_{2piper}), 2.78−2.88 (m, 2H, 6-CH_2), 3.04−3.16 (m, 2H, 8-CH_2), 3.19 (t, J = 5.0 Hz, 4H, 3-CH_{2piper}, 5-CH_{2piper}), 3.40 (td, J = 11.8/2.0 Hz, 2H, CH_{2axial}-O-CH_{2axial}), 4.05 (dd, J = 11.5/4.4 Hz, 2H, CH_{2equat}-O-CH_{2equat}), 6.92 (d, J = 9.0 Hz, 2H, 3-CH_{phenyl}, 5-CH_{phenyl}), 7.06−7.11 (m, 2H, 3-C*H*, 4-C*H*), 7.18 (s, 1H, 2-CH_{tolyl}), 7.20−7.29 (m, 1H, 5-CH_{tolyl}), 7.31−7.37 (m, 2H, 4-CH_{tolyl}, 6-CH_{tolyl}), 7.44 (s, 1H, N*H*), 7.46 (d, J = 9.0 Hz, 2H, 2-CH_{phenyl}, 6-CH_{phenyl}). ^{13}C NMR ($CDCl_3$): δ (ppm) 21.6 (1C, CH_{3tolyl}), 24.3 (1C, *C*-7), 29.8 (2C, *C*-3$_{pyran}$, *C*-5$_{pyran}$), 30.8 (1C, *C*-8) 30.9 (1C, *C*-6), 49.2 (2C, *C*-2$_{piper}$, *C*-6$_{piper}$), 50.0 (2C, *C*-3$_{piper}$, *C*-5$_{piper}$), 61.1 (1C, *C*-4$_{pyran}$), 67.6 (2C, *C*-2$_{pyran}$, *C*-6$_{pyran}$), 116.8 (2C, *C*-3$_{N\text{-}phenyl}$, *C*-5$_{N\text{-}phenyl}$), 121.6 (2C, *C*-2$_{N\text{-}phenyl}$, *C*-6$_{N\text{-}phenyl}$), 122.7 (1C, *C*-6$_{tolyl}$), 126.3 (1C, *C*-2$_{tolyl}$), 127.1 (1C, *C*-3), 127.2 (1C, *C*-4$_{tolyl}$), 128.4 (1C, *C*-4), 128.9 (1C, *C*-5$_{tolyl}$), 130.7 (1C, *C*-3$_{tolyl}$), 133.7 (1C, *C*-4$_{N\text{-}phenyl}$), 133.9 (1C, *C*-1$_{tolyl}$), 136.2 (1C, *C*-1$_{N\text{-}phenyl}$), 138.7 (1C, *C*-2), 140.4 (1C, *C*-3a), 143.5 (1C, *C*-5), 148.4 (1C, *C*-8a), 168.3 (1C, O=*C*-NH). FT-IR (neat): ν (cm^{-1}) = 3302 (N-H), 2839 (C-H$_{alkyl}$), 1639 (C=O), 1091, 1029 (C−O).

2-(4-Butylphenyl)-*N*-4-[*N*-methyl-*N*-(tetrahydro-2*H*-pyran-4-yl)aminomethyl]phenyl}-7,8-dihydro-6*H*-[7]annuleno[*b*]-thiophene-5-carboxamide (1cC). Primary amine **4C**[2] (68 mg, 0.31 mmol, 1.0 equiv) was added to a vigorously stirred mixture of acid **9c** (100 mg, 0.31 mmol), triethylamine (61 mg, 0.60 mmol, 2.0 equiv), and HATU (130 mg, 0.33 mmol. 1.1 equiv) in acetonitrile (5 mL). The mixture was stirred overnight at rt. The mixture was concentrated in vacuo, and the residue was purified by flash column chromatography (CH_2Cl_2/EtOAc + 5% MeOH = 2:1, d = 4 cm, l = 10 cm, V = 30 mL) to give a colorless solid. Recrystallization from acetonitrile afforded the amide **1cC** as a colorless solid. (R_f = 0.20, CH_2Cl_2/EtOAc + 5% MeOH = 2:1), mp 160−162 °C, yield 100 mg (64%). $C_{33}H_{40}N_2O_2S$ (528.7 g/mol). Purity (HPLC): 97%, t_R = 23.18 min. Exact MS (APCI): m/z = calcd for $C_{33}H_{41}N_2O_2S$ [MH^+] 529.2883, found 529.2916. ^{1}H NMR ($CDCl_3$): δ (ppm) 0.94 (t, J = 7.3 Hz, 3H, 4-$CH_{3n\text{-}butyl}$), 1.37 (sext., J = 7.3 Hz, 2H, 3-$CH_{2n\text{-}butyl}$), 1.54−1.80 (m, 6H, 3-CH_{2pyran}, 5-CH_{2pyran}, 2-$CH_{2n\text{-}butyl}$), 2.13 (quint, J = 5.5 Hz, 2H, 7-CH_2), 2.21 (s, 3H, N-CH_3), 2.61 (t, J = 7.7 Hz, 2H, 1-$CH_{2n\text{-}butyl}$), 2.62−2.70 (m 1H, 4-H_{pyran}), 2.83 (t, J = 5.7 Hz, 2H, 6-CH_2), 3.11 (t, J = 5.7 Hz, 2H, 8-CH_2), 3.37 (td, J = 11.6/2.3 Hz, 2H, CH_{2axial}-O-CH_{2axial}), 3.56 (s, 2H, Ph-CH_2-N), 4.04 (dd, J = 11.2/4.0 Hz, 2H, CH_{2equat}-O-CH_{2equat}), 7.06 (s, 1H, 3-C*H*), 7.14−7.19 (m, 3H, 4-C*H*, 3-$CH_{butylphen}$, 5-$CH_{butylphen}$), 7.30 (d, J = 8.4 Hz, 2H, 3-CH_{phenyl}, 5-CH_{phenyl}), 7.43 (d, J = 8.4 Hz, 2H, 2-$CH_{butylphen}$, 6-$CH_{butylphen}$), 7.53 (d, J = 8.5 Hz, 2H, 2-CH_{phenyl}, 6-CH_{phenyl}), 7.57 (s, 1H, N*H*). ^{13}C NMR ($CDCl_3$): δ (ppm) 14.1 (1C, *C*-4$_{butyl}$), 22.5 (1C, *C*-3$_{butyl}$), 24.3 (1C, *C*-7), 29.4 (2C, *C*-3$_{pyran}$, *C*-5$_{pyran}$), 30.8 (2C, *C*-8, *C*-6), 33.7 (1C, *C*-2$_{butyl}$), 35.5 (1C, *C*-1$_{butyl}$), 37.7 (1C, N-CH_3), 57.7 (1C, *C*-4$_{pyran}$), 59.7 (1C, Ph-CH_2-N), 67.8 (2C, *C*-2$_{pyran}$, *C*-6$_{pyran}$), 120.1 (2C, *C*-2$_{phenyl}$, *C*-6$_{phenyl}$), 125.5 (2C, *C*-3$_{butylphen}$, *C*-5$_{butylphen}$), 126.8 (2C, *C*-2$_{butylphen}$, *C*-6$_{butylphen}$) 127.4 (1C, *C*-3), 129.1 (1C, *C*-4), 129.5 (2C, *C*-3$_{phenyl}$, *C*-5$_{phenyl}$), 131.3 (1C, C-1$_{butylphen}$), 133.5 (1C, *C*-4$_{phenyl}$), 135.8 (1C, *C*-1$_{phenyl}$), 136.0 (1C, *C*-2), 137.1 (1C, *C*-3a), 140.5 (1C, *C*-5), 142.6 (1C, *C*-8a), 143.4 (1C, *C*-4$_{butylphen}$), 168.5 (1C, O=*C*-NH). FT-IR (neat): ν (cm^{-1}) = 3278 (N-H), 2846 (C-H$_{alkyl}$), 1647 (C=O), 1161 (C-O).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C and gHSQC NMR spectra, HPLC analysis, MS spectra, X-ray structure analysis of **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was performed within the framework of the International Research Training Group 'Complex Functional Systems in Chemistry: Design, Synthesis and Applications' in collaboration with the University of Nagoya. Financial support of this project by the IRTG Münster-Nagoya and the *Deutsche Forschungsgemeinschaft* and the Funding Program for Next Generation World-Leading Researchers from JSPS are gratefully acknowledged. We are very grateful to Dr. Yasutomo Segawa for performing the X-ray crystal structure analysis.

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