Regular Article

Bridged-Selective Intramolecular Diels–Alder Reactions in the Synthesis of Bicyclo[2.2.2]octanes

Mika Hanashima, Toshiki Matsumura, Yuta Asaji, Tomoyuki Yoshimura, and Jun-ichi Matsuo*

Division of Pharmaceutical Sciences, Graduate School of Medical Sciences, Kanazawa University, Kakuma-machi, Kanazawa, Ishikawa 920–1192, Japan.

Received July 20, 2020; accepted September 10, 2020

Regioselectivity for intramolecular Diels–Alder (IMDA) reactions of 6-acetoxy-6-alkenylcyclohexa-2,4-dien-1-ones that were formed by oxidation of 2-alkenylphenols with lead tetraacetate in acetic acid were studied. Bridged regioselectivity was observed in the IMDA reactions of 6-acetoxy-6-alkenylcyclohexa-2,4-dien-1-ones having a dienophile part which could conjugate with an aromatic group. Bridged seven- and eight-membered rings and bicyclo[2.2.2]octane skeletons were constructed by the present IMDA reactions. Density functional theory (DFT) calculations suggested that conjugation of the dienophile with neighboring aromatic groups lowered the highest occupied molecular orbital–lowest unoccupied molecular orbital (HOMO–LUMO) energy gap and preceded bridged [4 + 2] adducts.

Key words intramolecular Diels–Alder reaction; bridged regioselectivity; medium ring; bicyclo[2.2.2]octane; density functional theory (DFT) calculation

Introduction

Intramolecular Diels–Alder (IMDA) reactions^{1–6} are important reactions for organic synthesis of complex molecules having a six-membered ring with multiple stereogenic centers because of their predictable regiochemistry and stereochemistry. There are two modes in IMDA reactions, which give fused or bridged compounds (Chart 1).

Fused compounds are generally formed by IMDA reactions because of their straight arrangement between diene and dienophile parts.^{7–10} On the other hand, bridged compounds were obtained selectively in a few cases. Greuter reported that the IMDA reaction of (Z)-1 that was formed by isomerization (E)-1 gave a bridged seven-membered compound 2 in 35% yield as a main product along with a fused isomer 3 in 5% yield^{11–13} (Chart 2).

As another bridged-selective IMDA reaction, Cook and Danishefsky reported that oxidative dearomatization of a phenol^{14,15} in the presence of an allenyl alcohol gave a bridged compound 4 instead of a fused one 5¹⁶ (Chart 3). De Lera and colleagues proposed that stabilization of diradical species in the IMDA reaction was a key factor for the bridged selectivity.¹⁷

Although effects of a Lewis acid¹⁸ and effects of electronic factors¹⁹ for bridged selectivity have been reported, there has been limited information for favoring bridged products in IMDA reactions.²⁰ Here, we report the effects of the structure of the tether part between an alkene and a diene in 7, which were formed by oxidation of a 2-alkenyl phenol 6, in an IMDA reaction to a fused product 8 or a bridged one 9 (Chart 4).

Results and Discussion

Yates and Auksi reported that Wessely oxidation^{21–23} of 6a and 6b with Pb(OAc)₄ in acetic acid followed by IMDA reactions of 7a and 7b gave fused adducts 8a²⁴ and 8b¹⁸ in low yields (Table 1, entries 1 and 2). We investigated the effects of the length of a tether by using 2-alkenylphenol 6c. Wessely

oxidation of 6c was found to give the corresponding 7c in 28% yield (entry 3). However, an IMDA reaction of 7c gave complex mixtures probably due to flexibility of the tether part.

Next, IMDA reactions of phenols 6d, e, which had a 2-vinylphenyl group, were studied. Wessely oxidation of a phenol 6d at room temperature directly gave a fused Diels–Alder product 8d in 23% yield (entry 4). The corresponding dienone 7d and a bridged [4 + 2] adduct 9d were not obtained. The structure of 8d was determined unambiguously by its X-ray crystallography.²⁵ A one-carbon-homologated phenol 6e was oxidized to 7e and the IMDA reaction of 7e in refluxing xylenes gave a bridged product 9e in 73% yield without formation of a fused product 8e (entry 5). The structure of 9e was determined by heteronuclear multiple bond connectivity (HMBC) correlations.²⁵ Therefore, it was found that one-carbon homologation (7d to 7e) dramatically changed the fused or bridged selectivity in the IMDA reactions.

In order to study further effects of an extended tether, phenols 6f and 6g having a maleimide group and a 2-nitroethynyl group as a strong dienophile part were designed since difficulty of IMDA reactions of dienones 7 having a longer tether was expected (For structures of 6f and 6g, see Charts 5 and 6). Methoxy groups of 6g were introduced for synthesis of a colchicine²⁶-like structure, 8g or 9g.

Chart 1. Intramolecular Diels–Alder (IMDA) Reactions Affording Fused and Bridged Products

* To whom correspondence should be addressed. e-mail: jimatsuo@p.kanazawa-u.ac.jp

A phenol **6f** having a maleimide group was prepared as shown in Chart 5. Wittig reaction of aldehyde **10** with **11** gave a stilbene derivative **12** in 85% yield. Catalytic hydrogenation of **12** by H₂ and Pd/C or PtO₂ did not give a desired product **13**, but hydrogenation with TsNHNH₂/NaOAc afforded **13** in 90% yield.²⁷⁾ Heck reaction of aryl iodide **13** with maleimide gave a Heck product **14** in 29% yield by using 20 mol% of Pd(OAc)₂ and 20 mol% of DPEphos ((oxydi-2,1-phenylene)-

bis(diphenylphosphine)) in the presence of KOAc in ethylene carbonate.²⁸⁾ The use of dppe (ethylenebis(diphenylphosphine)) instead of DPEphos did not provide **14**. The low yield of **14** might result from a labile maleimide unit under the Heck reaction conditions. Removal of the *tert*-butyldimethylsilyl (TBS) group of **14** with HF-pyridine gave the phenol **15** in 95% yield.

Preparation of **6g** is shown in Chart 6. Wittig reaction of aldehyde **10** with **15** afforded a stilbene derivative **16** in 95%

Chart 2. A Bridged-Selective IMDA Reaction of (Z)-1

Chart 3. A Bridged-Selective IMDA Reaction Reported by Danishefsky *et al.*

Chart 4. Effects of the Tether Part for an IMDA Reaction of **7** to a Fused Product **8** or a Bridged One **9**

Chart 5. Preparation of **6f**

Table 1. Wessely Oxidation of **6** and IMDA Reactions of **7**

Entry	6	Ox cond.	7 (Yield) ^{a)}	DA cond.	8 or 9 (Yield) ^{a)}
1	6a	r.t., 12 h	Not isolated	Xylenes, reflux, 24 h	8a (28%) ^{b,c)}
2	6b	r.t., 24 h	7b (30%)	Xylenes, Δ	8b (16%) ^{d)}
3	6c	r.t., 24 h	7c (28%)	Neat, 170 °C, 20 h	complex
4	6d	r.t., 24 h	Not isolated	—	8d (23%) ^{c)}
5	6e	r.t., 1 h	7e (23%)	Xylenes, reflux, 16 h	9e (73%)

a) Isolated yield. b) Ref. 24. c) Yield for two steps. d) Ref. 18.

yield. Reduction of **16** using TsNHNH_2 and NaOAc gave a 1,2-diphenylethane **17** in 91% yield.²⁷⁾ Halogen-lithium exchange followed by a reaction with *N,N*-dimethylformamide (DMF) gave an aldehyde **18**. Nitro aldol reaction of **18** with nitromethane provided a nitroalkene **19** in 40% in two steps. Removal of the TBS group of **19** with tetrabutylammonium fluoride (TBAF) gave **6g** quantitatively.

With phenols **6f,g** having strong dienophiles in hand, fused/bridged regioselectivity in their IMDA reactions were investigated. Oxidation of **6f** with $\text{Pb}(\text{OAc})_4$ in AcOH afforded an acetoxy-2,4-cyclohexadien-1-one **7f** in 34% yield (Chart 7). The IMDA reaction of **7f** at 170°C for 3.5 h without using a solvent gave a bridged [4 + 2] adduct **9f** in 52% yield, and a fused adduct **8f** was not detected. The structure of **9f** was determined by HMBC correlations and nuclear Overhauser effect (NOE).²⁵⁾

Wessely oxidation of **6g** with $\text{Pb}(\text{OAc})_4$ gave dienone **7g** in 43% yield (Table 2). However, the IMDA reaction of **7g** did

Chart 6. Preparation of **6g** Chart 7. Wessely Oxidation of **6f** and the IMDA Reaction of **7f**Table 2. The IMDA Reaction of **7g**

Entry	Conditions	8g or 9g (Yield) ^{a)}
1	Neat, 165°C , 3 h	0
2	20 ^{b)} (20 mol%), toluene, reflux, 3 d	0
3	$\text{CF}_3\text{CH}_2\text{OH}$, 130°C , MW, 18 h	9g (25%)
4	$\text{CF}_3\text{CF}_2\text{CH}_2\text{OH}$, 130°C , MW, 18 h	9g (21%)
5	$(\text{CF}_3)_2\text{CHOH}$, 130°C , MW, 18 h	9g (12%)

a) Isolated yield. b)

not proceed at 165°C (entry 1). Attempted activation of the nitro group with a thiourea catalyst **20**^{29,30)} was not effective (entry 2). Danishefsky and colleagues reported that the use of 2,2,2-trifluoroethanol as a solvent improved the efficiency of Diels–Alder reactions of nitroalkenes.³¹⁾ Investigation of the effects of some fluoroalkyl alcohols as solvents revealed that 2,2,2-trifluoroethanol was the most effective for the IMDA reaction of **7g** (entry 3). In this case, a bridged IMDA product **9g** was formed selectively, and 19% of the starting material **7g** was recovered with many unidentified byproducts. It was assumed that 2,2,2-trifluoroethanol activated the nitro group of **7g** by its hydrogen bond.

Experimental results showed that the IMDA reaction of compound **7d** that had no methylene unit between a 2-vinyl-phenyl group and a dienone group gave the fused compound **8d** selectively, while the IMDA reaction of compounds **7e–g** that had the one or two methylene units afforded bridged compounds **9e–g**. In order to clarify the reason for the change of selectivity, density functional theory (DFT) calculations (B3LYP/6-31(d,p) or B3LYP/6-31G(d))^{32,33)} of IMDA reactions of **7d**, **e**, **b**, **f** were performed (Fig. 1). DFT calculation (B3LYP/6-31(d,p)) of the IMDA reaction of **7d** to the fused compound **8d** or the bridged compound **9d** is shown in Fig. 1(a). TS **21**, which gives fused **8d**, is 6.7 kcal/mol lower than TS **22**, which gives bridged **9d**. The fused compound **8d** is thermodynamically stable in 7.2 kcal/mol compared with the bridged compound **9d**. Therefore, the reaction path from **7d** to fused **8d** is preferred both in kinetic and thermodynamic aspects. In fact, the fused compound **8d** was selectively formed from **7d** (Table 1, entry 4).

DFT calculation (B3LYP/6-31(d)) of the IMDA reactions

Fig. 1. DFT Calculations of IMDA Reactions of **7d**, **e**, **b**, **f**

of **7e** indicated that TS **23**, which gives the fused compound **8e**, is less stable (2.2 kcal/mol) than TS **24**, which gives the bridged product **9e** (Fig. 1(b)). It was also pointed out that fused **8e** is more stable (5.5 kcal/mol) than bridged **9e**. The experimental result of selective formation of the bridged product **9e** from **7e** (Table 1, entry 5) suggests that the reaction path is kinetically controlled, reflecting the lower energy of TS **24**.

Judging from the result of DFT calculation (B3LYP/6-31(d)) of the IMDA reaction of **7b** (Fig. 1(c)), it is expected that a fused product **8b** would be preferably formed rather than a bridged product **9b** since TS **25**, which gives **8b**, is favored by 3.5 kcal/mol than TS **26**. This calculation is supported by the experimental result that the IMDA reaction of **7b** gave **8b** in 16% yield and **9b** was not isolated (Table 1, entry 2).¹⁸⁾ Therefore, experimental results and the calculations of IMDA reactions of **7b** and **7e** suggest that the presence of the phenyl ring in the tether structure of **7e** is important for favoring bridged selectivity through TS **24**.

As in the case of **7e**, DFT calculation (B3LYP/6-31(d)) of the IMDA reaction of **7f** (Fig. 1(d)) pointed out that TS **28**, which gives the bridged product **9f**, is lower in 3.7 kcal/mol than TS **27**, which gives a fused compound **8f**. The experimental result showing selective formation of **9f** (Chart 7) reflects the lower energy of TS **28**. In TS **28**, the phenyl group and the maleimide group have a highly co-planar conformation (see Supplementary Material, Figure S12), while these two groups are twisted in TS **27** (see Supplementary Material, Figure S11). Conjugation between the phenyl and maleimide groups lowers the lowest unoccupied molecular orbital (LUMO) energy of TS **28**, and this results in lowering the highest occupied

molecular orbital (HOMO)-LUMO energy gap for IMDA reactions. Similar conjugation between the phenyl group and the dienophile is considered in TS **24** from compound **7e**. However, in the case of **7d**, conjugation of the vinyl group with the phenyl group was difficult both in TS **21** and TS **22** because of their restricted transition states.

Conclusion

In conclusion, we found that the presence of a phenyl ring which could conjugate a dienophile part favored bridged-selective IMDA reactions of alkenyl dienones formed by oxidation of 2-alkenylphenols except in the case of a short tether. DFT calculations suggested that a transition state that gave a bridged product had a co-planar conformation between a phenyl ring and a dienophile part, and conjugation of the two co-planar groups lowered the HOMO-LUMO energy gap for IMDA reactions. Bridged-selective construction of an eight-membered ring in **9f**, **g** was performed by IMDA reactions. These results will help in the planning of bridged-selective IMDA reactions for synthesis of complex molecules.

Experimental

General All melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on Horiba IR-710. ¹H-NMR spectra were recorded on a JEOL JNM ECA600 (600 MHz) or a JEOL JNM ECS400 (400 MHz) spectrometer at room temperature (r.t.); chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; sept, septet; m, mul-

tiptet; br, broad. ^{13}C -NMR spectra were recorded on a JEOL JNM ECA600 (150 MHz) or a JEOL JNM ECS400 (100 MHz) spectrometer with complete proton decoupling. chemical shifts are reported in parts per million relative to tetramethylsilane with the solvent resonance as the internal standard CDCl_3 . High resolution (HR)MS were recorded on a JEOL JMS-T100TD. X-ray crystallographic analysis was performed on Rigaku R-Axis RAPIDII-S. Analytical TLC was performed on Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Silica gel column chromatography was carried out on silica gel 60N (Kanto Kagaku Co., Ltd., spherical neutral, 63–210 or 40–50 μm). Preparative thin-layer chromatography (PTLC) was carried out on silica gel Wakogel B-5F. All reactions were carried out under nitrogen in dried glassware with magnetic stirring. Microwave experiments were carried out in sealed vessels in a synthesis reactor (Biotage Initiator 2.5). Compounds **6b,c** were prepared by the reported method.³⁴⁾

Synthesis of 2-(2-Vinylphenyl)phenol (6d)³⁵⁾ To a cooled suspension of methyltriphenylphosphonium iodide (128 mg, 0.318 mmol) in tetrahydrofuran (THF) (3 mL) at 0 °C was added potassium *tert*-butoxide (56 mg, 0.50 mmol) under nitrogen. After 30 min, 6*H*-benzo[*c*]chromen-6-one³⁶⁾ (25 mg, 0.15 mmol) which was prepared from phenyl 2-bromobenzoate was added. The reaction was warmed to r.t. and the mixture was stirred for 15 h. After dropping 1 *N* HCl until pH below 7, the aqueous phase was separated and extracted with DCM. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (Hexane/EtOAc) to give the product **6d** (20 mg, 0.12 mmol, 81%). Compound **6d**: ^1H -NMR (CDCl_3 , 400 MHz) δ : 7.72 (1H, d, J = 7.2 Hz), 7.49–7.20 (4H, m), 7.13 (1H, d, J = 6.8 Hz), 6.99 (2H, d, J = 6.8 Hz), 6.56 (1H, dd, J = 17.6, 11.2 Hz), 5.75 (1H, d, J = 17.6 Hz), 5.22 (1H, d, J = 11.2 Hz), 4.80 (1H, s); ^{13}C -NMR (CDCl_3 , 100 MHz) δ : 152.6, 136.7, 134.9, 134.4, 130.9, 130.7, 129.4, 128.6, 128.4, 126.7, 125.6, 120.5, 115.9, 115.5.

Synthesis of 2-(2-Vinylbenzyl)-1-(*tert*-butyldimethylsilyloxy)benzene (6e) A mixture of 1-bromomethyl-2-*tert*-butyldimethylsilyloxybenzene (1.38 g, 4.59 mmol), 2-formylphenylboronic acid (688 mg, 4.59 mmol), $\text{Pd}(\text{PPh}_3)_4$ (133 mg, 0.115 mmol), K_2CO_3 (1.90 g, 13.8 mmol) in THF (15 mL) was heated at 95 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted by adding H_2O and ethyl acetate. The mixture was extracted with ethyl acetate (three times), and the combined organic extracts were dried over anhydrous Na_2SO_4 , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (hexanes/ethyl acetate = 10:1) to afford 2-(2-((*tert*-butyldimethylsilyloxy)benzyl)benzaldehyde (**29**) (1.20 g, 3.68 mmol, 80%). Compound **29**: ^1H -NMR (CDCl_3 , 600 MHz) δ : 10.26 (1H, s), 7.88 (1H, d, J = 7.6 Hz), 7.49 (1H, t, J = 6.8 Hz), 7.39 (1H, t, J = 7.2 Hz), 7.15–7.10 (2H, m), 6.85–6.83 (3H, m), 4.00 (2H, s), 0.92 (9H, s), 0.23 (6H, s); ^{13}C -NMR (CDCl_3 , 150 MHz) δ : 192.4, 153.3, 143.2, 134.0, 133.8, 131.1, 131.0, 130.7, 130.5, 127.4, 126.7, 121.2, 118.3, 32.6, 25.7, 18.2, –4.2; IR (CHCl_3 , cm^{-1}): 2958, 2931, 2860, 1693; HRMS (DART+): m/z [$\text{M} + \text{H}$] $^+$ Calcd for $\text{C}_{20}\text{H}_{26}\text{O}_2\text{Si}$: 327.17803. Found: 327.17867.

To a stirred mixture of methyltriphenylphosphonium iodide (1.95 g, 4.82 mmol), *t*-BuOK (800 mg, 7.13 mmol) in THF (50 mL) was added a solution of **29** (750 mg, 2.30 mmol) in THF (30 mL) at 0 °C for 4 h. The reaction was quenched by

addition of a solution of hydrochloric acid (<pH 7.0), and the mixture was extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (hexanes) to afford the corresponding Wittig product (528 mg, 1.63 mmol, 71%).

To a stirred solution of the Wittig product (500 mg, 1.54 mmol) in THF (10 mL) was added a solution of TBAF in THF (1.0 M, 2.3 mL, 2.3 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 25 min. The reaction was quenched by adding a solution of saturated aqueous NH_4Cl . The resulting mixture was extracted with ethyl acetate (three times), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated. The crude product was purified by column chromatography on silica gel (hexanes/ethyl acetate = 10:1) to afford **6e** (364 mg, 1.17 mmol, 76%). Compound **6e**: ^1H -NMR (CDCl_3 , 600 MHz) δ : 7.42 (1H, d, J = 7.2 Hz), 7.15–7.07 (2H, m), 7.01–6.95 (2H, m), 6.86 (1H, dd, J = 17.4, 11.4 Hz), 6.78 (1H, d, J = 7.2 Hz), 6.73 (1H, t, J = 7.8 Hz), 6.65 (1H, d, J = 8.4 Hz), 5.53 (1H, d, J = 17.4 Hz), 5.15 (1H, d, J = 11.4 Hz), 4.73 (1H, s), 3.92 (2H, s); ^{13}C -NMR (CDCl_3 , 150 MHz) δ : 153.4, 137.1, 136.6, 134.5, 130.5, 129.8, 128.0, 127.6, 126.8, 126.5, 126.0, 120.9, 116.0, 115.3, 33.0; IR (CHCl_3 , cm^{-1}): 3597, 3010; HRMS (DART+): m/z [$\text{M} + \text{H}$] $^+$ Calcd for $\text{C}_{14}\text{H}_{13}\text{O}_1$: 197.09664. Found: 197.09670.

The IMDA Reaction of 6d to 8d (Table 1, Entry 4) To a solution of **6d** (68 mg, 0.35 mmol) in AcOH (3 mL) was added $\text{Pb}(\text{OAc})_4$ (922 mg, 2.08 mmol) at 0 °C, and the reaction temperature was allowed to reach room temperature. After 72 h, the precipitate was filtered off with EtOAc, and the filtrate was washed with saturated aqueous solution of NaHCO_3 . The organic phase was dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (EtOAc/Hexane) to yield **8d** (21 mg, 0.08 mmol, 23%) as a yellow solid. Compound **8d**: mp: 128.0–129.0 °C (recryst. from CH_2Cl_2); ^1H -NMR (CDCl_3 , 600 MHz) δ : 7.26–7.18 (4H, m), 6.59 (1H, t, J = 6.0 Hz), 6.39 (1H, t, J = 6.6 Hz), 4.38–4.35 (1H, m), 3.42–4.39 (1H, m), 3.27–3.22 (1H, m), 2.16 (3H, s), 1.89–1.88 (2H, m); ^{13}C -NMR (CDCl_3 , 150 MHz) δ : 202.3, 169.2, 146.2, 139.3, 132.3, 131.5, 129.0, 127.2, 123.6, 122.6, 85.5, 52.1, 51.0, 38.4, 37.6, 21.5; IR (CHCl_3 , cm^{-1}): 2951, 1738; HRMS (DART+): m/z [$\text{M} + \text{H}$] $^+$ Calcd for $\text{C}_{16}\text{H}_{15}\text{O}_3$: 255.10212. Found: 255.10187.

6-Acetoxy-6-(2-vinylbenzyl)cyclohexa-2,4-dien-1-one (7e) To a solution of **6e** (54 mg, 0.24 mmol) in AcOH (1 mL) was added $\text{Pb}(\text{OAc})_4$ (317 mg, 0.715 mmol) at 0 °C, and the reaction temperature was allowed to reach room temperature. After 1 h, the precipitate was filtered off with EtOAc, and the filtrate was washed with saturated aqueous solution of NaHCO_3 . The organic phase was dried over anhydrous Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (EtOAc/Hexane/1% triethylammonium acetate (TEA)) to yield **7e** (15 mg, 0.055 mmol, 23%) as a yellow oil. Compound **7e**: ^1H -NMR (CDCl_3 , 600 MHz) δ : 7.52 (1H, d, J = 7.8 Hz), 7.19 (2H, d, J = 4.2 Hz), 7.11–7.06 (2H, m), 6.97–6.94 (1H, m), 6.27–6.25 (1H, m), 6.18 (1H, d, J = 9.6 Hz), 6.07 (1H, d, J = 9.0 Hz), 5.63 (1H, d, J = 16.8 Hz), 5.23 (1H, d, J = 10.8 Hz), 3.15 (1H, d, J = 13.8 Hz), 3.06 (1H, d, J = 13.8 Hz), 2.08 (3H, s); ^{13}C -NMR (CDCl_3 , 150 MHz) δ : 198.4, 169.3, 141.2, 140.5, 138.3, 135.3, 135.2, 132.3, 131.3, 127.7, 127.1, 125.9, 123.0, 115.8, 81.3, 40.1, 20.5;

IR (CHCl₃, cm⁻¹): 2927, 2856, 1739, 1676; HRMS (DART+): *m/z* [M + H]⁺ Calcd for C₁₇H₁₇O₃: 269.11777. Found: 269.11855.

The IMDA Reaction of 7e to 9e (Table 1, Entry 5) A solution of **7e** (59 mg, 0.22 mmol) in xylenes (1 mL) was refluxed for 16 h. After cooling to room temperature, the crude products were purified by column chromatography on silica gel (EtOAc/Hexane) to provide the product **9e** (43 mg, 0.16 mmol, 52%). Compound **9e**: mp: 97.5–98.5 °C (recryst. from CH₂Cl₂); ¹H-NMR (CDCl₃, 600 MHz) δ: 7.14–7.06 (4H, m), 6.66 (1H, t, *J* = 7.2 Hz), 6.21 (1H, t, *J* = 7.2 Hz), 4.28 (1H, d, *J* = 15.6), 3.86 (1H, t, *J* = 5.4 Hz), 3.56 (1H, t, *J* = 6.0 Hz), 3.15 (1H, d, *J* = 16.2 Hz), 2.99 (1H, dd, *J* = 10.2, 4.8 Hz), 2.29 (1H, dd, *J* = 13.2, 4.2 Hz), 2.12 (3H, s), 1.84 (1H, dd, *J* = 11.4, 12.6 Hz); ¹³C-NMR (CDCl₃, 150 MHz) δ: 203.1, 170.4, 144.3, 139.7, 134.9, 130.4, 128.1, 126.8, 126.6, 126.0, 80.8, 57.0, 43.7, 38.9, 36.3, 32.4, 22.0; IR (CHCl₃, cm⁻¹): 3024, 1736; HRMS (DART+): *m/z* [M + H]⁺ Calcd for C₁₇H₁₇O₃: 269.11777. Found: 269.11805.

1-(tert-Butyldimethylsilyloxy)-2-(2-iodostyryl)benzene (12) To a cooled suspension of triphenyl(2-vinylbenzyl)-phosphonium bromide (5.19 g, 9.28 mmol) in THF (46 mL) at 0 °C was added potassium *tert*-butoxide (1.21 g, 10.8 mmol) under argon. After 30 min, 2-*tert*-butyldimethylsilyloxybenzaldehyde **10** (1.83 g, 7.73 mmol) was added over 10 min. The reaction temperature was warmed to r.t. and the mixture was stirred for 12 h. After adding water (30 mL) slowly, the aqueous phase was separated and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (Hexane) to give the product **12** (2.77 g, 6.34 mmol, 82%, a mixture of (*E*)- and (*Z*)-**12**) as a yellow oil. Compound **12**: ¹H-NMR (CDCl₃, 600 MHz, *E/Z* = 5:1, data of (*E*)-**12** is shown here) δ: 7.87 (1H, d, *J* = 9.0 Hz), 7.69 (1H, d, *J* = 7.2 Hz), 7.60 (1H, d, *J* = 7.8 Hz), 7.37 (1H, d, *J* = 10.8 Hz), 7.34 (1H, dd, *J* = 7.8, 7.8 Hz), 7.24 (1H, d, *J* = 16.2 Hz), 7.17 (1H, dd, *J* = 6.6, 6.6 Hz), 7.00 (1H, dd, *J* = 7.8, 7.8 Hz), 6.94 (1H, dd, *J* = 6.6, 6.6 Hz), 6.84 (1H, d, *J* = 8.4 Hz), 1.04 (9H, s), 0.24 (6H, s); ¹³C-NMR (CDCl₃, 150 MHz, data of (*E*)-**12** is shown here) δ: 153.3, 140.7, 139.6, 131.9, 128.9, 128.7, 128.4, 126.7, 126.4, 126.0, 121.6, 119.7, 100.5, 25.8, 18.3, -4.1; IR (neat, cm⁻¹): 1597, 1252, 1011; HRMS (DART+): *m/z* [M + H]⁺ Calcd for C₂₀H₂₆IOSi: 437.07976. Found: 437.08039.

1-(tert-Butyldimethylsilyloxy)-2-(2-iodophenethyl)benzene (13) Tosylhydrazide (50 mg, 0.12 mmol) and sodium acetate (47 mg, 0.57 mmol) were added to a solution of **12** (50 mg, 0.12 mmol) in EtOH (0.5 mL). The mixture was refluxed for 2 h with stirring. When the reaction was complete, the mixture was cooled to room temperature. The mixture was diluted with Et₂O (5 mL) and washed with saturated solution of NaHCO₃ and brine. The organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/hexane) to give **13** (45.6 mg, 0.104 mmol, 90%) as a yellow oil. Compound **13**: ¹H-NMR (CDCl₃, 600 MHz) δ: 7.82 (1H, d, *J* = 7.8 Hz), 7.23 (1H, dd, *J* = 7.2, 7.2 Hz), 7.14 (1H, d, *J* = 6.0 Hz), 7.13 (1H, d, *J* = 7.8 Hz), 6.89–6.84 (2H, m), 6.81 (1H, d, *J* = 7.8 Hz), 2.98 (2H, dd, *J* = 10.8, 9.0 Hz), 2.87 (2H, dd, *J* = 10.8, 9.0 Hz), 1.03 (9H, s), 0.26 (6H, s); ¹³C-NMR (CDCl₃, 150 MHz) δ: 153.6, 144.5, 139.4, 131.7, 130.4, 129.4, 128.4, 128.2, 127.7, 127.0, 120.1, 118.4, 100.8, 41.2, 30.9, 25.9, 18.3, -4.1; IR (neat,

cm⁻¹): 1252, 1011; HRMS (DART+): *m/z* [M + H]⁺ Calcd for C₂₀H₂₈IOSi: 439.09541. Found: 439.09442.

3-(2-(2-((tert-Butyldimethylsilyloxy)phenethyl)phenyl)-1-phenyl-1*H*-pyrrole-2,5-dione (14) A dry 30 mL flask containing a magnetic stirring bar was charged with **13** (900 mg, 2.05 mmol), Pd(OAc)₂ (92 mg, 0.41 mmol), DPEphos (221 mg, 0.410 mmol), *N*-phenylmaleimide (1.78 g, 2.05 mmol), KOAc (604 mg, 6.15 mmol) and dry ethylene carbonate (5.4 g). The mixture was stirred at 60 °C for 6 h, and the mixture was cooled to room temperature. The crude product was purified by column chromatography on silica gel (EtOAc/Hexane) to give **14** (259 mg, 0.59 mmol, 29%) as a yellow oil. Compound **14**: ¹H-NMR (CDCl₃, 600 MHz) δ: 7.48 (2H, dd, *J* = 9.0, 9.0 Hz), 7.41–7.28 (7H, m), 7.07–7.04 (1H, m), 6.82–6.75 (3H, m), 3.03 (2H, t, *J* = 7.2 Hz), 2.90 (2H, t, *J* = 7.2 Hz), 0.99 (9H, s), 0.21 (6H, s); ¹³C-NMR (CDCl₃, 150 MHz) δ: 169.2, 169.1, 153.7, 145.7, 141.3, 131.7, 131.3, 130.6, 130.40, 130.35, 130.12, 130.09, 129.6, 129.0, 128.4, 128.2, 128.0, 127.6, 127.55, 127.46, 126.03, 125.91, 33.4, 32.6, 29.7, 25.8, 18.2, -4.1; IR (CHCl₃, cm⁻¹): 3473, 1768, 1714, 1623, 1598, 1502, 1257; HRMS (DART+): *m/z* [M + H]⁺ Calcd for C₃₀H₃₄NO₃Si: 484.23079. Found: 484.23058.

3-(2-(2-Hydroxyphenethyl)phenyl)-1-phenyl-1*H*-pyrrole-2,5-dione (6f) To a solution of **14** (50 mg, 0.10 mmol) in THF (1 mL) was added pyridine (0.15 mL) and HF-pyridine (0.15 mL) at 0 °C. The solution was stirred at 0 °C for 3 h. The reaction mixture was diluted with EtOAc and H₂O. The organic phase was washed with a saturated aqueous solution of NH₄Cl, a saturated aqueous solution of NaHCO₃, and brine. After the organic phase was concentrated under reduced pressure, the crude product was purified by column chromatography on silica gel (EtOAc/hexane) to yield **6f** (35 mg, 0.095 mmol, 95%) as a yellow oil. Compound **6f**: ¹H-NMR (CDCl₃, 600 MHz) δ: 7.49 (2H, dd, *J* = 9.0, 9.0 Hz), 7.45–7.37 (6H, m), 7.33–7.30 (1H, m), 7.07 (1H, dd, *J* = 9.0, 9.0 Hz), 7.00 (1H, dd, *J* = 7.2, 1.8 Hz), 6.82 (1H, dd, *J* = 6.6, 6.6 Hz), 6.69 (1H, s), 6.69 (1H, d, *J* = 6.6 Hz), 5.00 (1H, s), 3.00 (2H, dd, *J* = 10.2, 9.0 Hz), 2.90 (2H, dd, *J* = 10.8, 9.0 Hz); ¹³C-NMR (CDCl₃, 150 MHz) δ: 169.7, 169.6, 153.7, 145.5, 141.3, 131.6, 130.7, 130.45, 130.41, 130.3, 129.1, 128.6, 128.0, 127.8, 127.7, 127.1, 126.2, 126.0, 120.8, 115.3, 34.2, 33.0; IR (CHCl₃, cm⁻¹): 3588, 3473, 3286, 1770, 1712, 1596, 1502; HRMS (DART+): *m/z* [M + H]⁺ Calcd for C₂₄H₂₀NO₃: 370.14432. Found: 370.14448.

The Wessely Oxidation of 6f to 7f (Chart 7) To a solution of **6f** (98 mg, 0.26 mmol) in AcOH (4 mL) was added Pb(OAc)₄ (235 mg, 0.529 mmol) at 0 °C, and the reaction temperature was allowed to reach room temperature. After 30 min, the precipitate was filtered off with EtOAc, and the filtrate was washed with saturated aqueous solution of NaHCO₃. The organic phase was dried over anhydrous MgSO₄, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (EtOAc/Hexane) to yield **7f** (39 mg, 0.090 mmol, 34%) as a yellow oil. Compound **7f**: ¹H-NMR (CDCl₃, 600 MHz) δ: 7.52–7.50 (2H, m), 7.47–7.45 (2H, m), 7.41–7.39 (3H, m), 7.33–7.29 (2H, m), 6.77 (1H, s), 6.31–6.26 (2H, m), 6.15 (1H, d, *J* = 10.2 Hz), 2.82 (1H, ddd, *J* = 13.2, 13.2, 4.8 Hz), 2.73 (1H, ddd, *J* = 13.2, 13.2, 4.8 Hz), 2.14–2.07 (1H, m), 2.11 (3H, s); ¹³C-NMR (CDCl₃, 150 MHz) δ: 169.5, 169.4, 169.0, 145.6, 141.0, 140.5, 140.0, 130.6, 130.5, 130.0, 129.1, 128.6, 128.0, 127.9, 126.8, 126.6, 126.1, 123.0,

81.1, 39.0, 26.5, 20.4; IR (CHCl₃, cm⁻¹): 3473, 1770, 1737, 1716, 1675, 1502, 1390; HRMS (DART+): *m/z* [M + H]⁺ Calcd for C₂₆H₂₂NO₅: 428.14980. Found: 428.15020.

The IMDA Reaction of 7f to 9f (Chart 7) Compound **7f** (38 mg, 0.089 mmol) was heated at 170 °C in a vial without any solvent for 3.5 h. After cooling to room temperature, the crude products were purified by column chromatography on silica gel (EtOAc/Hexane) to provide the product **9f** (20 mg, 0.047 mmol, 52%). Compound **9f**: mp: 284.0–285.0 °C (recryst. from CH₂Cl₂); ¹H-NMR (CDCl₃, 600 MHz) δ: 8.61 (1H, d, *J* = 10.8 Hz), 7.49–7.47 (2H, m), 7.44–7.41 (1H, m), 7.34 (1H, dd, *J* = 7.2, 7.2 Hz), 7.27–7.20 (3H, m), 7.13 (1H, d, *J* = 7.8 Hz), 6.56 (1H, dd, *J* = 6.6, 6.6 Hz), 6.34 (1H, ddd, *J* = 7.8, 7.8, 1.2 Hz), 5.06 (1H, ddd, *J* = 5.1, 5.1, 1.8 Hz), 4.76 (1H, d, *J* = 4.2 Hz), 3.79 (1H, d, *J* = 6.0 Hz), 3.70–3.64 (1H, m), 3.17 (1H, ddd, *J* = 12.0, 6.6, 2.4 Hz), 2.92 (1H, ddd, *J* = 20.8, 6.6, 2.4 Hz), 2.73 (1H, ddd, *J* = 13.2, 13.2, 4.8 Hz), 2.36 (1H, ddd, *J* = 13.2, 13.2, 6.0 Hz), 2.00 (3H, s); ¹³C-NMR (CDCl₃, 150 MHz) δ: 201.0, 176.0, 174.0, 169.7, 136.5, 136.3, 134.6, 133.9, 131.5, 129.3, 129.1, 128.9, 128.5, 128.1, 126.5, 126.3, 79.6, 60.3, 51.4, 43.6, 39.2, 34.3, 33.9, 22.1; IR (CHCl₃, cm⁻¹): 3477, 1779, 1737, 1712, 1498, 1386; HRMS (DART+): *m/z* [M + H]⁺ Calcd for C₂₆H₂₂NO₅: 428.14980. Found: 428.14995.

***tert*-Butyl(2-(2-iodo-3,4,5-trimethoxystyryl)phenoxy)dimethylsilane (16)** To triphenylphosphine (2.1 g, 11 mmol) in a flask under a nitrogen atmosphere and heated to 100 °C in oil bath was added 1-(bromomethyl)-2-iodo-3,4,5-trimethoxybenzene (1.9 g, 4.9 mmol). After 10 min, to this was added CH₂Cl₂, and the mixture was concentrated, then filtered and washed extensively with EtOAc and CHCl₃ to yield the phosphonium salt (2.8 g, 4.8 mmol, 97%) as a white solid. mp: 224.0–225.0 °C (recryst. from CH₂Cl₂); ¹H-NMR (CDCl₃, 600 MHz) δ: 7.56–7.89 (15H, m), 7.16 (1H, brs), 5.54–5.79 (2H, brm), 3.84 (3H, brd, *J* = 1.4 Hz), 3.72 (3H, brd, *J* = 1.4 Hz), 3.58 (3H, brd, *J* = 2.1 Hz); ¹³C-NMR (CDCl₃, 150 MHz) δ: 142.2, 135.2, 134.5, 130.2, 125.6, 117.5, 117.0, 112.3, 92.8, 61.1, 60.6, 56.4, 35.6; IR (neat, cm⁻¹): 2939, 2854, 1482, 1483; HRMS (DART+): *m/z* [M-C₁₀H₁₂O₃I]⁺ Calcd for C₁₈H₁₆P: 263.0990. Found: 263.0980.

To a cooled suspension of a phosphonium bromide (2.0 g, 3.1 mmol) in THF (15 mL) was added potassium *tert*-butoxide (404 mg, 3.60 mmol) under nitrogen at 0 °C. After stirring the mixture for 30 min, 2-*tert*-butyldimethylsiloxybenzaldehyde **10** (607 mg, 2.57 mmol) was added over 10 min. The reaction temperature was warmed to room temperature and the mixture was stirred for 12 h. After adding water (30 mL), the aqueous phase was separated and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (Hexane) to give **16** (1.29 g, 2.44 mmol, 95%, a mixture of (*E*)-**16** and (*Z*)-**16**) as a colourless oil. Compound **16**: ¹H-NMR (CDCl₃, 400 MHz) δ: 7.71 (0.4H, d, *J* = 8.0 Hz), 7.32 (0.8H, s), 7.17 (0.4H, t, *J* = 8.0 Hz), 6.96–7.11 (2.0H, m), 6.66–6.86 (2.2H, m), 6.51–6.60 (1.2H, m), 3.90 (5.4H, s), 3.87 (1.8H, s), 3.42 (1.8H, s), 1.06 (3.6H, s), 1.02 (5.4H, s), 0.25 (2.4H, s), 0.24 (s, 3.6H); ¹³C-NMR (CDCl₃, 150 MHz) δ: 153.8, 153.6, 153.1, 153.0, 141.6, 141.0, 136.5, 133.1, 131.9, 130.5, 128.9, 128.5, 128.2, 127.9, 127.1, 126.1, 125.6, 121.6, 120.9, 119.5, 109.6, 104.9, 88.9, 87.8, 61.1, 61.0, 60.8, 60.7, 55.9, 55.6, 25.9, 25.8,

18.3, 4.08, -4.08, -4.22; IR (neat, cm⁻¹): 2932, 2856, 1596, 1255; HRMS (DART+): *m/z* [M + H]⁺ Calcd for C₂₃H₃₂IO₄Si: 527.1115. Found: 527.1106.

***tert*-Butyl(2-(2-iodo-3,4,5-trimethoxyphenethyl)phenoxy)dimethylsilane (17)** Tosylhydrazide (1.04 g, 5.58 mmol) and sodium acetate (1.21 g, 14.0 mmol) were added to a solution of **16** (1.47 g, 2.79 mmol) in EtOH (13 mL), and the mixture was refluxed for 4 h. The reaction temperature was cooled to room temperature, and the mixture was diluted with Et₂O. The mixture was washed with saturated aqueous solution of NaHCO₃ and brine. The organic phase was dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The products were purified by column chromatography on silica gel (EtOAc/Hexane) to give **17** (1.34 g, 2.54 mmol, 91%) as a colourless oil. Compound **17**: ¹H-NMR (CDCl₃, 600 MHz) δ: 7.13–7.18 (1H, m), 7.06–7.11 (m, 1H), 6.85–6.90 (m, 1H), 6.79–6.83 (1H, m), 6.51 (1H, s), 3.88 (3H, s), 3.86 (3H, s), 3.74 (3H, s), 2.95–3.02 (2H, m), 2.82–2.89 (2H, m), 1.05 (9H, s), 0.27 (6H, s); ¹³C-NMR (CDCl₃, 150 MHz) δ: 153.6, 153.3, 153.0, 140.3, 131.7, 130.6, 127.0, 121.1, 118.4, 108.8, 88.1, 61.0, 60.7, 55.9, 41.5, 31.0, 25.9, 18.3, -4.05; IR (CHCl₃, cm⁻¹): 2932, 2856, 1252; HRMS (DART+): *m/z* [M + H]⁺ Calcd for C₂₃H₃₄IO₄Si: 529.1271. Found: 529.1270.

6-(2-((*tert*-Butyldimethylsilyloxy)phenethyl)-2,3,4-trimethoxybenzaldehyde (18) To a solution of **17** (500 mg, 0.95 mmol) in THF (10 mL) was added a solution of *n*-butyllithium (1.62 M in hexane, 1.46 mL, 2.37 mmol) dropwise at -78 °C. After stirring for 30 min at -78 °C, anhydrous DMF (0.73 mL, 9.5 mmol) was added dropwise. The reaction mixture was stirred for another 1 h at -78 °C. The reaction was warmed to room temperature and stirred for another 2 h, followed by the addition of 3M HCl (3 mL). The resulting mixture was extracted with Et₂O, and the organic extracts were washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/Hexane) to afford compound **18** which was not completely pure. The crude product **18** was used without further purification in the next step.

(*E*)-*tert*-Butyldimethyl(2-(3,4,5-trimethoxy-2-(2-nitrovinyl)phenethyl)phenoxy)silane (19) The mixture of the crude **18**, nitromethane (3.62 g, 59.4 mmol) and ammonium acetate (15 mg, 0.19 mmol) was stirred at 100 °C for 3 h. After cooling the reaction mixture to room temperature, the mixture was concentrated, and then H₂O and dichloromethane were added. The mixture was washed with H₂O, 1N hydrochloric acid and brine, dried over Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (CH₂Cl₂/hexane) to yield **19** as a yellow solid (179 mg, 0.38 mmol, 40% yield for two steps). Compound **19**: mp: 73.5–74.5 °C (recryst. from CH₂Cl₂); ¹H-NMR (CDCl₃, 600 MHz) δ: 8.11 (1H, d, *J* = 13.4 Hz), 7.92 (1H, d, *J* = 13.4 Hz), 7.07 (1H, t, *J* = 6.9 Hz), 6.97 (1H, d, *J* = 6.5 Hz), 6.83 (1H, t, *J* = 7.4 Hz), 6.78 (1H, d, *J* = 7.9 Hz), 6.45 (1H, s), 3.91 (3H, s), 3.85 (3H, s), 3.80 (3H, s), 3.03 (3H, t, *J* = 7.6 Hz), 2.86 (2H, t, *J* = 7.6 Hz), 1.03 (9H, s), 0.26 (6H, s); ¹³C-NMR (CDCl₃, 150 MHz) δ: 156.0, 154.6, 153.6, 141.1, 140.6, 138.0, 132.2, 130.7, 130.6, 127.4, 121.2, 118.4, 115.3, 109.3, 60.9, 60.4, 55.8, 34.4, 32.9, 25.8, 18.2, -4.13; IR (CHCl₃, cm⁻¹): 2932, 2856, 1589, 1261; HRMS (DART+): *m/z* [M + H]⁺ Calcd for C₂₄H₃₆NO₆Si: 474.23119. Found: 474.2310.

(E)-2-(3,4,5-Trimethoxy-2-(2-nitrovinyl)phenethyl)phenol (6g) To a solution of **19** (140 mg, 0.30 mmol) in THF (6 mL) was added TBAF (1.0 M solution in THF, 0.36 mL, 0.36 mmol) dropwise at 0 °C. The solution was stirred at 0 °C for 30 min. Water was added to the reaction mixture, and the resulting mixture was extracted with Et₂O. The organic extracts were washed with brine, dried over anhydrous Na₂SO₄, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/Hexane) to yield **6g** (104 mg, 0.029 mmol, 98%) as a yellow oil. Compound **6g**: ¹H-NMR (CDCl₃, 600 MHz) δ: 8.27 (1H, d, *J* = 13.1 Hz), 7.94 (1H, d, *J* = 13.4 Hz), 7.05–7.10 (1H, m), 6.94 (1H, d, *J* = 7.6 Hz), 6.80 (1H, t, *J* = 7.4 Hz), 6.73 (1H, d, *J* = 7.9 Hz), 6.59 (1H, s), 5.18 (1H, brs), 3.90 (6H, s), 3.86 (3H, s), 3.06 (2H, t, *J* = 7.9 Hz), 2.86 (2H, t, *J* = 7.9 Hz); ¹³C-NMR (CDCl₃, 150 MHz) δ: 156.2, 154.7, 153.7, 141.5, 140.7, 138.0, 132.9, 130.6, 127.7, 126.8, 120.8, 115.7, 115.1, 109.3, 60.9, 60.4, 56.0, 34.3, 33.7; IR (CHCl₃, cm⁻¹): 3444, 2938, 2850, 1589; HRMS (DART+): *m/z* [M + H]⁺ Calcd for C₁₉H₂₂NO₆Si: 360.14471. Found: 360.14454.

The Wessely Oxidation of 6g to 7g (Table 2, Entry 1) Compound **6g** (300 mg, 0.84 mmol) in AcOH (5 mL) was added to a solution of Pb(OAc)₄ (556 mg, 1.25 mmol) in AcOH (5 mL) at 0 °C. The reaction temperature was warmed to room temperature, and the mixture was stirred for 2 h. The precipitate was filtered off with AcOEt and the filtrate was washed with saturated aqueous solution of NaHCO₃. The organic phase was washed with brine, dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (EtOAc/hexane) to yield **7g** (151 mg, 0.36 mmol, 43%) as a yellow amorphous. Compound **7g**: ¹H-NMR (CDCl₃, 600 MHz) δ: 8.11 (1H, d, *J* = 13.2 Hz), 7.98 (1H, d, *J* = 12.6 Hz), 7.04–7.09 (1H, m), 6.51 (1H, s), 6.44–6.48 (1H, m), 6.38–6.42 (1H, m), 6.24 (1H, d, *J* = 9.6 Hz), 3.94 (3H, s), 3.89 (3H, s), 3.84 (3H, s), 2.83–2.93 (1H, m), 2.74–2.82 (1H, m), 2.19 (3H, s), 1.99–2.01 (1H, m), 1.82–1.92 (1H, m); ¹³C-NMR (CDCl₃, 150 MHz) δ: 198.1, 169.6, 156.4, 155.0, 140.9, 140.8, 139.8, 138.5, 131.8, 126.8, 123.5, 114.9, 109.2, 80.9, 60.9, 60.5, 56.1, 39.6, 27.5, 20.4; IR (CHCl₃, cm⁻¹): 2927, 2854, 1749, 1716, 1595; HRMS (DART+): *m/z* [M + H]⁺ Calcd for C₂₁H₂₄NO₈: 418.1502. Found: 418.1507.

The IMDA Reaction of 7g to 9g (Table 2, Entry 3) A solution of **7g** (39 mg, 0.092 mmol) in 2,2,2-trifluoroethanol (1 mL) was heated in a vial at 130 °C under microwave irradiation for 18 h. After concentration, the crude product was purified by column chromatography on silica gel (EtOAc/CH₂Cl₂) to provide **9g** (9.6 mg, 0.023 mmol, 25%) as a brown solid. Compound **9g**: mp: 84.0–85.5 °C (recryst. from CH₂Cl₂); ¹H-NMR (CDCl₃, 600 MHz) δ: 6.38 (1H, t, *J* = 7.2 Hz), 6.35 (1H, s), 6.31 (1H, t, *J* = 6.9 Hz), 5.81 (1H, d, *J* = 3.6 Hz), 5.21 (1H, s), 4.89 (1H, d, *J* = 4.2 Hz), 3.97 (3H, s), 3.86 (3H, s), 3.83–3.89 (1H, m), 3.82 (3H, s), 3.39 (1H, t, *J* = 5.2 Hz), 3.23–3.35 (1H, m), 3.00–3.09 (1H, m), 2.71–2.81 (1H, m), 2.24–2.33 (1H, m), 2.02 (3H, s); ¹³C-NMR (CDCl₃, 150 MHz) δ: 202.3, 170.2, 152.8, 152.0, 141.8, 133.1, 131.9, 129.0, 121.8, 112.3, 82.9, 79.9, 61.8, 61.1, 56.1, 53.7, 42.5, 36.1, 33.3, 33.0, 22.5; IR (CHCl₃, cm⁻¹): 2940, 2838, 1736, 1552; HRMS (DART+): *m/z* [M + H]⁺ Calcd for C₂₁H₂₄NO₈: 418.1502. Found: 418.1505.

Computation Details Geometry optimization was performed with Spartan'18³⁷⁾ and the Gaussian 09 packages.³⁸⁾

The ground-state geometries of all compounds were determined by means of the following successive steps: Conformational search with MMFF94,³⁹⁾ then DFT calculation with B3LYP functionals.⁴⁰⁾ The transition-state geometries of all compounds were determined by the DFT calculation with B3LYP functionals followed by IRC calculations.^{41,42)} The basis set employed for DFT geometry optimization was the native 6–31G(d, p) for Fig. 1(a) or the native 6–31G(d) for Fig. 1(b)–(d).

Acknowledgments We thank Ms. Mizuki Yamazaki, Mr. Daichi Arai, and Ms. Akari Nakamura for assistance. This work was supported by JSPS KAKENHI Grant Number JP19K05473 and Kanazawa University SAKIGAKE project.

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

References

- 1) Brieger G., Bennett J. N., *Chem. Rev.*, **80**, 63–97 (1980).
- 2) Bear B. R., Sparks S. M., Shea K. J., *Angew. Chem. Int. Ed.*, **40**, 820–849 (2001).
- 3) Ciganek E., *Org. React.*, **32**, 1–374 (1984).
- 4) Fallis A. G., *Can. J. Chem.*, **62**, 183–234 (1984).
- 5) Craig D., *Chem. Soc. Rev.*, **16**, 187–238 (1987).
- 6) Takao K., Munakata R., Tadano K., *Chem. Rev.*, **105**, 4779–4807 (2005).
- 7) Deagostino A., Maddaluno J., Prandi C., Venturello P., *J. Org. Chem.*, **61**, 7597–7599 (1996).
- 8) Takasu K., Mizutani S., Ihara M., *J. Org. Chem.*, **67**, 2881–2884 (2002).
- 9) Corey E. J., Petrzilka M., *Tetrahedron Lett.*, **16**, 2537–2540 (1975).
- 10) Bailey S. J., Thomas E. J., Turner W. B., Jarvis J. A. J., *J. Chem. Soc. Chem. Commun.*, 474–475 (1978).
- 11) Greuter H., Schmid H., Fráter G., *Helv. Chim. Acta*, **60**, 1701–1729 (1977).
- 12) Greuter H., Fráter G., Schmid H., *Helv. Chim. Acta*, **55**, 526–531 (1972).
- 13) Greuter H., Schmid H., *Helv. Chim. Acta*, **55**, 2382–2400 (1972).
- 14) Liu X.-Y., Qin Y., *Nat. Prod. Rep.*, **34**, 1044–1050 (2017).
- 15) Hsu P.-Y., Peddinti R. K., Chittimalla S. K., Liao C.-C., *J. Org. Chem.*, **70**, 9156–9167 (2005).
- 16) Cook S. P., Danishefsky S. J., *Org. Lett.*, **8**, 5693–5695 (2006).
- 17) López C. S., Faza O. N., de Lera A. R., *J. Org. Chem.*, **73**, 467–473 (2008).
- 18) Bhamare N. K., Granger T., John C. R., Yates P., *Tetrahedron Lett.*, **32**, 4439–4442 (1991).
- 19) Iwasawa N., Inaba K., Nakayama S., Aoki M., *Angew. Chem. Int. Ed.*, **44**, 7447–7450 (2005).
- 20) For regioselectivity in construction of a bicyclo[2.2.2]octane skeleton by an IMDA reaction, see: Spangler J. E., Sorensen E. J., *Tetrahedron*, **65**, 6739–6745 (2009).
- 21) Wessely I. F., Lauterbach-Keil G., Sinwel F., *Monatsh. Chem.*, **81**, 811–818 (1950).
- 22) Wessely F., Sinwel F., *Monatsh. Chem.*, **81**, 1055–1070 (1950).
- 23) Yates P., Auksi H., *J. Chem. Soc. Chem. Commun.*, 1016–1017 (1976).
- 24) Yates P., Macas T. S., *Can. J. Chem.*, **66**, 1–10 (1988).
- 25) See supplementary materials.
- 26) Brossi A., *J. Med. Chem.*, **33**, 2311–2319 (1990).
- 27) Lin J., Zhang W., Jiang N., Niu Z., Bao K., Zhang L., Liu D., Pan

- C., Yao X., *J. Nat. Prod.*, **71**, 1938–1941 (2008).
- 28) Lim L. H., Zhou J., *Org. Chem. Front.*, **2**, 775–777 (2015).
- 29) Schreiner P. R., Wittkopp A., *Org. Lett.*, **4**, 217–220 (2002).
- 30) Wittkopp A., Schreiner P. R., *Chem. Eur. J.*, **9**, 407–414 (2003).
- 31) Kim W. H., Lee J. H., Danishefsky S. J., *J. Am. Chem. Soc.*, **131**, 12576–12578 (2009).
- 32) Becke A. D., *J. Chem. Phys.*, **98**, 5648–5652 (1993).
- 33) Lee C., Yang W., Parr R. G., *Phys. Rev. B Condens. Matter*, **37**, 785–789 (1988).
- 34) Han C., Fu Z., Guo S., Fang X., Lin A., Yao H., *ACS Catalysis*, **9**, 4196–4202 (2019).
- 35) Huang C.-G., Wan P., *J. Org. Chem.*, **56**, 4846–4853 (1991).
- 36) Harayama T., Yasuda H., *Heterocycles*, **46**, 61–64 (1997).
- 37) Shao Y., Molnar L. F., Jung Y., *et al.*, *Phys. Chem. Chem. Phys.*, **8**, 3172–3191 (2006).
- 38) Gaussian 09, Revision A. 02, Frisch M. J., Trucks G. W., Schlegel H. B., *et al.* Gaussian, Inc., Wallingford, CT (2009).
- 39) Halgren T. A., *J. Comput. Chem.*, **17**, 490–519 (1996).
- 40) Becke A. D., *J. Chem. Phys.*, **98**, 5648–5652 (1993).
- 41) Gonzalez C., Schlegel H. B., *J. Chem. Phys.*, **90**, 2154–2161 (1989).
- 42) Gonzalez C., Schlegel B., *J. Phys. Chem.*, **94**, 5523–5527 (1990).