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Tandem or Sequential Coupling−IMDA Cycloaddition Approach to Highly Fused Polycarbocycles

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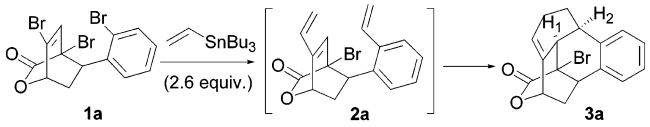
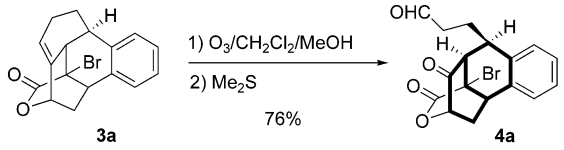
Abstract: The Diels−Alder cycloadduct made from 3,5-dibromo-2-pyrone and 2-bromo-styrene was successfully transformed stereoselectively into a series of novel benzotetracycles via a tandem or sequential Pd-catalyzed coupling−intramolecular Diels−Alder (IMDA) cycloaddition. The resulting polycarbocycles can be readily converted into a bicyclo[3.3.1]nonane system upon ozonolysis of the internal double bond.

Polycarbocycles are important structural frameworks for both their natural abundance and intriguing physiological activities.[1] A number of unique and efficient strategies and methods have been developed for their syntheses. In connection to our ongoing investigation on 3,5-dibromo-2-pyrone,[2] we have reported that it undergoes either normal or inverse electron demand Diels−Alder cycloadditions with a variety of electronically and sterically distinct dienophiles. The Diels−Alder cycloadditions with styrene derivatives[3] are of particular interest, as the resulting cycloadducts can be readily transformed into polycarbocycles, including tetrahydrofluorenes as we reported earlier.[4] Further manipulation into other fused carbocyclic systems could be envisaged through the introduction of vinyl units at the aryl bromide position and a subsequent radical cyclization process with the bridgehead bromine group. Attempted introduction of vinyl group with excess vinyltributyltin, however, did not produce the expected coupling product but instead provided **3a** as single diastereomer in 65% yield under the typical Stille conditions (Scheme 1). Evidently, the Stille coupling reaction took place at both vinyl and aryl bromide groups of **1a** to give rise to the divinyl intermediate **2a**, which further proceeded in an intramolecular Diels−Alder (IMDA) cycloaddition[5] to the benzotetracyclolactone **3a**.

SCHEME 1. Tandem Coupling−IMDA Cycloaddition



SCHEME 2. Ozonolysis of 3a for Synthesis of the Bicyclo[3.3.1]nonane System



Conformational rigidity of the diene and dienophile units in the intermediate **2a** led to the formation of single diastereomeric **3a**. Its NOESY spectrum shows strong correlation between H_1 and H_2, confirming its relative stereochemistry. Subsequent ozonolysis of **3a**, followed by a reductive workup with Me_2S, provided **4a** bearing a bicyclo[3.3.1]nonane skeleton, present in a number of natural products, including especially the family of hyperforins (Scheme 2).[6]

The potential synthetic applications toward the family of hyperforins and their analogues prompted us to investigate our new tandem process in depth.[7] The electronic match-up for the diene and dienophile, however, imposes a serious limitation on the type of vinyl electrophiles used. Sequential introduction of vinyl electrophiles onto the vinyl bromide and aryl halide groups would be more desirable for the structural diversity of the products. Fortunately, the Pd-catalyzed coupling reaction at the vinyl bromide of **1a** is significantly faster than at the aryl bromide, providing the dienes **5**−**8** in good to excellent yields (Table 1).

The tandem Stille coupling−IMDA reactions of **5** were then executed with various vinylstannanes (Table 2). The reaction with tributylvinyltin proceeded quite smoothly to give **3a** in 86% isolated yield (entry 1). The reactions with other stannanes, however, were not as efficient as those with vinyl tin. The isolated yields of the final

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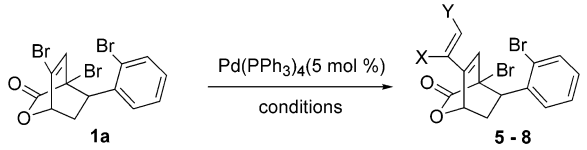
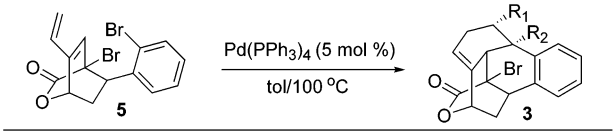
TABLE 1. Regioselective Coupling Reactions on 1a



entry	electrophile	conditions	product	yield
1	$SnBu_3$	toluene/50 °C/3 h	**5** (X = Y = H)	98%
2	OEt, $SnBu_3$	CuI/DMF/rt/0.5 h	**6** (X = OEt)	89%
3	Ph, $SnBu_3$	toluene/rt/3 h	**7** (Y = Ph)	86%
4	CO_2Me	DMF/Et_3N/50 °C/42 h[a]	**8** (Y = CO_2Me)	93%

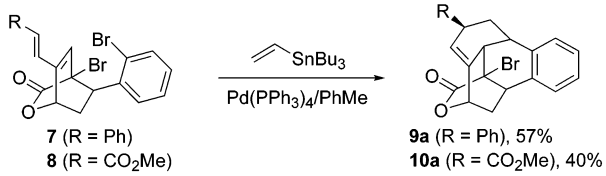
[a] Performed with a $Pd(OAc)_2$ (5 mol %)/PPh_3 (10 mol %) system.

TABLE 2. Tandem Stille Coupling−IMDA Cycloaddition of 5



entry	R-$SnBu_3$	time	product	yield
1	$SnBu_3$	27 h	**3a** (R_1= R_2= H)	86%
2	Ph, $SnBu_3$	6 h	**3b** (R_1= Ph)	31%
3	MeO_2C, $SnBu_3$	6 h	**3c** (R_2= CO_2Me)	23%
4	MeO_2C, $SnBu_3$	6 h	**3d** (R_1= CO_2Me)	33%

SCHEME 3. Tandem Reactions on 7 and 8



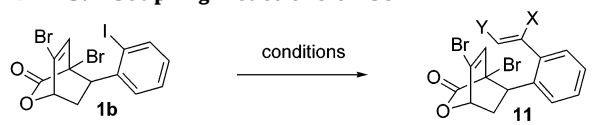
products dropped rather significantly as the size of the tin reagent increased.

The tandem reactions of **7** and **8** showed a similar trend, effective only with unsubstituted vinyl tin, furnishing **9a** and **10a** in reasonable yields (Scheme 3). The reactions with substituted vinyl stannanes gave the products only in 10−20% yields (data not shown). No desired reaction was observed with **6**, as the ethoxy vinyl group decomposed under the conditions.

To increase the reactivity at the aryl site for the second Stille coupling reaction, we prepared the cycloadduct **3b** where the aryl bromide was replaced with iodide.[8] The coupling reactions took place at aryl iodide this time, rather than at the desired vinyl bromide position, to give **11a**−**d** (Table 3). Unfortunately, however, the second Stille couplings of **11a** provided unidentifiable mixtures, due to the apparent interference of the styrene vinyl group.

Returning to the original system **5**−**8**, we studied tandem Suzuki coupling−IMDA reactions of **5** using

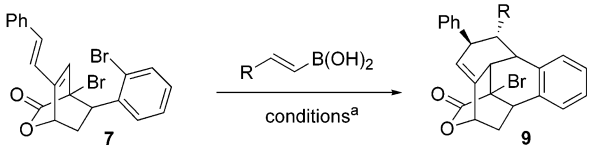
TABLE 3. Coupling Reactions on 3b



entry	electrophile	conditions	product	yields
1	$SnBu_3$	rt/3 d[a]	**11a** (X = Y = H)	65%
2	MeO_2C, $SnBu_3$	80 °C/2 h[a]	**11b** (X = CO_2Me)	50%
3	CO_2Me, $SnBu_3$	80 °C/2 h[a]	**11c** (X = OEt)	42%
4	CO_2Me	50 °C/2 h[b]	**11d** (Y = CO_2Me)	71%

[a] $Pd(PPh_3)_4$/CuI/DMF. [b] $Pd(OAc)_2$/PPh_3/DMF/Et_3N.

TABLE 4. Tandem Suzuki−IMDA Cycloadditions on 7



entry	boronic acids	time	product	yield
1	$B(OH)_2$	2 h	**9b** (R = Ph)	96%
2	Cl, $B(OH)_2$	4 h	**9c** (R = p-Cl-Ph)	83%
3	F, $B(OH)_2$	6 h	**9d** (R = p-F-Ph)	64%
4	H_3C, $B(OH)_2$	5 h	**9e** (R = p-Me)	72%
5	F_3C, $B(OH)_2$	5 h	**9f** (R = 4-CF3-Ph)	57%
6	nBu, $B(OH)_2$	12 h	**9g** (R = Bu)	10%

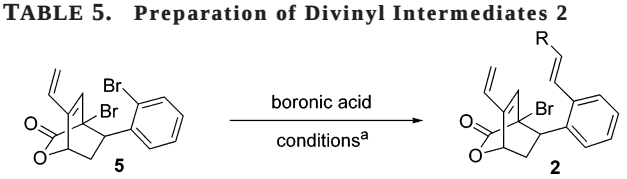
[a] $Pd(PPh_3)_4$ (5 mol %)/Na_2CO_3/toluene/100 °C.

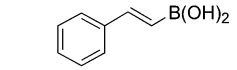
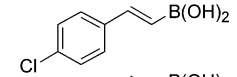
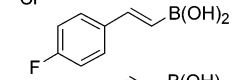
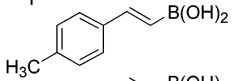
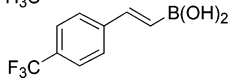
various substituted vinyl boronic acids, sterically less demanding than their stannyl counterparts. The results were still unsatisfactory, providing the desired polycyclic compounds in only 15−25% isolated yields. Meanwhile, the Suzuki−IMDA tandem reactions on **7** turned out to be much more effective, furnishing the benzotetracyclolactones **9b**−**f** in good to excellent isolated yields (Table 4). Only a small amount of the desired product **9g** was obtained when 1-hexenyl boronic acid was used (entry 6).

The success on **7** made us to look at the reactions of **5** (Table 2) more closely. A few sets of control experiments indicated that it is not the coupling reaction but the subsequent IMDA cycloaddition that lowers the overall product yield. The isolated divinyl intermediate **2b** proceeded in a facile IMDA cycloaddition when heated at 100 °C in toluene with no Pd catalyst, providing the desired product in good yield. We obtained the same product in less than 25% yield when **2b** was heated in the presence of Pd catalyst, indicating possible interference of the dienyl vinyl group. Various types of the divinyl intermediates were then prepared from the Suzuki

(8) Iodo derivative **1b** was prepared from the cycloaddition of 3,5-dibromo-2-pyrone with 2-iodo styrene upon heating at 100 °C in toluene (75% total yield with an 86:14 endo/exo ratio).

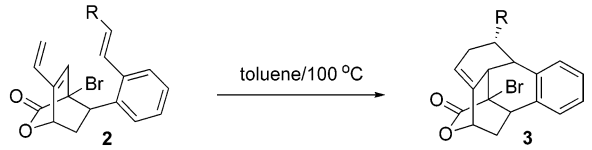
TABLE 5. Preparation of Divinyl Intermediates 2



entry	boronic acid	time	product	yield
1		0.5 h	**2b** (R = Ph)	77%
2		3 h	**2c** (R = p-Cl-Ph)	70%
3		2.5 h	**2d** (R = p-F-Ph)	71%
4		3 h	**2e** (R = p-Me)	60%
5		3.5 h	**2f** (R = 4-CF_3-Ph)	62%

[a] $Pd(PPh_3)_4$/CsF/DME/100 °C.

TABLE 6. IMDA Cycloadditions of Divinyl Intermediates



entry	time	product	yield
1	24 h	**3b** (R = Ph)	79%
2	24 h	**3e** (R = *p*-cl-ph)	58%
3	24 h	**3f** (R = *p*-F-Ph)	52%
4	24 h	**3g** (R = *p*-Me)	73%
5	12 h	**3h** (R = 4-CF3-Ph)	75%

couplings of **5** with alkenyl boronic acids (Table 5). The addition of CsF in this case greatly improved the product yields.[9]

The isolated divinyl intermediates **2b**−**f** furnished the corresponding benzotetracycles **3** in 52−79% isolated yields when heated at 100 °C in toluene (Table 6).

In summary, we have found that the cycloadduct **1a** can be efficiently converted into a series of structurally novel benzotetracyclic compounds with a complete control of diastereochemistry via tandem or sequential Pd-catalyzed coupling−IMDA cycloaddition reactions in good to excellent chemical yields. Ozonolysis of the internal double bond would generate the benzotricycles bearing a bicyclo[3.3.1]nonane core as demonstrated with **3a**. Their potential biological activities as well as synthetic applications toward various hyperforin derivatives are currently being investigated.

Experimental Section

General Methods. ^1H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz, with either TMS (δ = 0) or the signal for residual $CHCl_3$ in the $CDCl_3$ solvent (δ7.24) as internal standards. *J* values are reported in hertz. High-resolution mass spectra were measured by using the FAB method. Flash column chromatography was performed with Kieselgel 60 Art 9385 (230−400 mesh). All solvents used were purified according to standard procedures.

3a. A sealed tube was charged with **5** (86 mg, 0.224 mmol), tributylvinyltin (88 mg, 1.2 equiv), 0.05 equiv of tetrakis-(triphenylphosphine)palladium, and toluene (2 mL) under an Ar atmosphere. After 27 h at 100 °C, the reaction mixture was filtered through a plug of Celite. The filterate was concentrated in vacuo and chromatographed (hexanes/EtOAc = 9:1) to give 64 mg of **3a** (86% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 7.6 Hz, 1H), 7.26−7.17 (m, 2H), 7.05 (dd, J = 7.6, 1.2 Hz, 1H), 5.53 (dd, J = 6.0, 3.2 Hz, 1H), 4.94−4.93 (m, 1H), 3.60 (d, J = 10.4 Hz, 1H), 3.52 (dd, J = 7.6, 3.6 Hz, 1H), 3.05−3.02 (m, 1H), 2.67−2.61 (m, 1H), 2.54 (ddd, J = 14.4, 6.8, 3.6 Hz, 1H), 2.23−2.15 (m, 1H), 2.07−1.98 (m, 1H), 1.87−1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 138.0, 133.4, 132.9, 129.3, 127.4, 126.9, 126.6, 122.8, 76.7, 64.3, 43.4, 43.3, 42.8, 33.4, 24.7, 21.9; FT-IR ($CHCl_3$) 3080.1, 2882.7, 1778.2, 1647.1, 1498.7 cm^{-1}; HRMS (FAB) m/z $(M + 1)^+$ calcd for $C_{17}H_{16}BrO_2$ 331.0334, found 331.0343.

3b. A mixture of 20 mg of **2b** (0.049 mmol) in 1 mL of anhydrous toluene was heated at 100 °C in a sealed tube for 24 h. The reaction mixture was cooled to room temperature, concentrated, and chromatographed (hexanes/EtOAc = 9:1) to give 15.7 mg of **3b** in 79% yield: ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.6 Hz, 1H), 7.36−7.21 (m, 7H), 7.08 (dd, J = 7.6, 1.2 Hz, 1H), 5.77 (dd, J = 6.0, 3.2 Hz, 1H), 5.01 (dd, J = 2.8, 2.0 Hz, 1H), 3.90 (dd, 6.0, 2.8 Hz, 1H), 3.61−3.58 (m, 1H), 3.47−3.45 (m, 1H), 2.71−2.70 (m, 1H), 2.65 (d, J = 11.2 Hz, 1H), 2.48 (d, J = 19.2 Hz, 1H), 2.28−2.20 (m, 1H), 1.92 (ddd, J = 13.2, 3.2, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 143.9, 138.0, 133.91, 133.88, 129.5, 128.8, 127.7, 127.2, 127.1, 126.8, 126.4, 122.4, 77.2, 63.7, 43.5, 42.8, 41.1, 40.3, 38.9, 26.7; FT-IR ($CHCl_3$) 3060.8, 2883.4, 1751.2, 1492.8, 1170.7, 112.9 cm^{-1}; HRMS (FAB) m/z $(M + 1)^+$ calcd for $C_{23}H_{20}BrO_2$ 407.0647, found 407.0633.

3e. Prepared by using the same procedure as described for **3b**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 1H), 7.30−7.29 (m, 3H), 7.25−7.20 (m, 3H), 7.08 (dd, J = 7.6, 1.2 Hz, 1H), 5.76 (dd, J = 6.0, 3.2 Hz, 1H), 5.02 (dd, J = 2.8, 2.0 Hz, 1H), 3.88 (dd, 6.0, 2.8 Hz, 1H), 3.61 (d, J = 11.2 Hz, 1H), 3.43−3.41 (m, 1H), 2.71−2.65 (m, 2H), 2.43 (d, J = 19.6 Hz, 1H), 2.29−2.22 (m, 1H), 1.92 (ddd, J = 13.2, 3.2, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 142.3, 138.0, 134.0, 133.5, 132.6, 129.6, 128.9, 128.5, 127.8, 127.4, 126.3, 122.1, 77.3, 63.6, 43.4, 42.8, 41.0, 39.8, 38.8, 26.7; FT-IR ($CHCl_3$) 3010.7, 2883.4, 1753.2, 1490.9, 1159.1 cm^{-1}; HRMS (FAB) m/z $(M + 1)^+$ calcd for $C_{23}H_{19}BrClO_2$ 441.0257, found 441.0280.

3f. Prepared by using the same procedure as described for **3b**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.6 Hz, 1H), 7.32−7.21 (m, 4H), 7.08 (dd, J = 7.2, 0.8 Hz, 1H), 7.05−7.00 (m, 2H), 5.76 (dd, J = 6.0, 3.2 Hz, 1H), 5.02 (dd, J = 2.8, 2.0 Hz, 1H), 3.89 (dd, J = 6.0, 2.8 Hz, 1H), 3.60 (d, J = 11.6 Hz, 1H), 3.42−3.41 (m, 1H), 2.70−2.64 (m, 2H), 2.44 (d, J = 19.2 Hz, 1H), 2.29−2.22 (m, 1H), 1.92 (ddd, J = 13.2, 3.2, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 161.5 (d, J = 243.4 Hz), 139.5 (d, J = 3.0 Hz), 137.9, 133.9, 133.6, 129.5, 128.6 (d, J = 8.4 Hz), 127.7, 127.3, 126.3, 122.2, 115.6 (d, J = 20.7 Hz), 77.1, 63.6, 43.4, 42.8, 41.1, 39.5, 38.8, 26.8; FT-IR ($CHCl_3$) 3064.7, 2887.2, 1753.2, 1508.2, 1217.0, 1166.9 cm^{-1}; HRMS (FAB) m/z $(M + 1)^+$ calcd for $C_{23}H_{19}BrFO_2$ 425.0552, found 425.0561.

3g. Prepared by using the same procedure as described for **3b**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.6 Hz, 1H), 7.32−7.28 (m, 1H), 7.24−7.19 (m, 1H), 7.17−7.12 (m, 4H), 7.07 (dd, J = 7.6, 1.2 Hz, 1H), 5.75 (dd, J = 6.0, 3.2 Hz, 1H), 5.02−5.00 (m, 1H), 3.87−3.85 (m, 1H), 3.59 (d, J = 10.4 Hz, 1H), 3.44−3.42 (m, 1H), 2.71−2.70 (m, 1H), 2.65 (d, J = 10.4 Hz, 1H), 2.46 (d, J = 19.2 Hz, 1H), 2.35 (s, 3H), 2.26−2.20 (m, 1H), 1.92 (ddd, J = 13.2, 3.2, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 140.8, 138.0, 136.3, 134.0, 133.8, 129.5, 129.4, 127.7, 127.2, 126.9, 126.4, 122.5, 77.2, 63.8, 43.5, 42.8, 41.2, 39.8, 38.9, 26.8, 21.2; FT-IR ($CHCl_3$) 3018.4, 2883.4, 1753.2, 1490.9, 1166.9, 1108.9

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cm^{-1}; HRMS (FAB) m/z (M+1)$^+$ calcd for $C_{24}H_{22}BrO_2$ 421.0803, found 421.0780.

3h. Prepared by using the same procedure as described for **5b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.34−7.30 (m, 1H), 7.27−7.23 (m, 1H), 7.10 (dd, J = 7.6, 1.2 Hz, 1H), 5.79 (d, J = 6.4, 3.2 Hz, 1H), 5.04−5.03 (m, 1H), 3.96 (dd, J = 6.0, 2.8 Hz, 1H), 3.61 (d, J = 10.0 Hz, 1H), 3.48−3.46 (m, 1H), 2.72−2.63 (m, 2H), 2.48 (d, J = 19.2 Hz, 1H), 2.33−2.24 (m, 1H), 1.93 (ddd, J = 13.4, 3.0, 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 147.8, 137.9, 134.1, 133.3, 129.6, 129.2 (q, J = 31.1 Hz), 127. 8, 127.5, 127.4, 126.7 (q, J = 272 Hz), 126.2, 125.7 (q, J = 4.0 Hz), 122.0, 77.1, 63.4, 43.3, 42.7, 40.8, 40.2, 38.7, 26.5; FT-IR ($CHCl_3$) 3026.1, 2921.9, 1776.7, 1490.9, 1324.9, 1157.2 cm^{-1}; HRMS (FAB) m/z (M + 1)$^+$ calcd for $C_{24}H_{19}BrF_3O_2$ 475.0521, found 475.0526.

9a. A sealed tube was charged with **7** (34 mg, 0.074 mmol), tributylvinyltin (33 mg, 1.5 equiv), 0.05 equiv of tetrakis-(triphenylphosphine)palladium, 0.1 equiv of CuI, and toluene (1 mL) under an Ar atmosphere. After 12 h at 100 °C, the reaction mixture was filtered through a plug of Celite. The filtrate was concentrated and chromatographed (hexanes/EtOAc = 9:1) to give 17 mg of **9a** (57% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 7.2 Hz, 1H), 7.12−7.03 (m, 4H), 6.93−6.90 (m, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.64−6.61 (m, 2H), 5.93−5.91 (m, 1H), 5.08−5.07 (m, 1H), 3.67−3.62 (m, 2H), 3.54−3.50 (m, 1H), 3.10−3.07 (m, 1H), 2.83−2.77 (m, 1H), 2.74−2.67 (m, 1H), 2.42−2.36 (m, 1H), 2.02 (ddd, J = 13.9, 2.9, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 144.5, 136.7, 134.7, 134.6, 128.8, 128.0, 127.5, 127.4, 127.1, 126.65, 126.60, 126.0, 76.4, 63.5, 42.86, 42.84, 41.8, 39.1, 35.6, 32.8; FT-IR ($CHCl_3$) 3051.8, 2883.4, 1751.5, 1653.4, 1493.8 cm^{-1}; HRMS (FAB) m/z (M + 1)$^+$ calcd for $C_{23}H_{20}BrO_2$ 407.0647, found 407.0634.

9b. A sealed tube was charged with **7** (33.5 mg, 0.073 mmol), *trans*-2-phenylvinylboronic acid (33 mg, 3 equiv), 0.1 equiv of tetrakis(triphenylphosphine)palladium, toluene (1 mL), and 0.22 mL of aq Na_2CO_3 (1 M) under an Ar atmosphere. After 2 h at 100 °C, the reaction mixture was filtered through a plug of Celite. The filtrate was concentrated and chromatographed (hexanes/EtOAc = 9:1) to give 34 mg of **9b** (96% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.27 (m, 2H), 7.24−7.20 (m, 1H), 7.17−7.11 (m, 3H), 7.06−6.95 (m, 6H), 6.56 (dd, J = 7.8, 1.2 Hz, 2H), 6.12−6.11 (m, 1H), 5.15−5.14 (m, 1H), 3.77 (dd, J = 5.6, 4.0 Hz, 1H), 3.65−3.61 (m, 2H), 3.47 (dd, J = 6.4, 4.0 Hz, 1H), 3.21−3.18 (m, 1H), 2.88−2.81 (m, 1H), 2.11−2.07 (ddd, J = 13.6, 2.4, 2.0, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 145.2, 143.1, 136.4, 135.7, 135.4, 128.9, 128.7, 128.5, 128.0, 127.9, 127.8, 127.6, 126.95, 126.93, 126.7, 126.2, 76.7, 63.1, 54.9, 47.4, 42.7, 42.0, 41.4, 41.0; FT-IR ($CHCl_3$) 3020.3, 2881.4, 1770.5, 1488.9, 1157.2, 1108.8 cm^{-1}; HRMS (FAB) m/z (M + 1)$^+$ calcd for $C_{29}H_{24}BrO_2$ 483.0960, found 483.0963.

9c. Prepared by using the same procedure as described for **9b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.23 (m, 2H), 7.16−7.12 (m, 1H), 7.09−7.01 (m, 6H), 6.99 (d, J = 3.6 Hz, 2H), 6.58 (dd, J = 7.6, 1.2 Hz, 2H), 6.12−6.10 (m, 1H), 5.14−5.13 (m, 1H), 3.75 (dd, J = 6.4, 3.6 Hz, 1H), 3.64 (d, J = 10.8 Hz, 1H), 3.55−3.52 (m, 1H), 3.39 (dd, J = 6.4, 4.0 Hz, 1H), 3.20−3.17 (m, 1H), 2.89−2.82 (m, 1H), 2.10−2.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 143.9, 142.8, 136.5, 136.1, 135.6, 132.6, 129.4, 129.2, 129.1, 128.6, 129.4, 128.1, 127.9, 127.3, 127.2, 126.6, 77.3, 63.1, 55.2, 48.0, 42.8, 42.2, 41.4, 41.3; FT-IR ($CHCl_3$) 3024.1, 2929.7, 1766.7, 1488.9, 1159.1, 1108.9 cm^{-1}; HRMS (FAB) m/z (M + 1)$^+$ calcd for $C_{29}H_{23}BrClO_2$ 517.0570, found 517.0538.

9d. Prepared by using the same procedure as described for **9b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14−6.96 (m, 11H), 6.59−6.57 (m, 2H), 6.13−6.11 (m, 1H), 5.15−5.13 (m, 1H), 3.77 (dd, J = 6.4, 4.0 Hz, 1H), 3.66−3.63 (m, 1H), 3.56−3.53 (m, 1H), 3.40 (dd, J = 6.4, 4.0 Hz, 1H), 3.20 (dd, J = 6.0, 2.4 Hz, 1H), 2.89−2.83 (m, 1H), 2.08 (ddd, J = 13.2, 3.2, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 161.4 (d, J = 243.4 Hz), 142.8, 140.9 (d, J = 3.1 Hz), 136.4, 135.9, 135.5, 129.3 (d, J = 8.4 Hz), 129.0, 128.4, 128.1, 128.0, 127.7, 127.1, 127.0, 126.4, 115.7 (d, J = 21.2 Hz), 76.6, 62.9, 54.9, 48.0, 42.6, 42.1, 41.4, 41.3; FT-IR ($CHCl_3$) 3020.3, 2914.2, 1772.5, 1508.2, 1226.6, 1157.2 cm^{-1}; HRMS (FAB) m/z (M + 1)$^+$ calcd for $C_{29}H_{23}BrFO_2$ 501.0865, found 501.0849.

9e. Prepared by using the same procedure as described for **9b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13−6.93 (m, 11H), 6.56−6.54 (m, 2H), 6.10−6.09 (m, 1H), 5.14−5.13 (m, 1H), 3.71 (dd, J = 5.6, 3.6 Hz, 1H), 3.64−3.62 (m, 2H), 3.48 (dd, J = 5.6, 3.6 Hz, 1H), 3.18−3.14 (m, 1H), 2.87−2.80 (m, 1H), 2.33 (s, 3H), 2.09 (ddd, J = 13.2, 2.8, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 143.2, 142.1, 136.3, 136.1, 135.5, 135.2, 129.3, 128.8, 128.4, 127.9, 127.8, 127.7, 127.5, 127.4, 126.8, 126.0, 76.7, 63.0, 54.0, 47.1, 42.7, 41.9, 41.4, 40.8, 21.1; FT-IR ($CHCl_3$) 3020.3, 2879.5, 1770.5, 1488.9, 1157.2, 1108.9 cm^{-1}; HRMS (FAB) m/z (M + 1)$^+$ calcd for $C_{30}H_{26}BrO_2$ 497.1116, found 497.1090.

9f. Prepared by using the same procedure as described for **9b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.24−7.14 (m, 1H), 7.10−6.98 (m, 7H), 6.59−6.57 (m, 1H), 6.14−6.13 (m, 1H), 5.16−5.15 (m, 1H), 3.80 (dd, J = 5.8, 3.6 Hz, 1H), 3.66 (d, J = 11.2 Hz, 1H), 3.59−3.56 (m, 1H), 3.48 (dd, J = 6.4, 4.0 Hz, 1H), 3.22−3.19 (m, 1H), 2.91−2.84 (m, 1H), 2.09 (ddd, J = 13.8, 2.2, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 149.3, 142.4, 136,4, 136.1, 135.2, 129.1, 129.0 (d, J = 31.8 Hz), 128.4, 128.2, 127.9, 127.7, 127.2, 126.9, 126.8 (q, J = 271 Hz), 126.6, 125.8 (q, J = 3.8 Hz), 125.4, 76.5, 62.8, 55.5, 47.8, 42.6, 42.0, 41.3, 41.2; FT-IR ($CHCl_3$) 3022.2, 2931.6, 1772.5, 1490.9, 1328.9, 1161.7, 1108.9 cm^{-1}; HRMS (FAB) m/z (M + 1)$^+$ calcd for $C_{30}H_{23}BrF_3O_2$ 551.0834, found 551.0843.

10a. A sealed tube was charged with **8** (100 mg, 0.226 mmol), 0.05 equiv of tetrakis(triphenylphosphine)palladium, tributylvinyltin (108 mg, 1.5 equiv), and toluene (1 mL) under an Ar atmosphere. After 22 h at 100 °C, the reaction mixture was filtered through a plug of Celite. The filterate was concentrated and chromatographed (hexanes/EtOAc = 9:1) to give 35 mg of **10a** (40% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 7.0 Hz, 1H), 7.20−7.13 (m, 2H), 7.02 (dd, J = 7.3, 1.8 Hz, 1H), 5.86−5.84 (m, 1H), 5.03−5.02 (m, 1H), 3.60−3.57 (m, 2H), 3.43 (s, 3H), 3.19−3.15 (m, 1H), 3.12−3.06 (m, 1H), 3.01−2.98 (m, 1H), 2.71−2.65 (m, 1H), 2.40 (ddd, J = 15.0, 8.8, 4.8 Hz, 1H), 1.92 (ddd, J = 13.2, 2.6, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 169.5, 137.4, 134.5, 132.7, 129.2, 128.0, 127.2, 127.0, 120.5, 76.5, 65.5, 52.1, 43.2, 43.0, 41.9, 37.9, 32.5, 28.1; FT-IR ($CHCl_3$) 2966.3, 1766.7, 1728.1, 1176.5 cm^{-1}; HRMS (FAB) m/z (M + 1)$^+$ calcd for $C_{19}H_{18}BrO_4$ 389.0388, found 407.0397.

4a. A solution of **3a** (20 mg, 0.06 mmol) in 10 mL of CH_2Cl_2/MeOH (1:1 v/v) was purged with O_3 at −78 °C. After 5 min, the reaction mixture was purged with Ar for 30 min and treated with dimethyl sulfide at −78 °C. The reaction mixture was warmed to 0 °C and stirred for 3 h. After concentration in vacuo, the residue was purified by column chromatography (hexanes/EtOAc = 4:1) to give 17 mg of **4a** (76% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (t, J = 1.2 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.32−7.24 (m, 2H), 7.08 (dd, J = 7.3, 1.5 Hz, 1H), 4.55 (dd, J = 3.3, 2.6 Hz, 1H), 3.80 (dt, J = 10.8, 2.0 Hz, 1H), 3.68−3.62 (m, 1H), 3.13 (dd, J = 5.6, 2.0 Hz, 1H), 2.98−2.84 (m, 2H), 2.81−2.63 (m, 2H), 2.32−2.22 (m, 1H), 2.00 (dt, J = 14.8, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2, 200.9, 167.4, 135.2, 133.5, 129.0, 128.2, 128.0, 126.4, 78.2, 60.6. 49.0, 42.3, 41.7, 38.0, 36.4, 22.5; FT-IR ($CHCl_3$) 2923.9, 2853.9, 1773.9, 1740.6, 1720.6, 1330.6, 1050.6 cm^{-1}; HRMS (FAB) m/z (M + 1)$^+$ calcd for $C_{17}H_{16}BrO_4$ 363.0232, found 363.0241.

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Supporting Information Available: Spectral data of **3a**−**h**, **9a**−**f**, **10a**, and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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