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APPROACH TO PHENANTHROINDOLIZIDINE ALKALOIDS USING ORGANIC AZIDES WITH 1-ARYL ALLYLIC ALCOHOLS: UNEXPECTED TAMDEM REACTIONS TO INDENYL AZIRIDINES VIA NAZAROV CYCLIZATION

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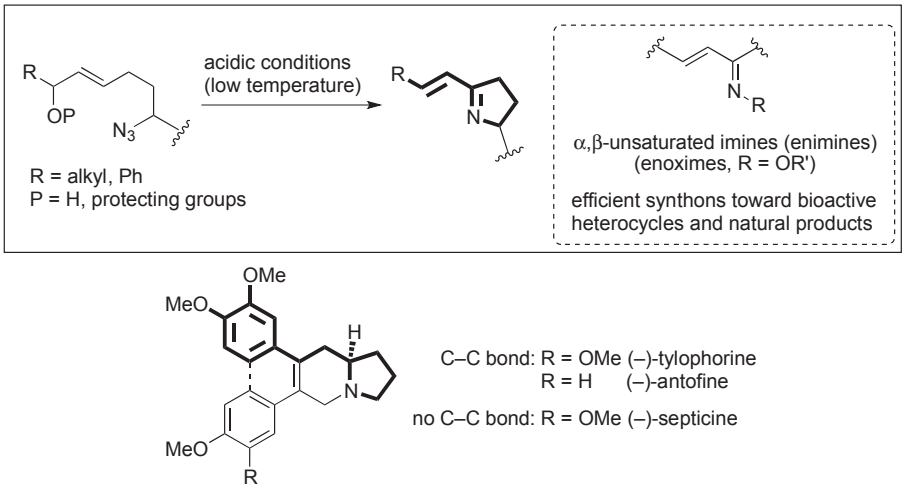
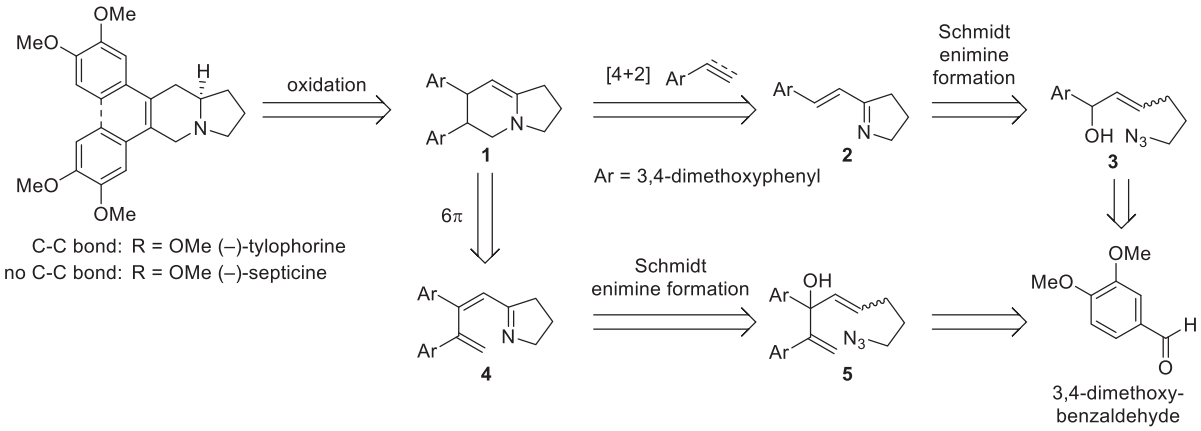
Abstract – Organic azide cyclization reactions with 1-aryl allylic alcohols were investigated in a synthetic study of phenanthroindolizidine alkaloids. Unsaturated imines (enimines) were effectively obtained from the allylic alcohol adjacent to electron-rich aromatic rings under thermal reaction conditions. The tandem aziridination-Nazarov reactions to indenyl aziridines were preferred to the acid-mediated enimine formation via Schmidt reaction in the case of 3-aryl diallylic alcohols.

α,β-Unsaturated imines (1-aza-1,3-butadienes, or enimines) and related compounds (like the corresponding oximes) are synthetically useful and show characteristic bioactivity.[1,2] These compounds can function as hetero-Diels-Alder dienes, dienophiles, and Michael acceptors. However, their use in organic synthesis is limited due to the tendency toward polymerization and hydrolysis resulting from high reactivity. Previously, we have developed a novel enimine synthesis from allylic alcohols and organic azides utilizing the allylic cation-mediated Schmidt reaction.[3] Our method was successfully used in the total syntheses of unstable α,β- and α,β,γ,δ-unsaturated imine Costa Rican ant venom alkaloids (Scheme 1). To further develop our methodology, approaches to more complex natural products should be examined, and we chose tylophorine and antofine as our synthetic targets. Tylophorine and antofine of the phenanthroindolizidine alkaloid family are known to exhibit anticancer activity and have attracted attention as synthetic targets for new and challenging strategies.[4,5] Herein, we report our approach utilizing the reactions of organic azides, and describe unexpected tandem aziridination-Nazarov cyclization reactions affording indenyl aziridines.



Scheme 1. Synthesis of unsaturated imines (enimines) from organic azides

Two retrosynthetic approaches for construction of the indolizidine alkaloid core are presented in Scheme 2. The first approach relies on the aza-[4+2] cycloaddition of enimine **2** with arylacetylene or styrene derivatives, which can be obtained from the 1-aryl allylic alcohol **3** using the developed enimine synthesis.[3] The second route involves 6π-electrocyclization of the α,β,γ,δ-unsaturated imine **4**, which could be similarly obtained from diallylic alcohol **5**. Compounds **3** and **5** could be prepared from the commercially available 3,4-dimethoxybenzaldehyde. In both routes, the electron-rich dimethoxyphenyl group was set at the β-carbon of enimines.

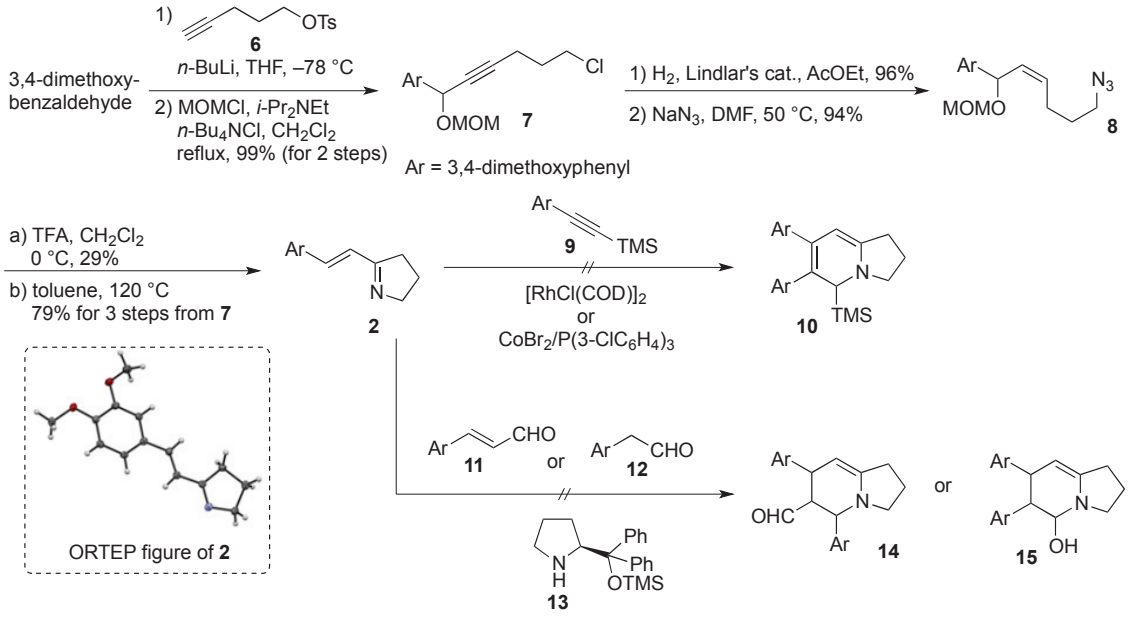


Scheme 2. Retrosynthetic routes to tylophorine and septicine

The first approach using the hetero-[4+2] cycloaddition started with the reaction of 3,4-dimethoxybenzaldehyde with tosyloxypentyne **6**,[3a] followed by protection of the alcohol with a methoxymethyl (MOM) group (Scheme 3). At this stage, the product partially reacted with chloride from MOMCl via an S_N2 substitution reaction to afford **7**, which was obtained in excellent yield by addition of tetrabutylammonium chloride. Reduction of the alkyne moiety using Lindlar's catalyst was followed by

azidation to yield the cyclization precursor **8**. When the hydroxy group was not protected, a 1,3-rearrangement to cinnamyl alcohol occurred under the reduction conditions. Next, we investigated the azide-allyl ether cyclization to enimine **2**. Although 1-phenyl allylic alcohol has previously been reported to afford the corresponding enimines,[3a,c] the typical conditions using TMSOTf or $BF_3 \cdot OEt_2$ did not give the desired product, probably due to the instability of the substrate under acidic conditions, imparted by the electron-rich dimethoxyphenyl group. When trifluoroacetic acid was used, **2** was obtained in 29% yield. Therefore, thermal cyclization conditions were tested, which were previously reported to be not effective.[3a,c] Under these conditions, **2** was successfully obtained in 79% yield over three steps.

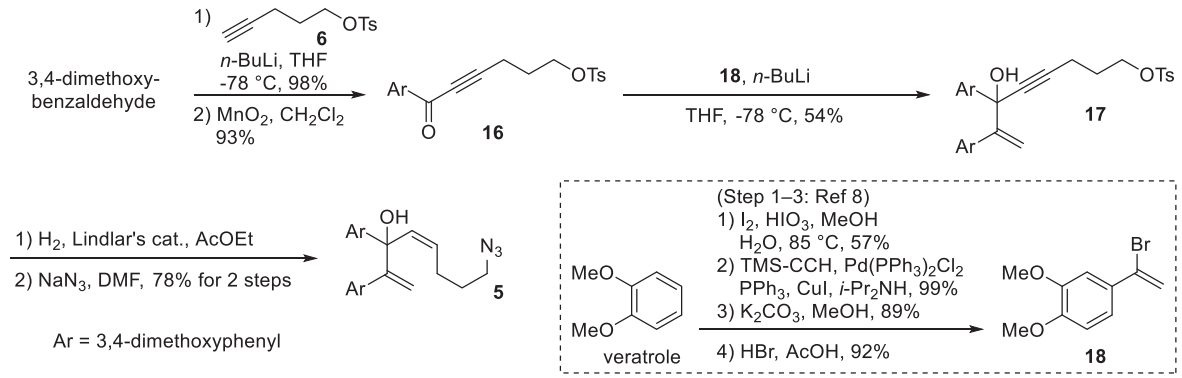
With the [4+2] cyclization precursor in hand, we examined hetero-[4+2] cyclizations. The initially attempted reaction with acrylonitrile and methyl enol ether derivatives in the presence or absence of Lewis acids did not occur. Following Yoshikai's[6] and Ellman's[7] procedures using cobalt or rhodium catalysts, cyclizations with arylalkyne **9**[8] to afford **10** were investigated. However, the starting material **2** was still unreactive. It should be noted that although typical enimines are unstable enough to decompose in 2–3 days, **2** was a bench stable crystalline compound with its structure confirmed by X-ray analysis. Thus, dienophiles for **2** were considered to be considerably more unreactive than typical enimines. We also tested organocatalytic [4+2] reactions with enal **11** (LUMO activation) and homobenzaldehyde **12** (HOMO activation).[9,10] Disappointingly, although the starting material was consumed, only trace amounts of aza-Michael addition or condensation products were observed.



Scheme 3. Synthesis of enimine **2** and related hetero-[4+2] cyclization reaction approaches

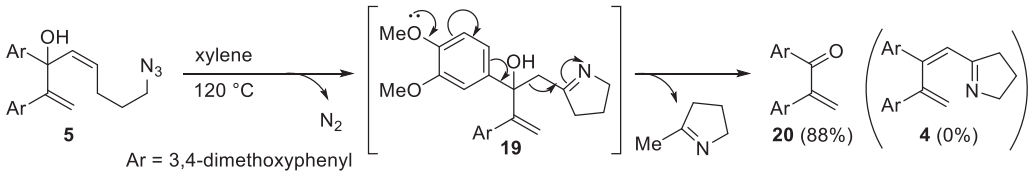
Therefore, we directed our efforts to the 6π-electrocyclization reaction (Scheme 4). The propargyl ketone **16** obtained from 3,4-dimethoxybenzaldehyde was reacted with the lithiated vinyl bromide **18** to afford

alcohol **17**. The alkyne moiety was reduced to olefin, and subsequent azidation afforded the cyclization precursor **5**.



Scheme 4. Synthesis of the diallylic alcohol **5** possessing an azido group

Based on the results of the conversion from **8** to **2**, a cyclization reaction under heating conditions was initially attempted with **5** (Scheme 5). Although all of the starting material was consumed, the only product obtained in good yield was the enone **20**, with no α,β,γ,δ-unsaturated imine **4** detected. This unexpected reaction is presumably explained by the retro-aldol transformation of the intermediate β-hydroxylimine **19**,[3a] accelerated by the electron donating aromatic group.

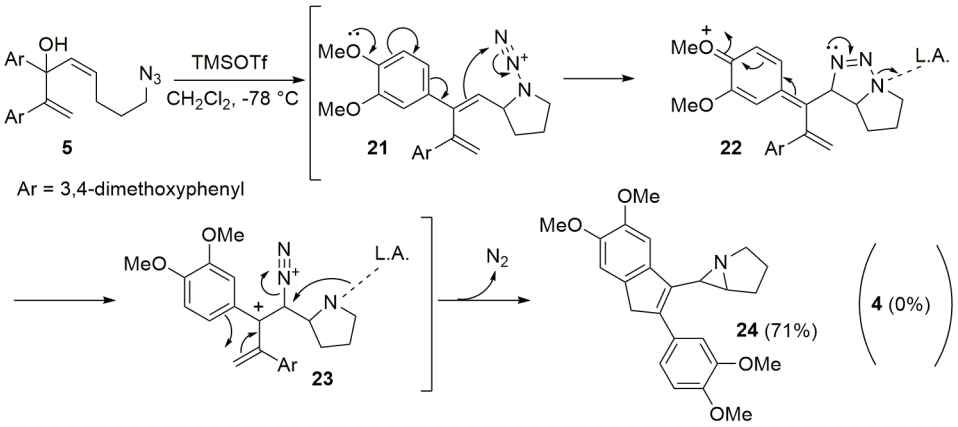


Scheme 5. Attempted cyclization of **5** under thermal conditions

Considering the above results, we switched back to acid-mediated conversion. After the investigation of reaction conditions, TMSOTf was found to give reproducible results. However, instead of the desired dienimine **4**, the reaction yielded the indenyl aziridine **24** in moderate yield (Scheme 6). The structure of **24** was unambiguously determined by X-ray crystallographic analysis (Figure 1).

A plausible mechanism is depicted in Scheme 6. After generation of the 1-pheny allylic cation by TMSOTf, a cyclization reaction with the azido moiety followed, to give the aminodiazonium intermediate **21**. In our previous study,[3a,c] including the case of 1-aryl allylic alcohol, the last step of the Schmidt reactions involved the loss of a proton[11] and nitrogen gas. However, in this case, the electron-rich dimethoxyphenyl group could induce a reaction with the diazonium moiety of **21** to afford triazoline **22**[12] prior to proton loss.[13] This is probably one of the reasons for the low yield and irreproducibility of the transformation of **8** to **2** under acidic conditions (Scheme 3), since the acid-labile triazoline structure

would be immediately decomposed to aziridine.[3a,12] Finally, Nazarov cyclization of the generated 1-aryl allylic cation **23** produced indene **24**.[14] The Nazarov reaction and aziridine formation could be performed independently.



Scheme 6. Tandem transformation of the azido diallylic alcohol **5** to indenyl aziridine **24**

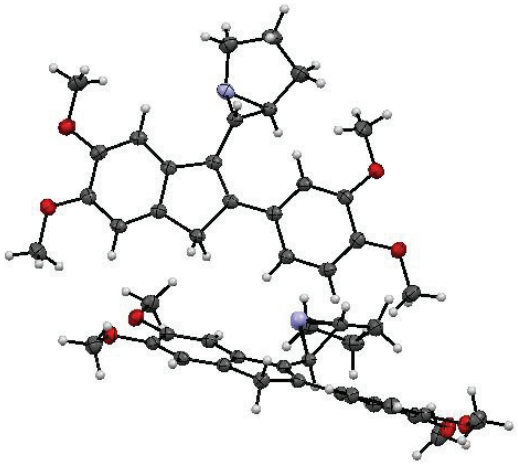
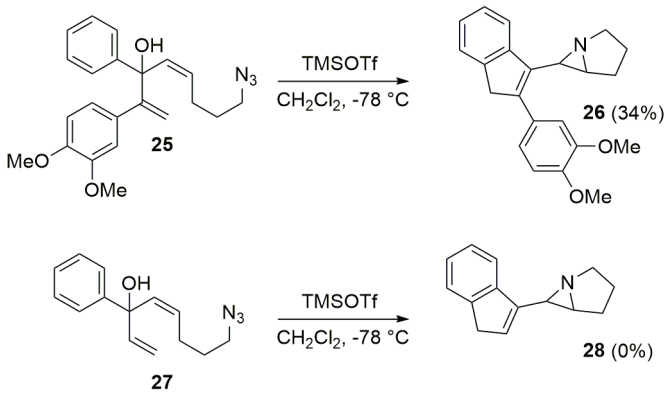


Figure 1. ORTEP figure of the indenyl aziridine **24**

In our previous study, a 1-phenyl allylic alcohol was successfully converted to the desired enimine. A model study to investigate the previously unobserved tandem reaction was set up (Scheme 7). Although product **26** was obtained in lower yield than **24** in Scheme 6, the tandem reaction occurred in the absence of electron-donating groups in the upper benzene ring. However, without an aromatic ring on the bottom side, the expected product **28** was not formed. These results indicate that the presence of aromatic moieties or electron-donating groups can strongly influence the aziridination-Nazarov reaction.

In conclusion, we investigated the cyclization reactions of organic azides and the influence of electron-rich benzene rings in a synthetic study of indolizidine alkaloids. In the case of a secondary benzyl alcohol, thermal reaction conditions were effective for obtaining the unsaturated imine. In the

presence of an electron-rich group, triazoline formation followed by aziridination was preferred to acid-mediated enimine formation via the Schmidt reaction. These results should facilitate the development of Schmidt reactions and an understanding of the behavior of organic azides. Further applications of the discovered reactions and the synthetic approach to alkaloids will follow in due course.



Scheme 7. Model study of tandem aziridination/Nazarov reaction

EXPERIMENTAL

General Information: ^{1}H and ^{13}C NMR spectra were recorded using a JEOL JNM-ECP500 spectrometer (500 MHz for ^{1}H NMR and 126 MHz for ^{13}C NMR). Chemical shifts are reported as δ values in ppm and calibrated with respect to the residual solvent peak ($CDCl_3$: δ 7.26 for ^{1}H NMR and δ 77.00 for ^{13}C NMR) or tetramethylsilane (δ 0 for ^{1}H NMR). The abbreviations used are as follows: s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (complex multiplet). Melting points were measured using a Yanaco Micro melting point apparatus. Infrared spectra were measured using a Jasco FT-IR-4200 spectrometer. Mass spectra were recorded using a Jeol JMS-700 MStaion [EI (70 eV), CI, FAB, and ESI]. Flash column chromatography was performed using Merck Silica gel 60. The progress of the reactions was monitored by silica gel thin layer chromatography (TLC) (Merck TLC Silica gel 60 F_{254}). The further purifications of the crude materials were performed using a LC-908 recycling gel permeation chromatography (GPC) equipped with a JAIGEL 2H-40 column ($CHCl_3$ elution) made by Japan Analytical Industry Co., Ltd. Phosphomolybdic acid was used for the TLC stains, and TLC was also monitored with UV lamp. All the reagents were purchased from Sigma-Aldrich, Wako Pure Chemical Industries, Ltd, TCI (Tokyo Chemical Industry, Co. Ltd), Kanto Chemical Co. Inc., and Nakalai Tesque. Anhydrous tetrahydrofuran (THF) was purchased from Kanto Chemical.

4-(6-Chloro-1-(methoxymethoxy)hex-2-yn-1-yl)-1,2-dimethoxybenzene (7): To a stirred solution of alkyne **6** (3.59 g, 15.1 mmol)[3a] in THF (45 mL) was added *n*-butyllithium (hexane solution, 10. mL, 1.63 M, 16.5 mmol) at -78 °C. After 14 min, 3,4-dimethoxybenzaldehyde (1.66 g, 10.0 mmol) dissolved in THF (40mL) was added to the mixture dropwise. After 2 h, saturated ammonium chloride aqueous

solution was added to stop the reaction. The mixture was extracted with EtOAc, and the extract was washed with water and brine. Drying collected organic layer was concentrated in vacuo to afford crude material (4.05 g) which was submitted to the next reaction without further purification due to the instability of the product.

To the stirred solution of the crude material (4.05g) in CH_2Cl_2 (100 mL) was added tetrabutylammonium chloride (6.63 g, 17.9 mmol), and the mixture was cooled to 0 °C. To the mixture were added diisopropylethylamine (5.2 mL, 30 mmol) and chloromethyl methyl ether (1.5 mL, 20 mmol) successively, and the mixture was stirred at room temperature for 18 h. Additional diisopropylethylamine (1.74 mL, 10.0 mmol) and chloromethyl methyl ether (0.75 mL, 9.9 mmol) were added, and the mixture was stirred at room temperature for 5 h, then heated at 50 °C for 3 h. The reaction mixture was extracted with CH_2Cl_2, and the extract was washed with water and brine. Drying collected organic layer followed by silica gel column chromatography (hexane/EtOAc = 5/1 to 2/1) to afford **7** (3.08 g, 99% for 2 steps). Colorless oil; R_f value 0.47 (hexane/EtOAc = 2/1); IR (NaCl, neat) ν_{max} 2951, 1516, 1260, 1234, 1146, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, 1H, *J* = 1.5 Hz), 7.02 (dd, 1H, *J* = 8.0, 2.0 Hz), 6.85 (d, 1H, *J* = 8.0 Hz), 5.33 (br-s, 1H), 4.96 (d, 1H, *J* = 7.0 Hz), 4.62 (d, 1H, *J* = 7.0 Hz), 3.91 (s, 3H), 3.89 (s, 3H), 3.65 (t, 2H, *J* = 6.5 Hz), 3.42 (s, 3H), 2.49 (dt, 2H, *J* = 7.0, 2.5 Hz), 1.99 (tt, 2H, *J* = 7.0, 6.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.13, 149.05, 131.4, 120.0, 110.7, 110.4, 93.6, 85.8, 79.0, 67.3, 55.9, 55.8, 55.7, 43.6, 31.2, 16.3; HRMS (ESI) calcd for $C_{16}H_{21}ClO_4Na$ [$(M+Na)^+$] 335.1026, found 335.1022.

Synthesis of (*E*)-5-(3,4-dimethoxystyryl)-3,4-dihydro-2*H*-pyrrole (2) by three-step sequence: To a stirred solution of **7** (2.86 g, 9.2 mmol) in EtOAc (91 mL) was added Lindlar's catalyst (286.6 mg). The atmosphere in the flask was replaced to hydrogen under balloon pressure, and the reaction mixture was vigorously stirred. After 26 h, the mixture was filtered through a pad of Celite to afford crude material of (*Z*)-4-(6-chloro-1-(methoxymethoxy)hex-2-en-1-yl)-1,2-dimethoxybenzene (2.88 g, 96%) which was submitted to the next reaction without further purification.

Analytical data of (*Z*)-4-(6-chloro-1-(methoxymethoxy)hex-2-en-1-yl)-1,2-dimethoxybenzene: Further purification was not necessary to collect analytical data. Colorless oil; R_f value 0.70 (hexane/EtOAc = 1/1); IR (NaCl, neat) ν_{max} 3000, 2934, 2839, 1515, 1464, 1261, 1145, 1094, 1028 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.92 (s, 1H), 6.91 (dd, 1H, *J* = 8.5, 1.5 Hz), 6.83 (d, 1H, *J* = 8.5 Hz), 5.66 (m, 1H), 5.57 (m, 1H), 5.40 (d, 1H, *J* = 9.0 Hz), 4.68 (d, 1H, *J* = 7.0 Hz), 4.59 (d, 1H, *J* = 7.0 Hz), 3.89 (s, 3H), 3.87 (s, 3H), 3.54 (m, 2H), 3.39 (s, 3H), 2.37 (td, 2H, *J* = 7.5, 7.5 Hz), 1.86 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.0, 148.4, 133.8, 131.3, 130.7, 119.1, 110.9, 109.6, 93.2, 72.1, 55.8, 55.8, 55.4, 44.3, 32.1, 24.7; LRMS (EI) *m*/*z* 314 (43%), 255 (40), 253 (100), 241 (45); HRMS (EI) calcd for $C_{16}H_{23}ClO_4$ (M^+) 314.1285, found 314.1287.

To a stirred solution of crude (*Z*)-4-(6-chloro-1-(methoxymethoxy)hex-2-en-1-yl)-1,2-dimethoxybenzene (2.88 g) in DMF (92 mL) was added sodium azide (777 mg, 12.0 mmol), and the mixture was heated to 50 °C. After 20 h, the mixture was extracted with Et_2O and the extract was washed with water and brine. Drying collected organic layer followed by concentration in vacuo afforded crude **8** (2.55 g) which was submitted to the next reaction without further purification. When purified, silica gel column chromatography (hexane/EtOAc = 5/1) afforded **8** (125.7 mg, 94%).

Analytical data of (*Z*)-4-(6-azido-1-(methoxymethoxy)hex-2-en-1-yl)-1,2-dimethoxybenzene (8): Colorless oil; R_f value 0.43 (hexane/EtOAc = 5/1×3); IR (NaCl, neat) ν_{max} 2938, 2097, 1516, 1261, 1147, 1030 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.91 (m, 1H), 6.89 (d, 1H, *J* = 1.5 Hz), 6.83 (m, 1H), 5.65 (m, 1H), 5.58 (td, 1H, *J* = 11.0, 7.5 Hz), 5.37 (d, 1H, *J* = 9.0 Hz), 4.68 (d, 1H, *J* = 6.5 Hz), 4.58 (d, 1H, *J* = 6.0 Hz), 3.89 (s, 3H), 3.87 (s, 3H), 3.40 (s, 3H), 3.28 (dt, 2H, *J* = 7.0, 1.5 Hz), 2.33–2.24 (m, 2H), 1.73–1.64 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.1, 148.5, 133.8, 131.04, 131.02, 119.2, 110.9, 109.6, 93.1, 72.1, 55.84, 55.79, 55.5, 50.7, 28.5, 24.7; HRMS (ESI) calcd for $C_{16}H_{23}N_3O_4Na$ $[(M+Na)^+]$ 344.1586, found 344.1585.

To a stirred solution of crude **8** (2.55 g) in toluene (79 mL) was heated to 120 °C. After 16 h, the mixture was concentrated in vacuo. The obtained residue was purified by silica gel column chromatography (hexane/EtOAc = 1/2 to $CHCl_3$/MeOH = 15/1) to afford **2** (1.68 g, 79% for 3 steps).

Analytical data of (*E*)-5-(3,4-dimethoxystyryl)-3,4-dihydro-2*H*-pyrrole (2, CCDC 1474594): White crystal; R_f value 0.39 (CH_2Cl_2/MeOH = 10/1); mp 119.3–120.6 °C; IR (NaCl, neat) ν_{max} 2958, 2932, 1632, 1590, 1513, 1265, 1139, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, 1H, *J* = 1.5 Hz), 7.04 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.00 (d, 1H, *J* = 16.5 Hz), 6.90 (d, 1H, *J* = 16.5 Hz), 6.86 (d, 1H, *J* = 8.0 Hz), 3.98 (t, 2H, *J* = 7.5 Hz), 3.91 (s, 3H), 3.90 (s, 3H), 2.77 (t, 2H, *J* = 8.0 Hz), 1.97 (tt, 2H, *J* = 8.0, 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 149.9, 149.1, 138.2, 129.0, 123.2, 121.1, 111.0, 108.8, 61.2, 55.9, 55.8, 33.4, 22.5; HRMS (ESI) calcd for $C_{14}H_{18}NO_2$ $[(M+H)^+]$ 232.1338, found 232.1339.

Compound 8 from 2 by TFA-mediated reaction: To a stirred solution of **2** (17.4 mg, 54.1 μmol) in CH_2Cl_2 (1 mL) was added trifluoroacetic acid (8 μL, 110 μmol) at 0 °C. After 1 h, the reaction was quenched with saturated sodium hydrogen carbonate aqueous solution. The mixture was extracted with EtOAc and washed with brine. Drying the collected organic layer over magnesium sulfate followed by concentration in vacuo and silica gel column chromatography (hexane/EtOAc = 7/2 to 1/1) afforded **8** (3.6 mg, 29%).

6-(3,4-Dimethoxyphenyl)-6-oxohex-4-yn-1-yl 4-methylbenzenesulfonate (16): To a stirred solution of **6** (2.26 g, 9.5 mmol)[3a] in THF (48 mL) was added *n*-butyllithium (hexane solution, 6.7 mL, 1.55 M, 10.4 mmol) at -78 °C. After 14 min, 3,4-dimethoxybenzaldehyde (1.05 g, 6.3 mmol) in THF (15 mL) was added dropwise at the same temperature. After 2 h, saturated ammonium chloride aqueous solution was

added to the mixture. The mixture was extracted with EtOAc, and was washed with water and brine. Drying collected organic layer over sodium sulfate followed by silica gel column chromatography (hexane/EtOAc = 2/1 to 1/1) afforded propargyl alcohol (2.49 g, 98%). The product was submitted to the next reaction due to the instability of the product.

To a vigorously stirred solution of the propargyl alcohol (2.47 g, 6.1 mmol) in CH_2Cl_2 (20 mL) was added manganese dioxide (2.13 g, 24.5 mmol) at room temperature. After 24 h, the mixture was filtrated through Celite. The obtained filtrate was concentrated in vacuo followed by silica gel column chromatography (hexane/EtOAc = 2/1 to 3/2) to afford **16** (2.28 g, 93%). Yellow oil; R_f value 0.17 (hexane/EtOAc = 2/1); IR (NaCl, neat) ν_{max} 1633, 1594, 1582, 1513, 1271, 1175 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78–7.76 (m, 3H), 7.55 (d, 1H, *J* = 2.0 Hz), 7.29 (d, 2H, *J* = 8.5 Hz), 6.92 (d, 1H, *J* = 8.5 Hz), 4.19 (t, 2H, *J* = 6.0 Hz), 3.96 (s, 3H), 3.93 (s, 3H), 2.58 (t, 2H, *J* = 6.0 Hz), 2.37 (s, 3H), 2.00 (tt, 2H, *J* = 6.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 154.3, 148.9, 145.0, 132.5, 130.1, 129.9, 127.8, 125.9, 110.0, 109.9, 92.6, 80.1, 68.4, 56.1, 56.0, 27.1, 21.6, 15.5; HRMS (ESI) calcd for $C_{21}H_{22}O_6SNa$ $[(M+Na)^+]$ 425.1035, found 425.1035.

Preparation of 1-bromo-1-(3,4-dimethoxyphenyl)ethene (18): To a stirred 3,4-dimethoxy-1-ethynylbenzene (713 mg, 4.4 mmol)[8] was added acetic acid (1 mL) and hydrogen bromide (acetic acid solution, 0.86 mL, 5.1 M, 4.4 mmol) successively. After 30 min, saturated sodium hydrogen carbonate aqueous solution was added to the mixture at 0 °C. The mixture was extracted with CH_2Cl_2, and the extract was washed with water and brine. Drying collected organic layer followed by silica gel column chromatography (hexane/EtOAc = 15/1 to 5/1) to afford **18** (984 mg, 92%) as a pale orange oil, which was soon submitted to the appropriate reactions due to its instability.

6,7-Bis(3,4-dimethoxyphenyl)-6-hydroxyoct-7-en-4-yn-1-yl 4-methylbenzenesulfonate (17): To a stirred solution of *n*-butlyllithium (hexane solution, 0.12 mL, 1.55 M, 0.19 mmol) in THF (0.3 mL) was added vinyl bromide **18** at -78 °C. After 20 min, **16** (50.7 mg, 0.13 mmol) dissolved in THF (0.5 mL) was added dropwise to the reaction mixture at the same temperature. After 3 h, satulated ammonium chloride aqueous solution was added. The mixture was extracted with EtOAc, and was washed with water and brine. Drying collected organic layer over $MgSO_4$ followed by silica gel column chromatography (hexane/EtOAc = 3/1 to 2/1) afforded **17** (38.6 mg, 54%). Pale yellow gum; R_f value 0.33 (hexane/EtOAc = 1/1); IR (NaCl, neat) ν_{max} 1935, 1653, 1514, 1262, 1142, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, 2H, *J* = 8.5 Hz), 7.31 (d, 2H, *J* = 8.0 Hz), 7.16 (dd, 1H, *J* = 8.0, 2.0 Hz), 7.11 (d, 1H, *J* = 1.5 Hz), 6.81 (d, 1H, *J* = 8.5 Hz), 6.70–6.67 (m, 2H), 6.60 (d, 1H, *J* = 1.0 Hz), 5.75 (d, 1H, *J* = 1.0 Hz), 5.31 (d, 1H, *J* = 1.0 Hz), 4.06 (t, 2H, *J* = 5.5 Hz), 3.87 (s, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.67 (s, 3H), 2.64 (s, 1H), 2.42 (s, 3H), 2.36 (t, 2H, *J* = 6.5 Hz), 1.81 (tt, 2H, *J* = 6.5, 6.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.3, 148.6, 148.6, 148.3, 147.7, 144.8, 135.4, 132.9, 131.7, 129.8, 127.8, 121.2, 118.9, 114.6, 112.0, 110.4, 110.2,

109.6, 86.0, 83.5, 74.8, 68.7, 55.9, 55.8, 55.7, 55.5, 27.8, 21.6, 15.2; HRMS (ESI) calcd for $C_{31}H_{34}O_8SNa$ [$(M+Na)^+$] 589.1872, found 589.1865.

(*Z*)-8-Azido-2,3-bis(3,4-dimethoxyphenyl)octa-1,4-dien-3-ol (5): To a stirred solution of **17** (763.0 mg, 1.4 mmol) in EtOAc (14 mL) was added Lindlar's catalyst (764.1 mg). The atmosphere in the flask was replaced to hydrogen under balloon pressure, and the reaction mixture was vigorously stirred. After 18 h, the mixture was filtered through a pad of Celite to afford crude material of allyl alcohol (733 mg) which was submitted to the next reaction due to the instability.

To a stirred solution of the allyl alcohol (733 mg) in DMF (13 mL) was added sodium azide (111.6 mg, 1.7 mmol). After 18 h, the mixture was extracted with Et_2O, and the organic layer was washed with water and brine. Drying collected organic layer over Na_2SO_4 followed by alumina column chromatography (hexane/EtOAc = 3/1 to 2/1 to 1/1) afforded **5** (459.7 mg, 78% for 2 steps). Pale yellow oil; R_f value 0.57 (hexane/EtOAc = 1/1); IR (NaCl, neat) ν_{max} 3508, 1095, 1513, 1254, 1141, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (s, 1H), 7.07 (d, 1H, *J* = 8.5 Hz), 6.84 (d, 1H, *J* = 8.5 Hz), 6.71 (d, 1H, *J* = 8.0 Hz), 6.67 (d, 1H, *J* = 8.5 Hz), 6.56 (s, 1H), 5.89 (d, 1H, *J* = 11.5 Hz), 5.56–5.50 (m, 2H), 5.32 (s, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.66 (s, 3H), 3.22 (t, 2H, *J* = 6.0 Hz), 2.39–2.26 (m, 2H), 1.63 (tt, 2H, *J* = 7.0, 6.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7, 148.7, 148.3, 148.02, 147.97, 138.3, 135.3, 132.4, 120.9, 118.7, 114.9, 111.7, 110.5, 110.4, 109.7, 79.7, 55.82, 55.80, 55.7, 55.5, 50.9, 28.3, 25.7; HRMS (ESI) calcd for $C_{24}H_{29}N_3O_5Na$ [$(M+Na)^+$] 462.2005, found 462.2006.

1,2-Bis(3,4-dimethoxyphenyl)prop-2-en-1-one (20): A stirred solution of **5** (5.6 mg, 0.013 mmol) in *o*-xylene (1 mL) was heated to 120 °C. After 3 h, the mixture was concentrated in vacuo, and the residue was purified by silica gel column chromatography (hexane/EtOAc = 3/1) to afford **20** (3.7 mg, 88%). Colorless oil; R_f value 0.43 (hexane/EtOAc = 1/1); IR (NaCl, neat) ν_{max} 2935, 2837, 1593, 1514, 1262, 1142, 1024 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, 1H, *J* = 2.0 Hz), 7.52 (dd, 1H, *J* = 8.0, 1.5 Hz), 6.98 (d, 1H, *J* = 2.0 Hz), 6.95 (dd, 1H, *J* = 8.5, 2.5 Hz), 6.83 (t, 2H, *J* = 7.5 Hz), 5.92 (s, 1H), 5.47 (s, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.6, 153.5, 149.3, 148.92, 148.89, 147.9, 130.0, 129.9, 125.7, 119.7, 117.3, 111.3, 111.0, 109.8, 109.6, 56.1, 56.0, 55.87, 55.85; HRMS (ESI) calcd for $C_{19}H_{20}O_5Na$ [$(M+Na)^+$] 351.1208, found 351.1193.

6-(2-(3,4-Dimethoxyphenyl)-5,6-dimethoxy-1*H*-inden-3-yl)-1-azabicyclo[3.1.0]hexane (24, CCDC 1474595): To a stirred solution of **5** (7.4 mg, 0.017 mmol) in CH_2Cl_2 (1 mL) was added TMSOTf (6 μL, 0.034 mmol) at -78 °C. After 15 min, saturated sodium hydrogen carbonate aqueous solution was added to the reaction mixture. The mixture was extracted with EtOAc and the organic layer was washed with water and brine. Drying collected organic layer followed by silica gel column chromatography (hexane/EtOAc = 1/1 to EtOAc elution) afforded **24** (4.7 mg, 71%). Pale yellow solid; R_f value 0.53 ($CHCl_3$/MeOH = 15/1); mp 99.1–99.7 °C; IR (NaCl, neat) ν_{max} 2936, 1514, 1488, 1238 cm^{-1}; ^1H NMR

(500 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.05 (dd, 1H, *J* = 8.0, 2.0 Hz), 7.02 (d, 1H, *J* = 2.0 Hz), 7.01 (s, 1H), 6.91 (d, 1H, *J* = 8.0 Hz), 3.95 (s, 3H), 3.93 (s, 3H), 3.92 (s, 3H), 3.90 (s, 3H), 3.68 (d, 1H, *J* = 22.5 Hz), 3.59 (d, 1H, *J* = 22.5 Hz), 3.25 (br-dd, 1H, *J* = 12.0, 8.0 Hz), 3.08 (dt, 1H, *J* = 11.5, 7.0 Hz), 2.57 (s, 1H), 2.54 (dd, 1H, *J* = 5.5, 3.0 Hz), 2.25 (dd, 1H, *J* = 13.0, 8.5 Hz), 2.00 (m, 1H), 1.76 (m, 1H), 1.63 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.5, 148.1, 148.0, 147.1, 141.3, 138.7, 135.0, 134.9, 130.0, 120.7, 111.5, 111.0, 107.4, 105.1, 56.2, 55.9, 53.3, 46.8, 41.1, 35.1, 26.3, 20.5; LRMS (EI) *m*/*z* 393 (M^+, 29%), 165 (40), 149 (100), 57 (79); HRMS (EI) calcd for $C_{24}H_{27}NO_4$ (M^+) 393.1940, found 393.1923.

Preparation of model substrates 25 and 27:

6-Oxo-6-phenylhex-4-yn-1-yl 4-methylbenzenesulfonate: To a vigorously stirred solution of 6-hydroxy-6-phenyl-4-propyn-1-yl 4-toluenesulfonate (377 mg, 1.1 mmol)[3a] in CH_2Cl_2 (11 mL) was added manganese dioxide (1.86 g, 21.7 mmol). After 12 h, the mixture was filtrated through Celite. The obtained filtrate was concentrated in vacuo followed by silica gel column chromatography (hexane/EtOAc = 3/1) to afford alkynyl ketone (262.5 mg, 70%). White solid; R_f value 0.3 (hexane/EtOAc = 3/1); mp 56–57 °C; IR (NaCl, neat) ν_{max} 2238, 2204, 1643, 1266, 1175, 930 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08–8.06 (m, 2H), 7.78 (d, 2H, *J* = 8.5 Hz), 7.62 (m, 1H), 7.50–7.47 (m, 2H), 7.28 (d, 2H, *J* = 7.0 Hz), 4.19 (t, 2H, *J* = 6.0 Hz), 2.60 (t, 2H, *J* = 7.0 Hz), 2.35 (s, 3H), 2.02 (tt, 2H, *J* = 7.5, 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 145.0, 136.5, 134.1, 132.5, 129.9, 129.5, 128.6, 127.9, 93.5, 80.2, 68.3, 27.1, 21.6, 15.5; LRMS (EI) *m*/*z* 342 (M^+, 100%), 170 (62), 141 (38); HRMS (EI) calcd for $C_{19}H_{18}O_4S$ (M^+) 342.0926, found 342.0920.

7-(3,4-Dimethoxyphenyl)-6-hydroxy-6-phenyloct-7-en-4-yn-1-yl 4-methylbenzenesulfonate: To a stirred solution of *n*-butyllithium (hexane solution, 0.92 mL, 1.54 M, 1.4 mmol) in THF (1.2 mL) was added THF solution (3 mL) of vinyl bromide **18** (318.4 mg, 1.3 mmol) was added dropwise at -78 °C. After 20 min, 6-oxo-6-phenylhex-4-yn-1-yl 4-methylbenzenesulfonate (247.6 mg, 0.72 mmol) dissolved in THF (3 mL) was added dropwise to the mixture. After 2 h, the reaction was stopped by addition of saturated ammonium chloride aqueous solution. The mixture was extracted with EtOAc and was washed with water and brine. Drying collected organic layer over $MgSO_4$ followed by silica gel column chromatography (hexane/EtOAc = 2/1 to 1/1) afforded the product (342.3 mg, 93%). Pale yellow oil; R_f value 0.1 (hexane/EtOAc = 3/1); IR (NaCl, neat) ν_{max} 3490, 1514, 1175, 1026, 930 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, 2H, *J* = 8.0 Hz), 7.59–7.57 (m, 2H), 7.34–7.26 (m, 5H), 6.72–6.67 (m, 2H), 6.48 (d, 1H, *J* = 2.0 Hz), 5.76 (d, 1H, *J* = 1.0 Hz), 5.31 (d, 1H, *J* = 1.0 Hz), 4.06 (t, 2H, *J* = 6.5 Hz), 3.81 (s, 3H), 3.61 (s, 3H), 2.64 (s, 1H), 2.42 (s, 3H), 2.36 (t, 2H, *J* = 7.0 Hz), 1.82 (tt, 2H, *J* = 7.0, 6.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 148.2, 147.6, 144.8, 142.9, 132.8, 131.6, 129.9, 128.1, 127.9, 127.8, 126.3, 121.2, 114.8, 111.8, 110.2, 86.2, 83.4, 68.8, 55.7, 55.4, 27.7, 21.6, 15.2; LRMS (EI) *m*/*z* 506 (M^+, 9%), 343 (96), 163 (100); HRMS (EI) calcd for $C_{29}H_{30}O_6S$ (M^+) 506.1763, found 506.1780.

(*Z*)-7-(3,4-Dimethoxyphenyl)-6-hydroxy-6-phenylocta-4,7-dien-1-yl 4-methylbenzenesulfonate: To a stirred solution of 7-(3,4-dimethoxyphenyl)-6-hydroxy-6-phenyloct-7-en-4-yn-1-yl 4-methylbenzenesulfonate in EtOAc (6.8 mL) was added Lindlar's catalyst (34.6 mg). The atmosphere in the flask was replaced to hydrogen under balloon pressure. After 23 h, the mixture was filtered through a pad of Celite and the filtrate was concentrated in vacuo followed by silica gel column chromatography (EtOAc/hexane = 3/1) to afford the product (267.5 mg, 78%). Pale yellow amorphous solid; R_f value 0.47 (hexane/EtOAc = 3/1×3); IR (NaCl, neat) ν_{max} 3519, 1514, 1357, 1252, 1175 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, 2H, *J* = 8.0 Hz), 7.52–7.50 (m, 2H), 7.35–7.31 (m, 4H), 7.26 (m, 1H), 6.73–6.67 (m, 2H), 6.43 (d, 1H, *J* = 2.5 Hz), 5.88 (d, 1H, *J* = 11.5 Hz), 5.58 (m, 1H), 5.47 (d, 1H, *J* = 1.0 Hz), 5.30 (d, 1H, *J* = 1.0 Hz), 3.96 (m, 2H), 3.83 (s, 3H), 3.60 (s, 3H), 2.94 (s, 3H), 2.34–2.20 (m, 2H), 1.64 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.5, 148.3, 147.9, 145.8, 144.6, 135.4, 133.0, 132.3, 132.2, 129.8, 128.2, 127.9, 127.1, 126.3, 121.0, 115.2, 111.5, 110.5, 79.9, 70.1, 55.7, 55.4, 28.5, 24.7, 21.6; HRMS (ESI) calcd for $C_{29}H_{32}O_6SNa$ [$(M+Na)^+$] 531.1817, found 531.1812.

(*Z*)-8-Azido-2-(3,4-dimethoxyphenyl)-3-phenylocta-1,4-dien-3-ol (25): To a stirred solution of (*Z*)-7-(3,4-dimethoxyphenyl)-6-hydroxy-6-phenylocta-4,7-dien-1-yl 4-methylbenzenesulfonate (126.2 mg, 0.25 mmol) in DMF (2.5 mL) was added sodium azide (21.8 mg, 0.34 mmol), and the mixture was heated at 50 °C. After 20 min, the mixture was extracted with Et_2O and was washed with water and brine. Drying collected organic layer over Na_2SO_4 followed by silica gel column chromatography (hexane/EtOAc = 4/1) gave **25** (77.6 mg, 82%). Pale yellow oil; R_f value 0.37 (hexane/EtOAc = 3/1); IR (NaCl, neat) ν_{max} 3504, 2935, 2095, 1514, 1252, 1027 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.56–7.54 (m, 2H), 7.37–7.34 (m, 2H), 7.28 (m, 1H), 6.71 (m, 2H), 6.47 (d, 1H, *J* = 1.5 Hz), 5.97 (br-d, 1H, *J* = 12.0 Hz), 5.55 (td, 1H, *J* = 11.5, 7.0 Hz), 5.50 (d, 1H, *J* = 1.0 Hz), 5.32 (d, 1H, *J* = 1.0 Hz), 3.83 (s, 3H), 3.62 (s, 3H), 3.20 (t, 2H, *J* = 7.0 Hz), 2.41–2.27 (m, 2H), 1.62 (tt, 2H, *J* = 7.0, 6.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.8, 148.3, 148.0, 145.9, 135.4, 132.6, 132.4, 128.2, 127.1, 126.4, 121.0, 115.2, 111.7, 110.5, 80.0, 55.7, 55.5, 50.9, 28.4, 25.8; HRMS (ESI) calcd for $C_{22}H_{25}N_3NaO_3$ [$(M+Na)^+$] 402.1794, found 402.1795.

(*Z*)-6-Oxo-6-phenylhex-4-en-1-yl 4-methylbenzenesulfonate: To a stirred solution of *cis*-6-azido-1-phenyl-2-propen-1-yl acetate (869.1 mg, 2.2 mmol)[3a] in CH_2Cl_2 (23 mL) was added diisobutylaluminium hydride (toluene solution, 3.3 mL, 1.01 M, 3.4 mmol) at -78 °C. After 1 h, the mixture was diluted with EtOAc followed by addition of saturated Rochell salt aqueous solution at room temperature. After 2 h with vigorous stir, the mixture was extracted with EtOAc and was washed with brine. Drying collected organic layer over Na_2SO_4 followed by silica gel column chromatography (hexane/EtOAc = 2/1) afforded the allyl alcohol (697.1 mg, 73%), which was submitted to the next reaction because of its instability.

To a vigorously stirred solution of the obtained allyl alcohol (659.1 mg, 1.9 mmol) in CH_2Cl_2 (19 mL) was added manganese dioxide (3.30 g, 37.9 mmol) at room temperature. After 11 h, the mixture was filtrated through Celite. The obtained filtrate was concentrated in vacuo followed by silica gel column chromatography (hexane/EtOAc = 4/1) to afford the product (425.1 mg, 65%). Colorless oil; R_f value 0.37 (hexane/EtOAc = 3/1); IR (NaCl, neat) ν_{max} 1665, 1359, 1230, 1175, 664, 554 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.92–7.90 (m, 2H), 7.77 (d, 2H, *J* = 8.0 Hz), 7.56 (m, 1H), 7.48–7.45 (m, 2H), 7.31 (d, 2H, *J* = 8.0 Hz), 6.83 (td, 1H, *J* = 11.0, 2.0 Hz), 6.25 (dt, 1H, *J* = 11.5, 7.5 Hz), 4.07 (t, 2H, *J* = 6.5 Hz), 2.65 (dtd, 2H, *J* = 7.5, 7.0, 2.0 Hz), 2.42 (s, 3H), 1.87 (tt, 2H, *J* = 7.5, 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.6, 146.9, 144.7, 138.2, 133.0, 132.9, 129.8, 128.6, 128.3, 127.9, 125.3, 70.0, 28.4, 25.8, 21.6; LRMS (EI) *m*/*z* 344 (M^+, 23%), 172 (47), 105 (100), 91 (87), 77 (69); HRMS (EI) calcd for $C_{19}H_{20}O_4S$ (M^+) 344.1082, found 344.1091.

(*Z*)-8-Azido-3-phenylocta-1,4-dien-3-ol (27): To a stirred solution of (*Z*)-6-oxo-6-phenylhex-4-en-1-yl 4-methylbenzenesulfonate (328.7 mg, 0.95 mmol) in THF (9.5 mL) was added vinylmagnesium bromide (THF solution, 3.8 mL, 1.0 M, 3.8 mmol) at -78 °C. After 1 h, saturated ammonium chloride aqueous solution was added to the mixture. The mixture was extracted with EtOAc and was washed with brine. Drying collected organic layer followed by silica gel column chromatography (hexane/EtOAc = 4/1) afforded the product as an inseparable mixture (248.9 mg).

To the stirred solution of the mixture (248.9 mg, 0.63 mmol) in DMF (6.3 mL) was added sodium azide (54.0 mg, 0.83 mmol), and the mixture was heated to 50 °C. After 40 min, the mixture was extracted with Et_2O, and was washed with water and brine. Drying collected organic layer followed by silica gel column chromatography (hexane/EtOAc = 6/1) afforded **27** (94.7 mg, 41% for 2 steps). Pale yellow oil; R_f value 0.57 (hexane/EtOAc = 3/1); IR (NaCl, neat) ν_{max} 3447, 2097, 1254, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2H), 7.34–7.31 (m, 2H), 7.24 (m, 1H), 6.19 (dd, 1H, *J* = 17.0, 10.0 Hz), 5.86 (td, 1H, *J* = 11.5, 2.0 Hz), 5.49 (dt, 1H, *J* = 11.5, 7.5 Hz), 5.34 (dd, 1H, *J* = 17.0, 1.0 Hz), 5.18 (dd, 1H, *J* = 10.0, 1.5 Hz), 3.11 (t, 2H, *J* = 6.5 Hz), 2.22–2.11 (m, 2H), 1.53 (tt, 2H, *J* = 7.5, 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.8, 143.5, 135.3, 132.0, 128.3, 127.2, 125.9, 112.6, 77.4, 50.7, 28.2, 25.2; HRMS (CI) calcd for $C_{14}H_{18}N_3O$ [$(M+H)^+$] 244.1450, found 244.1436.

6-(2-(3,4-Dimethoxyphenyl)-1*H*-inden-3-yl)-1-azabicyclo[3.1.0]hexane (26): To a stirred solution of **25** (18.6 mg, 0.049 mmol) in CH_2Cl_2 (0.5 mL) was added TMSOTf (18 μL, 0.1 mmol) at -78 °C. After 15 min, saturated ammonium chloride aqueous solution was added to stop the reaction. The mixture was extracted with CH_2Cl_2 and was washed with brine. Collected organic layer was dried over Na_2SO_4, and was concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 2/1 to 1/1) to afford **26** (5.5 mg, 34%). Pale yellow solid; R_f value 0.47 (hexane/EtOAc = 1/1); mp 79.9–80.7 °C; IR (NaCl, neat) ν_{max} 2958, 2935, 1515, 1461, 1262, 1244, 1026 cm^{-1}; ^1H NMR

(500 MHz, $CDCl_3$) δ 7.69 (d, 1H, *J* = 7.5 Hz), 7.41 (d, 1H, *J* = 7.5 Hz), 7.29 (t, 1H, *J* = 7.0 Hz), 7.17 (t, 1H, *J* = 7.5 Hz), 7.09 (dd, 1H, *J* = 8.0, 2.0 Hz), 7.05 (d, 1H, *J* = 1.5 Hz), 6.92 (d, 1H, *J* = 8.5 Hz), 3.94 (s, 3H), 3.93 (s, 3H), 3.82–3.59 (m, 2H), 3.28 (dd, 1H, *J* = 12.5, 8.0 Hz), 3.06 (dt, 1H, *J* = 11.5, 7.5 Hz), 2.58 (s, 1H), 2.54 (dd, 1H, *J* = 5.0, 3.0 Hz), 2.25 (dd, 1H, *J* = 13.0, 8.0 Hz), 2.02–1.94 (m, 1H), 1.76 (m, 1H), 1.63 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 148.2, 145.8, 142.6, 142.1, 135.2, 129.7, 126.4, 124.4, 123.2, 121.0, 111.6, 110.8, 55.9, 55.8, 53.3, 46.9, 41.2, 34.7, 26.3, 20.5; HRMS (ESI) calcd for $C_{22}H_{24}NO_2$ [$(M+H)^+$] 334.1807, found 334.1803.

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