JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Intramolecular [2 + 2] and [4 + 2] Cycloaddition Reactions of Cinnamylamides of Ethenetricarboxylate in Sequential Processes

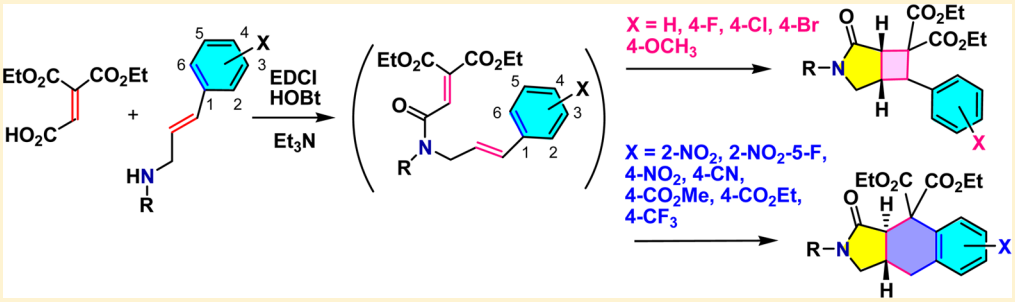
Shoko Yamazaki,*[,†] Hirotaka Sugiura,[†,‡] Shinnosuke Ohashi,[†] Keisuke Ishizuka,[†] Rina Saimu,[†] Yuji Mikata,[§] and Akiya Ogawa[‡]

[†]Department of Chemistry, Nara University of Education, Takabatake-cho, Nara 630-8528, Japan

[‡]Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, Gakuen-cho 1-1, Nakaku, Sakai, Osaka 599-8531, Japan

[§]KYOUSEI Science Center, Nara Women's University, Nara 630-8506, Japan

Supporting Information



ABSTRACT: Intramolecular [2 + 2] and [4 + 2] cycloaddition reactions of cinnamylamides of ethenetricarboxylate in sequential processes have been studied. Reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate and *trans*-cinnamylamines in the presence of EDCI/HOBt/Et_3N led to pyrrolidine products in one pot, via intramolecular [2 + 2], [4 + 2], and some other cyclizations. The types of the products depend on the substituents on the benzene ring and the reaction conditions. Reaction of cinnamylamines without substituents on the benzene ring and with halogens and OMe on the *para* position at room temperature gave cyclobutane-fused pyrrolidines as major products via [2 + 2] cycloaddition. The reaction at 80 °C in 1,2-dichloroethane gave *δ*-lactone fused pyrrolidines as major products, probably via ring-opening of the cyclobutanes. Interestingly, reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate and cinnamylamines bearing electron-withdrawing groups such as NO_2, CN, CO_2Me, CO_2Et, and CF_3 on *ortho* and *para* positions in the presence of EDCI/HOBt/Et_3N at room temperature or at 60−80 °C gave tetrahydrobenz[*f*]isoindolines via [4 + 2] cycloaddition as major products. DFT studies have been performed to explained the observed [2 + 2]/[4 + 2] selectivity.

INTRODUCTION

Sequential reactions allow multiple bond formations in one-pot and thus lead to high efficiency.[1] Intramolecular cycloaddition reactions are used for formation of various multicyclic systems. Intramolecular photochemical,[2] thermal,[3] and catalyzed [2 + 2] cycloadditions[4] have been reported. The reaction gives cyclobutane-fused cyclic skeletons. The reaction of substrates bearing styrene moiety also gave intramolecular [2 + 2] cycloadducts.[2a,4b]

The intramolecular [4 + 2] cycloaddition (Diels−Alder reaction) between alkenes and dienes leads to facile formation of multicyclic skeletons.[5] Furan is effectively utilized as diene moiety in intramolecular Diels−Alder reaction. Vinyl heterocycles such as vinyl furans,[6] pyrroles,[6a] imidazoles,[7] and benzothiophenes[8] have also been used as dienes. The intramolecular Diels−Alder reaction of vinylbenzene (styrene) as a diene requires relatively high temperature because it involves dearomatization of the benzene ring.[9]

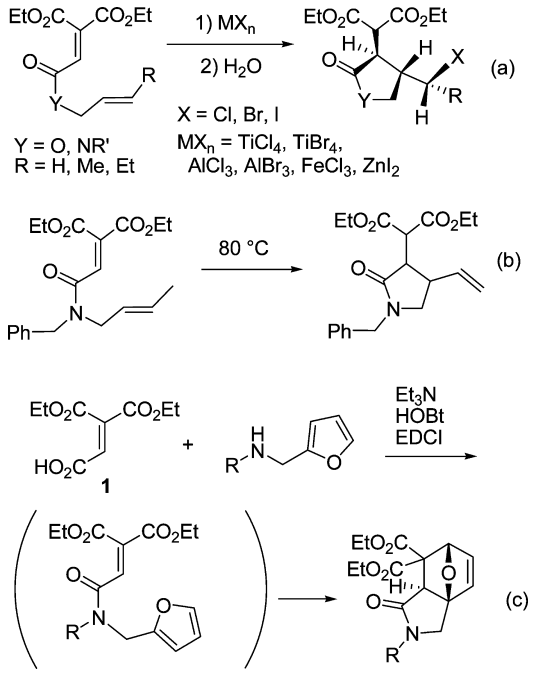
Thus, styrenes work as alkene or diene components in intramolecular [2 + 2] or [4 + 2] cycloadditions with electron-deficient alkenes. The both reactions may be useful for the construction of multicyclic skeletons and the question is how to control the selectivity.

Ethenetricarboxylate derivatives have been employed as highly electrophilic C═C components in various bond-forming reactions.[10] Ethenetricarboxylates allow facile derivatization at the 2-carboxyl group. Snider and Roush reported $FeCl_3$-promoted intramolecular reactions of alkenyl ethenetricarboxylates to give chlorinated *γ*-lactones.[11] Recently, we have developed Lewis acid (MX_n)-promoted cyclization/halogenation of alkenyl ethenetricarboxylates to give 3,4-*trans* five-membered rings stereoselectively with high generality (part a in Scheme 1).[12] 2-Alkenyl amides of ethenetricarboxylates also undergo facile intramolecular ene reactions (part b).[12c] In addition, reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** and 2-furylmethylamines in the presence of EDCI/HOBt/Et_3N at room

Received: August 8, 2016
Published: October 10, 2016

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

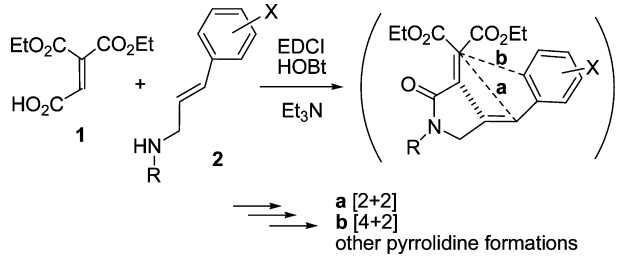
Scheme 1



temperature led directly to intramolecular Diels−Alder adducts (part c).[13]

It is of interest to examine the reaction of the highly electrophilic ethenetricarboxylates bearing aryl-substituted alkenyl groups as an extension of the alkene moiety and to examine the selectivity of styrenes. In this work, sequential intramolecular reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** with *trans*-cinnamylamines **2** under amide formation conditions have been studied (Scheme 2). Reaction of **1** and **2** in the presence of

Scheme 2



EDCI/HOBt/Et_3N led to pyrrolidine products in one pot, via intramolecular [2 + 2], [4 + 2], and some other cyclizations. The types of the products depend on the substituents on the benzene ring and the reaction conditions.

RESULTS AND DISCUSSION

Reaction of Cinnamylamines with *p*-H, Halogen, and MeO Groups: [2 + 2] Cycloaddition. Reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** and *trans*-cinnamylamines (X = H) **2a−c** in the presence of EDCI/HOBt/Et_3N have been examined first. It was found that the reaction gave cyclobutane-fused pyrrolidines **3a−c** in 41−51% yield as isolable major products (eq 1, Table 1). The products may be formed via amide formation/intramolecular [2 + 2] cycloaddition. Reaction of $RHNCH_2-CH{=}CH-C_6H_4-X$ (X = 4-halogen, 4-OCH_3) **2d−i** also gave cyclobutane-fused pyrrolidines **3d−i** in 39−51% yield

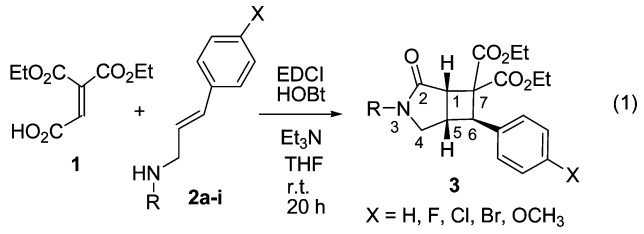


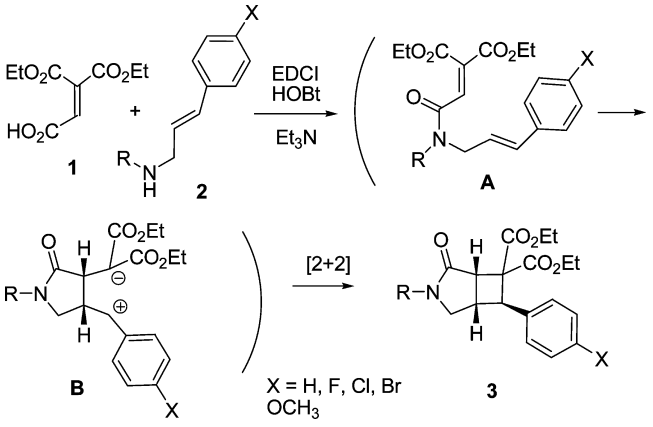
Table 1. Reactions of 1,1-Diethyl Ethenetricarboxylate 1 and Cinnamylamines 2

entry	2	R	X	product	3 yield (%)
1	**2a**	CH_2Ph	H	**3a**	43
2	**2b**	CH_2-cyclohexyl	H	**3b**	51
3	**2c**	$CH_2C_6H_4$-4-CF_3	H	**3c**	41
4	**2d**	$CH_2CH{=}CH_2$	H	**3d**	42
2	**2e**	CH_2Ph	F	**3e**	39
3	**2f**	$CH_2CH_2CH_3$	F	**3f**	51
4	**2g**	CH_2Ph	Cl	**3g**	40
5	**2h**	CH_2Ph	Br	**3h**	40
6	**2i**	CH_2Ph	OCH_3	**3i**	48

as isolable major products. The relative configuration of **3** was determined as shown in eq 1 by NOESY experiment (NOEs between C5−*H* and C1−*H*, Ar−H, etc.).

The intermediate amide **A** was not observed under the reaction conditions of amide formation (Scheme 3). The amide

Scheme 3

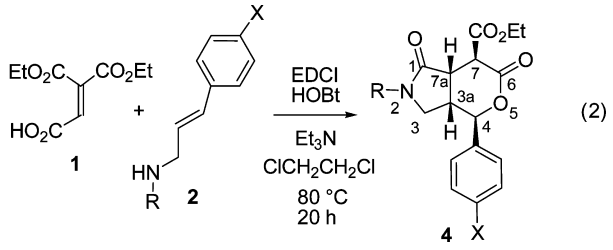


undergoes the first C−C bond formation to give a zwitter-ionic intermediate **B**, which is stabilized by the phenyl group. The second C−C bond formation proceeds, affording a highly strained cyclobutane-fused bicyclic compound **3**.

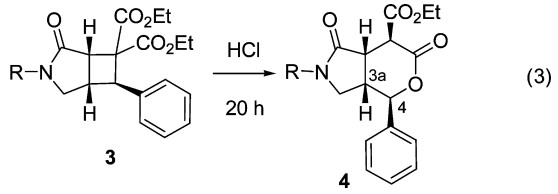
When the reaction of **1** and **2a** was carried out at 80 °C in 1,2-dichloroethane[14] or in α,α,α-trifluorotoluene, δ-lactone-fused pyrrolidine **4a** was obtained as a major product in 69% and 50% yields, respectively (eq 2, Table 2). The reaction of **1** and **2b,e−i** at 80 °C in 1,2-dichloroethane gave δ-lactone-fused pyrrolidines **4b,e−i** as major products. The relative configuration of **4** was determined as shown in eq 2 by NOEs.

Formation of **4** from **3** under the reaction conditions is likely. The reaction conditions may produce a small amount of HCl from EDCI along with formation of the byproducts $BtOCH_2CH_2Cl$ and $BtOCH_2CH_2OBt$.[14] Reaction of cyclobutane products **3** with HCl was next examined (eq 3). After examining various ring-opening conditions, the reaction of

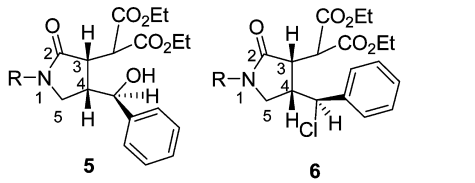
DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

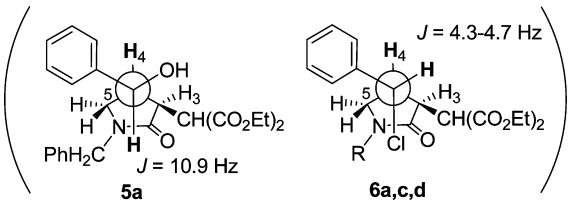


(2)



(3)

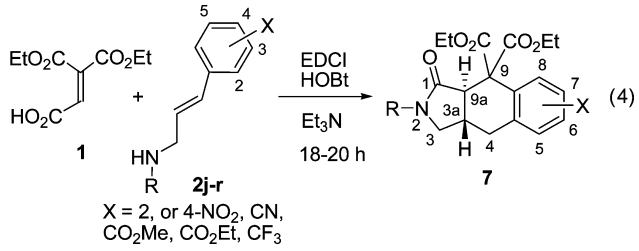




cyclobutane **3a** with 1 equiv of HCl/ether and 1 equiv of H_2O in $ClCH_2CH_2Cl$ at 80 °C for 20 h was found to give **4a** efficiently in 70% yield (Table 3, entry 1). The reaction of **3a** with 1 equiv of HCl/H_2O in THF at room temperature gave the mixture of alcohol **5a** and **4a** (entry 2). Treatment of alcohol **5a** with 1 equiv of HCl/ether in CH_2Cl_2 at room temperature overnight gave **4a** quantitatively. On the other hand, the reaction of **4** with 1 equiv of HCl/ether in CH_2Cl_2 or HCl/AcOEt at room temperature gave Cl-adduct **6** as a single diastereomer along with **4** (entries 3–5). The stereochemistries of **5a** and **6a,c,d** could be deduced as follows. The 3,4-cis stereochemistries of **5a** and **6a,c,d** were determined by NOEs. Preferred conformations of **5a** and **6a,c,d** may be as depicted in eq 3 from the coupling constants and consideration of steric effects, respectively. The coupling constant between C*H*(OH)Ph and C4–*H* of **5a** (J = 10.9 Hz) and those between C*H*ClPh and C4–*H* of **6a,c,d** (J = 4.3–4.7 Hz) suggest the configurations of the side chains as shown. The similarity in the coupling constant between C*H*OHPh and C4–*H* of **5a** and that between C4–*H* and C3a–*H* of **4a** (J = 11.3 Hz) supports the assignment of the configuration of **5a**.

Thus, δ-lactone **4** may form from cyclobutane **3** via intermediate **B**-H^+ and alcohol **5**, followed by transesterification (Scheme 4). Formation of **5** may proceed in two steps and formation of Cl-adducts **6** may proceed in one step ring opening based on their suggested stereochemistries.

Reaction of Cinnamylamines with *o,p*-Electron-Withdrawing Groups: [4 + 2] Cycloaddition. Next, the reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate **1** and cinnamylamines bearing electron-withdrawing groups on *ortho* and *para* positions in the presence of the amide condensation reagents was examined. Interestingly, reaction of **1** and $RHNCH_2$–CH═CH–C_6H_4–X (X = 2- or 4-NO_2, CN, CO_2Me, CO_2Et, or CF_3) **2j–r** with EDCI/HOBt/Et_3N at room temperature, 60 °C, and 80 °C gave tetrahydrobenz[*f*]isoindolines **7** as major products via [4 + 2] cycloaddition (eq 4, Table 4 and Table S1 of Supporting Information). The *trans*-fused pyrrolidine stereochemistry of **7** was determined by NOEs (in C_6D_6, CD_3CN, or $(CD_3)_2CO$, for some products).



(4)

Formation of the zwitterionic intermediate **B** corresponding to that in Scheme 3 may be strongly destabilized by the resonance and inductive effects of *ortho* and *para* electron-withdrawing group on the benzene ring (Scheme 5). Instead, the interaction between a styrene moiety and an alkene moiety of ethenetricarboxylate may lead to the intramolecular Diels–Alder adduct **C**. The 1,3-H transfer isomerization of **C** to the products **7** may proceed by a stepwise process via intermediate **D**-H^+.

Reaction of Cinnamylamines with *m*-CF_3 and F Groups: [2 + 2] or [4 + 2] Cycloaddition. It is interesting to examine the chemoselectivity of the *meta*-electron-withdrawing groups. Reaction of **1** and benzyl cinnamylamine (X = 3-CF_3) **2s** with EDCI/HOBt/Et_3N at room temperature gave tetrahydrobenz[*f*]isoindoline **7s** in 53% and cyclobutane-fused pyrrolidine

Table 2. Reactions of 1,1-Diethyl Ethenetricarboxylate 1 and Cinnamylamines 2

entry	2	solvent	R	X	product	4 yield (%)
1	**2a**	$ClCH_2CH_2Cl$[a]	CH_2Ph	H	**4a**	69
2	**2a**	C_6H_5–CF_3	CH_2Ph	H	**4a**	50
3	**2b**	$ClCH_2CH_2Cl$[a]	CH_2-cyclohexyl	H	**4b**	75
4	**2e**	$ClCH_2CH_2Cl$[a]	CH_2Ph	F	**4e**	55
5	**2f**	$ClCH_2CH_2Cl$[a]	$CH_2CH_2CH_3$	F	**4f**	38
6	**2g**	$ClCH_2CH_2Cl$[a]	CH_2Ph	Cl	**4g**	53
7	**2h**	$ClCH_2CH_2Cl$[a]	CH_2Ph	Br	**4h**	31
8	**2i**	$ClCH_2CH_2Cl$[a]	CH_2Ph	OCH_3	**4i**	41
9	**2c**	$ClCH_2CH_2Cl$[a]	$CH_2C_6H_4$-4-CF_3	H	*b*	
10	**2d**	$ClCH_2CH_2Cl$[a]	CH_2CH═CH_2	H	*b*	

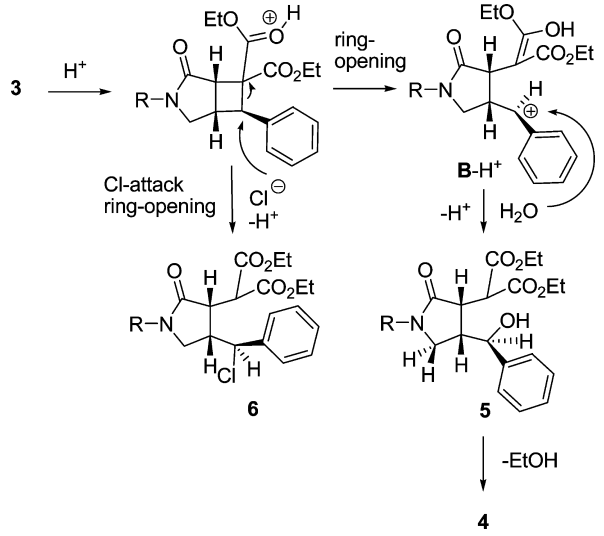
[a]The byproducts were removed by column chromatography.[14] [b]Complex mixtures containing **4** and small amounts of **3**.

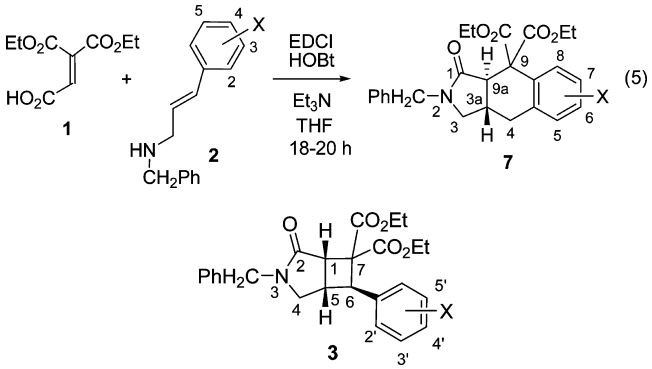
DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863–10886

Table 3. Ring-Opening Reactions of Cyclobutane-Fused Pyrrolidines 3

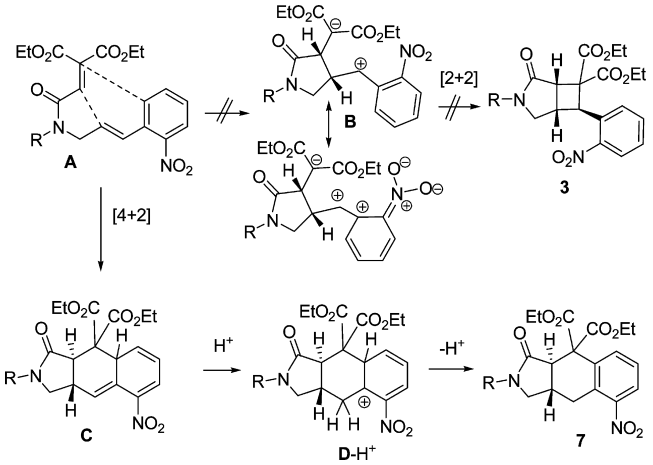
entry	3	R	conditions	product (yield)
1	**3a**	CH_2Ph	1 equiv of 1 M HCl/ether, 1 equiv of H_2O, $ClCH_2CH_2Cl$ 80 °C	**4a** (70%)
2	**3a**	CH_2Ph	1 equiv of 1 M HCl/H_2O, THF, rt	**5a** (42%), **4a** (47%)
3	**3a**	CH_2Ph	1 equiv of 1 M HCl/ether, CH_2Cl_2, rt	**6a** (60%), **4a** (27%)
4	**3c**	$CH_2C_6H_4$-4-CF_3	1 equiv of 1 M HCl/AcOEt, rt	**6c** (62%), **4c** (18%)
5	**3d**	$CH_2CH{=}CH_2$	1 equiv of 1 M HCl/ether, CH_2Cl_2, rt	**6d** (53%), **4d** (18%)

Scheme 4





Scheme 5



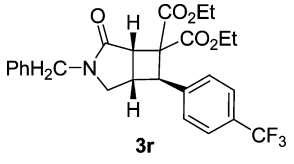
3s in 24% yields, respectively (eq 5, Table 5 and Table S2 of Supporting Information). The reaction of **1** and cinnamylamine (X = 3,5-diCF_3) **2t** at 60 °C gave cyclobutane-fused pyrrolidine **3t** as an isolable product in 13−30% yield and product **7** was not formed. One *meta*-CF_3 worked as an electron-withdrawing group by the inductive effect, and the reaction preferred [4 + 2] adduct **7s** to [2 + 2] adduct **3s**. The [4 + 2] adduct **7s** was obtained regioselectively. Cinnamylamine with two *meta*-CF_3 groups **2t** only gave cyclobutane **3t**, probably because steric hindrance of *meta*-CF_3 group interferes with [4 + 2] cycloaddition (Scheme 6).

Although the reaction of cinnamylamines with 4-F group **2e**,**f** gave cyclobutanes **3e**,**f** regioselectively (Table 1), reaction of **1** and cinnamylamine with 3-F group **2u** gave a mixture of 6-F- and 8-F-regioisomers of **7u** and cyclobutane-fused pyrrolidine **3u**.

Table 4. Reactions of 1,1-Diethyl Ethenetricarboxylate 1 and Cinnamylamines 2j−r[a]

entry	2	X	solvent	temp	R	7 yield (%)	X	3 yield (%)
1	**2j**	2-NO_2	THF	rt	CH_2Ph	**7j** (75)	5-NO_2	
2	**2k**	2-NO_2	benzene	80 °C	CH_2-cyclohexyl	**7k** (73)	5-NO_2	
3	**2l**	2-NO_2	THF	rt	$CH_2CH{=}CH_2$	**7l** (74)	5-NO_2	
4	**2m**	2-NO_2-5-F	THF	rt	CH_2Ph	**7m** (78)	5-NO_2-8-F	
5	**2n**	4-NO_2	THF	60 °C	CH_2Ph	**7n** (68)	7-NO_2	
6	**2o**	4-CN	THF	rt	CH_2Ph	**7o** (75)	7-CN	
7	**2p**	4-CO_2Me	THF	rt	CH_2Ph	**7p** (71)	7-CO_2Me	[b]
8	**2q**	4-CO_2Et	THF	rt	CH_2Ph	**7q** (57)	7-CO_2Et	[b]
9	**2r**	4-CF_3	benzene	80 °C	CH_2Ph	**7r** (51)	7-CF_3	**3r** (6)

[a]The best conditions for each compound are shown in this table, and the other conditions are described in Table S1 of Supporting Information. [b]A small amount of cyclobutane-fused pyrrolidine **3** was detected but could not be isolated.



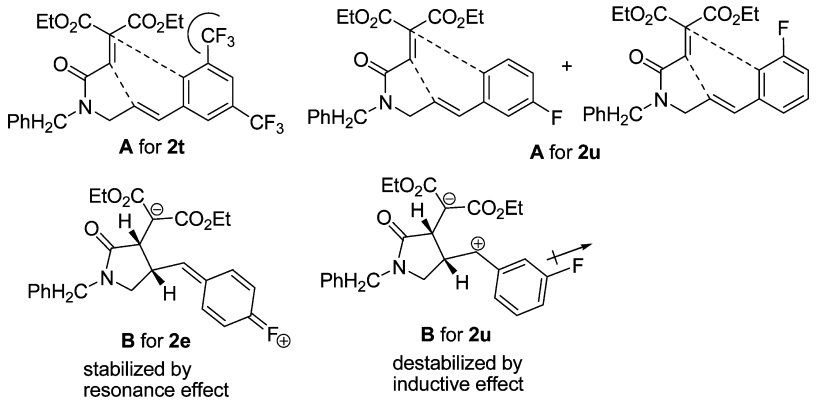
DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

Table 5. Reactions of 1,1-Diethyl Ethenetricarboxylate 1 and Cinnamylamines 2s−u[a]

entry	2	X	solvent	temp	7 yield (%)	X	3 yield (%)	X
1	**2s**	3-CF_3	THF	rt	**7s** (53)	6-CF_3	**3s** (24%)[b]	3′-CF_3
2	**2t**	3,5-diCF_3	THF	60 °C			**3t** (30%)	3′,5′-diCF_3
3	**2u**	3-F	THF	rt	6-F-**7u**, 8-F-**7u** (2.5:1, 37)[c]	6-F, 8-F	**3u** (29%)	3′-F

[a]The best conditions for each compound are shown in this table, and the other conditions are described in Table S2 of Supporting Information. [b]Reaction for 1 h at room temperature gave a complex mixture possibly containing intermediate amide **A**, which could not be isolated. [c]6-F-**7u** and 8-F-**7u** could not separated by column chromatography. The ratio was determined by ^{1}H NMR.

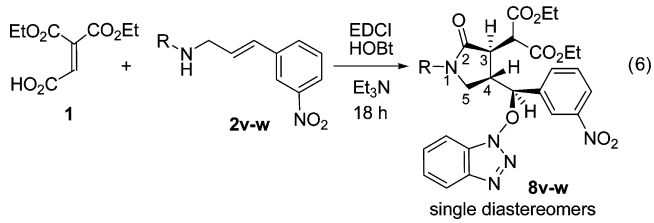
Scheme 6



F substituents destabilize **B** by inductive effect with high electronegativity, but *para*-F stabilizes benzylic cation intermediate **B** by resonance effect (Scheme 6). The steric hindrance of F is smaller than CF_3; therefore both 6-F- and 8-F-regioisomers of **7u** may be formed.

Thus, the reaction of **1** and cinnamylamines with *meta*-CF_3 and F groups **2s**,**t**,**u** gave [2 + 2] and [4 + 2] cycloadducts.

Reaction of Cinnamylamines with *m*-Nitro Group: Stereoselective Formation of HOBt-Incorporated Pyrrolidines. Reaction of cinnamylamines with *meta*-NO_2 group was carried out as examination of the inductive effect of a strong electron-withdrawing group. Unexpectedly, reaction of **1** and cinnamylamines (X = 3-NO_2) **2v**,**w** with EDCI/HOBt/Et_3N at room temperature, 60 °C, and 80 °C gave HOBt-incorporated 3,4-*trans*-pyrrolidines **8v**,**w** as single diastereomers in 53−75% yield selectively (eq 6, Table 6). The structure of **8w** was determined by X-ray analysis (Figure S1 of Supporting Information).[15]



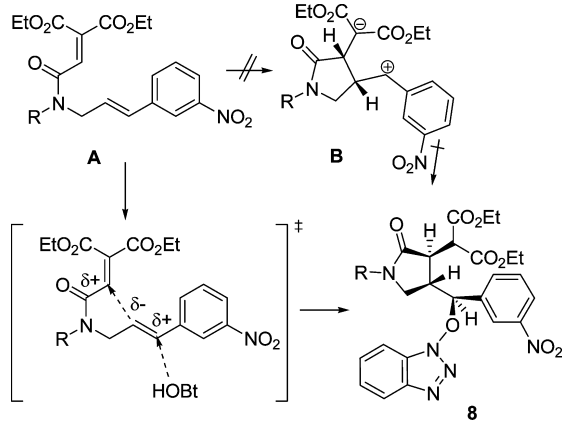
(6)

Table 6. Reactions of 1,1-Diethyl Ethenetricarboxylate 1 and Cinnamylamines 2v−w

entry	2	R	solvent	temp	8 yield (%)
1	**2v**	CH_2Ph	THF	rt	**8v** (53)
2	**2v**	CH_2Ph	THF	60 °C	**8v** (62)
3	**2v**	CH_2Ph	benzene	80 °C	**8v** (55)
4	**2w**	CH_2-cyclohexyl	THF	rt	**8w** (75)
5	**2w**	CH_2-cyclohexyl	THF	60 °C	**8w** (61)
6	**2w**	CH_2-cyclohexyl	benzene	80 °C	**8w** (61)

Stereospecific formation of **8v**,**w** is proposed as shown in Scheme 7. Formation of the zwitterionic intermediate **B** may be destabilized by the inductive effect of meta-NO_2 group on the benzene ring. Instead, the O−C bond formation and C−C bond formation from **A** occurred concertedly to lead to cyclized

Scheme 7

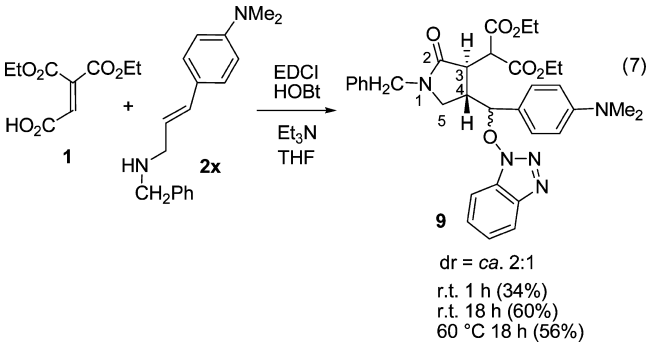


products **8v**−**w**. Intermolecular HOBt nucleophilic attack from outside leading to 3,4-*trans* cyclized product **8v**,**w** is proposed for steric reasons.

Reaction of Cinnamylamines with *p*-NMe_2 Group: Formation of HOBt-Incorporated Pyrrolidines. Reaction of cinnamylamine (X = 4-NMe_2 group) **2x** as a strong electron-donating group in *para* position was also examined. The reaction of **1** and **2x** with EDCI/HOBt/Et_3N at room temperature or 60 °C for 1 to 18 h gave HOBt-incorporated pyrrolidine **9** as ca. 2:1 diastereomer mixture in 34−60% yield and as an isolable product (eq 7). The 3,4-*trans*-stereochemistry of **9** was deduced

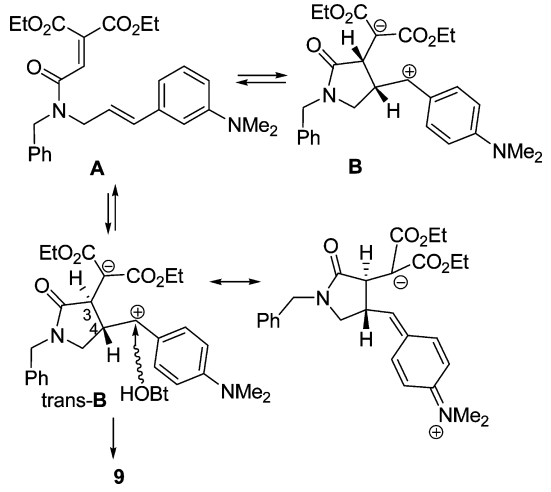
DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

by the absence of NOEs between C3−*H* and C4−*H* and between $CH(CO_2Et)_2$ and $CH(Ar)O$.



Formation of **9** could be explained by the intervention of the strongly stabilized zwitterionic intermediate *trans*-**B** by the resonance effect of *para*-NMe_2 group (Scheme 8). *trans*-**B** is a

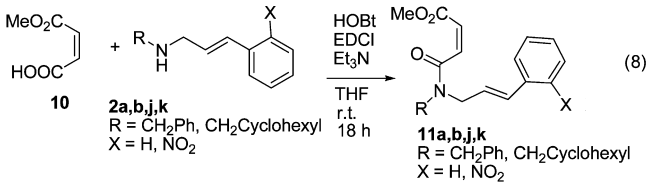
Scheme 8



3,4-*trans* isomer of intermediate **B**. The stabilized zwitterionic intermediates **B** may cause isomerization to sterically more stable intermediate *trans*-**B**. Stepwise nucleophilic attack of HOBt to zwitterionic intermediate *trans*-**B** gives product **9** with loss of stereochemistry at the side chain, 4-$CH(OBt)C_6H_4$-4-NMe_2.

The difference in reactivity may be related to the Hammet constants σ.[16] For [2 + 2] cycloaddition, σ_p ranges from −0.27 (*p*-OMe) to +0.23 (*p*-Cl, *p*-Br). For [4 + 2] cycloaddition, σ_p ranges from +0.78 (*p*-NO_2) to +0.45 (*p*-CO_2Et). σ_m +0.45 (*m*-CF_3) and +0.34 (*m*-F) gave [2 + 2] and [4 + 2] mixtures. Large negative value σ_p −0.83 (*p*-NMe_2) and large positive value σ_m +0.71 (*m*-NO_2) gave exceptional results, respectively.

Reaction of Other Electron-Deficient Olefins and Cinnamylamines with *o*-NO_2 Group: [4 + 2] Cycloaddition. In order to examine the effects of electron-withdrawing group in [4 + 2] cycloaddition of styrene moiety and the generality of the reaction, the reactions of other electron-deficient olefins with carboxyl group and cinnamylamines without substituents **2a,b** and with *o*-NO_2 group **2j,k** were carried out. Reaction of monomethyl maleate **10** and **2a,b** or **2j,k** with EDCI/HOBt/Et_3N at room temperature gave amides **11a,b** and **11j,k** as isolable products along with the corresponding trans isomers **13** (eq 8, Table 7). Formation of byproducts **13** may arise from partial isomerization of **10** to **12** under the reaction



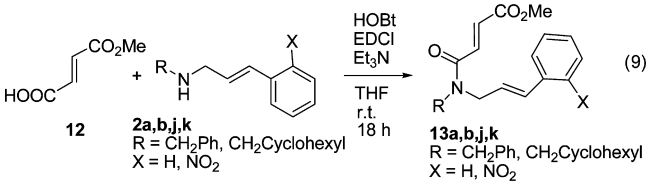


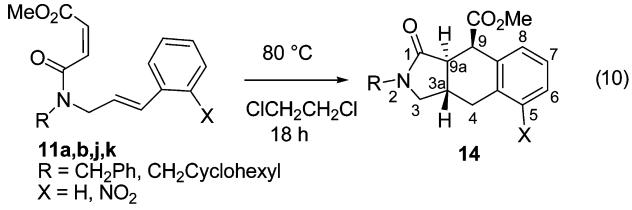
Table 7. Reactions of 10/12 and Cinnamylamines 2

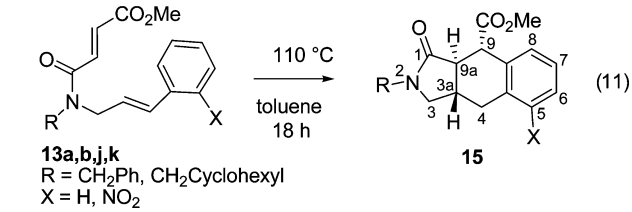
entry	10/12	2	R	X	yield (%)	isolated byproduct
1	**10**	**2a**	CH_2Ph	H	**11a** (40)[a]	[b]
2	**10**	**2b**	CH_2-cyclohexyl	H	**11b** (18)	**13b** (35)
3	**10**	**2j**	CH_2Ph	2-NO_2	**11j** (40)	**13j** (11)
4	**10**	**2k**	CH_2-cyclohexyl	2-NO_2	**11k** (31)	**13k** (39)
5	**12**	**2a**	CH_2Ph	H	**13a** (89)[a]	
6	**12**	**2b**	CH_2-cyclohexyl	H	**13b** (61)[a]	
7	**12**	**2j**	CH_2Ph	2-NO_2	**13j** (72)[a]	
8	**12**	**2k**	CH_2-cyclohexyl	2-NO_2	**13k** (63)	

[a]A small amount of impurity could not be removed. [b]**13a** could be formed but not confirmed.

conditions. Reaction of monomethyl fumarate **12** and **2a,b** or **2j,k** gave amides **13a,b** and **13j,k**, respectively (eq 9, Table 7).

Compound **11j,k** gradually changes to **14j,k** at room temperature. Heating **11j,k** at 80 °C in $ClCH_2CH_2Cl$ for 18 h gave **14j,k** via [4 + 2] cycloaddition/H-transfer (eq 10, Table 8).





On the other hand, heating **11a,b** at 80 °C in $ClCH_2CH_2Cl$ for 18 h gave complex mixtures. Heating trans isomer **13k** at 80 °C in $ClCH_2CH_2Cl$ for 18 h did not change. The reaction of **13j,k** at 110 °C in toluene for 18 h gave **15j,k** as isolable products (eq 11, Table 8). Reaction of **13a,b** at 80 °C in $ClCH_2CH_2Cl$ for 18 h gave remained starting materials, and the reaction at 110 °C in toluene for 18 h gave complex mixtures. The stereochemistries of **14j,k** and **15j,k** were determined by NOEs. The pyrrolidine ring junction is trans. Thermal [4 + 2] cycloaddition reaction of **11j,k** and **13j,k** proceeded stereospecifically, and the products

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

Table 8. Thermal Reactions of 11 and 13

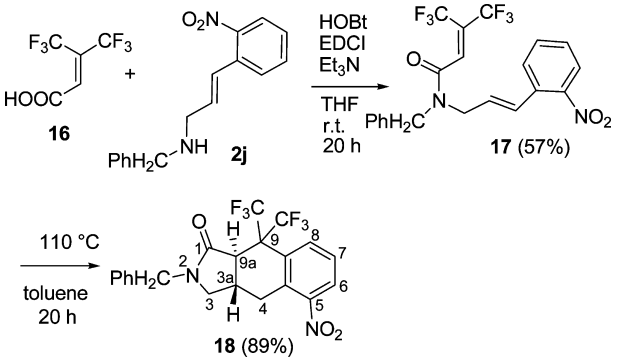
entry	11/13	R	X	temp (°C)	Yield (%)
1	**11a**	CH_2Ph	H	80	**14a** (0)[a]
2	**11b**	CH_2-cyclohexyl	H	80	**14b** (0)[a]
3	**11j**	CH_2Ph	2-NO_2	80	**14j** (33)
4	**11k**	CH_2-cyclohexyl	2-NO_2	80	**14k** (55)
5	**13a**	CH_2Ph	H	110	**15a** (0)[a]
6	**13b**	CH_2-cyclohexyl	H	110	**15b** (0)[a]
7	**13j**	CH_2Ph	2-NO_2	110	**15j** (31)
8	**13k**	CH_2-cyclohexyl	2-NO_2	110	**15k** (46)

[a]Complex mixtures.

retained the original cis and trans stereochemistries of C=C double bonds.

Furthermore, reaction of 4,4,4-trifluoro-3-(trifluoromethyl)-crotonic acid **16** and cinnamylamine with *o*-NO_2 group **2j** was examined. Reaction of **16** and **2j** with EDCI/HOBt/Et_3N at room temperature gave amide **17** in 57% yield (Scheme 9).

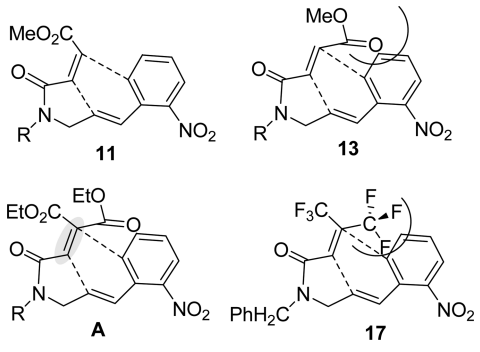
Scheme 9



Thermal reaction of **17** at 80 °C in $ClCH_2CH_2Cl$ for 22 h gave ca. 1:1 mixture of **17** and **18**. Heating **17** at 110 °C in toluene for 20 h completed the conversion, and **18** was obtained in 89% yield.

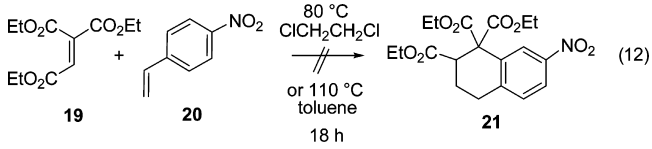
Higher reactivity of **11** than that of **13** may arise from preferable steric overlap on the transition states of [4 + 2] cycloaddition (Scheme 10). Much higher reactivity of ethenetricarboxylate

Scheme 10



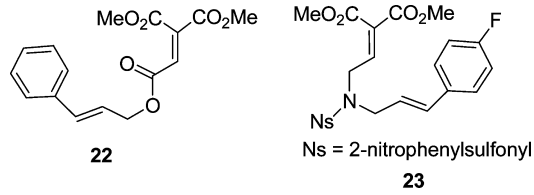
intermediates **A** compared to **11** and **13** may arise from activation of C=C double bond by three electron-withdrawing carbonyl groups. Lower reactivity of **17** than that of **A** could be due to the steric effect of CF_3 groups.

Finally, intermolecular reaction of ethenetricarboxylate triester **19** and nitrophenylstyrene **20** was attempted in order to examine the effect of electron-deficient substituents on the benzene ring on [4 + 2] cycloaddition of styrene as a diene component. However, heating **19** and **20** at 80 °C in $ClCH_2CH_2Cl$ or 110 °C in toluene did not produce any reaction, and only starting materials were recovered (eq 12).



Additional comparison with the results in the literature is discussed as follows. The difference in stability between **A** (in Scheme 3) and compound **22**, the oxygen analogue of **A**, is noteworthy (Scheme 11). Compound **22** was isolated as

Scheme 11



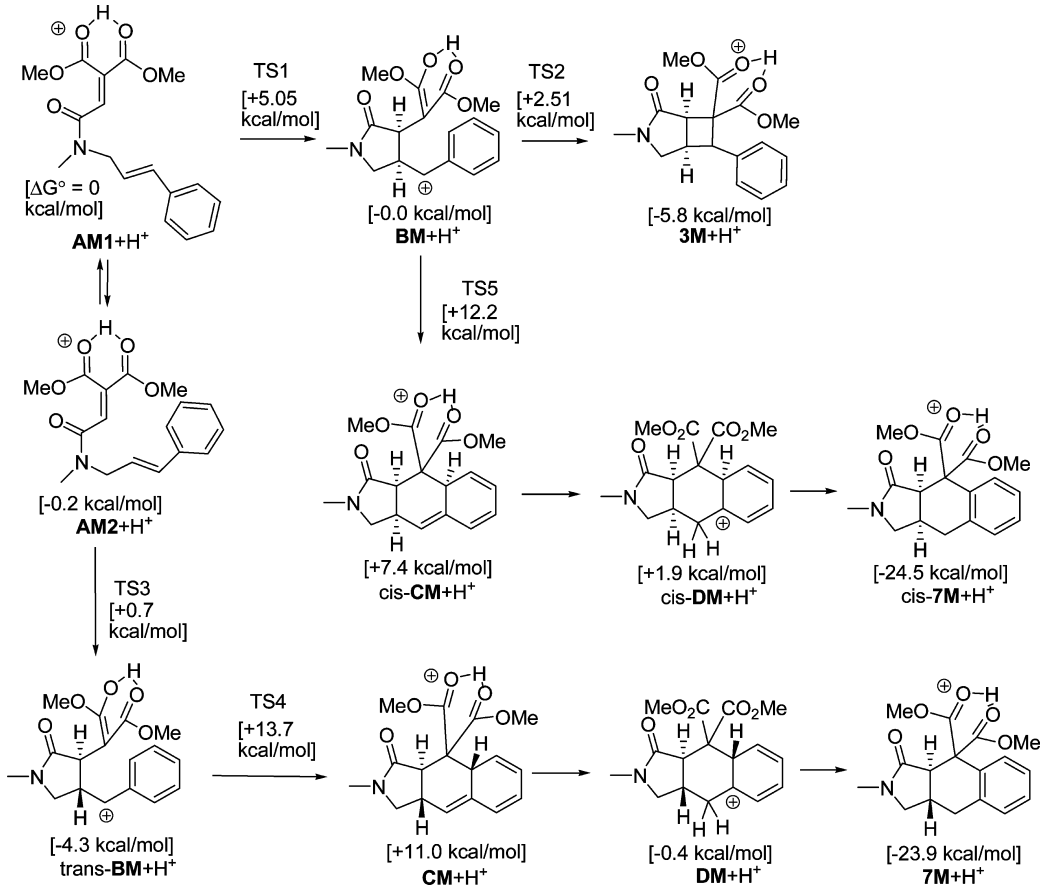
reported by Snider and his co-workers.[17] Heating compound **22** at 85 or 115 °C led to an equilibrium mixture of **22** and hetero-Diels–Alder adduct. They also reported that treatment of **22** with $FeCl_3$ underwent intramolecular reactions to give chlorinated γ-lactone with loss of stereochemistry on the side chain.[11] The difference in stability can be explained, similar to the cyclization of other ethenetricarboxylate derivatives.[12,13] Triester **22** may be more stable in s-*cis* conformation of O=C–O–CH_2 as shown in Scheme 11, probably because of the steric repulsion. In diester amide **A** (in Scheme 3), the energy differences of s-*cis* and s-*trans* conformations of O=C–NR–CH_2 may be small. The facile intramolecular reaction of amide probably originates from higher ratio of the reactive s-*trans* conformer. Amide-tethered alkylidene malonate **23** is also a stable compound, and scandium-catalyzed [2 + 2] cyclization to produce cyclobutane-fused pyrrolidine was reported.[5b] Higher reactivity of **A** compared to **23** may arise from the electron-withdrawing effect of the 2-carboxyl group and the steric effect of the restricted rotation of the C–N amide bond.

Theoretical Study. Understanding the detailed mechanism of the cycloadditions is important to find the factor to control the selectivity. In order to explain the observed [2 + 2]/[4 + 2] selectivity, the reaction mechanism was examined using B3LYP/6-31G*[18,19] calculations including the PCM[20] solvent effect (solvent = THF). TS geometry was characterized by vibrational analysis, which checked whether the obtained geometry has single imaginary frequencies ($\nu^{\ddagger}$). From TSs, reaction paths were traced by the intrinsic reaction coordinate (IRC) method[21] to obtain the energy-minimum geometries. Relative Gibbs free energies are of RB3LYP/6-31G* SCRF (PCM, solvent = THF) (T = 298.15 K, P = 1 atm).

Possible [2 + 2] cycloaddition paths could not be obtained using the neutral model systems. Alternatively, acid-catalyzed intramolecular [2 + 2] cycloaddition reaction models for **AM1** + H^+ were calculated (Scheme 12). The protonated six-membered ring intermediates with hydrogen bonding were assumed in models for **AM1** + H^+.[22] The acid *in situ*, possibly generated from EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) or

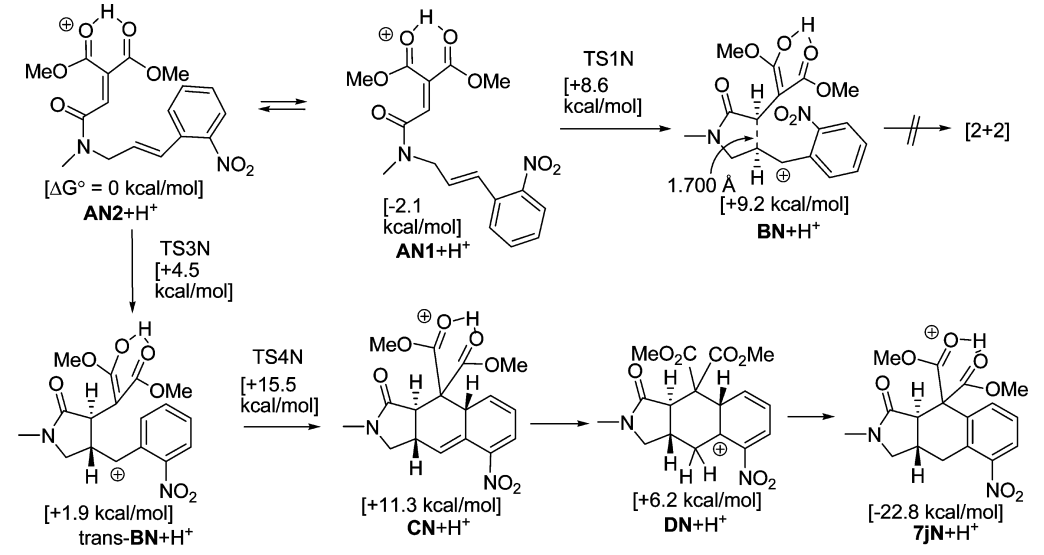
DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863–10886

Scheme 12. [2 + 2] and [4 + 2] Cycloaddition Reaction Paths of Protonated Intermediate Amides, AM1 + H^+ and AM2 + H^+[a]



[a]Gibbs free energies (T = 298.15 K, P = 1 atm) were obtained at the RB3LYP/6-31G* SCRF (PCM, solvent = THF) level and are relative to **AM1** + H^+.

Scheme 13. Acid-Catalyzed Reaction Path of *ortho*-Nitro Models[a]



[a]Gibbs free energies are relative to **AN2** + H^+.

starting material **1**, may catalyze the cycloaddition reactions. Stepwise [2 + 2] cycloaddition mechanism via benzylic cation intermediates **BM** + H^+ leads to cyclobutane-fused product **3M** + H^+. Stepwise [4 + 2] cycloaddition path via trans intermediate *trans*-**BM** + H^+ leading to **CM** + H^+ was also obtained. Intermolecular proton transfer of **CM** + H^+ to **DM** + H^+ possibly leads to rearomatized product **7M** + H^+. The path leading to the corresponding pyrrolidine cis-fused product *cis*-**7M** + H^+ via TS5 was also calculated.

The activation energies, $\Delta G^{\ddagger}$, of both TS4 and TS5 (13.7 and 12.2 kcal/mol) for [4 + 2] cycloadditions are higher than that of

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

TS1 (5.1 kcal/mol) for [2 + 2] cycloaddition. Thus, for cinnamylamine without electron-withdrawing group, [2 + 2] cycloaddition is more favorable than [4 + 2] cycloaddition.

Next, the effect of ortho electron-withdrawing group to [4 + 2] cycloaddition was examined. Acid-catalyzed reaction of *ortho*-nitro models were first calculated, and the results are shown in Scheme 13. The [2 + 2] cycloaddition path from unstable benzylic cation intermediate **BN** + H^+ could not be obtained. Alternatively, intermediate *trans*-**BN** + H^+ leads to [4 + 2] cycloaddition path.

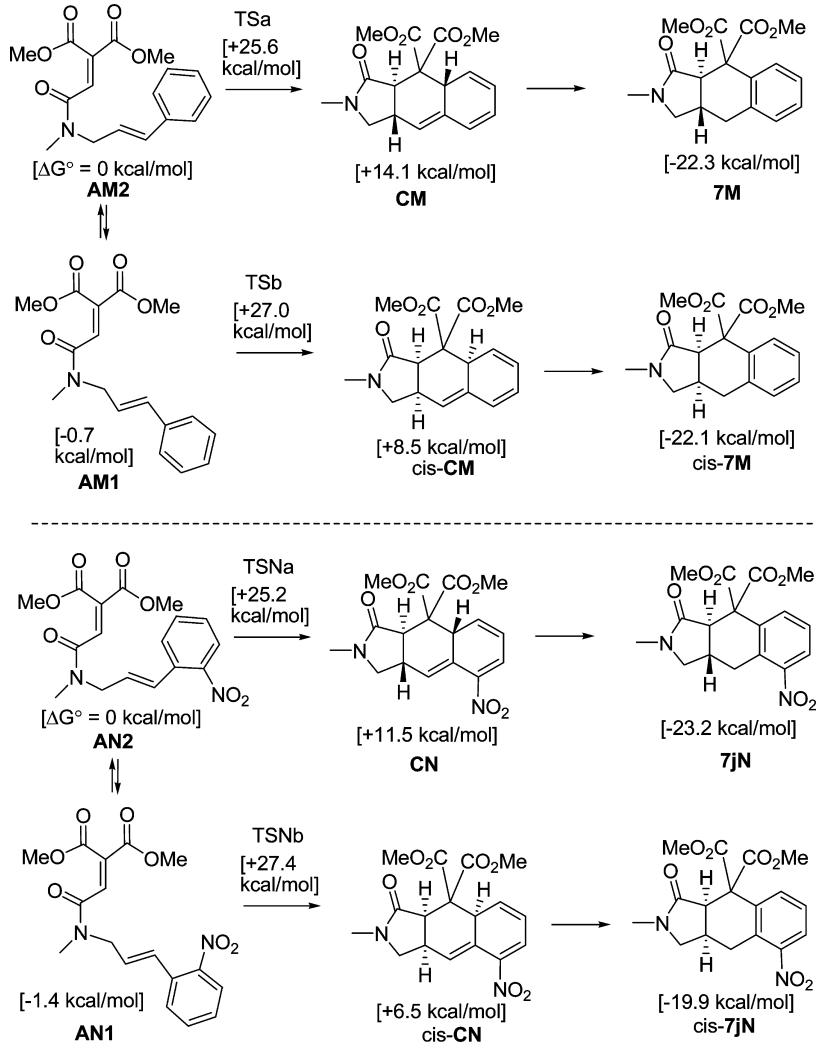
Concerted [4 + 2] cycloadditions without acid catalyst for cinnamyl and *ortho*-nitrocinnamyl amide models were also calculated, and the result is shown in Scheme 14. The concerted process of *ortho*-nitrocinnamyl amide (TSNa) is slightly energetically favored over that of cinnamyl amide (TSa). Substitution of a nitro group at one carbon away from the diene moiety may give little electronic effect to [4 + 2] cycloaddition. Thus, the [4 + 2] cycloaddition occurs in either acid-catalyzed path or concerted path under the one-pot reaction conditions.

The calculated results of the concerted path are also in agreement with observed preferable formation of trans-fused pyrrolidine ring to that of cis-fused pyrrolidine ring (TSNa < TSNb). The experimental result is similar to that reported for intramolecular [4 + 2] cycloaddition involving styrenes giving trans-fused heterocyclic five-membered rings mainly.[9e,f] The intramolecular [4 + 2] cycloaddition reaction may be governed by steric requirements.

These results suggest that an electron-withdrawing group on the benzene ring destabilizes the [2 + 2] cycloaddition path and alternatively the [4 + 2] cycloaddition path proceeds. The [4 + 2] cycloaddition of the styrene moiety involves dearomatization and rearomatization. Acceleration of dearomatization by nitro-substitution is reported in the reactions of the C=C component of a benzene ring.[23] However, whether there is any acceleration is unclear yet in the [4 + 2] cycloaddition of electron deficient olefin by substitution of an ortho NO_2 group to the styrene moiety as diene. Further mechanistic study is under investigation.

In summary, intramolecular [2 + 2] and [4 + 2] cycloaddition reactions of cinnamylamides and ethenetricarboxylate in sequential processes have been studied. Reaction of cinnamylamines without substituents on the benzene ring and with halogens and OMe on *para* positions at room temperature gave cyclobutane-fused pyrrolidines as major products via [2 + 2] cycloaddition. The reaction at 80 °C in 1.2-dichloroethane gave *δ*-lactone-fused

Scheme 14. [4 + 2] Cycloaddition Reaction Paths of AM2, AM1, and *ortho*-Nitro Models AN2 and AN1[a]



[a]Gibbs free energies are relative to **AM2** and **AN2**, respectively.

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

pyrrolidines as major products, possibly via ring-opening of the cyclobutanes. Interestingly, reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate and cinnamylamines bearing electron-withdrawing groups such as NO_2, CN, CO_2Me, CO_2Et, or CF_3 on *ortho* and *para* positions in the presence of EDCI/HOBt/Et_3N at room temperature or at 60−80 °C gave tetrahydrobenz-[*f*]isoindolines via [4 + 2] cycloaddition as major products. Diversity of the reaction pattern depending on the substituents of the benzene ring was found. Further transformation of the highly functionalized heterocyclic products to useful compounds are under investigation.

EXPERIMENTAL SECTION

General Methods. ^{1}H Chemical shifts are reported in ppm relative to Me_4Si. ^{13}C Chemical shifts are reported in ppm relative to $CDCl_3$ (77.1 ppm). ^{19}F Chemical shifts are reported in ppm relative to $CFCl_3$. ^{13}C Mutiplicities were determined by DEPT and HSQC. Mass spectra were recorded at an ionizing voltage of 70 eV by EI, FAB, CI, or ESI. Mass analyzer type used for EI, FAB, and CI is double-focusing and that for ESI is TOF in the HRMS measurements. All reactions were carried out under a nitrogen atmosphere. Column chromatography was performed on silica gel (75−150 μm).

Ethenetricarboxylate **1** was prepared according to the literature.[24] Cinnamylamines **2a**−**x** were prepared from the corresponding cinnamaldehydes and amines by reductive amination in methanol (for **2a**−**p**, **2r**−**x**) or ethanol (for **2q**) according to the literature procedure.[25] ^{1}H NMR of **2a** was in accord with the reported data.[26]

5-Fluoro-2-nitrocinnamaldehyde (90%), 4-cyanocinnamaldehyde (86%), and 3-nitrocinnamaldehyde (47%) were prepared from the corresponding benzaldehydes and acetoaldehyde according to the literature procedure.[27] ^{1}H NMR spectra of 4-cyanocinnamaldehyde and 3-nitrocinnamaldehyde were in accord with the reported data.[28] 4-(Methoxycarbonyl)cinnamaldehyde (59%) was prepared by the palladium-catalyzed reaction of the corresponding aryl iodides with acrolein diethyl acetal.[28] ^{1}H NMR spectra of 4-(methoxycarbonyl)cinnamaldehyde were in accord with the reported data.[29] 4-(Ethoxycarbonyl)-cinnamaldehyde and 3-fluorocinnamaldehyde were prepared according to the literature.[28] 4-(Trifluoromethyl)cinnamaldehyde (58%), 3-(trifluoromethyl)cinnamaldehyde (56%), 3,5-bis(trifluoromethyl)-cinnamaldehyde (81%) were prepared from the corresponding benzaldehydes and formylmethylenetriphenylphosphorane according to the literature procedure.[30] ^{1}H NMR of 3-(trifluoromethyl)cinnamaldehyde was in accord with the reported data.[28]

4-(Trifluoromethyl)cinnamaldehyde. (8.2 mmol scale, 0.951 g, 58%); R_f = 0.6 (hexane−ether = 1:1); pale yellow crystals; mp 60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.78 (dd, *J* = 16.0, 7.6 Hz, 1H), 7.52 (d, *J* = 16.0 Hz, 1H), 7.69 (s, 4H), 9.76 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 123.7 (C, q, J_{CF} = 272 Hz), 126.0 (CH, q, J_{CF} = 3.8 Hz), 128.6 (CH), 130.5 (CH), 132.4 (C, q, J_{CF} = 33 Hz), 137.3 (C, q, J_{CF} = 1.5 Hz), 150.3 (CH), 193.2 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −63.05; IR (KBr) 2817, 2733, 1680, 1324, 1172, 1122, 1066 cm^{-1}; MS (EI) *m*/*z* 200 (M^+, 38), 199 (32), 151 (47), 131 (100%); HRMS (EI) *m*/*z* M^+ 200.0448 (calcd for $C_{10}H_7F_3O$ 200.0449).

3,5-Bis(trifluoromethyl)cinnamaldehyde. (10 mmol scale, 2.17 g, 81%); R_f = 0.7 (hexane−ether = 1:1); pale yellow crystals; mp 80−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.85 (dd, *J* = 16.1, 7.4 Hz, 1H), 7.56 (d, *J* = 16.1 Hz, 1H), 7.94 (s, 1H), 8.02 (d, *J* = 0.4 Hz, 2H), 9.80 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 123.0 (C, q, J_{CF} = 273 Hz), 124.2 (CH, q, J_{CF} = 3.8 Hz), 128.1 (CH, q, J_{CF} = 3.1 Hz), 131.5 (CH), 132.8 (C, q, J_{CF} = 34 Hz), 136.2 (C), 148.1 (CH), 192.6 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −63.27; IR (KBr) 3088, 2834, 2749, 1696, 1379, 1279, 1178, 1123, 1107 cm^{-1}; MS (FAB) *m*/*z* 269 ($[M + H]^+$), 267 ($[M - H]^+$); HRMS (FAB) *m*/*z* $[M - H]^+$ 267.0245 (calcd for $C_{11}H_5F_6O$ 267.0245), $[M + H]^+$ 269.0402 (calcd for $C_{11}H_7F_6O$ 269.0401).

5-Fluoro-2-nitrocinnamaldehyde was prepared from 5-fluoro-2-nitrobenzaldehyde and acetoaldehyde according to the literature procedure.[28]

5-Fluoro-2-nitrocinnamaldehyde. (5.9 mmol scale, 1.04 g, 90%); colorless crystals; mp 139−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.61 (dd, *J* = 15.8, 7.6 Hz, 1H), 7.30 (ddd, J_{CH} = 9.1, 2.7 Hz, J_{FH} = 7.0 Hz, 1H), 7.35 (dd, J_{CH} = 2.7 Hz, J_{FH} = 8.6 Hz, 1H), 8.06 (d, *J* = 15.8 Hz, 1H), 8.21 (dd, J_{CH} = 9.1 Hz, J_{FH} = 5.0 Hz, 1H), 9.80 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 116.1 (CH, d, J_{CF} = 25 Hz), 118.0 (CH, d, J_{CF} = 23 Hz), 128.3 (CH, d, J_{CF} = 10 Hz), 133.42 (CH), 133.43 (C, d, J_{CF} = 10 Hz), 144.1 (C), 146.2 (CH, d, J_{CF} = 1.5 Hz), 165.0 (C, d, J_{CF} = 258 Hz), 192.7 (CH); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −101.91 (ddd, *J* = 8.6, 7.0, 5.0 Hz); IR (KBr) 3082, 2849, 1695, 1584, 1521, 1344, 1278, 1119, 979 cm^{-1}; MS (EI) *m*/*z* 195 (M^+, 1.3), 166 (100), 145 (86), 120 (52), 110 (69%); HRMS (EI) *m*/*z* M^+ 195.0327 (calcd for $C_9H_6FNO_3$ 195.0332).

Typical Experimental Procedure for Preparation of Cinnamylamines 2. A solution of *trans*-cinnamaldehyde (0.834 g, 10 mmol) and cyclohexylmethylamine (1.01 g, 8.9 mmol) in methanol (6.8 mL) was heated under reflux for 30 min, followed by the portionwise addition of $NaBH_4$ (567 mg, 15 mmol) in ice-cooled bath. The mixture was stirred overnight at room temperature. Excess sodium borohydride was quenched by the addition of acetone (3.7 mL). The mixture was concentrated, and the residue was dissloved in CH_2Cl_2 and water. The organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography over silica gel eluting with hexane−Et_2O to give **2b** (1.82 g, 89%).

*Cinnamyl Cyclohexylmethylamine (**2b**).* R_f = 0.4 (hexane−ether = 2:1); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.863−0.963 (m, 2H), 1.10−1.30 (m, 3H), 1.42−1.52 (m, 2H), 1.64−1.77 (m, 5H), 2.47 (d, *J* = 6.6 Hz, 2H), 3.37 (dd, *J* = 6.3, 1.5 Hz, 2H), 6.29 (dt, 15.9, 6.3 Hz, 1H), 6.51 (d, *J* = 15.9 Hz, 1H), 7.17−7.21 (m, 1H), 7.26−7.32 (m, 2H), 7.34−7.39 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 26.1 (CH_2), 26.7 (CH_2), 31.5 (CH_2), 38.1 (CH), 52.1 (CH_2), 56.3 (CH_2), 126.2 (CH), 127.2 (CH), 128.5 (CH), 128.8 (CH), 131.0 (CH), 137.2 (C); IR (neat) 3339, 3025, 2925, 2850, 1652, 1599, 1495, 1448, 1348, 1125, 966 cm^{-1}; MS (EI) *m*/*z* 229 (M^+, 17), 146 (26), 117 (100%); HRMS (EI) M^+ 229.1832 (calcd for $C_{16}H_{23}N$ 229.1830).

*Cinnamyl 4-(Trifluoromethyl)benzylamine (**2c**).* (8.9 mmol scale, 2.45 g, 95%); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.51 (bs, 1H), 3.42 (dd, *J* = 6.3, 1.5 Hz, 2H), 3.88 (s, 2H), 6.29 (dt, *J* = 15.9, 6.3 Hz, 1H), 6.53 (d, *J* = 15.9 Hz, 1H), 7.20−7.24 (m, 1H), 7.28−7.32 (m, 2H), 7.36−7.38 (m, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) 51.3 (CH_2), 52.7 (CH_2), 124.3 (C, q, J_{CF} = 272 Hz), 125.4 (CH, q, J_{CF} = 3.8 Hz), 126.3 (CH), 127.5 (CH), 128.1 (CH), 128.4 (CH), 128.6 (CH), 128.8 (C, q, J_{CF} = 32 Hz), 131.7 (CH), 137.0 (C), 144.5 (C); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −62.38; IR (neat) 3313, 3027, 2827, 1619, 1495, 1449, 1418, 1329, 1164, 1120, 1066, 1018, 967 cm^{-1}; MS (FAB) *m*/*z* 290 ($[M - H]^+$); HRMS (FAB) $[M - H]^+$ 290.1158 (calcd for $C_{17}H_{15}F_3N$ 290.1157).

*Allyl Cinnamylamine (**2d**).* (8.9 mmol scale, 1.48 g, 95%); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.23 (bs, 1H), 3.30 (ddd, *J* = 6.0, 1.6, 1.4 Hz, 2H), 3.41 (dd, *J* = 6.3, 1.5 Hz, 2H), 5.11 (ddt, *J* = 10.3, 1.6, 1.4 Hz, 1H), 5.20 (ddt, *J* = 17.1, 1.6, 1.6 Hz, 1H), 5.93 (ddt, *J* = 17.1, 10.3, 6.0 Hz, 1H), 6.29 (dt, *J* = 15.8, 6.3 Hz, 1H), 6.52 (d, *J* = 15.8 Hz, 1H), 7.19−7.23 (m, 1H), 7.27−7.32 (m, 2H), 7.35−7.38 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 51.2 (CH_2), 51.9 (CH_2), 116.0 (CH_2), 126.3 (CH), 127.4 (CH), 128.4 (CH), 128.6 (CH), 131.4 (CH), 136.8 (CH), 137.1 (C); IR (neat) 3316, 3025, 2816, 1643, 1598, 1494, 1448, 1114, 967 cm^{-1}; MS (FAB) *m*/*z* 174 ($[M + H]^+$); HRMS (FAB) *m*/*z* $[M + H]^+$ 174.1285 (calcd for $C_{12}H_{16}N$ 174.1283), $[M - H]^+$ 172.1130 (calcd for $C_{12}H_{14}N$ 172.1126).

*Benzyl 4-Fluorocinnamylamine (**2e**).* (6.9 mmol scale, 1.32 g, 79%); R_f = 0.4 (ether); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.70 (bs, 1H), 3.41 (dd, *J* = 6.3, 1.4 Hz, 2H), 3.82 (s, 2H), 6.22 (dt, *J* = 15.8, 6.3 Hz, 1H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.98 (dd-like, J_{HH} = 8.8 Hz, J_{FH} = 8.8 Hz, 2H), 7.23−7.35 (m, 7H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 51.1 (CH_2), 53.4 (CH_2), 115.4 (CH, d, J_{CF} = 21 Hz), 127.1 (CH), 127.8 (CH, d, J_{CF} = 7.7 Hz), 128.1 (CH, d, J_{CF} = 1.5 Hz), 128.2

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

(CH), 128.5 (CH), 130.3 (CH), 132.8 (C, d, J_{CF} = 3.1 Hz), 140.2 (C), 162.2 (C, d, J_{CF} = 246 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −114.86 (tt, J = 8.8, 5.7 Hz); IR (neat) 3312, 3028, 2819, 1602, 1508, 1453, 1228, 1158, 968 cm^{-1}; MS (EI) m/z 241 (M$^+$, 21), 196 (11), 132 (38), 106 (35), 91 (100%); HRMS (EI) m/z M$^+$ 241.1273 (calcd for $C_{16}H_{16}FN$ 241.1267).

*4-Fluorocinnamyl Propylamine (**2f**).* (8.9 mmol scale, 1.24 g, 72%); R_f = 0.2 (ether); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.935 (t, J = 7.4 Hz, 3H), 1.31 (bs, 1H), 1.55 (tq, J = 7.4, 7.4 Hz, 2H), 2.62 (t, J = 7.4 Hz, 2H), 3.39 (dd, J = 6.3, 1.4 Hz, 2H), 6.22 (dt, J = 15.8, 6.3 Hz, 1H), 6.48 (d, J = 15.8 Hz, 1H), 6.98 (dd-like, J_{HH} = 8.8 Hz, J_{FH} = 8.8 Hz, 2H), 7.32 (dd-like, J_{HH} = 8.8 Hz, J_{FH} = 5.5 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 11.8 (CH_3), 23.3 (CH_2), 51.5 (CH_2), 51.9 (CH_2), 115.4 (CH, d, J_{CF} = 22 Hz), 127.7 (CH, d, J_{CF} = 7.7 Hz), 128.4 (CH, d, J_{CF} = 2.3 Hz), 129.9 (CH), 133.4 (C, d, J_{CF} = 3.1 Hz), 162.2 (C, d, J_{CF} = 246 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −115.04 (tt, J = 8.8, 5.5 Hz); IR (neat) 3308, 2961, 1602, 1508, 1458, 1228, 1158, 1128, 967 cm^{-1}; MS (EI) m/z 193 (M$^+$, 29), 164 (20), 135 (100%); HRMS (EI) m/z M$^+$ 193.1272 (calcd for $C_{12}H_{16}FN$ 193.1267).

*Benzyl 4-Chlorocinnamylamine (**2g**).* (4.5 mmol scale, 0.794 g, 68%); R_f = 0.3 (hexane−ether = 2:1); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.62 (bs, 1H), 3.42 (dd, J = 6.3, 1.3 Hz, 2H), 3.82 (s, 2H), 6.23 (dt, J = 15.8, 6.3 Hz, 1H), 6.45 (dt, J = 15.8, 1.3 Hz, 1H), 7.23−7.28 (m, 5H), 7.32−7.33 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 51.1 (CH_2), 53.4 (CH_2), 127.1 (CH), 127.5 (CH), 128.2 (CH), 128.5 (CH), 128.7 (CH), 129.2 (CH), 130.1 (CH), 132.9 (C), 135.7 (C), 140.2 (C); IR (neat) 3311, 3027, 2818, 1491, 1453, 1404, 1360, 1091, 1012, 968 cm^{-1}; MS (EI) m/z 259 (M$^+$, 9.1), 257 (M$^+$, 22), 166 (16), 132 (52), 91 (100%); HRMS (EI) m/z M$^+$ 257.0971, 259.0980 (calcd for $C_{16}H_{16}ClN$ 257.0971, 259.0942).

*Benzyl 4-Bromocinnamylamine (**2h**).* (4.5 mmol scale, 1.15 g, 85%); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.60 (bs, 1H), 3.40 (dd, J = 6.2, 1.5 Hz, 2H), 3.82 (s, 2H), 6.28 (dt, J = 15.9, 6.2 Hz, 1H), 6.46 (d, J = 15.9 Hz, 1H), 7.20 (d-like, J = 8.5 Hz, 2H), 7.23−7.28 (m, 1H), 7.30−7.35 (m, 4H), 7.40 (d-like, J = 8.5 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 51.1 (CH_2), 53.4 (CH_2), 127.1 (CH), 127.8 (CH), 128.2 (CH), 128.5 (CH), 129.4 (CH), 130.1 (CH), 131.7 (CH), 136.1 (C), 140.1 (C); IR (neat) 3354, 3026, 2920, 2824, 1652, 1486, 1455, 1401, 1361, 1116, 1071, 1008, 967 cm^{-1}; MS (EI) m/z 303 (M$^+$, 4.5), 301 (M$^+$, 4.5), 196 (19), 132 (18), 106 (54), 91 (100%); HRMS (EI) m/z M$^+$ 301.0470, 303.0451 (calcd for $C_{16}H_{16}BrN$ 301.0466, 303.0446).

*Benzyl 4-Methoxycinnamylamine (**2i**).* (8.9 mmol scale, 2.13 g, 94%); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.78 (bs, 1H), 3.40 (dd, J = 6.4, 1.0 Hz, 2H), 3.77 (s, 3H), 3.82 (s, 2H), 6.17 (dt, J = 15.8, 6.4 Hz, 1H), 6.47 (d, J = 15.8 Hz, 1H), 6.83 (d-like, J = 8.6 Hz, 2H), 7.22−7.34 (m, 7H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 51.3 (CH_2), 53.3 (CH_2), 55.3 (CH_3), 114.0 (CH), 126.1 (CH), 127.0 (CH), 127.4 (CH), 128.2 (CH), 128.4 (CH), 129.9 (C), 131.0 (CH), 140.2 (C), 159.1 (C); IR (neat) 3313, 3028, 2932, 2834, 1607, 1511, 1453, 1249, 1174, 1107, 1034, 968 cm^{-1}; MS (EI) m/z 253 (M$^+$, 3.3), 196 (18), 162 (18), 106 (56), 91 (100%); HRMS (EI) m/z M$^+$ 253.1471 (calcd for $C_{17}H_{19}NO$ 253.1467).

*Benzyl 2-Nitrocinnamylamine (**2j**).* (8.9 mmol scale, 1.35 g, 56%); R_f = 0.4 (CH_2Cl_2−ether = 1:4); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.77 (bs, 1H), 3.47 (dd, J = 6.3, 1.6 Hz, 2H), 3.84 (s, 2H), 6.29 (dt, J = 15.6, 6.3 Hz, 1H), 7.01 (d, J = 15.6 Hz, 1H), 7.23−7.28 (m, 1H), 7.31−7.37 (m, 5H), 7.50−7.58 (m, 2H), 7.89 (dd, J = 8.2, 1.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 51.0 (CH_2), 53.3 (CH_2), 124.5 (CH), 126.5 (CH), 127.1 (CH), 127.9 (CH), 128.3 (CH), 128.5 (CH), 128.7 (CH), 132.8 (C), 133.0 (CH), 134.1 (CH), 140.0 (C), 147.8 (C); IR (neat) 3329, 3063, 3027, 2820, 1606, 1571, 1523, 1454, 1347, 1120, 966 cm^{-1}; MS (EI) m/z 269 ([M + H]$^+$, 1.5), 268 (M$^+$, 0.7), 267 ([M − H]$^+$, 2.8), 250 (13), 146 (28), 120 (48), 91 (100%); HRMS (EI) m/z [M + H]$^+$ 269.1284 (calcd for $C_{16}H_{17}N_2O_2$ 269.1290), M$^+$ 268.1179 (calcd for $C_{16}H_{16}N_2O_2$ 268.1212), [M − H]$^+$ 267.1138 (calcd for $C_{16}H_{15}N_2O_2$ 267.1134).

*Cyclohexylmethyl 2-Nitrocinnamylamine (**2k**).* (8.9 mmol scale, 1.76 g, 72%); R_f = 0.4 (CH_2Cl_2−ether = 1:4); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.891−0.981 (m, 2H), 1.10−1.30 (m, 3H), 1.43−1.53 (m, 1H), 1.55 (bs, 1H), 1.65−1.78 (m, 5H), 2.50 (d, J = 6.6 Hz, 2H), 3.44 (dd, J = 6.2, 1.5 Hz, 2H), 6.30 (dt, J = 15.8, 6.2, 1H), 6.99 (d, J = 15.8 Hz, 1H), 7.35 (ddd, J = 8.2, 7.4, 1.2 Hz, 1H), 7.53 (ddd, J = 7.8, 7.4, 1.0 Hz, 1H), 7.60 (dd, J = 7.8, 1.2 Hz, 1H), 7.87 (dd, J = 8.2, 1.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 26.0 (CH_2), 26.6 (CH_2), 31.3 (CH_2), 38.0 (CH), 51.8 (CH_2), 56.2 (CH_2), 124.3 (CH), 125.9 (CH), 127.7 (CH), 128.5 (CH), 132.7 (C), 132.8 (CH), 134.4 (CH), 147.6 (C); IR (neat) 2924, 2850, 1606, 1570, 1522, 1448, 1348, 1125, 966 cm^{-1}; MS (CI) m/z 275 ([M + H]$^+$) ; HRMS (CI) m/z [M + H]$^+$ 275.1759 (calcd for $C_{16}H_{23}N_2O_2$ 275.1760).

*Allyl 2-Nitrocinnamylamine (**2l**).* (8.9 mmol scale, 1.33 g, 69%); R_f = 0.3 (CH_2Cl_2−ether = 1:4); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.36 (bs, 1H), 3.32 (ddd, J = 4.5, 1.4, 1.4 Hz, 2H), 3.47 (dd, J = 6.1, 1.6 Hz, 2H), 5.13 (ddt, J = 10.4, 1.5, 1.5 Hz, 1H), 5.22 (ddt, J = 17.2, 1.5, 1.5 Hz, 1H), 5.93 (ddt, J = 17.2, 10.4, 6.1 Hz, 1H), 6.29 (dt, J = 15.8, 6.1 Hz, 1H), 7.00 (d, J = 15.8 Hz, 1H), 7.37 (ddd, J = 8.2, 7.3, 1.6 Hz, 1H), 7.53−7.57 (m, 1H), 7.60 (dd, J = 7.8, 1.6 Hz, 1H), 7.89 (dd, J = 8.2, 1.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 50.9 (CH_2), 51.7 (CH_2), 116.2 (CH_2), 124.4 (CH), 126.3 (CH), 127.8 (CH), 128.6 (CH), 132.7 (C), 133.0 (CH), 134.1 (CH), 136.5 (CH), 147.7 (C); IR (neat) 3325, 3072, 2817, 1643, 1606, 1571, 1522, 1442, 1350, 1307, 1144, 1115, 994, 967 cm^{-1}; MS (EI) m/z 218 (M$^+$, 1.2), 217 (6.8), 200 (26), 170 (42), 146 (84), 130 (43), 116 (100%); HRMS (EI) m/z M$^+$ 218.1046 (calcd for $C_{12}H_{14}N_2O_2$ 218.1055).

*Benzyl 5-Fluoro-2-nitrocinnamylamine (**2m**).* (5 mmol scale, 0.479 g, 33%); R_f = 0.2 (hexane−ether = 1:4); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.75 (bs, 1H), 3.48 (dd, J = 6.1, 1.6 Hz, 2H), 3.85 (s, 2H), 6.29 (dt, J = 15.8, 6.1 Hz, 1H), 7.03 (ddd, J_{FH} = 7.2 Hz, J_{HH} = 9.1, 2.7 Hz, 1H), 7.06 (bd, J = 15.8 Hz, 1H), 7.23 (dd, J_{FH} = 9.6 Hz, J_{HH} = 2.7 Hz, 1H), 7.24−7.28 (m, 1H), 7.32−7.36 (m, 4H), 7.99 (dd, J_{HH} = 9.1 Hz, J_{FH} = 5.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 50.8 (CH_2), 53.4 (CH_2), 115.0 (CH, d, J_{CF} = 23 Hz), 115.3 (CH, d, J_{CF} = 24 Hz), 125.9 (CH, d, J_{CF} = 1.5 Hz), 127.2 (CH), 127.5 (CH, d, J_{CF} = 10 Hz), 128.3 (CH), 128.5 (CH), 135.5 (CH), 136.4 (C, d, J_{CF} = 9.2 Hz), 134.0 (C), 143.8 (C, d, J_{CF} = 3.1 Hz), 164.7 (C, d, J_{CF} = 256 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −104.13 (ddd, J_{FH} = 9.6, 7.2, 5.2 Hz); IR (neat) 3324, 3028, 2821, 1645, 1616, 1581, 1520, 1345, 1273, 1221, 1132, 1075, 966 cm^{-1}; MS (CI) m/z 287 ([M + H]$^+$); HRMS (CI) m/z 287.1190 (calcd for $C_{16}H_{16}FN_2O_2$ [M + H]$^+$ 287.1196).

*Benzyl 4-Nitrocinnamylamine (**2n**).* (8.9 mmol scale, 1.08 g, 45%); R_f = 0.2 (hexane−ether = 1:4); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.68 (bs, 1H), 3.49 (dd, J = 5.9, 1.4 Hz, 2H), 3.85 (s, 2H), 6.50 (dt, J = 16.0, 5.9 Hz, 1H), 6.62 (d, J = 16.0 Hz, 1H), 7.24−7.30 (m, 1H), 7.31−7.35 (m, 4H), 7.47 (d-like, J = 8.9 Hz, 2H), 8.15 (d-like, J = 8.9 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 50.9 (CH_2), 53.5 (CH_2), 124.0 (CH), 126.7 (CH), 127.2 (CH), 128.2 (CH), 128.5 (CH), 129.1 (CH), 133.8 (CH), 134.0 (C), 143.7 (C), 146.8 (C); IR (neat) 3328, 3027, 2833, 1651, 1595, 1520, 1494, 1454, 1346, 1110, 971 cm^{-1}; MS (EI) m/z 268 (M$^+$, 6.9), 196 (16), 132 (23), 91 (100%); HRMS (EI) m/z M$^+$ 268.1207 (calcd for $C_{16}H_{16}N_2O_2$ 268.1212).

*Benzyl 4-Cyanocinnamylamine (**2o**).* (6.4 mmol scale, 0.837 g, 53%); R_f = 0.2 (hexane−ether = 1:4); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.55 (bs, 1H), 3.47 (dd, J = 5.9, 1.4 Hz, 2H), 3.84 (s, 2H), 6.44 (dt, J = 15.9, 5.9 Hz, 1H), 6.56 (d, J = 15.9 Hz, 1H), 7.24−7.30 (m, 1H), 7.32−7.35 (m, 4H), 7.42 (d-like, J = 8.4 Hz, 2H), 7.57 (d-like, J = 8.4 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 50.9 (CH_2), 53.5 (CH_2), 110.5 (C), 119.0 (C), 126.7 (CH), 127.2 (CH), 128.2 (CH), 128.5 (CH), 129.5 (CH), 132.4 (CH), 132.8 (CH), 140.0 (C), 141.7 (C); IR (neat) 3315, 3028, 2821, 2224, 1651, 1604, 1495, 1453, 1412, 1360, 1175, 1118, 971 cm^{-1}; MS (EI) m/z 248 (M$^+$, 13), 196 (10), 146 (32), 106 (34), 91 (100%); HRMS (EI) m/z M$^+$ 248.1317 (calcd for $C_{17}H_{16}N_2$ 248.1313).

*Benzyl 4-(Methoxycarbonyl)cinnamylamine (**2p**).* (5 mmol scale, 0.625 g, 44%); R_f = 0.2 (hexane−ether = 1:4); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.52 (bs, 1H), 3.46 (dd, J = 6.1, 1.4 Hz, 2H), 3.85 (s, 2H), 3.90 (s, 3H), 6.44 (dt, J = 15.9, 6.1 Hz, 1H), 6.58 (d, J = 15.9 Hz, 1H), 7.22−7.29 (m, 1H), 7.31−7.35 (m, 4H), 7.41 (d, J = 8.3 Hz, 2H), 7.97 (d-like, J = 8.3 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 51.1 (CH_2), 52.1 (CH_3), 53.5 (CH_2), 126.2 (CH),

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

127.1 (CH), 128.2 (CH), 128.5 (CH), 128.8 (C), 130.0 (CH), 130.4 (CH), 131.5 (CH), 140.2 (C), 141.7 (C), 167.0 (C); IR (neat) 3326, 3028, 2950, 1721, 1606, 1454, 1435, 1281, 1178, 1109, 1017, 971 cm^{-1}; MS (EI) m/z 281 (M^+, 14), 132 (35), 106 (25), 91 (100%); HRMS (EI) m/z M^+ 281.1417 (calcd for $C_{18}H_{19}NO_2$ 281.1416).

*Benzyl 4-(Ethoxycarbonyl)cinnamylamine (**2q**).* (6 mmol scale, 0.832 g, 47%); R_f = 0.2 (hexane−ether = 1:4); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.39 (t, J = 7.1 Hz, 3H), 1.56 (bs, 1H), 3.46 (dd, J = 6.1, 1.4 Hz, 2H), 3.85 (s, 2H), 4.36 (q, J = 7.1 Hz, 2H), 6.43 (dt, J = 15.9, 6.1 Hz, 1H), 6.58 (d, J = 15.9 Hz, 1H), 7.24−7.29 (m, 1H), 7.31−7.36 (m, 4H), 7.41 (d-like, J = 8.4 Hz, 2H), 7.98 (d-like, J = 8.4 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.4 (CH_3), 51.2 (CH_2), 53.5 (CH_2), 60.9 (CH_2), 126.1 (CH), 127.1 (CH), 128.2 (CH), 128.5 (CH), 129.2 (C), 129.9 (CH), 130.4 (CH), 131.3 (CH), 140.2 (C), 141.6 (C), 166.5 (C); IR (neat) 3316, 2980, 1713, 1607, 1495, 1453, 1413, 1366, 1275, 1178, 1105, 1020, 972 cm^{-1}; MS (EI) m/z 295 (M^+, 31), 204 (20), 132 (71), 91 (100%); HRMS (EI) m/z M^+ 295.1581 (calcd for $C_{19}H_{21}NO_2$ 295.1572).

*Benzyl 4-(Trifluoromethyl)cinnamylamine (**2r**).* (3.6 mmol scale, 0.996 g, 96%); R_f = 0.5 (hexane−ether = 1:1); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.55 (bs, 1H), 3.46 (dd, J = 6.1, 1.4 Hz, 2H), 3.84 (s, 2H), 6.41 (dt, J = 15.8, 6.1 Hz, 1H), 6.58 (d, J = 15.8 Hz, 1H), 7.25−7.30 (m, 1H), 7.32−7.35 (m, 4H), 7.44 (d, J = 8.2 Hz, 2H), 7.55 (d, J = 8.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 51.1 (CH_2), 53.5 (CH_2), 124.1 (C, q, J_{CF} = 272 Hz), 125.6 (CH, q, J_{CF} = 3.8 Hz), 126.5 (CH), 127.2 (CH), 128.3 (CH), 128.6 (CH), 129.2 (C, q, J = 32 Hz), 130.0 (CH), 131.4 (CH), 140.2 (C), 140.7 (C); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −62.50; IR (neat) 3310, 3029, 2823, 1652, 1615, 1495, 1455, 1415, 1327, 1163, 1120, 1067, 1016, 970 cm^{-1}; MS (EI) m/z 291 (M^+, 100), 200 (11), 185 (35), 132 (67), 91 (100%); HRMS (EI) m/z M^+ 291.1235 (calcd for $C_{17}H_{16}F_3N$ 291.1235).

*Benzyl 3-(Trifluoromethyl)cinnamylamine (**2s**).* (2.7 mmol scale, 0.656 g, 83%); R_f = 0.6 (hexane−ether = 1:1); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.55 (bs, 1H), 3.45 (dd, J = 6.2, 1.5 Hz, 2H), 3.84 (s, 2H), 6.38 (dt, J = 15.8, 6.2 Hz, 1H), 6.56 (d, J = 15.8 Hz, 1H), 7.24−7.29 (m, 1H), 7.31−7.36 (m, 4H), 7.40 (dd, J = 7.6, 7.4 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 7.4 Hz, 1H), 7.60 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 51.0 (CH_2), 53.5 (CH_2), 123.0 (CH, q, J_{CF} = 3.8 Hz), 123.9 (CH, q, J_{CF} = 3.8 Hz), 124.2 (C, q, J_{CF} = 272 Hz), 127.1 (CH), 128.2 (CH), 128.5 (CH), 129.0 (CH), 129.4 (CH), 129.9 (CH), 130.7 (CH), 131.0 (C, q, J_{CF} = 32 Hz), 138.0 (C), 140.2 (C); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −62.79; IR (neat) 3307, 3028, 2821, 1657, 1605, 1591, 1495, 1453, 1332, 1201, 1165, 1126, 1072, 966 cm^{-1}; MS (EI) m/z 291 (M^+, 24), 200 (14), 132 (42), 91 (100%); HRMS (EI) M^+ 291.1250 (calcd for $C_{17}H_{16}F_3N$ 291.1235).

*Benzyl 3-(Trifluoromethyl)cinnamylamine (**2t**).* (5.8 mmol scale, 1.84 g, 88%); R_f = 0.6 (hexane−ether = 1:1); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.63 (bs, 1H), 3.49 (dd, J = 5.9, 1.4 Hz, 2H), 3.86 (s, 2H), 6.47 (dt, J = 15.8, 5.9 Hz, 1H), 6.62 (d, J = 15.8 Hz, 1H), 7.25−7.29 (m, 1H), 7.30−7.37 (m, 4H), 7.71 (s, 1H), 7.76 (s, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 50.8 (CH_2), 53.5 (CH_2), 120.8 (CH, septet, J_{CF} = 3.8 Hz), 123.4 (C, q, J_{CF} = 273 Hz), 126.1 (CH), 127.2 (CH), 128.2 (CH), 128.4 (CH), 128.6 (CH), 131.9 (C, q, J_{CF} = 33 Hz), 133.1 (CH), 139.3 (C), 140.0 (C); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −63.09; IR (neat) 3296, 3030, 2832, 1657, 1616, 1496, 1455, 1382, 1276, 1135, 1028, 968 cm^{-1}; MS (EI) m/z 359 (M^+, 22), 132 (36), 91 (100%); HRMS (EI) M^+ 359.1131 (calcd for $C_{18}H_{15}F_6N$ 359.1109).

*Benzyl 3-Fluorocinnamylamine (**2u**).* (2.2 mmol scale, 0.221 g, 42%); R_f = 0.3 (ether); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.47 (bs, 1H), 3.44 (dd, J = 6.2, 1.5 Hz, 2H), 3.84 (s, 2H), 6.32 (dt, J = 16.0, 6.2 Hz, 1H), 6.51 (d, J = 16.0 Hz, 1H), 6.91 (ddd, J_{FH} = 8.6, J_{HH} = 8.6, 0.9 Hz, 1H), 7.06 (ddd, J_{FH} = 10.4, J_{HH} = 2.1, 2.1 Hz, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.22−7.28 (m, 2H), 7.23−7.35 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 51.1 (CH_2), 53.5 (CH_2), 112.8 (CH, d, J_{CF} = 21 Hz), 114.2 (CH, d, J_{CF} = 21 Hz), 122.2 (CH, d, J_{CF} = 3.1 Hz), 127.1 (CH), 128.3 (CH), 128.5 (CH), 130.0 (CH, d, J_{CF} = 3.8 Hz), 130.0 (CH, d, J_{CF} = 4.6 Hz), 130.3 (CH, d, J_{CF} = 3.1 Hz), 139.6 (C, d, J_{CF} = 7.7 Hz), 140.2 (C), 163.2 (C, d, J_{CF} = 245 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −113.66 (ddd, J_{FH} = 10.5, 8.6, 5.7 Hz); IR (neat) 3309, 3062, 3028, 2821, 1656, 1611, 1582, 1489, 1446, 1268, 1144, 965 cm^{-1}; MS (EI) m/z 241 (M^+, 66), 150 (33), 132 (62), 91 (100%); HRMS (EI) m/z M^+ 241.1261 (calcd for $C_{16}H_{16}FN$ 241.1267).

*Benzyl 3-Nitrocinnamylamine (**2v**).* (3.5 mmol scale, 0.723 g, 78%); R_f = 0.4 (ether); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.50 (bs, 1H), 3.48 (dd, J = 6.1, 1.4 Hz, 2H), 3.85 (s, 2H), 6.46 (dt, J = 15.8, 6.1 Hz, 1H), 6.60 (d, J = 15.8 Hz, 1H), 7.25−7.30 (m, 1H), 7.32−7.35 (m, 4H), 7.46 (dd, J = 8.2, 7.6 Hz, 1H), 7.65 (d, J = 7.6 Hz, 1H), 8.05 (ddd, J = 8.2, 2.2, 1.0 Hz, 1H), 8.20 (dd, J = 2.2, 2.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 50.9 (CH_2), 53.5 (CH_2), 120.9 (CH), 121.9 (CH), 127.1 (CH), 128.2 (CH), 128.5 (CH), 128.9 (CH), 129.5 (CH), 132.06 (CH), 132.10 (CH), 139.0 (C), 140.1 (C), 148.6 (C); IR (neat) 3329, 3028, 1656, 1522, 1453, 1350, 1119, 1028, 967 cm^{-1}; MS (FAB) m/z 269 ($[M + H]^+$), 268 (M^+), 267 ($[M - H]^+$); HRMS (FAB) m/z $[M + H]^+$ 269.1286 (calcd for $C_{16}H_{17}N_2O_2$ 269.1290), $[M - H]^+$ 267.1132 (calcd for $C_{16}H_{15}N_2O_2$ 267.1134).

*Benzyl 3-Nitrocinnamylamine (**2w**).* (4.2 mmol scale, 0.756 g, 66%); R_f = 0.2 (CH_2Cl_2−ether = 1:4); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.887−0.988 (m, 2H), 1.11−1.32 (m, 4H), 1.43−1.54 (m, 1H), 1.65−1.79 (m, 5H), 2.50 (d, J = 6.6 Hz, 2H), 3.44 (dd, J = 6.0, 1.4 Hz, 2H), 6.45 (dt, J = 15.8, 6.0 Hz, 1H), 6.59 (d, J = 15.8 Hz, 1H), 7.47 (dd, J = 8.2, 7.6 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 8.06 (ddd, J = 8.2, 2.1, 1.0 Hz, 1H), 8.21 (dd, J = 2.1, 2.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 26.1 (CH_2), 26.7 (CH_2), 31.5 (CH_2), 38.2 (CH), 51.8 (CH_2), 56.5 (CH_2), 120.9 (CH), 121.9 (CH), 128.6 (CH), 129.4 (CH), 132.1 (CH), 132.5 (CH), 139.1 (C), 148.6 (C); IR (neat) 3329, 2924, 2850, 1656, 1531, 1447, 1350, 1127, 966 cm^{-1}; MS (FAB) m/z 275 ($[M + H]^+$); HRMS (FAB) m/z $[M + H]^+$ 275.1765 (calcd for $C_{16}H_{23}N_2O_2$ 275.1760), M^+ 274.1678 (calcd for $C_{16}H_{22}N_2O_2$ 274.1681), $[M - H]^+$ 273.1606 (calcd for $C_{16}H_{21}N_2O_2$ 273.1603).

*Benzyl 4-Dimethylaminocinnamylamine (**2x**).* (4.5 mmol scale, 1.19 g, 98%); yellow crystals; mp 30−32 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.58 (bs, 1H), 2.93 (s, 6H), 3.40 (dd, J = 6.6, 1.4 Hz, 2H), 3.82 (s, 2H), 6.11 (dt, J = 15.8, 6.6 Hz, 1H), 6.44 (d, J = 15.8 Hz, 1H), 6.66 (d-like, J = 8.8 Hz, 2H), 7.22−7.28 (m, 3H), 7.30−7.34 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 40.6 (CH_3), 51.6 (CH_2), 53.3 (CH_2), 112.5 (CH), 124.0 (CH), 125.7 (C), 126.9 (CH), 127.2 (CH), 128.3 (CH), 128.4 (CH), 131.6 (CH), 140.4 (C), 150.0 (C); IR (neat) 3326, 3024, 2801, 1609, 1521, 1452, 1353, 1222, 1186, 1166, 1126, 1062, 965 cm^{-1}; MS (EI) m/z 266 (M^+, 63), 175 (73), 160 (51), 134 (100%); HRMS (EI) m/z M^+ 266.1793 (calcd for $C_{18}H_{22}N_2$ 266.1783).

Typical experimental procedure for eq 1,4-9 and preparationof 17 in Scheme 8 (eq 1, Table 1, entry 1). To a solution of 1,1-diethyl 2-hydrogen ethenetricarboxylate (**1**) (prepared from 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate (272 mg, 1 mmol) upon treatment with CF_3CO_2H (4 mL))[24] in THF (0.7 mL) were added benzyl cinnamylamine (**2a**) (223 mg, 1 mmol) in THF (0.7 mL), Et_3N (0.14 mL, 102 mg, 1 mmol), HOBt (1-hydroxybenzotriazole) (270 mg, 2 mmol) and EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) (199 mg, 1.04 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, and was allowed to warm to room temperature and stirred for 20 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$ solution, 2M aqueous citric acid, saturated aqueous $NaHCO_3$ and water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with hexane-Et_2O to give **3a** (180 mg, 43%).

3a: R_f = 0.1 (hexane-ether = 1 : 8); colorless crystals; mp 137−138.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29 (t, J = 7.0 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 2.39 (ddd, J = 10.7, 7.0, 5.9 Hz, 1H), 2.67 (d, J =10.7 Hz, 1H), 3.31 (dd, J = 10.7, 5.9 Hz, 1H), 3.89 (d, J = 7.0 Hz, 1H), 3.89 (d, J = 14.3 Hz, 1H), 4.03-4.17 (m, 2H), 4.22-4.36 (m, 3H), 4.89 (d, J = 14.3 Hz,1H), 6.75 (d-like, J = 7.6 Hz, 2H), 7.22-7.42 (m, 8H). Selected NOEs are between δ 2.39 (C5-*H*) and δ 3.31 (C4-H*H*), 6.75 (Ar-*H*), 3.89 (C1-*H*). Atom numbering is shown in eq 1.; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.5 (CH_3), 15.0 (CH_3), 36.1 (CH), 41.1 (CH), 44.8 (CH_2), 46.4 (CH_2), 59.9 (CH_2), 64.8 (CH_2), 79.2 (C),

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

79.8 (CH), 127.4 (CH), 127.9 (CH), 128.7 (CH), 128.9 (CH), 129.05 (CH), 129.11 (CH), 136.6 (C), 136.8 (C), 163.0 (C), 167.3 (C), 173.1 (C). Selected HMBC correlations are between δ 2.39 (C5-*H*), 2.67 (C4-*H*H), 3.89 (C1-*H*) and δ 173.1 (*C*2), between δ 2.39 (C5-*H*), 2.67 (C4-*H*H), 3.31 (C4-H*H*), 3.89 (C1-*H*) and δ 79.8 (*C*6), between δ 2.67 (C4-*H*H) and δ 41.1 (*C*1) and between δ 2.67 (C4-*H*H), 3.31 (C4-H*H*), 3.89 (C1-*H*) and δ 36.1 (*C*5).; IR (KBr) 2981, 1699, 1634, 1285, 1079 cm^{-1}; MS (EI) *m/z* 421 (M^+, 14), 222 (42), 199 (58), 132 (63), 91 (100%); HRMS *m/z* M^+ 421.1886 (calcd for $C_{25}H_{27}NO_5$ 421.1889).

3b: (1 mmol scale, 224 mg, 51%); R_f = 0.3 (ether); yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.908-1.01 (m, 2H), 1.14-1.26 (m, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.48-1.78 (m, 6H), 2.55 (ddd, *J* = 10.9, 7.0, 6.1 Hz, 1H), 2.86 (d, *J* = 10.7 Hz, 1H), 3.02 (dd, *J* = 13.6, 6.7 Hz, 1H), 3.13 (dd, *J* = 13.6, 7.7 Hz, 1H), 3.43 (dd, *J* = 10.7, 6.1 Hz, 1H), 3.84 (d, *J* = 7.0 Hz, 1H), 4.04-4.17 (m, 2H), 4.22-4.34 (m, 2H), 4.58 (d, *J* = 10.9 Hz, 1H), 7.30-7.32 (m, 2H), 7.42-7.48 (m, 3H). Selected NOEs are between δ 2.55 (C5-*H*) and δ 3.43 (C4-H*H*), 7.30-7.32 (Ar-*H*), 3.84 (C1-*H*) and between δ 4.58 (C6-*H*) and δ 2.86 (C4-*H*H).; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.4 (CH_3), 14.9 (CH_3), 25.7 (CH_2), 26.3 (CH_2), 30.7 (CH_2), 31.0 (CH_2), 35.7 (CH), 36.0 (CH), 41.1 (CH), 47.0 (CH_2), 49.1 (CH_2), 59.8 (CH_2), 64.8 (CH_2), 79.9 (C), 80.2 (CH), 127.7 (CH), 129.0 (CH), 129.4 (CH), 137.0 (C), 162.7 (C), 167.3 (C), 173.5 (C). Selected HMBC correlations are between δ 2.55 (C5-*H*), 2.86 (C4-*H*H), 3.84 (C1-*H*) and δ 173.5 (*C*2), between δ 2.55 (C5-*H*), 2.86 (C4-*H*H), 3.43 (C4-H*H*), 3.84 (C1-*H*) and δ 80.2 (*C*6), between δ 2.86 (C4-*H*H), 4.58 (C6-*H*) and δ 41.1 (*C*1) and between δ 2.86 (C4-*H*H), 3.43 (C4-H*H*), 3.84 (C1-*H*), 4.58 (C6-*H*) and δ 35.7 (*C*5).; IR (neat) 2978, 2924, 2852, 1699, 1634, 1447, 1377, 1285, 1078, 1026 cm^{-1}; MS (EI) *m/z* 427 (23), 268 (29), 228 (87), 117 (100%); HRMS *m/z* M^+ 427.2346 (calcd for $C_{25}H_{33}NO_5$ 427.2357).

3c: (1 mmol scale, 201 mg, 41%); R_f = 0.2 (ether); colorless crystals; mp 64-65 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29 (t, *J* = 7.1 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 2.45 (ddd, *J* = 10.9, 6.8, 6.0 Hz, 1H), 2.62 (d, *J* = 10.6 Hz, 1H), 3.34 (dd, *J* = 10.6, 6.0 Hz, 1H), 3.90 (d, *J* = 6.8 Hz, 1H), 4.00 (d, *J* = 14.4 Hz, 1H), 4.04-4.17 (m, 2H), 4.24 (d, *J* = 10.9 Hz, 1H), 4.26-4.36 (m, 2H), 4.91 (d, *J* = 14.4 Hz, 1H), 6.76 (d-like, *J* = 7.7 Hz, 2H), 7.24-7.29 (m, 2H), 7.30-7.34 (m, 1H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.66 (d, *J* = 8.0 Hz, 2H). Selected NOEs are between δ 2.45 (C5-*H*) and δ 3.34 (C4-H*H*), 6.76 (Ar-*H*), 3.90 (C1-*H*) and between δ 4.24 (C6-*H*) and δ 2.62 (C4-*H*H).; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.5 (CH_3), 15.0 (CH_3), 35.9 (CH), 41.0 (CH), 45.0 (CH_2), 46.0 (CH_2), 60.0 (CH_2), 64.8 (CH_2), 79.0 (C), 79.9 (CH), 124.1 (C, q, J_{CF} = 272 Hz), 125.9 (CH, q, J_{CF} = 3.8 Hz), 127.4 (CH), 128.8 (CH), 129.4 (CH), 130.4 (C, q, J_{CF} = 32 Hz), 136.5 (C), 140.7 (C), 163.1 (C), 167.3 (C), 173.2 (C). Selected HMBC correlations are between δ 2.45 (C5-*H*), 2.62 (C4-*H*H), 3.90 (C1-*H*) and δ 173.2 (*C*2), between δ 2.45 (C5-*H*), 2.62 (C4-*H*H), 3.34 (C4-H*H*), 3.90 (C1-*H*) and δ 79.9 (*C*6), between δ 2.62 (C4-*H*H), 4.24 (C6-*H*) and δ 41.0 (C1) and between δ 2.62 (C4-*H*H), 3.34 (C4-H*H*), 3.90 (C1-*H*), 4.24 (C6-*H*) and δ 35.9 (C5).; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -62.59; IR (KBr) 2983, 1701, 1618, 1416, 1326, 1167, 1125, 1066 cm^{-1}; MS (FAB) *m/z* 512 ($[M+Na]^+$), 490 ($[M+H]^+$); HRMS (FAB) *m/z* $[M+Na]^+$ 512.1657 (calcd for $C_{26}H_{26}F_3NO_5Na$ 512.1661).

3d: (1 mmol scale, 155 mg, 42%); R_f = 0.3 (ether); yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29 (t, *J* = 7.0 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 2.54 (ddd, *J* = 11.1, 7.0, 6.1 Hz, 1H), 2.85 (d, *J* = 10.8 Hz, 1H), 3.38 (dd, *J* = 10.8, 6.1 Hz, 1H), 3.70 (dd, *J* = 14.9, 6.9 Hz, 1H), 3.86 (d, *J* = 7.0 Hz, 1H), 4.02 (dd, *J* = 14.9, 6.1 Hz, 1H), 4.06-4.18 (m, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 4.55 (d, *J* = 11.1 Hz, 1H), 5.20 (ddd, *J* = 17.0, 1.4, 1.2 Hz, 1H), 5.23 (dd, *J* = 10.0, 1.2 Hz, 1H), 5.73 (dddd, *J* = 17.0, 10.0, 6.9, 6.1 Hz, 1H), 7.29-7.32 (m, 2H), 7.41-7.45 (m, 3H). Selected NOEs are between δ 2.54 (C5-*H*) and δ 3.38 (C4-H*H*), 7.29-7.32 (Ar-*H*), 3.86 (C1-*H*) and between δ 4.55 (C6-*H*) and δ 2.85 (C4-*H*H).; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.5 (CH_3), 15.0 (CH_3), 35.7 (CH), 41.1 (CH), 45.3 (CH_2), 45.7 (CH_2), 59.9 (CH_2), 64.9 (CH_2), 79.7 (C), 80.1 (CH), 119.0 (CH_2), 127.7 (CH), 129.0 (CH), 129.4 (CH), 132.3 (CH), 137.0 (C), 162.8 (C), 167.3 (C), 173.1 (C). Selected HMBC correlations are between δ 2.54 (C5-*H*), 2.85 (C4-*H*H), 3.86 (C1-*H*) and δ 173.1 (*C*2), between δ 2.54 (C5-*H*), 2.85 (C4-*H*H), 3.38 (C4-H*H*), 3.86 (C1-*H*) and δ 80.1 (*C*6), between δ 2.85 (C4-*H*H), 4.55 (C6-*H*) and δ 41.1 (C1) and between δ 2.85 (C4-*H*H), 3.38 (C4-H*H*), 3.86 (C1-*H*), 4.55 (C6-*H*) and δ 35.7 (C5).; IR (neat) 2982, 1699, 1626, 1489, 1443, 1378, 1285, 1185, 1078, 1027 cm^{-1}; MS (FAB) *m/z* 394 ($[M+Na]^+$), 372 ($[M+H]^+$); HRMS (FAB) *m/z* $[M+Na]^+$ 394.1629 (calcd for $C_{21}H_{25}NO_5Na$ 394.1630), $[M+H]^+$ 372.1804 (calcd for $C_{21}H_{26}NO_5$ 372.1811)

3e: (1 mmol scale, 172 mg, 39%); R_f = 0.3 (ether); colorless crystals; mp 107-108 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29 (t, *J* = 7.0 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 2.35 (ddd, *J* = 10.9, 6.8, 6.1 Hz, 1H), 2.62 (d, *J* = 10.8 Hz, 1H), 3.32 (dd, *J* = 10.8, 6.1 Hz, 1H), 3.85 (d, *J* = 14.3 Hz, 1H), 3.88 (d, *J* = 6.8 Hz, 1H), 4.03-4.15 (m, 2H), 4.23 (d, *J* = 10.9 Hz, 1H), 4.23-4.36 (m, 2H), 4.93 (d, *J* = 14.3 Hz, 1H), 6.72 (dd-like, J_{HH} = 8.6, J_{FH} = 5.2 Hz, 2H), 6.92 (dd-like, J_{HH} = 8.6, J_{FH} = 8.6 Hz, 2H), 7.27-7.30 (m, 2H), 7.37-7.42 (m, 3H). Selected NOEs are between δ 2.35 (C5-*H*) and δ 3.32 (C4-H*H*), 6.72 (Ar-*H*), 3.88 (C1-*H*) and between δ 4.23 (C6-*H*) and δ 2.62 (C4-*H*H).; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.5 (CH_3), 14.9 (CH_3), 36.2 (CH), 41.1 (CH), 44.6 (CH_2), 46.3 (CH_2), 59.9 (CH_2), 64.8 (CH_2), 79.1 (CH), 79.5 (C), 115.7 (CH, J_{CF} = 21 Hz), 128.0 (CH), 128.9 (CH), 129.1 (CH), 129.1 (CH, J_{CF} = 8.4 Hz), 132.7 (C, J_{CF} = 3.1 Hz), 136.6 (C), 162.8 (C), 163.0 (C, J_{CF} = 248 Hz), 167.2 (C), 172.9 (C). Selected HMBC correlations are between δ 2.35 (C5-*H*), 2.62 (C4-*H*H), 3.88 (C1-*H*) and δ 172.9 (*C*2), between δ 2.35 (C5-*H*), 2.62 (C4-*H*H), 3.32 (C4-H*H*), 3.88 (C1-*H*) and δ 79.1 (*C*6), between δ 2.62 (C4-*H*H), 4.23 (C6-*H*) and δ 41.1 (C1) and between δ 2.62 (C4-*H*H), 3.32 (C4-H*H*), 3.88 (C1-*H*), 4.23 (C6-*H*) and δ 36.2 (C5).; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −112.12 (tt, J_{FH} = 8.6, 5.2 Hz); IR (KBr) 2983, 1701, 1666, 1618, 1512, 1190, 1085 cm^{-1}; MS (EI) *m/z* 439 (M^+, 30), 366 (19), 277 (48), 240 (98), 91 (100%); HRMS (EI) *m/z* M^+ 439.1793 (calcd for $C_{25}H_{26}FNO_5$ 439.1795).

3f: (1 mmol scale, 201 mg, 51%, including a small amount of impurity); R_f = 0.3 (ether); colorless crystals; mp 85-86 °C; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.909 (t, *J* = 7.4 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.51 (qt, *J* = 7.4, 7.0 Hz, 2H), 2.54 (ddd, *J* = 11.1, 6.8, 6.1 Hz, 1H), 2.83 (d, *J* = 10.7 Hz, 1H), 3.14-3.29 (m, 2H), 3.46 (dd, *J* = 10.7, 6.1 Hz, 1H), 3.84 (d, *J* = 6.8 Hz, 1H), 4.03-4.16 (m, 2H), 4.26 (q, *J* = 7.1 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 1H), 4.55 (d, *J* = 11.1 Hz, 1H), 7.14 (dd-like, J_{FH} = 8.8, J_{HH} = 8.6 Hz, 2H), 7.32 (dd-like, J_{HH} = 8.6, J_{FH} = 5.3 Hz, 2H). Selected NOEs are between δ 2.54 (C5-*H*) and δ 3.46 (C4-H*H*), 7.32 (Ar-*H*), 3.84 (C1-*H*) and between δ 4.55 (C6-*H*) and δ 2.83 (C4-*H*H).; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 11.3 (CH_3), 14.4 (CH_3), 14.9 (CH_3), 20.6 (CH_2), 35.6 (CH), 41.0 (CH), 44.2 (CH_2), 46.1 (CH_2), 59.8 (CH_2), 64.9 (CH_2), 79.4 (CH), 80.0 (C), 116.0 (CH, J_{CF} = 21 Hz), 129.5 (CH, J_{CF} = 7.7 Hz), 132.9 (C, J_{CF} = 3.1 Hz), 162.6 (C), 163.2 (C, J_{CF} = 249 Hz), 167.2 (C), 173.1 (C). Selected HMBC correlations are between δ 2.54 (C5-*H*), 2.83 (C4-*H*H), 3.84 (C1-*H*) and δ 173.1 (*C*2), between δ 2.54 (C5-*H*), 2.83 (C4-*H*H), 3.46 (C4-H*H*), 3.84 (C1-*H*) and δ 79.4 (*C*6), between δ 2.83 (C4-*H*H), 4.55 (C6-*H*) and δ 41.0 (C1) and between δ 2.83 (C4-*H*H), 3.46 (C4-H*H*), 3.84 (C1-*H*), 4.55 (C6-*H*) and δ 35.6 (C5).; ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -116.48 (tt, J_{FH}= 8.8, 5.3 Hz); IR (neat) 2968, 1695, 1628, 1513, 1377, 1227, 1077, 1026 cm^{-1}; MS (EI) *m/z* 391 (M^+, 30), 318 (27), 277 (28), 232 (34), 192 (100%); HRMS (EI) *m/z* M^+ 391.1793 (calcd for $C_{21}H_{26}FNO_5$ 391.1795).

3g: (1 mmol scale, 182 mg, 40%); R_f = 0.3 (ether); colorless crystals; mp 58-59 °C; ^1H NMR (400MHz, $CDCl_3$) δ (ppm) 1.29 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 2.33 (ddd, *J* = 10.9, 6.8, 5.9 Hz, 1H), 2.62 (d, *J* = 10.8 Hz, 1H), 3.30 (dd, *J* = 10.8, 5.9 Hz, 1H), 3.82 (d, *J* = 14.2 Hz, 1H), 3.89 (d, *J* = 6.8 Hz, 1H), 4.02-4.15 (m, 2H), 4.21 (d, *J*= 10.9 Hz, 1H), 4.23-4.35 (m, 2H), 4.96 (d, *J* = 14.2 Hz, 1H), 6.63 (d-like, *J* = 8.4 Hz, 2H), 7.21 (d-like, *J* = 8.4 Hz, 2H), 7.26-7.32 (m, 2H), 7.37−7.41 (m, 3H). Selected NOEs are between δ 2.33 (C5-*H*) and δ 3.30 (C4-H*H*), 6.63 (Ar-*H*), 3.89 (C1-*H*) and between δ 4.21 (C6-*H*) and δ 2.62 (C4-*H*H).; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.5 (CH_3), 15.0 (CH_3), 36.1 (CH), 41.1 (CH), 44.5 (CH_2), 46.3 (CH_2), 60.0 (CH_2), 64.9 (CH_2), 79.0 (CH), 79.5 (C), 128.0 (CH), 128.7 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 135.1 (C), 135.2 (C), 136.6 (C), 162.8 (C), 167.2 (C), 172.8 (C). Selected HMBC correlations are between δ 2.33 (C5-*H*), 2.62 (C4-*H*H), 3.89 (C1-*H*) and δ 173.8 (*C*2),

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

between δ 2.33 (C5-*H*), 2.62 (C4-*H*H), 3.30 (C4-H*H*), 3.89 (C1-*H*) and δ 79.0 (*C*6), between δ 2.62 (C4-*H*H), 4.21 (C6-*H*) and δ 41.1 (*C*1) and between δ 2.62 (C4-*H*H), 3.30 (C4-H*H*), 3.89 (C1-*H*), 4.21 (C6-*H*) and δ 36.1 (*C*5).; IR (KBr) 2980, 1701, 1636, 1493, 1378, 1281, 1249, 1182, 1080 cm^{-1}; MS (EI) *m/z* 457 (M^+, 8.1), 455 (M^+, 19), 382 (13), 256 (45), 91 (100%); HRMS (EI) *m/z* M^+ 455.1502, 457.1485 (calcd for $C_{25}H_{26}ClNO_5$ 455.1500, 457.1470).

3h: (1 mmol scale, 202 mg, 40%); R_f = 0.4 (ether); colorless crystals; mp 55-56 °C; ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm) 1.28 (t, *J* = 7.0 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 2.33 (ddd, *J* = 10.9, 6.6, 6.0 Hz, 1H), 2.62 (d, *J* = 10.8 Hz, 1H), 3.32 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.81 (d, *J* = 14.2 Hz, 1H), 3.88 (d, *J* = 6.6 Hz, 1H), 4.02-4.15 (m, 2H), 4.19 (d, *J* = 10.9 Hz, 1H), 4.22-4.35 (m, 2H), 4.96 (d, *J* = 14.2 Hz, 1H), 6.56 (d-like, *J* = 8.4 Hz, 2H), 7.27-7.30 (m, 2H), 7.34-7.41 (m, 5H). Selected NOEs are between δ 2.33 (C5-*H*) and δ 3.32 (C4-H*H*), 6.56 (Ar-*H*), 3.88 (C1-*H*) and between δ 4.19 (C6-*H*) and δ 2.62 (C4-*H*H).; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.5 (CH_3), 14.9 (CH_3), 36.1 (CH), 41.1 (CH), 44.5 (CH_2), 46.3 (CH_2), 60.0 (CH_2), 64.9 (CH_2), 79.1 (CH), 79.4 (C), 123.2 (C), 128.00 (CH), 128.96 (CH), 128.98 (CH), 129.1 (CH), 131.9 (CH), 135.7 (C), 136.6 (C), 162.8 (C), 167.2 (C), 172.8 (C). Selected HMBC correlations are between δ 2.33 (C5-*H*), 2.62 (C4-*H*H), 3.88 (C1-*H*) and δ 172.8 (*C*2), between δ 2.33 (C5-*H*), 2.62 (C4-*H*H), 3.32 (C4-H*H*), 3.88 (C1-*H*) and δ 79.1 (*C*6), between δ 2.62 (C4-*H*H), 4.19 (C6-*H*) and δ 41.1 (*C*1) and between δ 2.62 (C4-*H*H), 3.32 (C4-H*H*), 3.88 (C1-*H*), 4.19 (C6-*H*) and δ 36.1 (*C*5).; IR (KBr) 2980, 1700, 1624, 1491, 1377, 1280, 1249, 1184, 1075, 1009 cm^{-1}; MS (EI) *m/z* 501 (M^+, 3.8), 499 (3.5), 404 (9.5), 302 (9.4), 277 (80), 91 (100%); HRMS (EI) *m/z* M^+ 499.0994, 501.0978 (calcd for $C_{25}H_{26}BrNO_5$ 499.0994, 501.0974).

3i: (1 mmol scale, 217 mg, 48%); R_f = 0.4 (ether); colorless crystals; mp 124-125 °C (ether-hexane = 1 : 19); ^{1}H NMR (400MHz, $CDCl_3$) δ (ppm) 1.28 (t, *J* = 7.0 Hz, 3H), 1.34 (t, *J* = 7.0 Hz, 3H), 2.38 (ddd, *J* = 10.9, 6.6, 6.0 Hz, 1H), 2.65 (d, *J* = 10.7 Hz, 1H), 3.31 (dd, *J* = 10.7, 6.0 Hz, 1H), 3.78 (s, 3H), 3.87 (d, *J* = 6.6 Hz, 1H), 3.89 (d, *J* = 14.2 Hz, 1H), 4.04-4.15 (m, 2H), 4.22 (d, *J* = 10.9 Hz, 1H), 4.24-4.36 (m, 2H), 4.89 (d, *J* = 14.2 Hz, 1H), 6.69 (d-like, *J* = 8.8 Hz, 2H), 6.76 (d-like, *J* = 8.8 Hz, 2H), 7.26-7.29 (m, 2H), 7.36-7.41 (m, 3H). Selected NOEs are between δ 2.38 (C5-*H*) and δ 3.31 (C4-H*H*), 6.69 (Ar-*H*), 3.87 (C1-*H*) and between δ 4.22 (C6-*H*) and δ 2.65 (C4-*H*H).; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.5 (CH_3), 15.0 (CH_3), 36.0 (CH), 41.1 (CH), 45.0 (CH_2), 46.4 (CH_2), 55.4 (CH_3), 59.9 (CH_2), 64.7 (CH_2), 79.2 (C), 79.6 (CH), 114.0 (CH), 127.9 (CH), 128.8 (CH), 128.9 (CH), 128.9 (C), 129.1 (CH), 136.7 (C), 160.2 (C), 163.1 (C), 167.4 (C), 173.1 (C). Selected HMBC correlations are between δ 2.38 (C5-*H*), 2.65 (C4-*H*H), 3.87 (C1-*H*) and δ 173.1 (*C*2), between δ 2.38 (C5-*H*), 2.65 (C4-*H*H), 3.31 (C4-H*H*), 3.87 (C1-*H*) and δ 79.6 (*C*6), between δ 2.65 (C4-*H*H), 4.22 (C6-*H*) and δ 41.1 (*C*1) and between δ 2.65 (C4-*H*H), 3.87 (C1-*H*), 4.22 (C6-*H*) and δ 36.0 (*C*5).; IR (KBr) 2982, 2901, 1700, 1680, 1646, 1612, 1516, 1249, 1179, 1081, 1028 cm^{-1}; MS (FAB) *m/z* 474 ($[M+Na]^+$), 452 ($[M+H]^+$); HRMS (FAB) *m/z* $[M+Na]^+$ 474.1898 (calcd for $C_{26}H_{29}NO_6Na$ 474.1893). Anal. Calcd for $C_{26}H_{29}NO_6$: C, 69.16; H, 6.47; N, 3.10. Found: C, 69.03; H, 6.56; N, 3.17.

Typical Experimental Procedure for Eq 2 (Table 2, Entry 1). To a solution of 1,1-diethyl 2-hydrogen ethenetricarboxylate (**1**) (prepared from 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate (272 mg, 1 mmol) upon treatment with CF_3CO_2H (4 mL))[24] in 1,2-dichloroethane (0.7 mL) were added benzyl cinnamylamine (**2a**) (201 mg, 0.90 mmol) in 1,2-dichloroethane (0.7 mL), Et_3N (0.14 mL, 102 mg, 1 mmol), HOBt (1-hydroxybenzotriazole) (270 mg, 2 mmol), and EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) (199 mg, 1.04 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, and was allowed to warm to 80 °C and stirred for 20 h. The reaction mixture was diluted with CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$ solution, 2 M aqueous citric acid, saturated aqueous $NaHCO_3$, and water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with hexane−Et_2O to give **4a** (246 mg, 69%).

4a: R_f = 0.1 (hexane−ether = 1:4); colorless crystals; mp 107.5−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.39 (t, *J* = 7.1 Hz, 3H), 2.78−2.86 (m, 2H), 3.28 (dd, *J* = 11.2, 7.9 Hz, 1H), 3.26−3.78 (m, 2H), 4.33 (d, *J* = 14.4 Hz, 1H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.55 (d, *J* = 14.4 Hz, 1H), 4.78 (d, *J* = 11.3 Hz, 1H), 7.07 (d-like, *J* = 8.0 Hz, 2H), 7.21−7.24 (m, 2H), 7.29−7.39 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.2 (CH_3), 37.2 (CH), 41.1 (CH), 45.9 (CH_2), 46.8 (CH_2), 47.1 (CH), 62.5 (CH_2), 81.4 (CH), 127.6 (CH), 128.2 (CH), 128.5 (CH), 129.0 (CH), 129.1 (CH), 129.7 (CH), 135.2 (C), 135.7 (C), 167.5 (C), 167.6 (C), 172.2 (C); ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) 1.33 (t, *J* = 7.1 Hz, 3H), 2.70 (dd, *J* = 10.8, 1.9 Hz, 1H), 3.00 (dddd, *J* = 11.7, 10.1, 8.2, 1.9 Hz, 1H), 3.26 (dd, *J* = 10.8, 8.2 Hz, 1H), 3.65 (dd, *J* = 10.6, 10.1 Hz, 1H), 3.83 (d, *J* = 10.6 Hz, 1H), 4.30 (d, *J* = 14.8 Hz, 1H), 4.317 (q, *J* = 7.1 Hz, 1H), 4.320 (q, *J* = 7.1 Hz, 1H), 4.48 (d, *J* = 14.8 Hz, 1H), 5.10 (d, *J* = 11.7 Hz, 1H), 7.22−7.26 (m, 4H), 7.30−7.40 (m, 6H). Selected NOEs are between δ 3.00 (C3a−*H*) and δ 3.26 (C3−H*H*), 3.65 (C7a−*H*) and between δ 2.70 (C3−*H*H) and δ 5.10 (C4−*H*). Atom numbering is shown in eq 2. ^{13}C NMR (100.6 MHz, CD_3CN) δ (ppm) 14.5 (CH_3), 36.8 (CH), 41.9 (CH), 46.8 (CH_2), 46.9 (CH_2), 48.2 (CH), 62.7 (CH_2), 82.1 (CH), 128.6 (CH), 128.8 (CH), 129.0 (CH), 129.7 (CH), 129.8 (CH), 130.4 (CH), 137.0 (C), 137.4 (C), 169.0 (C), 169.3 (C), 173.2 (C). Selected HMBC correlations are between δ 2.70 (C3−*H*H), 3.26 (C3−H*H*), 3.00 (C3a−*H*), 3.65 (C7a−*H*) and δ 82.1 (*C*4), between δ 3.65 (C7a−*H*) and δ 48.2 (*C*7), and between δ 2.70 (C3−*H*H), 5.10 (C4−*H*) and δ 41.9 (*C*7a). IR (KBr) 3448, 2929, 1752, 1740, 1691, 1449, 1375, 1266, 1156, 1045, 1021 cm^{-1}; MS (EI) *m/z* 393 (M^+, 16), 186 (30), 91 (61), 57 (100%); HRMS (EI) *m/z* M^+ 393.1574 (calcd for $C_{23}H_{23}NO_5$ 393.1576).

4b: (1 mmol scale, 298 mg, 75%); R_f = 0.4 (ether); colorless crystals; mp 59−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.882−0.996 (m, 2H), 1.13−1.22 (m, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.50−1.76 (m, 6H), 2.89−2.97 (m, 2H), 3.04 (dd, *J* = 13.6, 6.8 Hz, 1H), 3.18 (dd, *J* = 13.6, 7.5 Hz, 1H), 3.43 (dd, *J* = 11.2, 8.1 Hz, 1H), 3.69−3.75 (m, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 4.94 (d, *J* = 11.3 Hz, 1H), 7.34−7.36 (m, 2H), 7.42−7.45 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.1 (CH_3), 25.6 (CH_2), 25.7 (CH_2), 26.2 (CH_2), 30.6 (CH_2), 30.8 (CH_2), 35.6 (CH), 36.9 (CH), 41.0 (CH), 47.1 (CH), 47.5 (CH_2), 49.0 (CH_2), 62.3 (CH_2), 81.6 (CH), 127.7 (CH), 129.1 (CH), 129.8 (CH), 135.3 (C), 167.6 (C), 167.7 (C), 172.3 (C); ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) 0.841−0.960 (m, 2H), 1.15−1.26 (m, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.47−1.75 (m, 6H), 2.84 (dd, *J* = 10.7, 1.8 Hz, 1H), 2.98−3.10 (m, 3H), 3.38 (dd, *J* = 10.7, 8.6 Hz, 1H), 3.58 (dd, *J* = 10.5, 10.4 Hz, 1H), 3.73 (d, *J* = 10.5 Hz, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 5.17 (d, *J* = 11.7 Hz, 1H), 7.41−7.50 (m, 5H). Selected NOEs are between δ 2.84 (C3−*H*H) and δ 5.17 (C4−*H*), 3.73 (C7−*H*) and between δ 5.17 (C4−*H*) and δ 3.73 (C7−*H*). ^{13}C NMR (100.6 MHz, CD_3CN) δ (ppm) 14.5 (CH_3), 26.4 (CH_2), 26.5 (CH_2), 27.1 (CH_2), 31.3 (CH_2), 31.5 (CH_2), 36.2 (CH), 36.7 (CH), 41.9 (CH), 48.1 (CH_2), 48.3 (CH), 49.4 (CH_2), 62.6 (CH_2), 82.3 (CH), 128.9 (CH), 129.9 (CH), 130.5 (CH), 137.1 (C), 169.0 (C), 169.4 (C), 173.2 (C). Selected HMBC correlations are between δ 2.84 (C3−*H*H), 3.38 (C3−H*H*), 3.58 (C7a−*H*), and δ 82.3 (*C*4), between δ 3.58 (C7a−*H*) and δ 48.3 (*C*7), between δ 5.17 (C4−*H*) and δ 48.1 (*C*3) and between δ 2.84 (C3−*H*H), 5.17 (C4−*H*) and δ 41.9 (*C*7a). IR (KBr) 2922, 2850, 1757, 1741, 1688, 1502, 1452, 1375, 1344, 1146, 1037 cm^{-1}; MS (EI) *m/z* 399 (M^+, 48), 317 (22), 149 (32), 117 (65), 84 (100%); HRMS (EI) *m/z* M^+ 399.2056 (calcd for $C_{23}H_{29}NO_5$ 399.2046).

4e: (1 mmol scale, 228 mg, 55%); R_f = 0.4 (ether); colorless crystals; mp 70−71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.38 (t, *J* = 7.1 Hz, 3H), 2.73−2.82 (m, 2H), 3.29 (dd, *J* = 11.1, 7.8 Hz, 1H), 3.72−3.78 (m, 2H), 4.28 (d, *J* = 14.5 Hz, 1H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.58 (d, *J* = 14.5 Hz, 1H), 4.77 (d, *J* = 11.3 Hz, 1H), 6.97−7.06 (m, 4H), 7.21−7.24 (m, 2H), 7.34−7.39 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.1 (CH_3), 37.3 (CH), 41.1 (CH), 45.7 (CH_2), 46.7 (CH_2), 47.0 (CH), 62.5 (CH_2), 80.6 (CH), 116.0 (CH, d, J_{CF} = 22 Hz), 128.2 (CH), 128.5 (CH), 129.1 (CH), 129.4 (CH, d, J_{CF} = 8.4 Hz), 131.2 (C, d, J_{CF} = 3.1 Hz), 135.7 (C), 163.3 (C, d, J_{CF} = 249 Hz), 167.3 (C), 167.5 (C), 172.0 (C); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −111.13 (tt, J_{FH} = 8.6, 5.7 Hz); ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ (ppm) 1.31 (t, *J* = 7.1 Hz, 3H), 2.83 (dd, *J* = 10.7, 1.8 Hz, 1H), 3.13 (dddd, *J* = 11.5, 9.3, 8.2, 1.8 Hz, 1H), 3.40 (dd, *J* = 10.7, 8.2 Hz, 1H), 3.70 (dd, *J* = 10.2, 9.9 Hz, 1H), 4.03 (d, *J* = 10.2 Hz, 1H), 4.25−4.33 (m, 2H), 4.36 (d, *J* = 14.8 Hz,

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

1H), 4.51 (d, J = 14.8 Hz, 1H), 5.39 (d, J = 11.5 Hz, 1H), 7.15 (dd-like, J_{HH} = 8.8 Hz, J_{FH} = 8.8 Hz, 2H), 7.28−7.32 (m, 2H), 7.34−7.41 (m, 5H). Selected NOEs are between δ 3.13 (C3a−*H*) and δ 3.40 (C3−H*H*), 3.70 (C7a−*H*), 7.34−7.41 (Ar-*H*), and δ 2.83 (C3−*H*H), 4.03 (C7−*H*) and δ 5.39 (C4−*H*). ^{13}C NMR (100.6 MHz, $(CD_3)_2CO$) δ (ppm) 14.4 (CH_3), 37.0 (CH), 41.6 (CH), 46.5 (CH_2), 46.7 (CH_2), 47.9 (CH), 62.0 (CH_2), 81.0 (CH), 116.3 (CH, d, J_{CF} = 22 Hz), 128.4 (CH), 128.9 (CH), 129.5 (CH), 131.0 (CH, d, J_{CF} = 8.4 Hz), 133.5 (C, d, J_{CF} = 3.1 Hz), 137.4 (C), 163.9 (C, d, J_{CF} = 247 Hz), 168.56 (C), 168.61 (C), 172.8 (C). Selected HMBC correlations are between δ 2.83 (C3−*H*H), 3.40 (C3−H*H*), 3.13 (C3a−*H*), 3.70 (C7a−*H*), and δ 81.0 (*C*4), between δ 3.70 (C7a−*H*) and δ 47.9 (*C*7), and between δ 2.83 (C3−*H*H), 5.39 (C4−*H*), and δ 41.6 (*C*7a). IR (KBr) 2935, 1758, 1735, 1697, 1513, 1233, 1156, 1045 cm^{-1}; MS (EI) m/z 411 (M^+, 87), 366 (11), 240 (19), 174 (27), 135 (85), 91 (100%); HRMS (EI) m/z M^+ 411.1492 (calcd for $C_{23}H_{22}FNO_5$ 411.1482).

4f: (1 mmol scale, 139 mg, 38%); R_f = 0.4 (ether); colorless crystals; mp 78−79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.899 (t, J = 7.3 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H), 1.52 (qt, J = 7.3, 7.3 Hz, 2H), 2.89−2.95 (m, 2H), 3.17−3.34 (m, 2H), 3.45 (dd, J = 11.1, 8.2 Hz, 1H), 3.68−3.75 (m, 2H), 4.35−4.40 (m, 2H), 4.93 (d, J = 11.1 Hz, 1H), 7.14 (dd, J_{HH} = 8.5 Hz, J_{FH} = 8.5 Hz, 2H), 7.36 (dd, J_{HH} = 8.5 Hz, J_{FH} = 5.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 11.3 (CH_3), 14.1 (CH_3), 20.4 (CH_2), 36.9 (CH), 41.0 (CH), 44.4 (CH_2), 46.8 (CH_2), 47.1 (CH), 62.5 (CH_2), 80.9 (CH), 116.3 (CH, d, J_{CF} = 22 Hz), 129.7 (CH, d, J_{CF} = 8.4 Hz), 131.4 (C, d, J_{CF} = 3.1 Hz), 163.5 (C, d, J_{CF} = 250 Hz), 167.5 (C), 172.1 (C); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −110.83 (tt, J = 8.5, 5.2 Hz); ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) 0.847 (t, J = 7.2 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.47 (qt, J = 7.2, 7.2 Hz, 2H), 2.83 (dd, J = 10.8, 2.1 Hz, 1H), 3.03 (dddd, J = 11.5, 10.4, 8.5, 2.1 Hz, 1H), 3.08−3.26 (m, 2H), 3.39 (dd, J = 10.8, 8.5 Hz, 1H), 3.56 (dd, J = 10.7, 10.4 Hz, 1H), 3.71 (d, J = 10.7 Hz, 1H), 4.25−4.31 (m, 2H), 5.18 (d, J = 11.5 Hz, 1H), 7.19 (dd-like, J_{HH} = 8.8 Hz, J_{FH} = 8.8 Hz, 2H), 7.46 (dd-like, J_{HH} = 8.8 Hz, J_{FH} = 5.3 Hz, 2H). Selected NOEs are between δ 3.03 (C3a−*H*) and δ 3.39 (C3−H*H*), 3.56 (C7a−*H*), 7.46 (Ar-*H*), and between δ 2.83 (C3−*H*H), 3.71 (C7−*H*), and δ 5.18 (C4−*H*). ^{13}C NMR (100.6 MHz, CD_3CN) δ (ppm) 11.5 (CH_3), 14.5 (CH_3), 20.9 (CH_2), 36.6 (CH), 41.9 (CH), 44.8 (CH_2), 47.4 (CH_2), 48.3 (CH), 62.6 (CH_2), 81.5 (CH), 116.7 (CH, d, J_{CF} = 22 Hz), 131.2 (CH, d, J_{CF} = 8.4 Hz), 133.5 (C, d, J_{CF} = 3.8 Hz), 164.2 (C, d, J_{CF} = 247 Hz), 167.0 (C), 169.3 (C), 172.9 (C). Selected HMBC correlations are between δ 2.83 (C3−*H*H), 3.39 (C3−H*H*), 3.03 (C3a−*H*), 3.56 (C7a−*H*), and δ 81.5 (*C*4), between δ 3.56 (C7a−*H*) and δ 48.3 (*C*7), between δ 5.18 (C4−*H*) and 47.4 (*C*3), and between δ 2.83 (C3−*H*H), 3.39 (C3−H*H*), 5.18 (C4−*H*), and δ 41.9 (*C*7a). IR (neat) 2968, 2876, 1754, 1689, 1607, 1514, 1492, 1455, 1375, 1348, 1319, 1268, 1233, 1159, 1095, 1041 cm^{-1}; MS (EI) m/z 363 (M^+, 45), 318 (17), 277 (100%); HRMS (EI) m/z M^+ 363.1497 (calcd for $C_{19}H_{22}FNO_5$ 363.1482).

4g: (1 mmol scale, 226 mg, 53%); R_f = 0.3 (ether); colorless crystals; mp 53−54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.38 (t, J = 7.1 Hz, 3H), 2.72−2.78 (m, 2H), 3.28 (dd, J = 11.3, 7.8 Hz, 1H), 3.72−3.78 (m, 2H), 4.26 (d, J = 14.5 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 4.60 (d, J = 14.5 Hz, 1H), 4.74 (d, J = 11.3 Hz, 1H), 6.96 (d-like, J = 8.4 Hz, 2H), 7.22−7.24 (m, 2H), 7.28 (d-like, J = 8.4 Hz, 2H), 7.35−7.40 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.1 (CH_3), 37.4 (CH), 41.1 (CH), 45.6 (CH_2), 46.7 (CH_2), 47.0 (CH), 62.6 (CH_2), 80.5 (CH), 128.3 (CH), 128.5 (CH), 128.8 (CH), 129.1 (CH), 129.2 (CH), 133.8 (C), 135.66 (C), 135.68 (C), 167.3 (C), 167.5 (C), 172.0 (C); ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) 1.32 (t, J = 7.1 Hz, 3H), 2.68 (dd, J = 10.9, 1.8 Hz, 1H), 2.95 (dddd, J = 11.5, 10.0, 8.3, 1.8 Hz, 1H), 3.26 (dd, J = 10.9, 8.3 Hz, 1H), 3.63 (dd, J = 10.4, 10.0 Hz, 1H), 3.80 (d, J = 10.4 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 4.32 (d, J = 14.8 Hz, 1H), 4.44 (d, J = 14.8 Hz, 1H), 5.08 (d, J = 11.5 Hz, 1H), 7.19 (d-like, J = 8.4 Hz, 2H), 7.23−7.25 (m, 2H), 7.30−7.39 (m, 5H). Selected NOEs are between δ 2.95 (C3a−*H*) and δ 3.26 (C3−H*H*), 3.63 (C7a−*H*), 7.19 (Ar-*H*), and between δ 2.68 (C3−*H*H), 3.80 (C7−*H*), and δ 5.08 (C4−*H*). ^{13}C NMR (100.6 MHz, CD_3CN) δ (ppm) 14.5 (CH_3), 36.9 (CH), 41.8 (CH), 46.7 (CH_2), 46.9 (CH_2), 48.2 (CH), 62.7 (CH_2), 81.2 (CH), 128.6 (CH), 129.0 (CH), 129.7 (CH), 129.8 (CH), 130.5 (CH), 135.7 (C), 135.8 (C), 137.3 (C), 168.9 (C), 169.1 (C), 173.1 (C). Selected HMBC correlations are between δ 2.68 (C3−*H*H), 3.26 (C3−H*H*), 2.95 (C3a−*H*), 3.63 (C7a−*H*), and δ 81.2 (*C*4), between δ 3.63 (C7a−*H*) and δ 48.2 (*C*7), between δ 5.08 (C4−*H*) and 46.7 (*C*3), and between δ 2.68 (C3−*H*H), 5.08 (C4−*H*), and δ 41.8 (*C*7a). IR (KBr) 2938, 1756, 1733, 1684, 1489, 1452, 1260, 1191, 1051, 1012 cm^{-1}; MS (EI) m/z 429 (M^+, 8.9), 427 (M^+, 24), 345 (15), 271 (20), 256 (21), 151 (47), 91 (100%); HRMS (EI) m/z M^+ 427.1204, 429.1180 (calcd for $C_{23}H_{22}ClNO_5$ 427.1187, 429.1157).

4h: (1 mmol scale, 147 mg, 31%); R_f = 0.5 (ether); colorless crystals; mp 68−69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.38 (t, J = 7.1 Hz, 3H), 2.71−2.78 (m, 2H), 3.28 (dd, J = 11.2, 7.7 Hz, 1H), 3.72−3.77 (m, 2H), 4.25 (d, J = 14.5 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 4.61 (d, J = 14.5 Hz, 1H), 4.72 (d, J = 11.1 Hz, 1H), 6.89 (d-like, J = 8.4 Hz, 2H), 7.22−7.24 (m, 2H), 7.35−7.39 (m, 3H), 7.44 (d-like, J = 8.4 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.1 (CH_3), 37.4 (CH), 41.1 (CH), 45.6 (CH_2), 46.7 (CH_2), 47.0 (CH), 62.6 (CH_2), 80.6 (CH), 123.9 (C), 128.3 (CH), 128.6 (CH), 129.08 (CH), 129.10 (CH), 132.2 (CH), 134.3 (C), 135.7 (C), 167.2 (C), 167.5 (C), 172.0 (C); ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) 1.32 (t, J = 7.0 Hz, 3H), 2.68 (dd, J = 10.9, 2.0 Hz, 1H), 2.95 (dddd, J = 11.5, 10.0, 8.2, 2.0 Hz, 1H), 3.27 (dd, J = 10.9, 8.2 Hz, 1H), 3.62 (dd, J = 10.4, 10.0 Hz, 1H), 3.79 (d, J = 10.4 Hz, 1H), 4.28−4.33 (m, 3H), 4.45 (d, J = 14.8 Hz, 1H), 5.07 (d, J = 11.5 Hz, 1H), 7.14 (d-like, J = 8.4 Hz, 2H), 7.23−7.25 (m, 2H), 7.30−7.41 (m, 3H), 7.53 (d-like, J = 8.4 Hz, 2H). Selected NOEs are between δ 2.95 (C3a−*H*) and δ 3.27 (C3−H*H*), 3.62 (C7a−*H*), 7.14 (Ar-*H*), and between δ 2.68 (C3−*H*H), 3.79 (C7−*H*), and δ 5.07 (C4−*H*). ^{13}C NMR (100.6 MHz, CD_3CN) δ (ppm) 14.5 (CH_3), 36.8 (CH), 41.8 (CH), 46.7 (CH_2), 46.9 (CH_2), 48.2 (CH), 62.7 (CH_2), 81.3 (CH), 128.6 (CH), 129.0 (CH), 129.7 (CH), 130.7 (CH), 132.8 (CH), 133.9 (C), 136.3 (C), 137.4 (C), 168.9 (C), 169.1 (C), 173.1 (C). Selected HMBC correlations are between δ 2.68 (C3−*H*H), 3.27 (C3−H*H*), 3.62 (C7a−*H*), and δ 81.3 (*C*4), between δ 3.62 (C7a−*H*) and δ 48.2 (*C*7), and between δ 2.68 (C3−*H*H), 5.07 (C4−*H*), and δ 41.8 (*C*7a). IR (KBr) 2938, 1752, 1734, 1685, 1488, 1260, 1191, 1051, 1009 cm^{-1}; MS (EI) m/z 473 (M^+, 44), 471 (M^+, 43), 344 (16), 300 (15), 174 (39), 91 (100%); HRMS (EI) m/z M^+ 471.0688, 473.0667 (calcd for $C_{23}H_{22}BrNO_5$ 471.0681, 473.0661).

4i: (1 mmol scale, 173 mg, 41%); R_f = 0.5 (ether); colorless crystals; mp 66−67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.38 (t, J = 7.1 Hz, 3H), 2.75−2.85 (m, 2H), 3.28 (dd, J = 11.0, 7.9 Hz, 1H), 3.70−3.76 (m, 2H), 3.78 (s, 3H), 4.34 (d, J = 14.5 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 4.51 (d, J = 14.5 Hz, 1H), 4.75 (d, J = 11.1 Hz, 1H), 6.82 (d-like, J = 8.8 Hz, 2H), 7.01 (d-like, J = 8.8 Hz, 2H), 7.20−7.23 (m, 2H), 7.31−7.38 (m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.1 (CH_3), 37.0 (CH), 41.0 (CH), 46.0 (CH_2), 46.7 (CH_2), 47.0 (CH), 55.4 (CH_3), 62.4 (CH_2), 81.2 (CH), 114.3 (CH), 127.2 (C), 128.1 (CH), 128.4 (CH), 128.9 (CH), 129.0 (CH), 135.7 (C), 160.6 (C), 167.6 (C), 167.7 (C), 172.2 (C); ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) 1.33 (t, J = 7.1 Hz, 3H), 2.68 (dd, J = 10.8, 1.9 Hz, 1H), 2.99 (dddd, J = 11.5, 10.0, 8.3, 1.9 Hz, 1H), 3.27 (dd, J = 10.8, 8.3 Hz, 1H), 3.63 (dd, J = 10.4, 10.0 Hz, 1H), 3.77 (s, 3H), 3.81 (d, J = 10.4 Hz, 1H), 4.28−4.35 (m, 2H), 4.30 (d, J = 14.8 Hz, 1H), 4.47 (d, J = 14.8 Hz, 1H), 5.05 (d, J = 11.5 Hz, 1H), 6.90 (d-like, J = 8.8 Hz, 2H), 7.17 (d-like, J = 8.8 Hz, 2H), 7.23−7.25 (m, 2H), 7.29−7.39 (m, 3H). Selected NOEs are between δ 2.99 (C3a−*H*) and δ 3.27 (C3−H*H*), 3.63 (C7a−*H*), 7.17 (Ar-*H*), and between δ 2.68 (C3−*H*H), 3.81 (C7−*H*), and δ 5.05 (C4−*H*). ^{13}C NMR (100.6 MHz, CD_3CN) δ (ppm) 14.5 (CH_3), 36.6 (CH), 41.8 (CH), 46.9 (CH_2), 47.0 (CH_2), 48.2 (CH), 56.0 (CH_3), 62.6 (CH_2), 81.9 (CH), 115.0 (CH), 128.6 (CH), 128.8 (C), 129.0 (CH), 129.7 (CH), 130.3 (CH), 137.4 (C), 161.4 (C), 169.1 (C), 169.2 (C), 173.3 (C). Selected HMBC correlations are between δ 2.68 (C3−*H*H), 3.27 (C3−H*H*), 2.99 (C3a−*H*), 3.63 (C7a−*H*), and δ 81.9 (*C*4), between δ 3.63 (C7a−*H*) and δ 48.2 (*C*7), between δ 5.05 (C4−*H*) and 46.9 (*C*3), and between δ 2.68 (C3−*H*H), 5.05 (C4−*H*), and δ 41.8 (*C*7a). IR (KBr) 2936, 1752, 1735, 1685, 1508, 1262, 1194, 1049 cm^{-1}; MS (EI) m/z 423 (M^+, 29), 173 (77), 147 (41), 135 (28), 91 (100%); HRMS (EI) m/z M^+ 423.1687 (calcd for $C_{24}H_{25}NO_6$ 423.1682).

Transformation of 3a to 4a (Table 3, entry 1). To a solution of **3a** (210 mg, 0.5 mmol) in $ClCH_2CH_2Cl$ (0.7 mL) were added 1 M HCl/ether (0.5 mL, 0.5 mmol) and H_2O (9 mg, 0.5 mmol). The mixture was

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

stirred at 80 °C for 20 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel eluting with hexane−Et_2O to give **4a** (139 mg, 70%).

Transformation of 3a to 5a and 4a (Table 3, entry 2). To a solution of **3a** (245 mg, 0.58 mmol) in THF (0.8 mL) was added 1 M HCl/H_2O (0.58 mL, 0.58 mmol). The mixture was stirred at room temperature for 20 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with CH_2Cl_2. The organic phase was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by column chromatography over silica gel eluting with hexane−Et_2O to give **5a** (111 mg, 42%) and **4a** (107 mg, 47%).

5a: R_f = 0.6 (ether); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.27 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 2.15 (bs, 1H), 2.54 (dd, J = 10.3, 2.6 Hz, 1H), 2.87 (dddd, J = 10.9, 7.4, 6.6, 2.6 Hz, 1H), 2.97 (dd, J = 10.2, 6.6 Hz, 1H), 3.67 (dd, J = 10.2, 7.4 Hz, 1H), 4.06 (d, J = 14.5 Hz, 1H), 4.08 (d, J = 10.2 Hz, 1H), 4.19−4.39 (m, 5H), 4.58 (d, J = 14.5 Hz, 1H), 6.87−6.89 (m, 2H), 7.16−7.23 (m, 5H), 7.29−7.35 (m, 3H). Selected NOEs are between δ 3.67 (C3−*H*) and δ 2.87 (C4−*H*), 2.97 (C5−H*H*) and between δ 2.54 (C5−*H*H), 2.97 (C5−H*H*), and δ 6.87−6.89 (Ph−*H*). Atom numbering is shown in eq 3. ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.2 (CH_3), 42.2 (CH), 46.0 (CH), 46.6 (CH_2), 47.5 (CH_2), 51.1 (CH), 61.6 (CH_2), 61.8 (CH_2), 74.0 (CH), 126.7 (CH), 127.8 (CH), 128.4 (CH), 128.69 (CH), 128.76 (CH), 128.77 (CH), 136.4 (C), 142.5 (C), 168.6 (C), 169.4 (C), 172.8 (C). Selected HMBC correlations are between δ 2.54 (C5−*H*H), 2.87 (C4−*H*), 3.67 (C3−*H*), and δ 172.8 (*C*2), between δ 2.54 (C5−*H*H), 2.87 (C4−*H*), 2.97 (C5−H*H*), and δ 74.0 (*C*H(OH)Ph), and between δ 2.54 (C5−*H*H), 2.97 (C5−H*H*), 3.67 (C3−*H*), and δ 42.2 (*C*4). IR (neat) 3419, 2981, 1747, 1732, 1684, 1494, 1455, 1376, 1301, 1032 cm^{-1}; MS (EI) m/z 439 (M^+, 15), 393 (13), 332 (33), 174 (70), 84 (100%); HRMS (EI) m/z M^+ 439.2003 (calcd for $C_{25}H_{29}NO_6$ 439.1995).

Transformation of 3a to 6a (Table 3, entry 3). To a solution of **3a** (178 mg, 0.42 mmol) in CH_2Cl_2 (0.6 mL) was added 1 M HCl/ether (0.42 mL, 0.42 mmol). The mixture was stirred at room temperature for 20 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography over silica gel eluting with hexane−Et_2O to give **6a** (117 mg, 60%) and **4a** (45 mg, 27%).

6a: R_f = 0.7 (hexane−ether = 1:8); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.28 (t, J = 7.1 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H), 3.19 (dd, J = 10.4, 2.7 Hz, 1H), 3.24 (dd, J = 10.4, 7.1 Hz, 1H), 3.32 (dddd, J = 8.7, 7.1, 4.3, 2.7 Hz, 1H), 3.62 (dd, J = 10.5, 8.7 Hz, 1H), 3.85 (d, J = 10.5 Hz, 1H), 4.15−4.41 (m, 5H), 4.67 (d, J = 14.7 Hz, 1H), 4.95 (d, J = 4.3 Hz, 1H), 7.26−7.36 (m, 10H). Selected NOEs are between δ 3.62 (C3−*H*) and δ 3.32 (C4−*H*), 3.24 (C5−H*H*) and between δ 3.85 (*CH*(CO_2Et)$_2$), 3.19 (C5−*H*H), and δ 4.95 (*CH*ClPh). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.1 (CH_3), 14.2 (CH_3), 41.4 (CH), 44.7 (CH), 46.6 (CH_2), 46.9 (CH_2), 49.8 (CH), 61.95 (CH), 61.98 (CH_2), 62.2 (CH_2), 127.0 (CH), 127.8 (CH), 128.5 (CH), 128.66 (CH), 128.72 (CH), 128.8 (CH), 135.8 (C), 138.9 (C), 168.4 (C), 168.5 (C), 171.9 (C). Selected HMBC correlations are between δ 3.19 (C5−*H*H), 3.24 (C5−H*H*), 3.62 (C3−*H*), and δ 171.9 (*C*2), between δ 3.19 (C5−*H*H), 3.24 (C5−H*H*), 3.62 (C3−*H*), and δ 61.95 (*C*HClPh), and between δ 3.19 (C5−*H*H), 3.24 (C5−H*H*), and δ 41.4 (*C*4). IR (neat) 2981, 1747, 1732, 1689, 1604, 1495, 1447, 1371, 1028 cm^{-1}; MS (EI) m/z 459 (M^+, 6.3), 457 (M^+, 17), 332 (33), 198 (52), 72 (100%); HRMS (EI) m/z M^+ 457.1655, 459.1647 (calcd for $C_{25}H_{28}ClNO_5$ 457.1656, 459.1627).

6c: (0.41 mmol scale, 134 mg, 62%); R_f = 0.7 (ether); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.28 (t, J = 7.1 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H), 3.19 (dd, J = 10.4, 2.9 Hz, 1H), 3.29 (dd, J = 10.4, 7.3 Hz, 1H), 3.37 (dddd, J = 8.9, 7.3, 4.7, 2.9 Hz, 1H), 3.62 (dd, J = 10.3, 8.9 Hz, 1H), 3.84 (d, J = 10.3 Hz, 1H), 4.16−4.41 (m, 5H), 4.67 (d, J = 14.5 Hz, 1H), 4.96 (d, J = 4.7 Hz, 1H), 7.26−7.37 (m, 5H), 7.40 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H). Selected NOEs are between δ 3.62 (C3−*H*) and δ 3.37 (C4−*H*), 3.29 (C5−H*H*), between δ 3.84 (*CH*(CO_2Et)$_2$), 3.19 (C5−*H*H), and δ 4.96 (*CH*ClPh), and between δ 3.19 (C5−*H*H) and δ 7.26−7.37 (Ph−*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (CH_3), 14.1 (CH_3), 41.3 (CH), 44.4 (CH), 46.5 (CH_2), 46.8 (CH_2), 49.7 (CH), 61.96 (CH), 62.00 (CH_2), 62.2 (CH_2), 124.1 (q, J = 272 Hz), 125.6 (q, J = 3.8 Hz), 126.9 (CH), 128.6 (CH), 128.89 (CH), 128.90 (CH), 130.0 (q, J = 32 Hz), 138.6 (C), 140.0 (C), 168.30 (C), 168.32 (C), 172.2 (C). Selected HMBC correlations are between δ 3.19 (C5−*H*H), 3.29 (C5−H*H*), 3.62 (C3−*H*), and δ 172.2 (*C*2), between δ 3.19 (C5−*H*H), 3.29 (C5−H*H*), 3.62 (C3−*H*), and δ 61.96 (CHClPh), and between δ 3.19 (C5−*H*H), 3.29 (C5−H*H*), 3.62 (C3−*H*), and δ 41.3 (*C*4). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −62.57; IR (neat) 2983, 1747, 1732, 1696, 1620, 1486, 1448, 1418, 1372, 1327, 1234, 1165, 1124, 1066, 1019 cm^{-1}; MS (FAB) m/z 550 ([M + Na]$^+$), 548 ([M + Na]$^+$), 528 ([M + H]$^+$), 526 ([M + H]$^+$); HRMS (FAB) m/z [M + H]$^+$ 526.1608, 528.1593, (calcd for $C_{26}H_{28}ClF_3NO_5$ 526.1608, 528.1579), [M + Na]$^+$ 548.1430, 550.1421 (calcd for $C_{26}H_{27}ClF_3NO_5Na$ 548.1428, 550.1398).

6d: (0.42 mmol scale, 90 mg, 53%); R_f = 0.8 (ether); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.27 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.2 Hz, 3H), 3.28−3.41 (m, 3H), 3.59 (dd, J = 10.5, 8.5 Hz, 1H), 3.81 (d, J = 10.5 Hz, 1H), 3.87 (dd, J = 15.0, 6.4 Hz, 1H), 3.95 (dd, J = 15.0, 6.4 Hz, 1H), 4.15−4.38 (m, 2H), 4.96 (d, J = 4.3 Hz, 1H), 5.22 (dddd, J = 10.1, 1.2, 1.2, 1.2 Hz, 1H), 5.24 (dddd, J = 17.1, 1.5, 1.5, 1.2 Hz, 1H), 5.78 (dddd, J = 17.1, 10.1, 6.4, 6.4 Hz, 1H), 7.31−7.41 (m, 5H). Selected NOEs are between δ 3.81 (*CH*(CO_2Et)$_2$) and δ 4.96 (*CH*ClPh). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (CH_3), 14.1 (CH_3), 41.4 (CH), 44.6 (CH), 45.5 (CH_2), 46.5 (CH_2), 49.7 (CH), 61.9 (CH_2), 62.0 (CH), 62.1 (CH_2), 118.7 (CH_2), 127.0 (CH), 128.5 (CH), 128.9 (CH), 132.3 (CH), 138.9 (C), 168.3 (C), 168.4 (C), 171.7 (C). Selected HMBC correlations are between δ 3.59 (C3−*H*) and δ 171.7 (*C*2), between δ 3.59 (C3−*H*) and δ 62.0 (*C*HClPh), between δ 4.96 (*CH*ClPh) and δ 46.5 (*C*5), and between δ 3.81 (*CH*(CO_2Et)$_2$) and δ 41.4 (*C*4). IR (neat) 2981, 1747, 1726, 1695, 1486, 1448, 1371, 1279, 1186, 1027 cm^{-1}; MS (EI) m/z 409 (M^+, 2.4), 407 (M^+, 7.1), 362 (5.9), 282 (47), 198 (33), 86 (100%); HRMS (EI) m/z M^+ 407.1493, 409.1480 (calcd for $C_{21}H_{26}ClNO_5$ 407.1500, 409.1470).

7j: *(Table 4, entry 1).* (1 mmol scale, 352 mg, 75%); R_f = 0.8 (CH_2Cl_2−ether = 1:1); colorless crystals; mp 148−150 °C (ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.24 (t, J = 7.1 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H), 2.41 (ddddd, J = 12.9, 11.7, 9.6, 7.5, 5.5 Hz, 1H), 3.05−3.19 (m, 4H), 3.49 (dd, J = 9.3, 7.5 Hz, 1H), 4.11−4.19 (m, 1H), 4.27−4.47 (m, 4H), 4.68 (d, J = 14.8 Hz, 1H), 7.27−7.37 (m, 5H), 7.41 (dd, J = 8.0, 8.0 Hz, 1H), 7.67 (dd, J = 8.0, 1.4 Hz, 1H), 7.82 (dd, J = 8.0, 1.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.9 (CH_3), 14.1 (CH_3), 31.2 (CH_2), 31.8 (CH), 46.5 (CH_2), 49.3 (CH), 50.3 (CH_2), 60.9 (C), 62.5 (CH_2), 63.0 (CH_2), 124.5 (CH), 127.0 (CH), 127.7 (CH), 128.2 (CH), 128.8 (CH), 130.5 (C), 135.6 (CH), 136.5 (C), 136.9 (C), 150.4 (C), 167.7 (C), 170.0 (C), 171.1 (C); ^{1}H NMR (400 MHz, C_6D_6) δ (ppm) 0.968 (t, J = 7.1 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H), 1.95 (ddddd, J = 13.1, 12.2, 9.4, 8.0, 5.0 Hz, 1H), 2.17 (dd, J = 9.4, 8.8 Hz, 1H), 2.40 (dd, J = 17.2, 12.2 Hz, 1H), 2.56 (dd, J = 17.2, 5.0 Hz, 1H), 2.69 (dd, J = 8.8, 8.0 Hz, 1H), 2.87 (d, J = 13.1 Hz, 1H), 3.90−3.98 (m, 1H), 4.03 (d, J = 14.7 Hz, 1H), 4.06−4.14 (m, 1H), 4.19−4.27 (m, 2H), 4.48 (d, J = 14.7 Hz, 1H), 6.75 (dd, J = 8.0, 7.8 Hz, 1H), 7.07 (t-like, J = 7.2 Hz, 1H), 7.12−7.21 (m, 4H), 7.34 (d-like, J = 7.8 Hz, 1H), 7.71 (d-like, J = 8.0 Hz, 1H). Selected NOEs are between δ 1.95 (C3a−*H*) and δ 2.69 (C3−H*H*), 2.56 (C4−H*H*), between δ 2.17 (C3−*H*H) and δ 2.40 (C4−*H*H), 2.87 (C9a−*H*), and between δ 2.40 (C4−*H*H) and δ 2.87 (C9a−*H*). Atom numbering is shown in eq 4. ^{13}C NMR (100.6 MHz, C_6D_6) δ (ppm) 13.8 (CH_3), 14.0 (CH_3), 30.9 (CH_2), 31.6 (CH), 46.4 (CH_2), 49.3 (CH), 49.6 (CH_2), 61.2 (C), 62.1 (CH_2), 62.7 (CH_2), 124.1 (CH), 126.7 (CH), 127.6 (CH), 128.4 (CH), 128.8 (CH), 130.8 (C), 135.4 (CH), 137.4 (C), 137.6 (C), 151.0 (C), 167.8 (C), 170.1 (C), 170.4 (C). Selected HMBC correlations are between δ 2.40 (C4−*H*H), 2.56 (C4−H*H*), 2.69 (C3−H*H*), 2.87 (C9a−*H*), and δ 31.6 (*C*3a), δ 2.17 (C3−*H*H), 2.87 (C9a−*H*), and δ 30.9 (*C*4), and between δ 2.87 (C9a−*H*) and δ 61.2 (*C*9). IR (KBr) 3307, 1745, 1726, 1700, 1528, 1363, 1250, 1198, 1030 cm^{-1}; MS (EI) m/z 466 (M^+, 35), 436 (14), 363 (18), 118 (15), 91 (100%); HRMS (EI) m/z M^+ 466.1747 (calcd for $C_{25}H_{26}N_2O_7$ 466.1740). Anal. Calcd for $C_{25}H_{26}N_2O_7$: C, 64.37; H, 5.62; N, 6.01. Found: C, 64.14; H, 5.63; N, 5.94.

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

7k: (Table 4, entry 2). (1 mmol scale, 343 mg, 73%); R_f = 0.8 (CH_2Cl_2−ether = 1:1); colorless crystals; mp 118−119 °C (AcOEt−hexane = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.937−1.03 (m, 2H), 1.14−1.27 (m, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H), 1.62−1.81 (m, 6H), 2.42 (ddddd, J = 13.1, 11.7, 9.8, 7.4, 5.5 Hz, 1H), 3.00−3.30 (m, 6H), 3.62 (dd, J = 9.2, 7.4 Hz, 1H), 4.11−4.44 (m, 4H), 7.41 (dd, J = 8.0, 8.0 Hz, 1H), 7.65 (dd, J = 8.0, 1.4 Hz, 1H), 7.82 (dd, J = 8.0, 1.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.9 (CH_3), 14.0 (CH_3), 25.77 (CH_2), 25.80 (CH_2), 26.4 (CH_2), 30.8 (CH_2), 30.9 (CH_2), 31.2 (CH_2), 31.9 (CH), 36.2 (CH), 49.1 (CH_2), 49.3 (CH), 51.9 (CH_2), 60.8 (C), 62.4 (CH_2), 62.9 (CH_2), 124.4 (CH), 126.9 (CH), 130.5 (C), 135.5 (CH), 137.0 (C), 150.4 (C), 167.8 (C), 169.9 (C), 171.2 (C); ^{1}H NMR (400 MHz, C_6D_6) δ (ppm) 0.807−0.924 (m, 2H), 0.975 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 7.0 Hz, 3H), 1.03−1.19 (m, 3H), 1.38−1.48 (m, 1H), 1.50−1.68 (m, 5H), 2.00 (ddddd, J = 13.1, 12.0, 9.4, 7.5, 5.2 Hz, 1H), 2.26 (dd, J = 9.4, 9.4 Hz, 1H), 2.54 (dd, J = 17.3, 12.0 Hz, 1H), 2.68 (dd, J = 17.3, 5.2 Hz, 1H), 2.74−2.80 (m, 2H), 2.88 (d, J = 13.1 Hz, 1H), 3.18 (dd, J = 13.6, 7.5 Hz, 1H), 3.91−3.99 (m, 1H), 4.02−4.10 (m, 1H), 4.14−4.26 (m, 2H), 6.74 (dd, J = 8.0, 8.0 Hz, 1H), 7.34 (dd, J = 8.0, 1.2 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H). Selected NOEs are between δ 2.00 (C3a−*H*) and δ 2.68 (C4−H*H*), between δ 2.26 (C3−*H*H) and δ 2.54 (C4−*H*H), 2.88 (C9a−*H*), and between δ 2.54 (C4−*H*H) and δ 2.88 (C9a−H). ^{13}C NMR (100.6 MHz, C_6D_6) δ (ppm) 13.8 (CH_3), 14.0 (CH_3), 26.1 (CH_2), 26.2 (CH_2), 26.7 (CH_2), 30.9 (CH_2), 31.0 (CH_2), 31.1 (CH_2), 31.8 (CH), 36.5 (CH), 48.9 (CH), 49.4 (CH), 51.2 (CH_2), 61.2 (C), 62.0 (CH_2), 62.6 (CH_2), 124.1 (CH), 126.8 (CH), 130.7 (C), 135.5 (CH), 137.6 (C), 151.0 (C), 167.8 (C), 170.1 (C), 170.5 (C). Selected HMBC correlations are between δ 2.54 (C4−*H*H), 2.68 (C4−H*H*), and δ 31.8 (*C*3a), δ 2.26 (C3−*H*H), 2.88 (C9a−*H*), and δ 31.1 (*C*4), and between δ 2.88 (C9a−*H*) and δ 61.2 (*C*9). IR (KBr) 2924, 2852, 1743, 1728, 1702, 1529, 1447, 1365, 1249, 1197, 1031 cm^{-1}; MS (EI) m/z 472 (M^+, 24), 390 (100), 191 (74), 162 (60%); HRMS (EI) m/z M^+ 472.2210 (calcd for $C_{25}H_{32}N_2O_7$ 472.2210). Anal. Calcd for $C_{25}H_{32}N_2O_7$: C, 63.54; H, 6.83; N, 5.93. Found: C, 63.43; H, 6.89; N, 5.92.

7l: (Table 4, entry 3). (1 mmol scale, 307 mg, 74%); R_f = 0.8 (CH_2Cl_2−ether = 1:1); colorless crystals; mp 114−115 °C (AcOEt−hexane = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.24 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 2.44 (ddddd, J = 13.1, 11.9, 9.8, 7.4, 5.5 Hz, 1H), 3.02 (d, J = 13.1 Hz, 1H), 3.08−3.25 (m, 3H), 3.60 (dd, J = 9.4, 7.4 Hz, 1H), 3.85 (dd, J = 15.2, 6.1 Hz, 1H), 4.04−4.16 (m, 2H), 4.25−4.44 (m, 3H), 5.22 (dddd, J = 10.2, 1.4, 1.4, 1.2 Hz, 1H), 5.26 (dddd, J = 17.2, 1.6, 1.4, 1.4 Hz, 1H), 5.78 (dddd, J = 17.2, 10.2, 6.1, 5.9 Hz, 1H), 7.41 (dd, J = 8.0, 8.0 Hz, 1H), 7.66 (dd, J = 8.0, 1.4 Hz, 1H), 7.83 (dd, J = 8.0, 1.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.9 (CH_3), 14.1 (CH_3), 31.3 (CH_2), 31.9 (CH), 45.2 (CH_2), 49.4 (CH), 50.5 (CH_2), 60.9 (C), 62.5 (CH_2), 63.0 (CH_2), 118.2 (CH_2), 124.5 (CH), 127.0 (CH), 130.6 (C), 132.5 (CH), 135.6 (CH), 136.9 (C), 150.5 (C), 167.8 (C), 170.0 (C), 170.9 (C); ^{1}H NMR (400 MHz, C_6D_6) δ (ppm) 0.951 (t, J = 7.1 Hz, 3H), 1.06 (t, J = 7.1 Hz, 3H), 1.99 (ddddd, J = 13.1, 11.7, 9.8, 7.4, 5.4 Hz, 1H), 2.15−2.21 (m, 1H), 2.53 (dd, J = 17.4, 11.7 Hz, 1H), 2.61 (dd, J = 17.4, 5.4 Hz, 1H), 2.73−2.78 (m, 1H), 2.86 (d, J = 13.1 Hz, 1H), 3.42 (dd, J = 15.4, 6.1 Hz, 1H), 3.88−3.96 (m, 2H), 4.01−4.09 (m, 1H), 4.14−4.26 (m, 2H), 4.96 (dd, J = 10.2, 1.4 Hz, 1H), 5.00 (dd, J = 17.2, 1.6 Hz, 1H), 5.52 (dddd, J = 17.2, 10.2, 6.1, 5.7 Hz, 1H), 6.70−6.75 (m, 1H), 7.34 (dd, J = 8.0, 1.4 Hz, 1H), 7.72 (dd, J = 8.0, 1.4 Hz, 1H). Selected NOEs are between δ 1.99 (C3a−*H*) and δ 2.73−2.78 (C3−H*H*), 2.61 (C4−H*H*) and between δ 2.15−2.21 (C3−*H*H), 2.53 (C4−*H*H), and δ 2.86 (C9a−*H*). ^{13}C NMR (100.6 MHz, C_6D_6) δ (ppm) 13.8 (CH_3), 14.0 (CH_3), 31.1 (CH_2), 31.7 (CH), 44.9 (CH_2), 49.4 (CH), 49.8 (CH_2), 61.2 (C), 62.0 (CH_2), 62.6 (CH_2), 117.0 (CH_2), 124.1 (CH), 126.8 (CH), 130.8 (C), 133.3 (CH), 135.5 (CH), 137.5 (C), 151.0 (C), 167.8 (C), 170.0 (C), 170.1 (C). Selected HMBC correlations are between δ 2.53 (C4−*H*H), 2.61 (C4−H*H*), 2.73−2.78 (C3−H*H*), 2.86 (C9a−*H*), and δ 31.7 (*C*3a), δ 1.99 (C3a−*H*), 2.86 (C9a−*H*), and δ 31.1 (*C*4), and between δ 2.86 (C9a−*H*) and δ 61.2 (*C*9). IR (KBr) 2984, 1743, 1723, 1702, 1644, 1529, 1364, 1251, 1197, 1023 cm^{-1}; MS (EI) m/z 416 (M^+, 100), 343 (74), 297 (89%); HRMS (EI) m/z M^+ 416.1588 (calcd for $C_{21}H_{24}N_2O_7$ 416.1584). Anal. Calcd for $C_{21}H_{24}N_2O_7$: C, 60.57; H, 5.81; N, 6.73. Found: C, 60.38; H, 5.84; N, 6.80.

7m: (Table 4, entry 4). (1 mmol scale, 380 mg, 78%); R_f = 0.4 (hexane−ether = 1:4); colorless crystals; mp 157−158 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.25 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 2.36 (ddddd, J = 13.1, 12.1, 9.6, 7.5, 5.5 Hz, 1H), 2.91 (d, J = 13.1 Hz, 1H), 3.08 (dd, J = 9.6, 9.3 Hz, 1H), 3.11 (dd, J = 17.8, 12.1 Hz, 1H), 3.25 (dd, J = 17.8, 5.5 Hz, 1H), 3.48 (dd, J = 9.3, 7.5 Hz, 1H), 4.14 (dq, J = 10.7, 7.1 Hz, 1H), 4.30−4.52 (m, 4H), 4.64 (d, J = 14.8 Hz, 1H), 7.14 (dd, J_{FH} = 9.2, J_{HH} = 9.0 Hz, 1H), 7.27−7.37 (m, 5H), 7.93 (dd, J_{FH} = 4.9, J_{HH} = 9.0 Hz, 1H). Selected NOEs are between δ 2.36 (C3a−*H*) and δ 3.48 (C3−H*H*), 3.25 (C4−H*H*) and between δ 3.08 (C3−*H*H), 3.11 (C4−*H*H), and δ 2.91 (C9a−*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.89 (CH_3), 13.93 (CH_3), 31.6 (CH), 31.8 (CH_2), 46.6 (CH_2), 49.8 (CH), 50.2 (CH_2), 58.3 (C), 62.6 (CH_2), 63.0 (CH_2), 115.0 (CH, d, J_{CF} = 26 Hz), 126.0 (C, d, J_{CF} = 16 Hz), 127.0 (CH, d, J_{CF} = 11.5 Hz), 127.8 (CH), 128.3 (CH), 128.8 (CH), 134.2 (C, d, J_{CF} = 4.6 Hz), 136.4 (C), 146.4 (C), 164.0 (C), 167.1 (C), 169.5 (C), 170.5 (C). Selected HMBC correlations are between δ 3.11 (C4−*H*H), 3.25 (C4−H*H*), and δ 50.2 (*C*3), between δ 3.11 (C4−*H*H), 3.25 (C4−H*H*), and δ 49.8 (*C*9a), and between δ 2.91 (C9a−*H*) and δ 58.3 (*C*9). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −100.82 (J_{FH} = 9.2, 4.9 Hz); IR (KBr) 2983, 1746, 1727, 1699, 1527, 1360, 1268, 1251, 1198, 1023 cm^{-1}; MS (EI) m/z 484 (M^+, 53), 454 (31), 381 (31), 337 (18), 310 (20), 119 (23), 91 (100%); HRMS (EI) m/z M^+ 484.1661 (calcd for $C_{25}H_{25}FN_2O_7$ 484.1646).

7n: (Table 4, entry 5). (1 mmol scale, 317 mg, 68%); R_f = 0.3 (hexane−ether = 1:8); colorless crystals; mp 133−134.5 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.25 (t, J = 7.1 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H), 2.55 (ddddd, J = 12.9, 12.1, 9.6, 7.5, 5.1 Hz, 1H), 2.90 (dd, J = 17.0, 12.1 Hz, 1H), 3.04 (d, J = 12.9 Hz, 1H), 3.07 (dd, J = 9.6, 9.3 Hz, 1H), 3.14 (dd, J = 17.0, 5.1 Hz, 1H), 3.48 (dd, J = 9.3, 7.5 Hz, 1H), 4.15 (dq, J = 10.7, 7.1 Hz, 1H), 4.28−4.51 (m, 4H), 4.68 (d, J = 14.8 Hz, 1H), 7.27−7.37 (m, 6H), 8.08 (dd, J = 8.6, 2.3 Hz, 1H), 8.30 (d, J = 2.3 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.9 (CH_3), 14.1 (CH_3), 32.3 (CH), 34.4 (CH_2), 46.6 (CH_2), 50.1 (CH), 50.2 (CH_2), 60.4 (C), 62.5 (CH_2), 63.2 (CH_2), 122.8 (CH), 126.2 (CH), 127.7 (CH), 128.2 (CH), 128.8 (CH), 130.7 (CH), 135.9 (C), 136.6 (C), 143.1 (C), 146.6 (C), 167.6 (C), 169.9 (C), 171.0 (C); ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ (ppm) 1.19 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.54 (ddddd, J = 12.9, 11.9, 9.6, 7.6, 5.3 Hz, 1H), 3.06 (dd, J = 17.8, 11.9 Hz, 1H), 3.11 (d, J = 12.9 Hz, 1H), 3.22 (dd, J = 9.6, 9.0 Hz, 1H), 3.26 (dd, J = 17.8, 5.3 Hz, 1H), 3.54 (dd, J = 9.0, 7.6 Hz, 1H), 4.08−4.42 (m, 5H), 4.69 (d, J = 15.0 Hz, 1H), 7.27−7.32 (m, 1H), 7.33−7.37 (m, 4H), 7.50 (d, J = 8.6 Hz, 1H), 8.11 (dd, J = 8.6, 2.3 Hz, 1H), 8.23 (d, J = 2.3 Hz, 1H). Selected NOEs are between δ 2.54 (C3a−*H*) and δ 3.54 (C3−H*H*), 3.26 (C4−H*H*). ^{13}C NMR (100.6 MHz, $(CD_3)_2CO$) δ (ppm) 14.1 (CH_3), 14.3 (CH_3), 33.1 (CH), 34.7 (CH_2), 46.6 (CH_2), 50.3 (CH), 50.6 (CH_2), 61.4 (C), 62.6 (CH_2), 63.0 (CH_2), 123.2 (CH), 126.2 (CH), 128.1 (CH), 128.7 (CH), 129.3 (CH), 132.0 (CH), 137.0 (C), 138.4 (C), 145.3 (C), 147.1 (C), 168.2 (C), 170.4 (C), 171.3 (C). Selected HMBC correlations are between δ 3.06 (C4−*H*H), 3.11 (C9a−*H*), and δ 50.6 (*C*3), between δ 3.22 (C3−*H*H), 3.54 (C3−H*H*), and δ 50.3 (*C*9a), between δ 3.06 (C4−*H*H), 3.26 (C4−H*H*), 3.11 (C9a−*H*), 3.54 (C3−H*H*), and δ 33.1 (*C*3a), and between δ 3.11 (C9a−*H*) and δ 61.4 (*C*9). IR (KBr) 2982, 2936, 1747, 1732, 1699, 1520, 1347, 1255, 1190, 1098, 1029 cm^{-1}; MS (EI) m/z 466 (M^+, 96), 363 (53), 91 (100%); HRMS (EI) m/z M^+ 466.1734 (calcd for $C_{25}H_{26}N_2O_7$ 466.1740). Anal. Calcd for $C_{25}H_{26}N_2O_7$: C, 64.37; H, 5.62; N, 6.01. Found: C, 64.68; H, 5.34; N, 5.97.

7o: (Table 4, entry 6). (1 mmol scale, 334 mg, 75%); R_f = 0.2 (hexane−ether = 1:4); colorless crystals; mp 118.5−119.5 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.25 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 2.52 (ddddd, J = 13.3, 12.1, 9.7, 7.4, 5.3 Hz, 1H), 2.87 (dd, J = 16.6, 12.1 Hz, 1H), 3.01 (d, J = 13.3 Hz, 1H), 3.05 (dd, J = 9.7, 9.4 Hz, 1H), 3.08 (dd, J = 16.6, 5.3 Hz, 1H), 3.47 (dd, J = 9.4, 7.4 Hz, 1H), 4.14 (dq, J = 10.7, 7.1 Hz, 1H), 4.28−4.49 (m, 4H), 4.67 (d, J = 14.8 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.27−7.37 (m, 5H), 7.50 (dd, J = 8.0, 1.7 Hz, 1H), 7.70 (d, J = 1.7 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (CH_3), 14.1 (CH_3), 32.2 (CH), 34.5 (CH_2),

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

46.5 (CH_2), 50.1 (CH), 50.2 (CH_2), 60.3 (C), 62.5 (CH_2), 63.1 (CH_2), 110.7 (C), 118.6 (C), 127.7 (CH), 128.2 (CH), 128.8 (CH), 130.8 (CH), 131.1 (CH), 134.9 (CH), 135.7 (C), 136.6 (C), 141.3 (C), 167.6 (C), 170.0 (C), 171.2 (C); ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) 1.17 (t, J = 7.0 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 2.44 (ddddd, J = 12.9, 11.9, 9.4, 7.6, 5.3 Hz, 1H), 2.91 (dd, J = 17.2, 11.9 Hz, 1H), 3.02 (d, J = 12.9 Hz, 1H), 3.11 (dd, J = 9.4, 9.2 Hz, 1H), 3.11 (dd, J = 17.2, 5.3 Hz, 1H), 3.46 (dd, J = 9.2, 7.6 Hz, 1H), 4.07 (dq, J = 10.7, 7.0 Hz, 1H), 4.19–4.38 (m, 4H), 4.62 (d, J = 15.2 Hz, 1H), 7.28–7.39 (m, 6H), 7.60 (dd, J = 8.0, 1.6 Hz, 1H), 7.66 (d, J = 1.6 Hz, 1H). Selected NOEs are between δ 2.44 (C3a–*H*) and δ 3.46 (C3–H*H*), and between δ 2.91 (C4–*H*H) and δ 3.02 (C9a–*H*). ^{13}C NMR (100.6 MHz, CD_3CN) δ (ppm) 14.2 (CH_3), 14.3 (CH_3), 32.9 (CH), 34.7 (CH_2), 46.7 (CH_2), 50.4 (CH), 51.0 (CH_2), 61.4 (C), 62.9 (CH_2), 63.4 (CH_2), 110.8 (C), 119.3 (C), 128.3 (CH), 128.8 (CH), 129.5 (CH), 132.0 (CH), 132.1 (CH), 135.3 (CH), 136.7 (C), 138.4 (C), 143.3 (C), 168.6 (C), 170.9 (C), 171.9 (C). Selected HMBC correlations are between δ 2.91 (C4–*H*H) and δ 51.0 (*C*3), between δ 3.46 (C3–H*H*) and δ 50.4 (*C*9a), δ 2.91 (C4–*H*H), 3.02 (C9a–*H*), 3.46 (C3–H*H*), and δ 32.9 (*C*3a), and between δ 3.02 (C9a–*H*) and δ 61.4 (*C*9). IR (KBr) 2981, 2937, 2229, 1742, 1730, 1696, 1496, 1442, 1366, 1252, 1190, 1029 cm^{-1}; MS (EI) m/z 446 (M^+, 100), 343 (58), 149 (60), 91 (92%); HRMS (EI) m/z M^+ 446.1846 (calcd for $C_{26}H_{26}N_2O_5$ 446.1842). Anal. Calcd for $C_{26}H_{26}N_2O_5$: C, 69.94; H, 5.87; N, 6.27. Found: C, 69.59; H, 5.96; N, 6.15.

7p: *(Table 4, entry 7)*. (1 mmol scale, 342 mg, 71%); R_f = 0.3 (hexane–ether = 1:4); colorless crystals; mp 145–146 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.23 (t, J = 7.1 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H), 2.53 (ddddd, J = 13.2, 12.1, 9.6, 7.4, 5.1 Hz, 1H), 2.86 (dd, J = 16.6, 12.1 Hz, 1H), 3.04 (d, J = 13.2 Hz, 1H), 3.05 (dd, J = 9.6, 9.2 Hz, 1H), 3.08 (dd, J = 16.6, 5.1 Hz, 1H), 3.46 (dd, J = 9.2, 7.4 Hz, 1H), 3.90 (s, 3H), 4.14 (dq, J = 10.7, 7.1 Hz, 1H), 4.26–4.50 (m, 4H), 4.68 (d, J = 14.8 Hz, 1H), 7.19 (d, J = 8.1 Hz, 1H), 7.26–7.36 (m, 5H), 7.89 (dd, J = 8.1, 1.7 Hz, 1H), 8.09 (d, J = 1.7 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.9 (CH_3), 14.1 (CH_3), 32.4 (CH), 34.4 (CH_2), 46.5 (CH_2), 50.28 (CH), 50.32 (CH_2), 52.2 (CH_3), 60.4 (C), 62.2 (CH_2), 62.7 (CH_2), 127.6 (CH), 128.2 (CH), 128.6 (C), 128.7 (CH), 128.9 (CH), 129.9 (CH), 132.2 (CH), 134.5 (C), 136.7 (C), 140.8 (C), 166.6 (C), 168.2 (C), 170.4 (C), 171.5 (C); ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) 1.16 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 2.44 (ddddd, J = 13.1, 11.9, 9.8, 7.6, 5.3 Hz, 1H), 2.89 (dd, J = 17.0, 11.9 Hz, 1H), 3.04 (d, J = 13.1 Hz, 1H), 3.11 (dd, J = 17.0, 5.3 Hz, 1H), 3.11 (dd, J = 9.8, 9.2 Hz, 1H), 3.47 (dd, J = 9.2, 7.6 Hz, 1H), 3.87 (s, 3H), 4.07 (dq, J = 10.7, 7.1 Hz, 1H), 4.17–4.38 (m, 5H), 4.62 (d, J = 15.0 Hz, 1H), 7.28–7.33 (m, 4H), 7.36–7.39 (m, 2H), 7.86 (dd, J = 8.0, 1.8 Hz, 1H), 7.94 (d, J = 1.8 Hz, 1H). Selected NOEs are between δ 2.44 (C3a–*H*) and δ 3.47 (C3–H*H*). ^{13}C NMR (100.6 MHz, CD_3CN) δ (ppm) 14.2 (CH_3), 14.4 (CH_3), 33.1 (CH), 34.6 (CH_2), 46.7 (CH_2), 50.6 (CH), 51.1 (CH_2), 52.8 (CH_3), 61.6 (C), 62.8 (CH_2), 63.1 (CH_2), 128.3 (CH), 128.8 (CH), 129.2 (C), 129.4 (CH), 129.6 (CH), 131.3 (CH), 132.4 (CH), 135.8 (C), 138.4 (C), 142.8 (C), 167.2 (C), 169.1 (C), 171.3 (C), 172.1 (C). Selected HMBC correlations are between δ 2.89 (C4–*H*H) and δ 51.1 (*C*3), between δ 3.47 (C3–H*H*) and δ 50.6 (*C*9a), between δ 2.89 (C4–*H*H), 3.47 (C3–H*H*), and δ 33.1 (*C*3a), and between δ 3.04 (C9a–*H*) and δ 61.6 (*C*9). IR (KBr) 2984, 2918, 1749, 1726, 1686, 1613, 1483, 1431, 1254, 1191, 1138, 1023 cm^{-1}; MS (FAB) m/z 502 ([M + Na]$^+$), 480 ([M + H]$^+$); HRMS (FAB) m/z [M + H]$^+$ 480.2026 (calcd for $C_{27}H_{30}NO_7$ 480.2022), [M + Na]$^+$ 502.1856 (calcd for $C_{27}H_{29}NO_7Na$ 502.1842). Anal. Calcd for $C_{27}H_{29}NO_7$: C, 67.63; H, 6.10; N, 2.92. Found: C, 67.58; H, 6.12; N, 2.89.

7q: *(Table 4, entry 8)*. (1 mmol scale, 282 mg, 57%); R_f = 0.4 (hexane–ether = 1:8); colorless crystals; mp 128–129.5 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.23 (t, J = 7.1 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H), 1.38 (t, J = 7.1 Hz, 3H), 2.53 (ddddd, J = 12.9, 12.1, 9.8, 7.5, 5.1 Hz, 1H), 2.86 (dd, J = 16.6, 12.1 Hz, 1H), 3.05 (d, J = 12.9 Hz, 1H), 3.05 (dd, J = 9.8, 9.3 Hz, 1H), 3.08 (dd, J = 16.6, 5.1 Hz, 1H), 3.46 (dd, J = 9.3, 7.5 Hz, 1H), 4.13 (dq, J = 10.7, 7.1 Hz, 1H), 4.27–4.51 (m, 6H), 4.68 (d, J = 14.8 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.26–7.36 (m, 5H), 7.89 (dd, J = 8.0, 1.8 Hz, 1H), 8.10 (d, J = 1.8 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.9 (CH_3), 14.1 (CH_3), 14.3 (CH_3), 32.3 (CH), 34.3 (CH_2), 46.5 (CH_2), 50.2 (CH), 50.3 (CH_2), 60.4 (C), 61.0 (CH_2), 62.1 (CH_2), 62.7 (CH_2), 127.6 (CH), 128.2 (CH), 128.7 (CH), 128.85 (CH), 128.92 (C), 129.8 (CH), 132.1 (CH), 134.5 (C), 136.7 (C), 140.6 (C), 166.1 (C), 168.2 (C), 170.4 (C), 171.6 (C); ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) 1.16 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.0 Hz, 3H), 2.44 (ddddd, J = 13.1, 11.9, 9.6, 7.4, 5.3 Hz, 1H), 2.89 (dd, J = 16.8, 11.9 Hz, 1H), 3.04 (d, J = 13.1 Hz, 1H), 3.11 (dd, J = 9.6, 9.2 Hz, 1H), 3.11 (dd, J = 16.8, 5.3 Hz, 1H), 3.47 (dd, J = 9.2, 7.4 Hz, 1H), 4.07 (dq, J = 10.7, 7.1 Hz, 1H), 4.18–4.39 (m, 6H), 4.62 (d, J = 15.0 Hz, 1H), 7.28–7.33 (m, 4H), 7.35–7.39 (m, 2H), 7.87 (dd, J = 8.0, 1.8 Hz, 1H), 7.95 (d, J = 1.8 Hz, 1H). Selected NOEs are between δ 2.44 (C3a–*H*) and δ 3.47 (C3–H*H*), and between δ 2.89 (C4–*H*H) and δ 3.04 (C9a–*H*). ^{13}C NMR (100.6 MHz, CD_3CN) δ (ppm) 14.9 (CH_3), 15.0 (CH_3), 15.2 (CH_3), 33.8 (CH), 35.3 (CH_2), 47.4 (CH_2), 51.2 (CH), 51.7 (CH_2), 62.2 (C), 62.5 (CH_2), 63.4 (CH_2), 63.8 (CH_2), 128.9 (CH), 129.4 (CH), 130.0 (CH), 130.2 (CH), 131.9 (CH), 133.0 (CH), 136.4 (C), 139.1 (C), 143.3 (C), 167.3 (C), 169.7 (C), 172.0 (C), 172.8 (C). Selected HMBC correlations are between δ 2.89 (C4–*H*H) and δ 51.7 (*C*3), between δ 3.47 (C3–H*H*), 2.89 (C4–*H*H), and δ 51.2 (*C*9a), between δ 2.89 (C4–*H*H), 3.04 (C9a–*H*), 3.47 (C3–H*H*), and δ 33.8 (*C*3a), and between δ 3.04 (C9a–*H*) and δ 62.2 (*C*9). IR (KBr) 2983, 1728, 1611, 1482, 1443, 1366, 1280, 1259, 1193, 1027 cm^{-1}; MS (EI) m/z 493 (M^+, 100), 390 (72), 91 (55%); HRMS (EI) m/z M^+ 493.2094 (calcd for $C_{28}H_{31}NO_7$ 493.2101).

7r:*(Table 4, entry 9)*. (0.5 mmol scale, 125 mg, 51%); R_f = 0.7 (ether); colorless crystals; mp 124–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.23 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 2.54 (ddddd, J = 14.1, 12.2, 9.8, 7.5, 5.3 Hz, 1H), 2.87 (dd, J = 16.5, 12.2 Hz, 1H), 3.04 (d, J = 14.1 Hz, 1H), 3.06 (dd, J = 9.8, 9.3 Hz, 1H), 3.08 (dd, J = 16.5, 5.3 Hz, 1H), 3.47 (dd, J = 9.3, 7.5 Hz, 1H), 4.13 (dq, J = 10.7, 3.1 Hz, 1H), 4.26–4.47 (m, 4H), 4.69 (d, J = 14.8 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.27–7.37 (m, 5H), 7.48 (dd, J = 8.0, 1.4 Hz, 1H), 7.67 (bs, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.8 (CH_3), 14.1 (CH_3), 32.4 (CH), 34.2 (CH_2), 46.5 (CH_2), 50.2 (CH), 50.3 (CH_2), 60.4 (C), 62.3 (CH_2), 62.8 (CH_2), 124.0 (C, q, J_{CF} = 272 Hz), 124.7 (CH, q, J_{CF} = 3.8 Hz), 127.6 (CH), 127.9 (CH, q, J_{CF} = 3.8 Hz), 128.2 (CH), 128.8 (CH), 128.9 (C, q, J_{CF} = 33 Hz), 130.3 (CH), 134.9 (C), 136.6 (C), 139.7 (C), 167.9 (C), 170.2 (C), 171.4 (C); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −62.71; ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) 1.16 (t, J = 7.0 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 2.46 (ddddd, J = 13.1, 12.1, 9.6, 7.4, 5.1 Hz, 1H), 2.91 (dd, J = 16.8, 12.1 Hz, 1H), 3.05 (d, J = 13.1 Hz, 1H), 3.12 (dd, J = 9.6, 9.2 Hz, 1H), 3.12 (dd, J = 16.8, 5.1 Hz, 1H), 3.48 (dd, J = 9.2, 7.4 Hz, 1H), 4.07 (dq, J = 10.7, 7.0 Hz, 1H), 4.18–4.37 (m, 4H), 4.63 (d, J = 15.0 Hz, 1H), 7.28–7.40 (m, 6H), 7.58 (d, J = 8.4 Hz, 1H), 7.59 (s, 1H). Selected NOEs are between δ 2.46 (C3a–*H*) and δ 3.48 (C3–H*H*), and between δ 2.91 (C4–*H*H) and δ 3.05 (C9a–*H*). ^{13}C NMR (100.6 MHz, CD_3CN) δ (ppm) 14.1 (CH_3), 14.3 (CH_3), 33.1 (CH), 34.5 (CH_2), 46.7 (CH_2), 50.5 (CH), 51.0 (CH_2), 61.5 (C), 62.9 (CH_2), 63.2 (CH_2), 125.2 (C, q, J_{CF} = 271 Hz), 125.4 (CH, q, J_{CF} = 3.8 Hz), 128.2 (CH, q, J_{CF} = 4.6 Hz), 128.3 (CH), 128.7 (C, q, J_{CF} = 32 Hz), 128.8 (CH), 129.6 (CH), 131.9 (CH), 136.3 (C), 138.4 (C), 142.2 (C), 168.8 (C), 171.1 (C), 172.0 (C). Selected HMBC correlations are between δ 2.91 (C4–*H*H) and δ 51.0 (*C*3), between δ 3.48 (C3–H*H*), 2.91 (C4–*H*H), and δ 50.5 (*C*9a), between δ 2.91 (C4–*H*H), 3.05 (C9a–*H*), 3.48 (C3–H*H*), and δ 33.1 (*C*3a), and between δ 3.05 (C9a–*H*) and δ 61.5 (*C*9). IR (KBr) 2927, 1747, 1726, 1699, 1334, 1261, 1162, 1128 cm^{-1}; MS (EI) m/z 489 (M^+, 25), 386 (15), 333 (14), 242 (29), 226 (36), 200 (100%); HRMS (EI) m/z M^+ 489.1772 (calcd for $C_{26}H_{26}F_3NO_5$ 489.1763).

3r:*(Table 4, entry 9)*. (0.5 mmol scale, 14 mg, 6%); R_f = 0.4 (ether); colorless crystals; mp 164–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.30 (t, J = 7.0 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 2.36 (ddd, J = 10.9, 6.6, 5.9 Hz, 1H), 2.64 (d, J = 10.9 Hz, 1H), 3.33 (dd, J = 10.9, 5.9 Hz, 1H), 3.82 (d, J = 14.3 Hz, 1H), 3.91 (d, J = 6.6 Hz, 1H), 4.03–4.16 (m, 2H), 4.24–4.37 (m, 3H), 5.00 (d, J = 14.3 Hz, 1H), 6.79 (d, J = 8.1 Hz, 2H), 7.30–7.32 (m, 2H), 7.40–7.44 (m, 3H), 7.49 (d, J = 8.1 Hz, 2H). Selected NOEs are between δ 2.36 (C5–*H*) and δ 3.33 (C4–H*H*), 6.79 (Ar-*H*), 3.91 (C1–*H*) and between δ 3.33 (C4–H*H*) and δ 3.91 (C1–*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.5 (CH_3), 15.0 (CH_3), 36.3 (CH), 41.1 (CH), 44.4 (CH_2), 46.3 (CH_2), 60.1 (CH_2),

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863–10886

65.0 (CH_2), 79.0 (CH), 79.7 (C), 123.8 (C, q, J_{CF} = 272 Hz), 125.7 (CH, q, J_{CF} = 3.8 Hz), 127.7 (CH), 128.1 (CH), 129.1 (CH), 129.2 (CH), 131.3 (C, q, J_{CF} = 33 Hz), 136.7 (C), 140.7 (C), 162.7 (C), 167.1 (C), 172.8 (C). Selected HMBC correlations are between δ 2.36 (C5−*H*), 2.64 (C4−*H*H), 3.91 (C1−*H*), and δ 172.8 (*C*2), between δ 2.36 (C5−*H*), 2.64 (C4−*H*H), 3.33 (C4−H*H*), 3.91 (C1−*H*), and δ 79.0 (*C*6), between δ 2.64 (C4−*H*H) and δ 41.1 (*C*1), and between δ 2.64 (C4−*H*H), 3.91 (C1−*H*), and δ 36.3 (*C*5). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −62.85; IR (KBr) 2984, 2931, 1699, 1668, 1621, 1327, 1164, 1124, 1068, 1020 cm^{-1}; MS (EI) *m*/*z* 489 (M^+, 21), 291 (43), 205 (92), 200 (63), 91 (100%); HRMS (EI) *m*/*z* M^+ 489.1789 (calcd for $C_{26}H_{26}F_3NO_5$ 489.1763).

7s: *(Table 5, entry 1).* (1 mmol scale, 258 mg, 53%); R_f = 0.6 (hexane−ether = 1:8); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.24 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 2.53 (ddddd, *J* = 13.3, 12.1, 9.6, 7.5, 5.3 Hz, 1H), 2.88 (dd, *J* = 16.3, 12.1 Hz, 1H), 3.04 (d, *J* = 13.3 Hz, 1H), 3.07 (dd, *J* = 9.6, 9.3 Hz, 1H), 3.09 (dd, *J* = 16.3, 5.3 Hz, 1H), 3.48 (dd, *J* = 9.3, 7.5 Hz, 1H), 4.13 (dq, *J* = 10.7, 7.1 Hz, 1H), 4.26−4.47 (m, 4H), 4.69 (d, *J* = 14.8 Hz, 1H), 7.26−7.37 (m, 5H), 7.39 (bs, 1H), 7.47 (broad d, *J* = 8.2 Hz, 1H), 7.52 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.9 (CH_3), 14.1 (CH_3), 32.3 (CH), 34.1 (CH_2), 46.4 (CH_2), 50.2 (CH), 50.3 (CH_2), 60.5 (C), 62.2 (CH_2), 62.7 (CH_2), 123.1 (CH, q, J_{CF} = 3.8 Hz), 123.9 (C, q, J_{CF} = 272 Hz), 126.7 (CH, q, J_{CF} = 3.8 Hz), 127.6 (CH), 128.2 (CH), 128.7 (CH), 130.2 (C, q, J_{CF} = 32 Hz), 131.3 (CH), 136.5 (C), 136.6 (C), 137.8 (C), 167.9 (C), 170.2 (C), 171.4 (C); ^{1}H NMR (400 MHz, CD_3CN) δ (ppm) 1.17 (t, *J* = 7.0 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 2.46 (ddddd, *J* = 13.1, 12.1, 9.2, 7.7, 5.4 Hz, 1H), 2.91 (dd, *J* = 16.6, 12.1 Hz, 1H), 3.04 (d, *J* = 13.1 Hz, 1H), 3.12 (dd, *J* = 9.2, 9.1 Hz, 1H), 3.13 (dd, *J* = 16.6, 5.4 Hz, 1H), 3.48 (dd, *J* = 9.1, 7.7 Hz, 1H), 4.07 (dq, *J* = 10.7, 7.0 Hz, 1H), 4.19−4.37 (m, 4H), 4.63 (d, *J* = 15.0 Hz, 1H), 7.28−7.39 (m, 5H), 7.50−7.55 (m, 3H). Selected NOEs are between δ 2.46 (C3a−*H*) and δ 3.48 (C3−H*H*), and between δ 2.91 (C4−*H*H) and δ 3.04 (C9a−*H*). ^{13}C NMR (100.6 MHz, CD_3CN) δ (ppm) 14.2 (CH_3), 14.3 (CH_3), 33.1 (CH), 34.4 (CH_2), 46.7 (CH_2), 50.5 (CH), 51.0 (CH_2), 61.7 (C), 62.9 (CH_2), 63.2 (CH_2), 123.6 (CH, q, *J* = 3.8 Hz), 125.1 (C, q, *J* = 271 Hz), 127.7 (CH, q, *J* = 3.8 Hz), 128.3 (CH), 128.8 (CH), 129.6 (CH), 130.3 (C, q, *J* = 32 Hz), 132.4 (CH), 138.4 (C), 138.7 (C), 139.5 (C), 168.8 (C), 171.1 (C), 172.1 (C). Selected HMBC correlations are between δ 2.91 (C4−*H*H) and δ 51.0 (*C*3), between δ 3.48 (C3−H*H*), 2.91 (C4−*H*H), and δ 50.5 (*C*9a), between δ 2.91 (C4−*H*H), 3.04 (C9a−*H*), 3.48 (C3−H*H*), and δ 33.1 (*C*3a), and between δ 3.04 (C9a−*H*) and δ 61.7 (*C*9). IR (neat) 2980, 1747, 1733, 1684, 1651, 1426, 1337, 1250, 1164, 1083, 1031 cm^{-1}; MS (FAB) *m*/*z* 512 ($[M + Na]^+$), 490 ($[M + H]^+$); HRMS (FAB) *m*/*z* $[M + Na]^+$ 512.1661 (calcd for $C_{26}H_{26}F_3NO_5Na$ 512.1661).

3s: *(Table 5, entry 1).* (1 mmol scale, 119 mg, 24%); R_f = 0.1 (hexane−ether = 1:8); colorless crystals; mp 130−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.30 (t, *J* = 7.0 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 2.40 (ddd, *J* = 10.9, 6.6, 6.0 Hz, 1H), 2.62 (d, *J* = 10.9 Hz, 1H), 3.35 (dd, *J* = 10.9, 6.0 Hz, 1H), 3.79 (d, *J* = 14.3 Hz, 1H), 3.92 (d, *J* = 6.6 Hz, 1H), 4.03−4.16 (m, 2H), 4.25−4.37 (m, 3H), 5.02 (d, *J* = 14.3 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 7.03 (s, 1H), 7.28−7.31 (m, 2H), 7.35−7.43 (m, 4H), 7.57 (d, *J* = 7.8 Hz, 1H). Selected NOEs are between δ 2.40 (C5−*H*) and δ 3.35 (C4−H*H*), 6.90 (Ar-*H*), 7.03 (Ar-*H*), 3.92 (C1−*H*) and between δ 3.35 (C4−H*H*) and δ 3.92 (C1−*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.5 (CH_3), 15.0 (CH_3), 36.1 (CH), 41.0 (CH), 44.5 (CH_2), 46.4 (CH_2), 60.1 (CH_2), 65.1 (CH_2), 79.0 (CH), 79.8 (C), 123.7 (C, q, J_{CF} = 273 Hz), 124.2 (CH, q, J_{CF} = 3.8 Hz), 126.1 (CH, q, J_{CF} = 3.8 Hz), 128.2 (CH), 129.0 (CH), 129.1 (CH), 129.3 (CH), 130.8 (CH), 131.3 (C, q, J_{CF} = 32 Hz), 136.5 (C), 138.0 (C), 162.6 (C), 167.1 (C), 172.7 (C). Selected HMBC correlations are between δ 2.40 (C5−*H*), 2.62 (C4−*H*H), 3.92 (C1−*H*), and δ 172.7 (*C*2), between δ 2.40 (C5−*H*), 2.62 (C4−*H*H), 3.35 (C4−H*H*), 3.92 (C1−*H*), and δ 79.0 (*C*6), between δ 2.62 (C4−*H*H) and δ 41.0 (*C*1), and between δ 2.62 (C4−*H*H), 3.92 (C1−*H*), and δ 36.1 (*C*5). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −62.56; IR (KBr) 2983, 2929, 1701, 1666, 1625, 1494, 1413, 1331, 1164, 1083 cm^{-1}; MS (FAB) *m*/*z* 512 ($[M + Na]^+$), 490 ($[M + H]^+$); HRMS (FAB) *m*/*z* $[M + Na]^+$ 512.1660 (calcd for $C_{26}H_{26}F_3NO_5Na$ 512.1661).

3t: *(Table 5, entry 2).* (0.5 mmol scale, 85 mg, 30%); R_f = 0.5 (ether); colorless crystals; mp 170−171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.31 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 2.42 (ddd, *J* = 11.0, 6.8, 6.1 Hz, 1H), 2.58 (d, *J* = 11.0 Hz, 1H), 3.39 (dd, *J* = 11.0, 6.1 Hz, 1H), 3.72 (d, *J* = 14.2 Hz, 1H), 3.95 (d, *J* = 6.8 Hz, 1H), 4.03−4.16 (m, 2H), 4.25−4.38 (m, 2H), 5.12 (d, *J* = 14.2 Hz, 1H), 7.21 (s, 2H), 7.29−7.31 (m, 2H), 7.39−7.43 (m, 3H), 7.83 (s, 1H). Selected NOEs are between δ 2.42 (C5−*H*) and δ 3.39 (C4−H*H*), 7.21 (Ar-*H*), 3.95 (C1−*H*) and between δ 3.39 (C4−H*H*) and δ 3.95 (C1−*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.5 (CH_3), 14.9 (CH_3), 36.2 (CH), 40.9 (CH), 44.2 (CH_2), 46.3 (CH_2), 60.2 (CH_2), 65.4 (CH_2), 78.3 (CH), 80.3 (C), 122.8 (C, q, J_{CF} = 273 Hz), 123.2 (CH, septet, J_{CF} = 3.8 Hz), 127.6 (CH), 128.5 (CH), 128.8 (CH), 129.1 (CH), 132.3 (C, q, J_{CF} = 34 Hz), 136.3 (C), 139.8 (C), 162.1 (C), 166.9 (C), 172.4 (C). Selected HMBC correlations are between δ 2.42 (C5−*H*), 2.58 (C4−*H*H), 3.95 (C1−*H*), and δ 172.4 (*C*2), between δ 2.42 (C5−*H*), 2.58 (C4−*H*H), 3.39 (C4−H*H*), 3.95 (C1−*H*), and δ 78.3 (*C*6), between δ 2.58 (C4−*H*H) and δ 40.9 (*C*1), and between δ 2.58 (C4−*H*H), 3.39 (C4−H*H*), 3.95 (C1−*H*), and δ 36.2 (*C*5). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −62.75; IR (KBr) 2989, 2935, 1701, 1680, 1646, 1341, 1279, 1176, 1123, 1087 cm^{-1}; MS (FAB) *m*/*z* 580 ($[M + Na]^+$), 558 ($[M + H]^+$); HRMS (FAB) *m*/*z* M^+ 557.1636 (calcd for $C_{27}H_{25}F_6NO_5$ 557.1637), $[M + H]^+$ 558.1706 (calcd for $C_{27}H_{26}F_6NO_5$ 558.1715), $[M + Na]^+$ 580.1535 (calcd for $C_{27}H_{25}F_6NO_5Na$ 580.1535).

6-F-7u/8-F-7u: *(Table 5, entry 3).* (0.83 mmol scale, 134 mg, 37%, 2.5:1 regioisomers); R_f = 0.6 (ether); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.23 (t, *J* = 7.1 Hz, 3H × 0.7, major isomer), 1.24 (t, *J* = 7.1 Hz, 3H × 0.3, minor isomer), 1.35 (t, *J* = 7.1 Hz, 3H × 0.7), 1.37 (t, *J* = 7.1 Hz, 3H × 0.3), 2.44−2.56 (m, 1H), 2.81 (dd, *J* = 15.8, 12.3 Hz, 1H), 2.94 (d, *J* = 12.9 Hz, 1H × 0.3), 2.97−3.10 (m, 4H + 1H × 0.7), 3.42−3.47 (m, 1H), 4.07−4.17 (m, 1H), 4.26−4.51 (m, 4H), 4.64 (d, *J* = 14.7 Hz, 1H × 0.3), 4.68 (d, *J* = 14.8 Hz, 1H × 0.7), 6.81 (dd, J_{FH} = 9.5, J_{HH} = 2.6 Hz, 1H × 0.7), 6.91−6.96 (m, 1H + 1H × 0.3), 7.19−7.38 (m, 5H + 1H × 0.7 + 1H × 0.3). Selected NOEs are between δ 2.44−2.56 (C3a−*H* for 6-F-**7u** and 8-F-**7u**) and δ 3.42−3.47 (C3−H*H* for 6-F-**7u** and 8-F-**7u**). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.89 (CH_3), 13.94 (CH_3), 14.1 (CH_3), 32.28 (CH), 32.31 (CH), 34.0 (CH_2), 34.3 (CH_2), 46.5 (CH_2), 50.3 (CH_2), 50.5 (CH), 50.9 (CH), 57.9 (C), 60.0 (C), 62.00 (CH_2), 62.04 (CH_2), 62.5 (CH_2), 62.6 (CH_2), 113.9 (CH, d, J_{CF} = 21 Hz), 114.0 (CH, d, J_{CF} = 23 Hz), 115.8 (CH, d, J_{CF} = 21 Hz), 123.3 (C, d, J_{CF} = 15 Hz), 125.3 (C, d, J_{CF} = 3.1 Hz), 127.6 (CH), 128.2 (CH), 128.7 (CH), 129.4 (CH, d, J_{CF} = 9.2 Hz), 129.9 (C, d, J_{CF} = 3.1 Hz), 132.4 (CH, d, J_{CF} = 8.4 Hz), 136.65 (C), 136.69 (C), 138.0 (C, d, J_{CF} = 7.7 Hz), 161.8 (C, d, J_{CF} = 250 Hz), 162.08 (C, d, J_{CF} = 248 Hz), 168.10 (C), 168.5 (C), 170.5 (C), 170.7 (C), 171.4 (C), 171.7 (C). Selected HMBC correlations are between δ 2.81 (C4−*H*H for 6-F-**7u** and 8-F-**7u**), 3.42−3.47 (C3−H*H* for 6-F-**7u** and 8-F-**7u**), and δ 32.28 (*C*3a for 6-F-**7u**), 32.31 (*C*3a for 8-F-**7u**). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −107.29 (dd, J_{FH} = 10.3, 5.7 Hz, minor isomer), −114.44 (ddd, J_{FH} = 9.5, 8.6, 5.7 Hz, major isomer); IR (neat) 2982, 2935, 1732, 1699, 1683, 1615, 1583, 1495, 1435, 1366, 1298, 1194, 1108, 1030 cm^{-1}; MS (EI) *m*/*z* 439 (M^+, 13), 336 (13), 321 (48), 91 (100%); HRMS (EI) *m*/*z* M^+ 439.1788 (calcd for $C_{25}H_{26}FNO_5$ 439.1795).

3u: *(Table 5, entry 3).* (0.83 mmol scale, 107 mg, 29%); R_f = 0.3 (ether); colorless crystals; mp 146−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.30 (t, *J* = 7.1 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H), 2.35 (ddd, *J* = 10.9, 6.6, 5.9 Hz, 1H), 2.67 (d, *J* = 10.9 Hz, 1H), 3.33 (dd, *J* = 10.9, 5.9 Hz, 1H), 3.85 (d, *J* = 14.2 Hz, 1H), 3.89 (d, *J* = 6.6 Hz, 1H), 4.04−4.17 (m, 2H), 4.22 (d, *J* = 10.9 Hz, 1H), 4.24−4.36 (m, 2H), 4.95 (d, *J* = 14.2 Hz, 1H), 6.44−6.47 (m, 2H), 7.00 (dddd, J_{FH} = 8.4, J_{HH} = 8.2, 1.2, 1.2 Hz, 1H), 7.20 (ddd, J_{FH} = 5.5, J_{HH} = 8.2, 8.0 Hz, 1H), 7.28−7.31 (m, 2H), 7.36−7.43 (m, 3H). Selected NOEs are between δ 2.35 (C5−*H*) and δ 3.33 (C4−H*H*), 6.44−6.47 (Ar-*H*), 3.89 (C1−*H*) and between δ 3.33 (C4−H*H*) and δ 3.89 (C1−*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.5 (CH_3), 15.0 (CH_3), 36.2 (CH), 41.1 (CH), 44.5 (CH_2), 46.3 (CH_2), 60.0 (CH_2), 64.9 (CH_2), 79.0 (CH, d, J_{CF} = 1.5 Hz), 79.5 (C), 114.3 (CH, d, J_{CF} = 22 Hz), 116.1 (CH, d, J_{CF} = 21 Hz), 123.0 (CH, d, J_{CF} = 3.1 Hz), 128.1 (CH), 129.0 (CH), 129.1 (CH), 130.3 (CH, d, J_{CF} = 7.7 Hz), 136.6 (C), 139.2 (C, d, J_{CF} = 7.7 Hz), 162.70 (C),

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

162.73 (C, d, J_{CF} = 248 Hz), 167.2 (C), 172.8 (C). Selected HMBC correlations are between δ 2.35 (C5−*H*), 2.67 (C4−*H*H), 3.89 (C1−*H*), and δ 172.8 (*C*2), between δ 2.35 (C5−*H*), 2.67 (C4−*H*H), 3.33 (C4−H*H*), 3.89 (C1−*H*), and δ 79.0 (*C*6), between δ 2.67 (C4−*H*H) and δ 41.1 (*C*1), and between δ 2.67 (C4−*H*H), 3.33 (C4−H*H*), 3.89 (C1−*H*), and δ 36.2 (*C*5). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −111.80 (ddd, J_{FH} = 9.2, 8.4, 5.5 Hz); IR (KBr) 2980, 2905, 1697, 1649, 1618, 1494, 1435, 1379, 1335, 1278, 1178, 1076, 1028 cm^{-1}; MS (EI) *m*/*z* 439 (M^+, 19), 240 (54), 157 (42), 91 (100%); HRMS (EI) *m*/*z* M^+ 439.1790 (calcd for $C_{25}H_{26}FNO_5$ 439.1795).

8v: *(Table 6, entry 2).* (0.5 mmol scale, 188 mg, 62%); R_f = 0.5 (ether); colorless crystals; mp 153−154 °C (AcOEt−hexane = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.25 (t, *J* = 7.0 Hz, 3H), 1.28 (t, *J* = 7.0 Hz, 3H), 3.27 (dddd, *J* = 9.2, 7.0, 5.7, 5.7 Hz, 1H), 3.44 (dd, *J* = 7.0, 4.1 Hz, 1H), 3.51 (dd, *J* = 10.2, 9.2 Hz, 1H), 3.81 (dd, *J* = 10.2, 5.7 Hz, 1H), 3.83 (d, *J* = 4.1 Hz, 1H), 4.09−4.28 (m, 4H), 4.52 (d, *J* = 14.8 Hz, 1H), 4.65 (d, *J* = 14.8 Hz, 1H), 5.90 (d, *J* = 5.7 Hz, 1H), 7.27−7.43 (m, 8H), 7.50 (dd, *J* = 8.2, 7.8 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 9.2 Hz, 1H), 8.16 (ddd, *J* = 8.2, 2.1, 1.0 Hz, 1H), 8.32 (dd, *J* = 2.1, 2.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (CH_3), 14.1 (CH_3), 39.7 (CH), 44.2 (CH), 45.9 (CH_2), 47.0 (CH_2), 51.2 (CH), 62.1 (CH_2), 62.2 (CH_2), 91.4 (CH), 108.4 (CH), 120.4 (CH), 121.9 (CH), 124.4 (CH), 124.8 (CH), 127.4 (C), 127.9 (CH), 128.2 (CH), 128.5 (CH), 128.9 (CH), 130.2 (CH), 133.5 (CH), 135.7 (C), 138.3 (C), 143.3 (C), 148.4 (C), 167.7 (C), 168.5 (C), 171.7 (C); ^{1}H NMR (400 MHz, C_6D_6) δ (ppm) 0.896 (t, *J* = 7.1 Hz, 3H), 0.946 (t, *J* = 7.0 Hz, 3H), 3.21 (dddd, *J* = 9.0, 7.8, 6.8, 6.2 Hz, 1H), 3.31 (dd, *J* = 7.8, 4.3 Hz, 1H), 3.41 (dd, *J* = 9.9, 9.0 Hz, 1H), 3.57 (dd, *J* = 9.9, 6.2 Hz, 1H), 3.65 (d, *J* = 4.3 Hz, 1H), 3.86−4.05 (m, 4H), 4.21 (d, *J* = 14.8 Hz, 1H), 4.69 (d, *J* = 14.8 Hz, 1H), 5.59 (d, *J* = 6.8 Hz, 1H), 6.46 (dd, *J* = 7.9, 7.9 Hz, 1H), 6.73 (ddd, *J* = 8.4, 7.0, 1.1 Hz, 1H), 6.87 (ddd, *J* = 8.2, 7.0, 0.9 Hz, 1H), 7.02 (dd, *J* = 9.4, 1.0 Hz, 1H), 7.05−7.09 (m, 2H), 7.16−7.20 (m, 2H), 7.31 (d, *J* = 8.4 Hz, 1H), 7.51 (ddd, *J* = 8.2, 2.0, 1.0 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 8.22 (dd, *J* = 2.0, 1.9 Hz, 1H). Selected NOEs are between δ 3.31 (C3−*H*) and δ 5.59 (C*H*(Ar)O), between δ 3.21 (C4−*H*), and δ 3.65 (C*H*(CO_2Et)$_2$), 3.41 (C5−*H*H), and between 3.57 (C5−H*H*) and δ 5.59 (C*H*(Ar)O). ^{13}C NMR (100.6 MHz, C_6D_6) δ (ppm) 13.8 (CH_3), 13.9 (CH_3), 39.9 (CH), 44.2 (CH), 46.5 (CH_2), 46.9 (CH_2), 51.5 (CH), 61.8 (CH_2), 61.9 (CH_2), 91.9 (CH), 108.5 (CH), 120.6 (CH), 121.9 (CH), 124.2 (CH), 124.6 (CH), 127.9 (CH), 128.1 (CH), 128.6 (CH), 129.0 (CH), 129.8 (CH), 133.5 (CH), 136.8 (C), 138.3 (C), 143.7 (C), 148.5 (C), 167.9 (C), 168.4 (C), 171.2 (C). Selected HMBC correlations are between δ 3.41 (C5−*H*H), 3.57 (C5−H*H*), 3.31 (C3−*H*), and δ 171.2 (*C*2), between δ 3.41 (C5−*H*H), 3.57 (C5−H*H*), 3.31 (C3−*H*), and δ 39.9 (*C*4), and between δ 3.41 (C5−*H*H), 3.57 (C5−H*H*), and δ 91.9 (*C*H(Ar)O). IR (KBr) 3074, 2985, 2939, 1746, 1724, 1697, 1616, 1513, 1489, 1444, 1354, 1256, 1180, 1079, 1027, 958 cm^{-1}; MS (FAB) *m*/*z* 624 ([M + Na]$^+$), 602 ([M + H]$^+$); HRMS (FAB) *m*/*z* [M + Na]$^+$ 624.2066 (calcd for $C_{31}H_{31}N_5O_8Na$ 624.2070), [M + H]$^+$ 602.2244 (calcd for $C_{31}H_{32}N_5O_8$ 602.2251). Anal. Calcd for $C_{31}H_{31}N_5O_8$: C, 61.89; H, 5.19; N, 11.64. Found: C, 61.75; H, 5.24; N, 11.50.

8w: *(Table 6, entry 4).* (0.5 mmol scale, 227 mg, 75%); R_f = 0.8 (CH_2Cl_2−ether = 1:1); colorless crystals; mp 134−136 °C (AcOEt−hexane = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.949−1.04 (m, 2H), 1.15−1.31 (m, 3H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.26 (t, *J* = 7.0 Hz, 3H), 1.66−1.75 (m, 6H), 3.23 (d, *J* = 7.2 Hz, 2H), 3.30−3.38 (m, 2H), 3.66 (dd, *J* = 10.1, 9.2 Hz, 1H), 3.83 (d, *J* = 3.7 Hz, 1H), 3.96 (dd, *J* = 10.1, 5.2 Hz, 1H), 4.05−4.24 (m, 4H), 5.93 (d, *J* = 5.1 Hz, 1H), 7.32 (dd, *J* = 8.4, 7.1 Hz, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.43 (dd, *J* = 8.4, 7.1 Hz, 1H), 7.55 (dd, *J* = 8.2, 7.6 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 8.20 (ddd, *J* = 8.2, 1.2, 0.8 Hz, 1H), 8.42 (dd, *J* = 1.2, 1.2 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (CH_3), 25.71 (CH_2), 25.74 (CH_2), 26.3 (CH_2), 30.7 (CH_2), 30.8 (CH_2), 35.8 (CH), 39.7 (CH), 44.3 (CH), 47.3 (CH_2), 49.5 (CH_2), 51.2 (CH), 61.9 (CH_2), 62.1 (CH_2), 91.6 (CH), 108.4 (CH), 120.4 (CH), 121.9 (CH), 124.4 (CH), 124.8 (CH), 127.4 (C), 128.5 (CH), 130.1 (CH), 133.7 (CH), 138.5 (C), 143.3 (C), 148.4 (C), 167.7 (C), 168.4 (C), 171.6 (C); IR (KBr) 2921, 2852, 1746, 1722, 1695, 1536, 1346, 1251, 1171, 1082, 1027, 957 cm^{-1}; MS (FAB) *m*/*z* 630 ([M + Na]$^+$), 608 ([M + H]$^+$); HRMS (FAB) *m*/*z* [M + Na]$^+$ 630.2537 (calcd for $C_{31}H_{37}N_5O_8Na$ 630.2540), [M + H]$^+$ 608.2720 (calcd for $C_{31}H_{38}N_5O_8$ 608.2720). Anal. Calcd for $C_{31}H_{37}N_5O_8$: C, 61.27; H, 6.14; N, 11.53. Found: C, 61.14; H, 6.13; N, 11.47.

9: *(eq 7, rt, 18 h).* (1 mmol scale, 361 mg, 60%, dr = 2:1); R_f = 0.2 (CH_2Cl_2−ether = 1:1); pale yellow crystals; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.19 (t, *J* = 7.1 Hz, 3H × 0.33, minor isomer), 1.24 (t, *J* = 7.1 Hz, 6H × 0.67, major isomer), 1.30 (t, *J* = 7.1 Hz, 3H × 0.33), 2.91 (s, 6H × 0.67), 2.93 (s, 6H × 0.33), 2.96 (d, *J* = 3.9 Hz, 1H × 0.67), 3.06 (dd, *J* = 9.7, 5.4 Hz, 1H × 0.67), 3.10 (dd, *J* = 7.7, 3.9 Hz, 1H × 0.67), 3.16 (dd, *J* = 5.7, 4.3 Hz, 1H × 0.33), 3.43 (dd, *J* = 9.3, 3.2 Hz, 1H × 0.33), 3.52−3.64 (m, 2H × 0.67), 3.98 (d, *J* = 4.3 Hz, 1H × 0.33), 4.08−4.34 (m, 4H), 4.41−4.51 (m, 2H), 5.37 (d, *J* = 9.8 Hz, 1H × 0.67), 5.75 (d, *J* = 5.9 Hz, 1H × 0.33), 6.53 (d, *J* = 8.8 Hz, 2H × 0.33), 6.59 (d, *J* = 8.8 Hz, 2H × 0.67), 7.07−7.12 (m, 3H × 0.33), 7.19−7.36 (m, 6H +2H × 0.67), 7.44−7.51 (m, 1H), 7.90−7.94 (m, 1H). Selected NOEs are between δ 3.10 (major), 3.16 (minor) (C3−*H*), and δ 5.37 (major), 5.75 (minor) (C*H*(Ar)O), and between δ 3.52−3.64 (C4−*H*, C5−H*H*) and δ 2.96 (major), 3.98 (minor) (C*H*(CO_2Et)$_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.97 (CH_3), 14.01 (CH_3), 14.09 (CH_3), 14.12 (CH_3), 38.1 (CH), 39.2 (CH), 40.2 (CH_3), 45.5 (CH), 45.7 (CH), 46.8 (CH_2), 46.9 (CH_2), 47.6 (CH_2), 49.2 (CH_2), 51.7 (CH), 52.3 (CH), 61.6 (CH_2), 61.8 (CH_2), 61.9 (CH_2), 62.1 (CH_2), 65.4 (CH), 67.4 (CH), 110.6 (CH), 111.1 (CH), 112.3 (CH), 112.4 (CH), 115.6 (CH), 115.7 (CH), 121.0 (C), 122.5 (C), 124.5 (CH), 124.6 (CH), 127.6 (CH), 127.7 (CH), 128.0 (CH), 128.2 (CH), 128.3 (CH), 128.65 (CH), 128.73 (CH), 128.9 (CH), 130.3 (CH), 130.43 (C), 130.46 (C), 130.50 (CH), 134.05 (C), 134.10 (C), 135.8 (C), 135.9 (C), 150.7 (C), 150.8 (C), 167.6 (C), 167.8 (C), 168.0 (C), 168.7 (C), 171.8 (C); IR (KBr) 2981, 2906, 1745, 1690, 1612, 1527, 1497, 1460, 1424, 1362, 1256, 1181, 1031 cm^{-1}; MS (ESI) *m*/*z* 622 ([M + Na]$^+$); HRMS (ESI) *m*/*z* [M + Na]$^+$ 622.2641 (calcd for $C_{33}H_{37}N_5O_6Na$ 622.2642).

9 (major): Major diastereoisomer could be isolated by recrystallization. Colorless crystals; mp 152−155 °C (AcOEt−hexane = 1:19); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.24 (t, *J* = 7.1 Hz, 6H), 2.93 (s, 6H), 3.00 (d, *J* = 3.9 Hz, 1H), 3.06−3.10 (m, 2H), 3.52−3.63 (m, 2H), 4.09−4.24 (m, 4H), 4.43 (d, *J* = 14.8 Hz, 1H), 4.49 (d, *J* = 14.8 Hz, 1H), 5.39 (d, *J* = 9.4 Hz, 1H), 6.65 (broad d, *J* = 7.8 Hz, 2H), 7.21−7.35 (m, 9H), 7.49 (m, 1H), 7.92 (dd, *J* = 7.8, 1.4 Hz, 1H). Selected NOEs are between δ 3.06−3.10 (C3−*H*, C5−*H*H) and δ 5.39 (C*H*(Ar)O) and between δ 3.52−3.63 (C4−*H*, C5−H*H*) and δ 3.00 (C*H*(CO_2Et)$_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (CH_3), 14.2 (CH_3), 39.2 (CH), 40.6 (CH_3), 45.7 (CH), 46.9 (CH_2), 49.1 (CH_2), 51.7 (CH), 61.6 (CH_2), 61.8 (CH_2), 67.3 (CH), 110.6 (CH), 112.9 (CH), 115.8 (CH), 124.7 (CH), 127.7 (CH), 128.1 (CH), 128.3 (CH), 128.8 (CH), 130.5 (C), 130.6 (CH), 134.2 (C), 135.7 (C), 167.7 (C), 168.0 (C), 171.8 (C). Selected HMBC correlations are between δ 3.00 (C*H*(CO_2Et)$_2$) and δ 171.8 (*C*2) and between δ 5.39 (C*H*(Ar)O) and δ 39.2 (*C*4). IR (KBr) 2980, 2911, 1740, 1704, 1613, 1527, 1359, 1256, 1194, 1031 cm^{-1}; MS (ESI) *m*/*z* 622 ([M + Na]$^+$); HRMS (ESI) *m*/*z* [M + Na]$^+$ 622.2641 (calcd for $C_{33}H_{37}N_5O_6Na$ 622.2642).

11a: *(Table 7, entry 1).* (1 mmol scale, 134 mg, 40%, including a small amount of impurity); R_f = 0.5 (hexane−ether = 1:4); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ratio 1.2:1) δ (ppm) 3.68 (s, 3H × 0.55, major rotamer), 3.76 (s, 3H × 0.45, minor rotamer), 3.97 (dd, *J* = 6.0, 1.5 Hz, 2H × 0.55), 4.19 (dd, *J* = 6.6, 1.2 Hz, 2H × 0.45), 4.52 (s, 2H × 0.45), 4.73 (s, 2H × 0.55), 6.02 (dt, *J* = 16.0, 6.0 Hz, 1H × 0.55), 6.05 (d, *J* = 11.9 Hz, 1H × 0.45), 6.06 (d, *J* = 12.0 Hz, 1H × 0.55), 6.23 (dt, *J* = 15.9, 6.6 Hz, 1H × 0.45), 6.42 (ddd, *J* = 16.0, 1.5, 1.5 Hz, 1H × 0.55), 6.51 (d, *J* = 15.9 Hz, 1H × 0.45), 6.62 (d, *J* = 11.9 Hz, 1H × 0.45), 6.66 (d, *J* = 12.0 Hz, 1H × 0.55), 7.20−7.41 (m, 10H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 46.0 (CH_2), 47.2 (CH_2), 49.4 (CH_2), 50.9 (CH_2), 51.98 (CH_3), 52.02 (CH_3), 123.5 (CH), 123.7 (CH), 123.8 (CH), 126.46 (CH), 126.52 (CH), 127.2 (CH), 127.6 (CH), 127.8 (CH), 128.0 (CH), 128.1 (CH), 128.63 (CH), 128.67 (CH), 128.74 (CH), 128.8 (CH), 129.0 (CH), 133.0 (CH), 133.7 (CH), 136.1 (C), 136.2 (C), 136.7 (C), 136.8 (C), 137.7 (CH), 137.8 (CH), 165.1 (C), 165.2 (C), 167.2 (C), 167.3 (C); IR (neat) 3028, 2974, 2950, 1728, 1645, 1496, 1451, 1221, 1173 cm^{-1}; MS (EI) *m*/*z* 335 (M^+, 35),

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

91 (100%); HRMS (EI) m/z M^+ 335.1515 (calcd for $C_{21}H_{21}NO_3$ 335.1521).

11b: *(Table 7, entry 2).* (1 mmol scale, 60 mg, 18%); R_f = 0.5 (hexane−ether = 1:4); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ratio 1.1:1) δ (ppm) 0.783−1.05 (m, 2H), 1.12−1.26 (m, 3H), 1.58−1.79 (m, 6H), 3.11 (d, J = 7.4 Hz, 2H × 0.52, major rotamer), 3.32 (d, J = 7.0 Hz, 2H × 0.48, minor rotamer), 3.707 (s, 3H × 0.48), 3.714 (s, 3H × 0.52), 4.05 (dd, J = 5.9, 1.6 Hz, 2H × 0.48), 4.22 (dd, J = 6.5, 1.1 Hz, 2H × 0.52), 6.00 (d, J = 11.9 Hz, 1H × 0.48), 6.01 (d, J = 11.9 Hz, 1H × 0.52), 6.07 (dt, J = 16.0, 5.9 Hz, 1H × 0.48), 6.26 (dt, J = 16.0, 6.5 Hz, 1H × 0.52), 6.45 (d, J = 16.0 Hz, 1H × 0.48), 6.58 (d, J = 11.9 Hz, 1H × 0.52), 6.60 (d, J = 11.9 Hz, 1H × 0.48), 6.61 (d, J = 16.0 Hz, 1H × 0.52), 7.21−7.42 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 25.85 (CH_2), 25.94 (CH_2), 26.4 (CH_2), 26.5 (CH_2), 30.9 (CH_2), 31.0 (CH_2), 36.2 (CH), 36.5 (CH), 46.8 (CH_2), 50.9 (CH_2), 51.1 (CH_2), 51.9 (CH_3), 53.9 (CH_2), 122.8 (CH), 122.9 (CH), 124.3 (CH), 124.4 (CH), 126.4 (CH), 126.5 (CH), 127.7 (CH), 128.0 (CH), 128.6 (CH), 128.7 (CH), 132.4 (CH), 133.0 (CH), 136.2 (C), 136.8 (C), 138.1 (CH), 138.2 (CH), 165.14 (C), 165.17 (C), 167.18 (C), 167.24 (C); IR (neat) 2927, 2852, 1732, 1689, 1633, 1450, 1367, 1217, 1174, 1141, 967 cm^{-1}; MS (FAB) m/z 364 ([M + Na]$^+$), 342 ([M + H]$^+$); HRMS (FAB) m/z [M − H]$^+$ 340.1915 (calcd for $C_{21}H_{26}NO_3$ 340.1913).

11j: *(Table 7, entry 3).* (1 mmol scale, 152 mg, 40%); R_f = 0.3 (hexane−ether = 1:4); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ratio 1.1:1) δ (ppm) 3.69 (s, 3H × 0.48, minor rotamer), 3.73 (s, 3H × 0.52, major rotamer), 4.02 (dd, J = 6.2, 1.5 Hz, 2H × 0.48), 4.21 (dd, J = 6.3, 1.2 Hz, 2H × 0.52), 4.58 (s, 2H × 0.52), 4.76 (s, 2H × 0.48), 5.96 (dt, J = 15.7, 6.2 Hz, 1H × 0.48), 6.08 (d, J = 11.9 Hz, 1H × 0.52), 6.10 (d, J = 11.9 Hz, 1H × 0.48), 6.22 (dt, J = 15.7, 6.3 Hz, 1H × 0.52), 6.65 (d, J = 11.9 Hz, 1H × 0.52), 6.70 (d, J = 11.9 Hz, 1H × 0.48), 6.91 (d, J = 15.7 Hz, 1H × 0.48), 7.00 (d, J = 15.7 Hz, 1H × 0.52), 7.25−7.44 (m, 6H + 1H × 0.48), 7.54−7.62 (m, 1H + 1H × 0.52), 7.93 (dd, J = 8.1, 1.1 Hz, 1H × 0.52), 7.97 (dd, J = 8.1, 0.9 Hz, 1H × 0.48); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 45.6 (CH_2), 47.4 (CH_2), 49.5 (CH_2), 51.0 (CH_2), 51.9 (CH_3), 52.0 (CH_3), 123.4 (CH), 123.8 (CH), 124.5 (CH), 124.7 (CH), 127.4 (CH), 127.6 (CH), 128.60 (CH), 128.69 (CH), 128.76 (CH), 128.79 (CH), 128.99 (CH), 129.07 (CH), 129.09 (CH), 129.4 (CH), 132.3 (C), 132.7 (C), 133.2 (CH), 133.4 (CH), 135.9 (C), 136.7 (C), 137.7 (CH), 137.9 (CH), 147.6 (C), 147.7 (C), 165.07 (C), 165.12 (C), 167.2 (C), 167.3 (C); IR (neat) 3030, 2951, 1728, 1694, 1639, 1570, 1520, 1438, 1345, 1291, 1220, 1173, 1081 cm^{-1}; MS (EI) m/z 380 (M^+, 1.1), 205 (9.4), 119 (22), 83 (100%); HRMS (EI) m/z M^+ 380.1384 (calcd for $C_{21}H_{20}N_2O_5$ 380.1372).

11k: *(Table 7, entry 4).* (1 mmol scale, 119 mg, 31%); R_f = 0.5 (ether); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ratio 1.8:1) δ (ppm) 0.802−1.32 (m, 5H), 1.62−1.80 (m, 6H), 3.15 (d, J = 7.2 Hz, 2H × 0.64, major rotamer), 3.35 (d, J = 7.0 Hz, 2H × 0.36, minor rotamer), 3.70 (s, 3H × 0.64), 3.71 (s, 3H × 0.36), 4.10 (dd, J = 6.0, 1.3 Hz, 2H × 0.36), 4.27 (d, J = 6.0 Hz, 2H × 0.64), 6.01−6.08 (m, 1H + 1H × 0.36), 6.28 (dt, J = 15.8, 6.0 Hz, 1H × 0.64), 6.58 (d, J = 11.9 Hz, 1H × 0.64), 6.65 (d, J = 12.1 Hz, 1H × 0.36), 6.94 (d, J = 15.8 Hz, 1H × 0.36), 7.07 (d, J = 15.8 Hz, 1H × 0.64), 7.36−7.45 (m, 1H), 7.52−7.61 (m, 1H + 1H × 0.36), 7.66 (dd, J = 7.8, 0.6 Hz, 1H × 0.64), 7.93 (d, J = 8.2 Hz, 1H × 0.64), 7.97 (d, J = 8.4 Hz, 1H × 0.36); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 25.8 (CH_2), 25.9 (CH_2), 26.3 (CH_2), 26.4 (CH_2), 30.85 (CH_2), 30.90 (CH_2), 36.1 (CH), 36.3 (CH), 46.8 (CH_2), 50.9 (CH_2), 51.0 (CH_2), 51.85 (CH_3), 51.87 (CH_3), 54.1 (CH_2), 122.8 (CH), 122.9 (CH), 124.5 (CH), 124.7 (CH), 128.2 (CH), 128.6 (CH), 129.0 (CH), 129.1 (CH), 129.76 (CH), 129.79 (CH), 132.3 (C), 132.7 (C), 133.2 (CH), 133.4 (CH), 138.1 (CH), 138.4 (CH), 147.6 (C), 147.8 (C), 165.1 (C), 165.2 (C), 167.3 (C), 167.4 (C); IR (neat) 2925, 2852, 1733, 1694, 1645, 1570, 1520, 1447, 1348, 1292, 1217, 1172, 1142 cm^{-1}; MS (EI) m/z 386 (M^+, 24), 304 (57), 303 (52), 113 (100%); HRMS (EI) m/z M^+ 386.1843 (calcd for $C_{21}H_{26}N_2O_5$ 386.1842).

13a: *(Table 7, entry 5).* (1 mmol scale, 299 mg, 89%, including a small amount of impurity); R_f = 0.5 (hexane−ether = 1:4); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ratio 1.2:1) δ (ppm) 3.76 (s, 3H × 0.45, minor rotamer), 3.78 (s, 3H × 0.55, major rotamer), 4.09 (dd, J = 5.5, 1.6 Hz, 2H × 0.55), 4.21 (dd, J = 6.6, 1.1 Hz, 2H × 0.45), 4.63 (s, 2H × 0.45), 4.72 (s, 2H × 0.55), 6.07 (dt, J = 16.0, 5.5 Hz, 1H × 0.55), 6.17 (dt, J = 15.9, 6.6 Hz, 1H × 0.45), 6.45 (d, J = 15.9 Hz, 1H × 0.45), 6.46 (d, J = 16.0 Hz, 1H × 0.55), 6.928 (d, J = 15.2 Hz, 1H × 0.45), 6.933 (d, J = 15.4 Hz, 1H × 0.55), 7.18−7.39 (m, 10H), 7.41 (d, J = 15.2 Hz, 1H × 0.45), 7.44 (d, J = 15.4 Hz, 1H × 0.55); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 47.8 (CH_2), 48.88 (CH_2), 48.93 (CH_2), 50.3 (CH_2), 52.2 (CH_3), 123.5 (CH), 123.6 (CH), 126.48 (CH), 126.54 (CH), 126.7 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 128.2 (CH), 128.4 (CH), 128.6 (CH), 128.7 (CH), 128.8 (CH), 129.1 (CH), 131.7 (CH), 131.8 (CH), 132.7 (CH), 133.89 (CH), 133.96 (CH), 134.00 (CH), 135.9 (C), 136.1 (C), 136.4 (C), 136.8 (C), 165.0 (C), 165.1 (C), 166.06 (C), 166.12 (C); IR (neat) 3028, 2951, 1728, 1652, 1634, 1495, 1435, 1361, 1294, 1166, 1029, 969 cm^{-1}; MS (EI) m/z 335 (M^+, 9.8), 303 (21), 244 (26), 218 (34), 77 (100%); HRMS (EI) m/z M^+ 335.1500 (calcd for $C_{21}H_{21}NO_3$ 335.1521).

13b: *(Table 7, entry 6).* (1 mmol scale, 209 mg, 61%, including a small amount of impurity); R_f = 0.7 (hexane−ether = 1:4); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ratio 1.2:1) δ (ppm) 0.878−1.04 (m, 2H), 1.18−1.27 (m, 3H), 1.60−1.76 (m, 6H), 3.23 (d, J = 7.2 Hz, 2H × 0.55, major rotamer), 3.33 (d, J = 7.2 Hz, 2H × 0.45, minor rotamer), 3.77 (s, 3H × 0.45), 3.81 (s, 3H × 0.55), 4.16 (dd, J = 6.4, 1.0 Hz, 2H × 0.45), 4.21 (dd, J = 5.3, 1.6 Hz, 2H × 0.55), 6.11 (dt, J = 15.9, 5.3 Hz, 1H × 0.45), 6.18 (dt, J = 15.9, 6.4 Hz, 1H × 0.55), 6.46 (d, J = 15.9 Hz, 1H × 0.45), 6.51 (d, J = 15.9 Hz, 1H × 0.55), 6.85 (d, J = 15.2 Hz, 1H × 0.45), 6.88 (d, J = 15.2 Hz, 1H × 0.55), 7.21−7.38 (m, 5H), 7.40 (d, J = 15.2 Hz, 1H × 0.45), 7.42 (d, J = 15.2 Hz, 1H × 0.55); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 25.79 (CH_2), 25.83 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 30.8 (CH_2), 30.9 (CH_2), 36.6 (CH), 37.6 (CH), 48.7 (CH_2), 50.6 (CH_2), 52.07 (CH_3), 52.12 (CH_3), 52.6 (CH_2), 53.6 (CH_2), 124.0 (CH), 126.4 (CH), 126.5 (CH), 127.7 (CH), 128.0 (CH), 128.6 (CH), 128.7 (CH), 130.9 (CH), 131.0 (CH), 132.1 (CH), 133.0 (CH), 134.2 (CH), 134.3 (CH), 136.0 (C), 136.4 (C), 164.5 (C), 165.0 (C), 166.2 (C), 166.3 (C); IR (neat) 2927, 2852, 1729, 1653, 1626, 1449, 1293, 1165, 970 cm^{-1}; MS (FAB) m/z 364 ([M + Na]$^+$), 342 ([M + H]$^+$); HRMS (FAB) m/z [M + Na]$^+$ 364.1888 (calcd for $C_{21}H_{27}NO_3Na$ 364.1889), [M + H]$^+$ 342.2070 (calcd for $C_{21}H_{28}NO_3$ 342.2069).

13j: *(Table 7, entry 7).* (1 mmol scale, 273 mg, 72%, including a small amount of impurity); R_f = 0.6 (hexane−ether = 1:4); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ratio 1.2:1) δ (ppm) 3.78 (s, 3H × 0.55, major rotamer), 3.80 (s, 3H × 0.45, minor rotamer), 4.13 (dd, J = 5.6, 1.5 Hz, 1H × 0.45), 4.24 (dd, J = 6.4, 1.2 Hz, 1H × 0.55), 4.70 (s, 2H × 0.55), 4.76 (s, 2H × 0.45), 6.05 (dt, J = 15.8, 5.6 Hz, 1H × 0.45), 6.13 (dt, J = 15.8, 6.4 Hz, 1H × 0.55), 6.91−7.07 (m, 2H), 7.24−7.60 (m, 9H), 7.96 (dd, J = 8.2, 1.2 Hz, 1H × 0.55), 7.99 (dd, J = 8.1, 1.1 Hz, 1H × 0.45); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 47.5 (CH_2), 48.82 (CH_2), 48.84 (CH_2), 50.5 (CH_2), 52.2 (CH_3), 52.3 (CH_3), 124.6 (CH), 124.8 (CH), 126.9 (CH), 127.8 (CH), 128.1 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 128.82 (CH), 128.86 (CH), 128.93 (CH), 129.03 (CH), 129.07 (CH), 129.12 (CH), 129.2 (CH), 131.8 (CH), 132.0 (CH), 132.2 (C), 132.4 (C), 133.35 (CH), 133.41 (CH), 133.7 (CH), 133.8 (CH), 135.9 (C), 136.7 (C), 147.6 (C), 165.96 (C), 165.01 (C), 166.0 (C), 166.1 (C); IR (neat) 3064, 3031, 2951, 1732, 1651, 1634, 1571, 1520, 1455, 1360, 1163, 1115, 1081, 1029, 968 cm^{-1}; MS (EI) m/z 380 (M^+, 13), 218 (79), 91 (100%); HRMS (EI) m/z M^+ 380.1375 (calcd for $C_{21}H_{20}N_2O_5$ 380.1372).

13k: *(Table 7, entry 8).* (1 mmol scale, 245 mg, 63%); R_f = 0.6 (ether); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ratio 1.9:1) δ (ppm) 0.908−1.06 (m, 2H), 1.12−1.29 (m, 3H), 1.68−1.77 (m, 6H), 3.29 (d, J = 7.0 Hz, 2H × 0.66, major rotamer), 3.38 (d, J = 7.2 Hz, 2H × 0.34, minor rotamer), 3.79 (s, 3H × 0.34), 3.82 (s, 3H × 0.66), 4.23 (dd, J = 5.4, 1.5 Hz, 2H × 0.34), 4.27 (dd, J = 6.3, 1.1 Hz, 2H × 0.66), 6.07 (dt, J = 15.8, 5.5 Hz, 1H × 0.34), 6.17 (dt, J = 15.8, 6.3 Hz, 1H × 0.66), 6.85 (d, J = 15.2 Hz, 1H × 0.34), 6.87 (d, J = 15.2 Hz, 1H × 0.66), 6.98 (d, J = 15.8 Hz, 1H), 7.39−7.46 (m, 2H), 7.53−7.62 (m, 2H), 7.95 (d, J = 8.1 Hz, 1H × 0.66), 7.98 (dd, J = 8.2, 1.0 Hz, 1H × 0.34); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 25.7 (CH_2), 25.8 (CH_2), 26.2 (CH_2), 26.3 (CH_2), 30.7 (CH_2), 30.9 (CH_2), 36.4 (CH), 37.5 (CH), 48.8 (CH_2), 50.5 (CH_2), 52.08 (CH_3), 52.11 (CH_3), 52.5 (CH_2), 54.0 (CH_2), 124.5 (CH), 124.7 (CH), 128.3 (CH),

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

128.57 (CH), 128.60 (CH), 128.9 (CH), 129.0 (CH), 129.4 (CH), 129.5 (CH), 131.1 (CH), 132.1 (C), 132.4 (C), 133.2 (CH), 133.3 (CH), 133.9 (CH), 134.1 (CH), 147.6 (C), 164.6 (C), 164.9 (C), 166.10 (C), 166.14 (C); IR (neat) 2925, 2848, 1728, 1651, 1572, 1520, 1435, 1344, 1163 cm^{-1}; MS (EI) *m/z* 386 (M^+, 14), 304 (24), 251 (33), 250 (29), 162 (47), 84 (100%); HRMS (EI) *m/z* M^+ 386.1811 (calcd for $C_{21}H_{26}N_2O_5$ 386.1842).

Typical Experimental Procedure (Table 8, Entry 3). A solution of **11j** (152 mg, 0.40 mmol) in 1,2-dichloroethane (1.0 mL) was heated at 80 °C for 18 h. The mixture was concentrated *in vacuo*. The residue was purified by column chromatography over silica gel with CH_2Cl_2–ether as eluent to give **14j** (69 mg, 45%).

14j: R_f = 0.5 (ether); pale yellow crystals; mp 91–93 °C (AcOEt–hexane = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.49 (dd, *J* = 12.6, 5.5 Hz, 1H), 2.92 (dd, *J* = 16.4, 11.5 Hz, 1H), 3.05 (m, 1H), 3.10–3.16 (m, 2H), 3.48 (dd, *J* = 8.8, 6.6 Hz, 1H), 3.76 (s, 3H), 4.35 (d, *J* = 5.5 Hz, 1H), 4.45 (d, *J* = 14.9 Hz, 1H), 4.62 (d, *J* = 14.9 Hz, 1H), 7.25–7.40 (m, 6H), 7.77 (dd, *J* = 8.1, 1.3 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H). Selected NOEs are between δ 3.05 (C3a–*H*) and δ 3.48 (C3–H*H*) and between δ 2.92 (C4–*H*H), 4.35 (C9–*H*), and δ 2.49 (C9a–*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 30.5 (CH_2), 31.9 (CH), 43.3 (CH), 45.8 (CH), 46.6 (CH_2), 50.6 (CH_2), 52.6 (CH_3), 123.9 (CH), 127.2 (CH), 127.7 (CH), 128.0 (CH), 128.8 (CH), 131.1 (C), 135.49 (CH), 135.52 (C), 136.5 (C), 150.9 (C), 171.2 (C), 172.7 (C). Selected HMBC correlations are between δ 2.92 (C4–*H*H) and δ 50.6 (*C*3), between δ 3.48 (C3–H*H*) and δ 45.8 (*C*9a), between δ 2.92 (C4–*H*H), 3.48 (C3–H*H*), and δ 31.9 (*C*3a), and between δ 2.49 (C9a–*H*) and δ 43.3 (*C*9). IR (KBr) 2925, 1734, 1695, 1527, 1436, 1346, 1250, 1197, 1166 cm^{-1}; MS (EI) *m/z* 380 (M^+, 36), 149 (34), 84 (100%); HRMS (EI) *m/z* M^+ 380.1370 (calcd for $C_{21}H_{20}N_2O_5$ 380.1372).

14k: *(Table 8, entry 4).* (0.92 mmol scale, 194 mg, 55%); R_f = 0.5 (ether); pale yellow crystals; mp 80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.934–1.03 (m, 2H), 1.12–1.28 (m, 3H), 1.62–1.75 (m, 6H), 2.47 (dd, *J* = 12.7, 5.7 Hz, 1H), 2.96 (dd, *J* = 16.1, 11.8 Hz, 1H), 3.05 (m, 1H), 3.17–3.27 (m, 4H), 3.59 (dd, *J* = 9.2, 6.8 Hz, 1H), 3.71 (s, 3H), 4.30 (d, *J* = 5.7 Hz, 1H), 4.38 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.79 (d, *J* = 7.9 Hz, 1H). Selected NOEs are between δ 4.30 (C9–*H*) and δ 2.47 (C9a–*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 25.70 (CH_2), 25.72 (CH_2), 26.3 (CH_2), 30.4 (CH_2), 30.60 (CH_2), 30.64 (CH_2), 31.9 (CH), 36.1 (CH_2), 43.1 (CH), 45.7 (CH), 48.9 (CH_2), 51.8 (CH_2), 52.4 (CH_3), 123.7 (CH), 127.0 (CH), 131.0 (C), 135.3 (CH), 135.6 (C), 150.8 (C), 171.2 (C), 172.6 (C). Selected HMBC correlations are between δ 2.96 (C4–*H*H) and δ 51.8 (*C*3), between δ 3.59 (C3–H*H*) and δ 45.7 (*C*9a), between δ 2.96 (C4–*H*H), 3.59 (C3–H*H*), and δ 31.9 (*C*3a), and between δ 2.47 (C9a–*H*) and δ 43.1 (*C*9). IR (KBr) 2926, 2848, 1743, 1695, 1528, 1162 cm^{-1}; MS (EI) *m/z* 386 (M^+, 6.1), 345 (41), 271 (100%); HRMS (EI) *m/z* M^+ 386.1816 (calcd for $C_{21}H_{26}N_2O_5$ 386.1842).

15j: *(Table 8, entry 7).* (0.60 mmol scale, 72 mg, 31%); R_f = 0.3 (hexane–ether = 1:1); colorless crystals; mp 133–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.14 (ddddd, *J* = 13.1, 9.8, 8.2, 8.2, 7.0 Hz, 1H), 2.91 (dd, *J* = 13.1, 11.9 Hz, 1H), 3.08 (d, *J* = 8.2 Hz, 2H), 3.19 (dd, *J* = 9.8, 9.5 Hz, 1H), 3.40 (dd, *J* = 9.5, 7.0 Hz, 1H), 3.90 (s, 3H), 4.02 (d, *J* = 11.9 Hz, 1H), 4.46 (d, *J* = 14.8 Hz, 1H), 4.51 (d, *J* = 14.8 Hz, 1H), 7.23–7.38 (m, 6H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H). Selected NOEs are between δ 2.14 (C3a–*H*) and δ 3.40 (C3–H*H*), 4.02 (C9–*H*), and between δ 3.19 (C3–*H*H) and δ 2.91 (C9a–*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 30.5 (CH_2), 35.6 (CH), 46.2 (CH), 46.6 (CH_2), 47.2 (CH), 50.3 (CH_2), 52.9 (CH_3), 123.7 (CH), 127.6 (CH), 127.8 (CH), 128.2 (CH), 128.8 (CH), 130.8 (C), 132.6 (CH), 136.20 (C), 136.22 (C), 150.9 (C), 172.6 (C), 172.7 (C). Selected HMBC correlations are between δ 3.08 (C4–H_2) and δ 50.3 (*C*3), between δ 3.19 (C3–*H*H), 3.40 (C3–H*H*), and δ 46.2 (*C*9a), between δ 3.08 (C4–H_2), 3.19 (C3–*H*H), 3.40 (C3–H*H*), and δ 35.6 (*C*3a), and between δ 2.91 (C9a–*H*) and δ 47.2 (*C*9). IR (KBr) 2953, 2859, 1736, 1699, 1523, 1427, 1360, 1313, 1245, 1206 cm^{-1}; MS (FAB) *m/z* 381 ($[M + H]^+$); HRMS (FAB) *m/z* $[M + H]^+$ 381.1452 (calcd for $C_{21}H_{21}N_2O_5$ 381.1450), $[M + Na]^+$ 403.1270 (calcd for $C_{21}H_{20}N_2O_5Na$ 403.1270). Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36. Found: C, 66.22; H, 5.50; N, 7.07.

15k: *(Table 8, entry 8).* (0.63 mmol scale, 113 mg, 46%); R_f = 0.7 (ether); pale yellow crystals; mp 130–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.910–0.998 (m, 2H), 1.10–1.26 (m, 3H), 1.56–1.74 (m, 6H), 2.17 (ddddd, *J* = 13.0, 9.8, 8.4, 8.4, 7.0 Hz, 1H), 2.88 (dd, *J* = 13.0, 11.9 Hz, 1H), 3.09 (dd, *J* = 13.8, 6.7 Hz, 1H), 3.14 (d, *J* = 8.4 Hz, 2H), 3.18 (dd, *J* = 13.8, 7.3 Hz, 1H), 3.33 (dd, *J* = 9.8, 9.6 Hz, 1H), 3.50 (dd, *J* = 9.6, 7.0 Hz, 1H), 3.88 (s, 3H), 3.97 (d, *J* = 11.9 Hz, 1H), 7.36 (dd, *J* = 8.0, 7.8 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.79 (ddd, *J* = 8.0, 1.0, 1.0 Hz, 1H). Selected NOEs are between δ 2.17 (C3a–*H*) and δ 3.50 (C3–H*H*), 3.97 (C9–*H*), and between δ 3.33 (C3–*H*H) and δ 2.88 (C9a–*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 25.8 (CH_2), 26.4 (CH_2), 30.6 (CH_2), 30.9 (CH_2), 31.0 (CH_2), 36.0 (CH), 36.4 (CH), 46.3 (CH), 47.3 (CH), 49.2 (CH_2), 52.0 (CH_2), 52.9 (CH_3), 123.7 (CH), 127.6 (CH), 130.8 (C), 132.7 (CH), 136.5 (C), 151.0 (C), 172.89 (C), 172.92 (C). Selected HMBC correlations are between δ 3.14 (C4–H_2), 3.50 (C3–H*H*), and δ 46.3 (*C*9a), δ 3.33 (C3–*H*H), 3.50 (C3–H*H*), and δ 36.0 (*C*3a), and between δ 2.88 (C9a–*H*) and δ 47.3 (*C*9). IR (KBr) 2923, 2846, 1739, 1700, 1526, 1362, 1313, 1203, 1157 cm^{-1}; MS (EI) *m/z* 386 (M^+, 5.9), 304 (24), 205 (28), 108 (57), 84 (100%); HRMS (EI) *m/z* 386.1841 (calcd for $C_{21}H_{26}N_2O_5$ 386.1842). Anal. Calcd for $C_{21}H_{26}N_2O_5$: C, 65.27; H, 6.78; N, 7.25. Found: C, 65.14; H, 6.83; N, 7.21.

17: (1 mmol scale, 261 mg, 57%, including a small amount of impurity); R_f = 0.5 (hexane–ether = 1:2); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ratio 1:1) δ (ppm) 3.95 (dd, *J* = 6.2, 1.4 Hz, 2H × 0.5), 4.20 (dd, *J* = 6.6, 1.0 Hz, 2H × 0.5), 4.50 (s, 2H × 0.5), 4.74 (s, 2H × 0.5), 5.90 (dt, *J* = 15.6, 6.2 Hz, 1H × 0.5), 6.06 (dt, *J* = 15.6, 6.6 Hz, 1H × 0.5), 6.95 (d, *J* = 15.6 Hz, 1H × 0.5), 6.98 (d, *J* = 15.6 Hz, 1H × 0.5), 7.15 (s, 1H × 0.5), 7.23–7.54 (m, 7H+1H × 0.5), 7.58–7.62 (m, 1H), 7.98 (dd, *J* = 8.2, 1.2 Hz, 1H × 0.5), 8.00 (dd, *J* = 8.2, 1.2 Hz, 1H × 0.5); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 46.1 (CH_2), 47.7 (CH_2), 49.1 (CH_2), 51.1 (CH_2), 120.1 (C, q, J_{CF} = 275 Hz), 120.3 (C, broad q, J_{CF} = 275 Hz), 124.7 (CH), 123.45–124.46 (C, m), 124.8 (CH), 127.4 (CH), 127.5 (CH), 127.6 (CH), 128.1 (CH), 128.6 (CH), 128.7 (CH), 128.8 (CH), 128.95 (CH), 129.00 (CH), 129.1 (CH), 129.3 (CH), 130.35 (CH), 130.43 (CH), 131.9 (C), 132.3 (C), 133.5 (CH), 133.6 (CH), 134.5 (C), 135.7 (C), 136.0 (CH, m), 136.2 (CH, m), 147.59 (C), 147.63 (C), 162.6 (C), 162.7 (C); ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −66.43 (q, J_{FF} = 6.5 Hz), −66.65 (q, J_{FF} = 6.5 Hz), −69.89 (q, J_{FF} = 6.5 Hz), −69.99 (q, J_{FF} = 6.5 Hz); IR (neat) 3068, 3032, 2931, 1651, 1608, 1524, 1435, 1386, 1348, 1286, 1221, 1166, 985 cm^{-1}; MS (EI) *m/z* 458 (M^+, 3.8), 296 (28), 106 (34), 91 (100%); HRMS (EI) *m/z* 458.1057 (calcd for $C_{21}H_{16}F_6N_2O_3$ 458.1065).

18: (0.57 mmol scale, 231 mg, 89%); R_f = 0.2 (hexane–ether = 2:1); colorless crystals; mp 219–220 °C (AcOEt); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.64 (ddddd, *J* = 13.5, 12.1, 9.6, 7.2, 4.3 Hz, 1H), 2.81 (dd, *J* = 13.5, 1.2 Hz, 1H), 2.95 (dd, *J* = 17.2, 12.1 Hz, 1H), 3.06 (dd, *J* = 9.6, 9.4 Hz, 1H), 3.12 (dd, *J* = 17.2, 4.3 Hz, 1H), 3.28 (dd, *J* = 9.4, 7.2 Hz, 1H), 4.44 (d, *J* = 14.8 Hz, 1H), 4.62 (d, *J* = 14.8 Hz, 1H), 7.25 (d-like, *J* = 7.4 Hz, 2H), 7.28–7.37 (m, 3H), 7.51 (dd, *J* = 8.4, 8.0 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.11 (d. *J* = 8.4 Hz, 1H). Selected NOEs are between δ 2.64 (C3a–*H*) and δ 3.28 (C3–H*H*) and between δ 2.95 (C4–*H*H) and δ 2.81 (C9a–*H*). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 30.9 (CH_2), 32.4 (CH, q, J_{CF} = 2.3 Hz), 46.6 (CH), 47.2 (CH_2), 48.7 (CH_2), 56.9 (C, septet, J_{CF} = 27 Hz), 123.6 (C, q, J_{CF} = 288 Hz), 124.3 (C, q, J_{CF} = 285 Hz), 125.5 (CH), 127.6 (CH), 128.0 (CH), 128.3 (CH), 129.0 (CH), 129.5 (C), 132.9 (C), 135.5 (CH, septet, J_{CF} = 3.8 Hz), 136.0 (C), 151.1 (C), 167.4 (C). Selected HMBC correlations are between δ 3.28 (C3–H*H*) and 2.95 (C4–*H*H), between δ 46.6 (*C*9a), δ 2.95 (C4–*H*H), 3.28 (C3–H*H*), and δ 32.4 (*C*3a), and between δ 2.81 (C9a–*H*) and δ 56.9 (*C*9). ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −66.23 (q, J_{FF} = 6.9 Hz), −70.27 (q, J_{FF} = 6.9 Hz); IR (KBr) 3033, 2929, 1699, 1530, 1431, 1349, 1263, 1245, 1195, 1080 cm^{-1}; MS (EI) *m/z* 458 (M^+, 71), 91 (100%); HRMS (EI) *m/z* 458.1064 (calcd for $C_{21}H_{16}F_6N_2O_3$ 458.1065). Anal. Calcd for $C_{21}H_{16}F_6N_2O_3$: C, 55.03; H, 3.52; N, 6.11. Found: C, 55.01; H, 3.55; N, 6.15.

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863–10886

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01947.

Additional data for Tables 4 and 5, optimized structures of Schemes 12−14, Cartesian coordinates of the optimized geometries, and crystallographic data (PDF)
Copies of the ^{1}H and ^{13}C NMR (PDF)
2D NOESY spectra (PDF)
Crystal structure of **8w** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yamazaks@nara-edu.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Ministry of Education, Culture, Sports, Science, and Technology (MEXT), Japan, and JSPS KAKENHI Grant Number JP26410048. This work was partly supported by Nanotechnology Platform Program of MEXT. We thank Nara Institute of Science and Technology (NAIST) and Prof. K. Kakiuchi (NAIST) for mass spectrometry.

■ REFERENCES

(1) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (c) Parvatkar, P. T.; Kadam, H. K.; Tilve, S. G. *Tetrahedron* **2014**, *70*, 2857.

(2) (a) Bach, T.; Pelkmann, C.; Harms, K. *Tetrahedron Lett.* **1999**, *40*, 2103. (b) Bach, T.; Krüger, C.; Harms, K. *Synthesis* **2000**, *2000*, 305.

(3) (a) Kriis, K.; Ausmees, K.; Pehk, T.; Lopp, M.; Kanger, T. *Org. Lett.* **2010**, *12*, 2230. (b) Ausmees, K.; Kriis, K.; Pehk, T.; Werner, F.; Järving, I.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2012**, *77*, 10680. (c) Reinart-Okugbeni, R.; Ausmees, K.; Kriis, K.; Werner, F.; Rinken, A.; Kanger, T. *Eur. J. Med. Chem.* **2012**, *55*, 255. (d) Araki, T.; Ozawa, T.; Yokoe, H.; Kanematsu, M.; Yoshida, M.; Shishido, K. *Org. Lett.* **2013**, *15*, 200. (e) Hoshikawa, T.; Tanji, K.; Matsuo, J.; Ishibashi, H. *Chem. Pharm. Bull.* **2012**, *60*, 548. (f) Padwa, A.; Lipka, H.; Watterson, S. H.; Murphree, S. S. *J. Org. Chem.* **2003**, *68*, 6238. (g) Brummond, K. M.; Chen, D. *Org. Lett.* **2005**, *7*, 3473. (h) Ovaska, T. V.; Kyne, R. E. *Tetrahedron Lett.* **2008**, *49*, 376.

(4) (a) Ko, C.; Feltenberger, J. B.; Ghosh, S. K.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 1971. (b) Nakano, S.; Kakugawa, K.; Nemoto, T.; Hamada, Y. *Adv. Synth. Catal.* **2014**, *356*, 2088. (c) Luzung, M. R.; Mauleón, P.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12402. (d) Ranieri, B.; Obradors, C.; Mato, M.; Echavarren, A. M. *Org. Lett.* **2016**, *18*, 1614. (e) Gulías, M.; Collado, A.; Trillo, B.; López, F.; Oñate, E.; Esteruelas, M. A.; Mascareñas, J. L. *J. Am. Chem. Soc.* **2011**, *133*, 7660.

(5) (a) Ciganek, E. *Org. React.* **1984**, *32*, 1. (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon, 1991, Vol. *5*, p 513. (c) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179.

(6) (a) Hayakawa, K.; Yodo, M.; Ohsuki, S.; Kanematsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 6735. (b) Horak, Y. I.; Lytvyn, R. Z.; Homza, Y. V.; Zaytsev, V. P.; Mertsalov, D. F.; Babkina, M. N.; Nikitina, E. V.; Lis, T.; Kinzhybalo, V.; Matiychuk, V. S.; Zubkov, F. I.; Varlamov, A. V.; Obushak, M. D. *Tetrahedron Lett.* **2015**, *56*, 4499. (c) Patre, R. E.; Gawas, S.; Sen, S.; Parameswaran, P. S.; Tilve, S. G. *Tetrahedron Lett.* **2007**, *48*, 3517. (d) Kotsuki, H.; Kawamura, A.; Ochi, M.; Tokoroyama, T. *Chem. Lett.* **1981**, *10*, 917. (e) Drew, M. G. B.; Jahans, A.; Harwood, L. M.; Apoux, S. A. B. H. *Eur. J. Org. Chem.* **2002**, *2002*, 3589.

(7) He, Y.; Chen, Y.; Wu, H.; Lovely, C. J. *Org. Lett.* **2003**, *5*, 3623.

(8) Kim, P.; Tsuruda, J. M.; Olmstead, M. M.; Eisenberg, S.; Kurth, M. J. *Tetrahedron Lett.* **2002**, *43*, 3963.

(9) (a) Klemm, L. H.; McGuire, T. M.; Gopinath, K. W. *J. Org. Chem.* **1976**, *41*, 2571. (b) Kocsis, L. S.; Benedetti, E.; Brummond, K. M. *Org. Lett.* **2012**, *14*, 4430. (c) Benedetti, E.; Veliz, A. B. E.; Charpenay, M.; Kocsis, L. S.; Brummond, K. M. *Org. Lett.* **2013**, *15*, 2578. (d) Ozawa, T.; Kurahashi, T.; Matsubara, S. *Org. Lett.* **2011**, *13*, 5390. (e) Sun, S.; Turchi, I. J.; Xu, D.; Murray, W. V. *J. Org. Chem.* **2000**, *65*, 2555. (f) Pedrosa, R.; Andrés, C.; Nieto, J. *J. Org. Chem.* **2002**, *67*, 782.

(10) (a) Yamazaki, S.; Yamamoto, Y.; Fukushima, Y.; Takebayashi, M.; Ukai, T.; Mikata, Y. *J. Org. Chem.* **2010**, *75*, 5216. (b) Yamazaki, S.; Takebayashi, M.; Miyazaki, K. *J. Org. Chem.* **2010**, *75*, 1188. (c) Yamazaki, S.; Iwata, Y.; Fukushima, Y. *Org. Biomol. Chem.* **2009**, *7*, 655. (d) Morikawa, S.; Yamazaki, S.; Tsukada, M.; Izuhara, S.; Morimoto, T.; Kakiuchi, K. *J. Org. Chem.* **2007**, *72*, 6459. (e) Yamazaki, S.; Iwata, Y. *J. Org. Chem.* **2006**, *71*, 739. (f) Yamazaki, S.; Ueda, K.; Fukushima, Y.; Ogawa, A.; Kakiuchi, K. *Eur. J. Org. Chem.* **2014**, *2014*, 7023. (g) Yamazaki, S.; Maenaka, Y.; Fujinami, K.; Mikata, Y. *RSC Adv.* **2012**, *2*, 8095.

(11) Snider, B. B.; Roush, D. M. *J. Org. Chem.* **1979**, *44*, 4229.

(12) (a) Yamazaki, S.; Fujinami, K.; Maitoko, Y.; Ueda, K.; Kakiuchi, K. *J. Org. Chem.* **2013**, *78*, 8405. (b) Fukushima, Y.; Yamazaki, S.; Ogawa, A. *Org. Biomol. Chem.* **2014**, *12*, 3964. (c) Yamazaki, S.; Wada, J.; Kakiuchi, K. *Can. J. Chem.* **2015**, *93*, 1122.

(13) Yamazaki, S.; Sugiura, H.; Niina, M.; Mikata, Y.; Ogawa, A. *Heterocycles* **2016**, *92*, 485.

(14) The byproducts by the reaction of CH_2ClCH_2Cl and HOBt in the presence of Et_3N were formed and removed by column chromatography. (a) Ji, J.-G.; Zhang, D.-Y.; Ye, Y.-H.; Xing, Q.-Y. *Tetrahedron Lett.* **1998**, *39*, 6515. (b) Feld, W. A.; Evans, D. G. *J. Chem. Eng. Data* **1983**, *28*, 138.

(15) Crystallographic data for **8w** have been deposited with the Cambridge Crystallographic Data Centre (no. CCDC 1495967).

(16) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

(17) Snider, B. B.; Roush, D. M.; Killinger, T. A. *J. Am. Chem. Soc.* **1979**, *101*, 6023.

(18) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter Mater. Phys.* **1988**, *37*, 785.

(19) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, revision D.01; Gaussian, Inc.: Wallingford, CT, 2009.

(20) (a) Cancès, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032. (b) Cossi, M.; Barone, V.; Mennucci, B.; Tomasi, J. *Chem. Phys. Lett.* **1998**, *286*, 253. (c) Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *106*, 5151.

(21) (a) Fukui, K. *J. Phys. Chem.* **1970**, *74*, 4161. (b) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154.

(22) Duan, S.; Jana, R.; Tunge, J. A. *J. Org. Chem.* **2009**, *74*, 4612.

(23) (a) Paredes, E.; Biolatto, B.; Kneeteman, M.; Mancini, P. M. *Tetrahedron Lett.* **2000**, *41*, 8079. (b) Paredes, E.; Biolatto, B.; Kneeteman, M.; Mancini, P. *Tetrahedron Lett.* **2002**, *43*, 4601. (c) Trost, B. M.; Ehmke, V.; O'Keefe, B. M.; Bringley, D. A. *J. Am. Chem. Soc.* **2014**, *136*, 8213.

(24) Yamazaki, S.; Ohmitsu, K.; Ohi, K.; Otsubo, T.; Moriyama, K. *Org. Lett.* **2005**, *7*, 759.

(25) (a) Anan, H.; Tanaka, A.; Tsuzuki, R.; Yokota, M.; Yatsu, T.; Fujikura, T. *Chem. Pharm. Bull.* **1996**, *44*, 1865. (b) Abdel-Magid, A. F.;

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886

Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.
(26) Singh, K. K.; Mathela, C. S. *Indian J. Chem.* **2014**, *53B*, 907.
(27) Nishimura, T. *Bull. Chem. Soc. Jpn.* **1952**, *25*, 54.
(28) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2003**, *5*, 777.
(29) Zhu, J.; Liu, J.; Ma, R.; Xie, H.; Li, J.; Jiang, H.; Wang, W. *Adv. Synth. Catal.* **2009**, *351*, 1229.
(30) (a) Saikachi, H.; Taniguchi, Y.; Ogawa, H. *Yakugaku Zasshi* **1963**, *83*, 578; *Chem. Abstr.* **1963**, *59*, 11397. (b) Cresp, T. M.; Sargent, M. V.; Vogel, P. *J. Chem. Soc., Perkin Trans. 1* **1974**, 37. (c) Olstein, R.; Stephenson, E. F. M. *Aust. J. Chem.* **1979**, *32*, 681.

DOI: 10.1021/acs.joc.6b01947
J. Org. Chem. 2016, 81, 10863−10886