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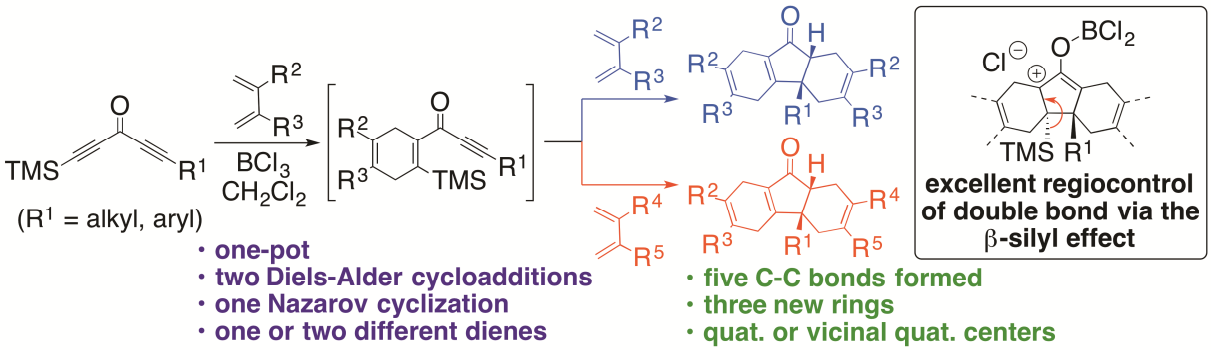
Graphical Abstract:



One-pot Synthesis of [6-5-6] Tricyclic Products via a Double Diels-Alder/Nazarov Tandem Reaction of Unsymmetrically Substituted Cross-conjugated Diynones

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Abstract: A highly concise one-pot method towards biologically pertinent compounds having a [6-5-6] tricyclic framework has been established. The multicomponent reaction utilizes a tandem, double Diels-Alder cycloaddition followed by a Nazarov reaction to furnish the [6-5-6] backbone. This method produces three fused rings evolving from the construction of five new carbon-carbon bonds, a quaternary carbon, and stereogenic centers in a one-pot reaction. The products are produced with excellent regio- and diastereocontrol.

Keywords: Diels-Alder cycloaddition; Nazarov reaction; multicomponent reaction; tandem reaction; terpenes

1. Introduction

Pharmaceutical endeavors toward biologically important molecules rely heavily on cost-effective and economical synthetic methodologies.[1] The use of relatively high-energy starting materials to achieve multiple carbon-carbon bond formation in a single pot reaction is a highly efficient technique to rapidly access advanced intermediates.[2,3] A number of efficacious examples targeting useful polycyclic substructures have recently been reported in the literature.[4–6] Five- and six-membered rings are highly prevalent in biologically active compounds, therefore routes towards these polycyclic structures receive considerable attention.[7,8] Cycloaddition reactions are one of the most innovative and influential strategies for synthesizing desirable cyclic target molecules. Since its discovery in 1928, the Diels-Alder reaction has been modified to meet current needs in chemistry, particularly by increasing functionality in the products.[9–11] The Nazarov cyclization is perhaps one of the most effective routes for the stereoselective formation of cyclopentenones.[12–16] Utilizing the Nazarov and Diels-Alder reactions in a cascade process to generate multiple rings in a one-pot reaction is a very pragmatic approach towards important biological scaffolds.[17,18] A number of biologically germane molecules: Hirsutellone B, taiwaniaquinol D, and gibberellic acid are characterized by a [6-5-6]-carbotricyclic skeleton, all of which involve numerous steps to construct (Figure 1).[19–22] Hirsutellone B displays potent activity against tuberculosis,[19] taiwaniaquinol D was found to exhibit potent cytotoxic activity against KB epidermoid carcinoma cancer cells,[23] and gibberellic acid is an important plant hormone. Therefore, the development of efficient methods to obtain the [6-5-6]-tricyclic core shared by these molecules is of value.

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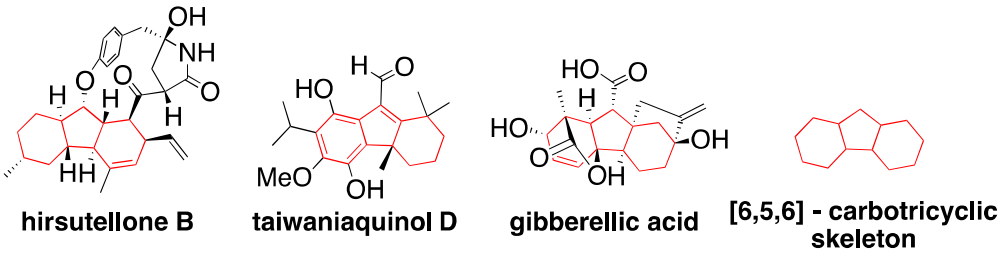


Figure 1. Biologically pertinent, naturally occurring compounds bearing a [6-5-6]-carbotricyclic skeleton.

2. Results and Discussion

We recently reported the multicomponent double Diels-Alder/Nazarov tandem reaction of symmetric cross-conjugated diynones **1** that could be conducted within a single reaction pot (Figure 2a).[17] When 1,5-bis(TMS)-1,4-diyn-3-one is employed as a substrate, desilylation of one TMS group occurs to ultimately provide product **2** with excellent regio- and diastereoselectivity. If the TMS groups in the substrate are exchanged for other groups (R^1 = aryl, alkyl) then products **3**, which contain vicinal quaternary centers, are produced. Unfortunately, the scope of products **2** that contain a single quaternary center is limited to trialkylsilyl-substituted adducts. To mend this limitation, we envisioned using unsymmetrically substituted TMS-substituted diynones **4** as substrates, where the TMS will be cleaved during the reaction and the R^4 group retained in the product (Figure 2b). Intermediate **5** can undergo a second cyclization with a second equivalent of the same diene to give product **6** where various substituents (R^4) can be envisioned at the quaternary center. An added advantage of this method is that one can also utilize a second equivalent of a different diene to afford an even broader scope of products such as **7**. Herein, we report a one-pot double Diels-Alder/Nazarov tandem reaction of unsymmetrically substituted diynones to produce [6-5-6]-tricyclic products with excellent regio- and diastereoselectivity.

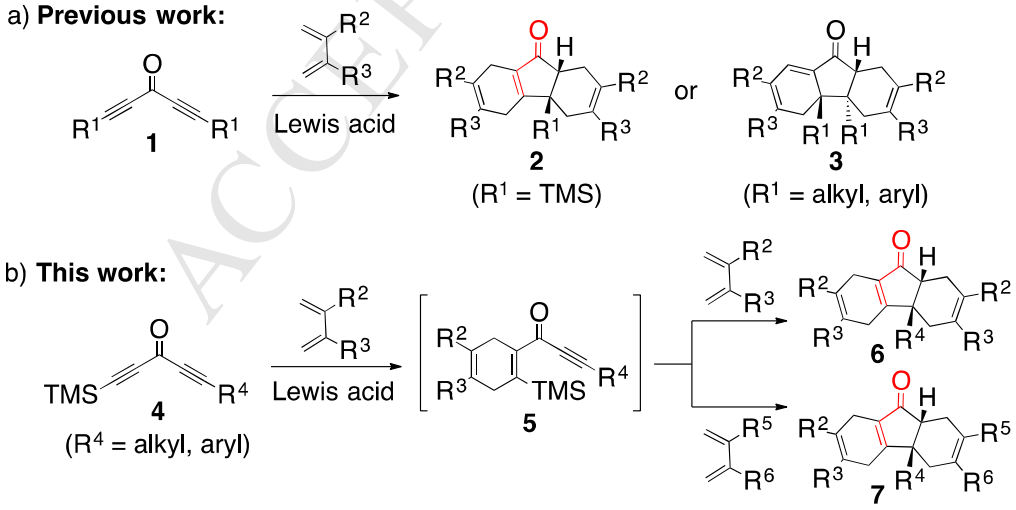


Figure 2. a) A double Diels-Alder/Nazarov reaction of symmetric diynones to produce [6-5-6] products with a quaternary (**2**) or vicinal quaternary (**3**) centers.[17] b) Proposed use of unsymmetrically substituted diynones **4** and various dienes to broaden the scope of this reaction.

Regiochemical control is a common obstacle that plagues the utility of the Nazarov reaction.[24] The utilization of the β-silyl effect in the Nazarov reaction to elicit high regiocontrol of the products has proven to be an exceedingly valuable tool.[17,25–27] The incorporation of a TMS-substituent in substrate **4** not only stabilizes the oxyallyl cation intermediate **8** through the β-silyl effect but also results in a very regioselective elimination of the TMS group to provide product **6** (Figure 3). Using this as the foundation for this work, we set out to survey unsymmetrically substituted cross-conjugated diynones in a one-pot double Diels-Alder/Nazarov tandem reaction.

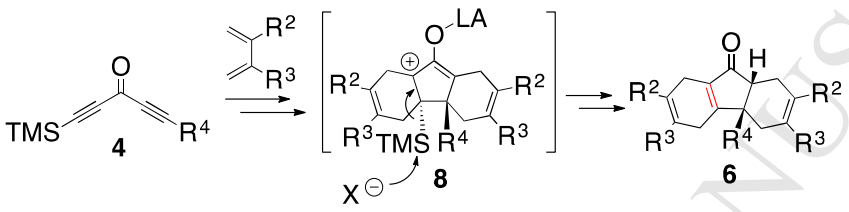
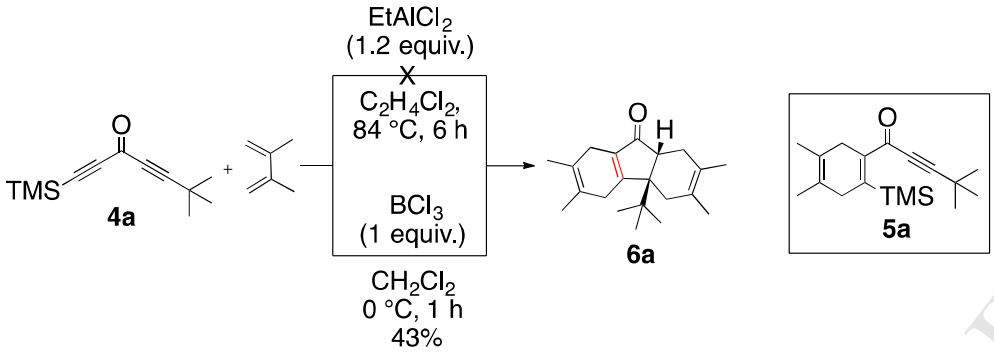


Figure 3. Nazarov cyclization and stabilization of the carbocation intermediate via the β-silyl effect.

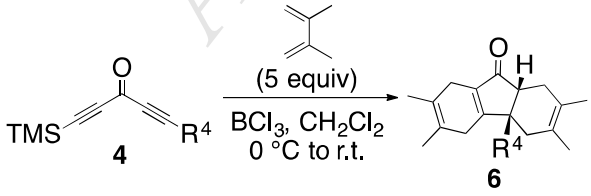
We chose to explore the cyclization reaction of bulky diynone **4a** due to its stability and ease of handling. Use of this diynone also allowed for a direct comparison of the double Diels-Alder cycloaddition with respect to substituents of similar size (TMS vs *tert*-butyl). We initially attempted to use our previously reported conditions to invoke the tandem cyclization reaction.[17] Unfortunately, compound **4a** only produced monocyclized product **5a** in the presence of ethylaluminum dichloride with no detection of **6a**, even at elevated temperatures (Scheme 1). The high regioselectivity of the single Diels-Alder reaction product was interesting as we envisioned that this might prove useful for mixed Diels-Alder reactions (*vide infra*). Nonetheless, it seemed that ethylaluminum dichloride was not sufficiently strong enough for this one-pot reaction. Thus, we turned to using boron trichloride since we have recently reported the successful use of this catalyst for the cyclization of challenging symmetric diynones.[17] Indeed, boron trichloride worked well to provide **6a** in 43% yield (Scheme 1). One should note that this modest overall yield is the product of two separate Diels-Alder reactions and a Nazarov cyclization that equates to roughly 75% yield per reaction accompanied by the formation of five new carbon-carbon bonds, three new rings, and vicinal quaternary centers. As we had predicted, the elimination of the TMS group provided excellent regioselectivity for the newly formed double bond in compound **6b** (shown in red). The major diastereomer contains a *syn* relationship between the methine hydrogen and the *tert*-butyl group and was assigned based on NOESY NMR experiments. This result is also consistent with what was reported for compound **2** (Figure 2).[17]



Scheme 1. Double Diels-Alder/Nazarov tandem reaction of sterically hindered diynone **4a** and 2,3-dimethyl-1,3-butadiene to generate [6-5-6]-carbotricyclic product **6a** catalyzed by BCl_3.

We synthesized a variety of TMS-substituted diynones **4** to establish the scope of the unsymmetrically substituted diynone system and its applicability for targeting a wide range of [6-5-6]-carbotricyclic derivatives (Table 1). Interestingly, we determined that the product with the larger *tert*-butyl substituent (**6a**, entry 1) was actually obtained in higher yield versus the smaller methyl-substituted derivative (**6b**, entry 2). Diynone **4c** provided product **6c** in a moderate 32% yield (entry 3). Not surprisingly, electron-rich aryl groups on substrates **4d** and **4e** proved to be more difficult for the Diels-Alder cycloaddition but nevertheless generated the desired tricyclic products **6d** and **6e** in modest yields of 24% and 32%, respectively (entries 4 and 5). It should be noted that the skipped cyclohexadiene moiety in product **6d** (entry 4) had partially oxidized to an aromatic ring over the course of the reaction and this side-product was separated and isolated in 6% yield (see supporting information for details). The bromine-substituted aryl derivatives **4f** and **4g** (entries 6 and 7) underwent the tandem double Diels-Alder/Nazarov reaction rapidly to generate the corresponding products **6f** and **6g** in relatively good yields of 29% and 42%, respectively. The fluorine-substituted aryl derivatives **4h** and **4i** (entries 8 and 9) also performed well to give **6h** and **6i** in 38% and 43% yield, respectively. All of the tricyclic products **6a-i** were generated with excellent regio- and diastereoselectivity. As is common with cyclic "skipped dienes", we observed that products **6a-i** would begin to oxidize if exposed to air under the reaction conditions or if left under an air atmosphere for an extended period of time.[10,11] For many of the reactions, only the two expected diastereomeric products were detected by GC-MS analysis. However, in entries 1 and 2 we observed an additional minor isomer (uncharacterized) that is possibly the result of double bond migration.[17]

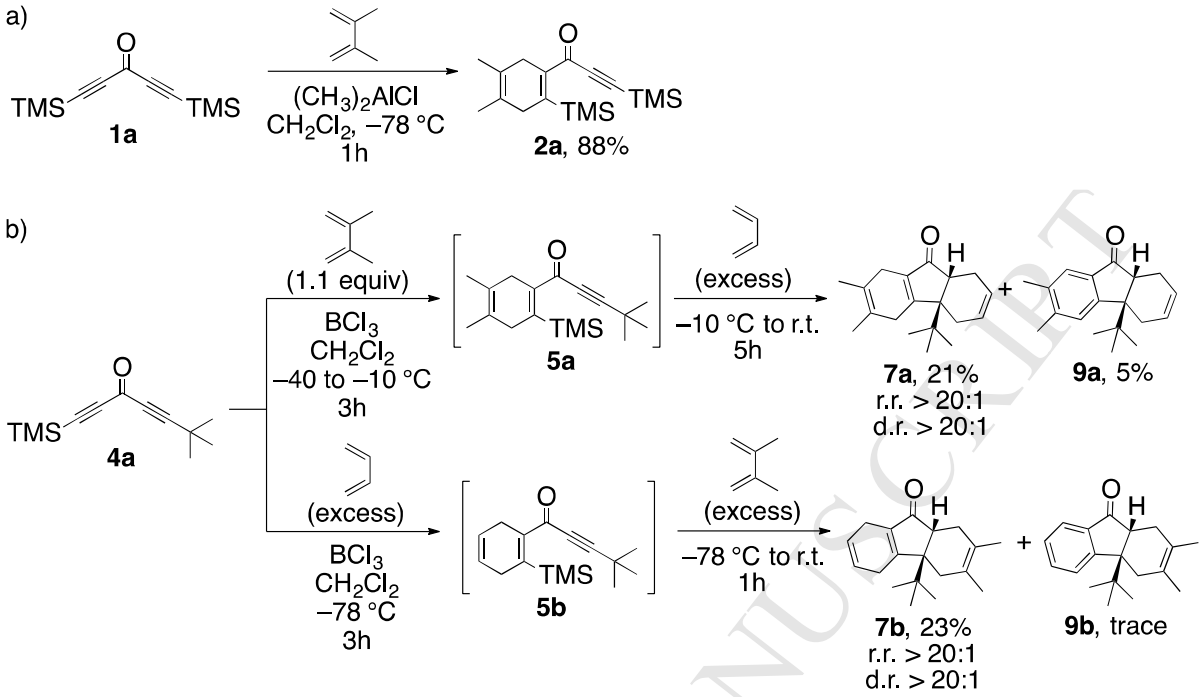
Table 1. Substrate scope of diynone **4**.



Entry	Substrate	R^4	Product	Yield [%][a]	Isomeric ratio[b]
1	**4a**	*t*-butyl	**6a**	43	15:2:1[c]
2	**4b**	Me	**6b**	17	15:1:1[c]
3	**4c**	C_6H_5	**6c**	32	>20:1
4	**4d**	*o*-MeO-C_6H_4	**6d**	24[d,e]	>20:1
5	**4e**	*p*-MeO-C_6H_4	**6e**	32	>20:1
6	**4f**	*o*-Br-C_6H_4	**6f**	29[e]	12:1
7	**4g**	*p*-Br-C_6H_4	**6g**	42	>20:1
8	**4h**	*o*-F-C_6H_4	**6h**	38[e]	>20:1
9	**4i**	*p*-F-C_6H_4	**6i**	43	>20:1

[a] Isolated yield of major isomer. [b] Crude diastereomeric ratio of products determined by GC-MS analysis. [c] An uncharacterized third minor isomer was detected possibly due to double bond migration in the product. [d] Oxidized/aromatized side-product (**S10**) was also isolated in 6% yield. [e] The NOESY data was ambiguous; therefore, the stereochemistry was assigned by analogy.

In a previous study, we noted that at low temperatures we could selectively form the monocyclized product **2a** in good yield, even in the presence of excess diene (Scheme 2a).[17] With this result we imagined that we could employ a timed double Diels-Alder reaction between compound **4** and two different dienes to arrive at highly functionalized [6-5-6]-tricyclic products with excellent regiocontrol. We were thrilled to find that by carrying out the reaction between unsymmetrically substituted diynone **4a** and 1.1 equivalents of 2,3-dimethyl-1,3-butadiene at low temperature, the Diels-Alder cycloaddition occurred exclusively with the silyl-substituted alkyne to generate the monocyclic intermediate **5a** (Scheme 2b). Corey and coworker have also observed that silyl-substituted alkynes react faster as dienophiles than alkyl-substituted alkynes in an analogous Diels-Alder reaction.[28] After the formation of **5a**, the addition of an excess amount of a second diene (1,3-butadiene) in the same reaction pot, followed by warming to room temperature, provided asymmetric product **7a** in a modest 21% yield with excellent regio- and diastereoselectivity. We could also change the order of diene addition to provide **7b** in 23% yield with excellent regio- and diastereoselectivity. We should point out that the expected side-product from the double cycloaddition of 1,3-butadiene was not detected upon workup. Presumably, this is because the relative rate of cycloaddition is much higher for 2,3-dimethyl-1,3-butadiene during the second Diels-Alder reaction. This proof-of-concept demonstrates that we can indeed arrive at a host of [6-5-6]-tricyclic products using this timed double Diels-Alder method with a high level of regiocontrol.



Scheme 2. a) Formation and isolation of monocyclized product **2a** at low temperatures suggesting a timed double Diels-Alder reaction is possible.[17] b) Demonstration of a timed double Diels-Alder cycloaddition with two different dienes followed by a Nazarov cyclization to generate **7a** and **7b** as the major isomers along with a small amount of oxidized products **9a** and **9b**.

3. Conclusions

In summary, we have demonstrated a double Diels-Alder/Nazarov tandem reaction of unsymmetrically substituted diynones to yield biologically important [6-5-6] tricyclic scaffolds in a one-pot reaction. Additionally, we have demonstrated that a controlled, multicomponent diene system can undergo a timed double Diels-Alder cycloaddition to generate highly functionalized [6-5-6]-carbotricyclic products in a single reaction pot. The one-pot double Diels-Alder/Nazarov tandem reaction is highly regioselective and diastereoselective, providing very concise and efficient access to important molecules, while also imparting useful functional handles (isolated and conjugated double bonds and a ketone) for further chemical elaboration.

4. Experimental

4.1. General Methods

Reagents were purchased reagent grade from commercial suppliers and used without further purification unless otherwise noted. CH_2Cl_2 and THF were purified using a PureSolv MD 5 solvent purification system. Ethynyltrimethylsilane was distilled before use. Evaporation and concentration in vacuo by rotary evaporation. Where appropriate, reactions were performed in standard, dry glassware under an inert atmosphere of N_2. Column chromatography: Silica gel

irregular 60 Å (40-60 micron) from VWR International. The bulb-to-bulb distillation was performed using a kugelrohr apparatus, Büchi GKR-51. Thin-layer chromatography (TLC): glass sheets covered with silica gel 60 F_{254} from Millipore a Corporation; visualization by UV light, anisaldehyde stain or $KMnO_4$ stain. Mp: Mel-Temp apparatus; uncorrected. IR spectra (cm^{-1}): Thermo Nicolet 6700 FT-IR (diamond ATR), data are reported as cm^{-1}. ^1H and ^{13}C NMR: Varian NMR 400 MHz, 500 MHz at r.t. in $CDCl_3$; solvent peaks (7.26 ppm and 77.16 ppm for ^1H and ^{13}C, respectively) or C_6D_6; solvent peaks (7.16 ppm and 128.06 ppm for ^1H and ^{13}C, respectively) as reference. GCMS (EI): Agilent 7890A with a 5970C mass spectrometer with triple axis detector using a 122-5532UI DB-5MS Ui column (30m x 0.25mm). ESI-TOF and APCI-TOF MS: Agilent G6230A instrument with purine and HP-Ø921 as internal calibrants.

4.2. General experimental procedure for 1,4-pentadiyn-3-ols (S1-S9)

General procedure A:[29] To a solution of *n*-butyllithium (1.0 equiv.) in tetrahydrofuran (15 mL) at –78 ºC under N_2 atmosphere was added terminal alkyne (1.0 equiv.). After 15 minutes of stirring 3-(trimethylsilyl)-2-propynal (1.1 equiv.) was added slowly and the reaction was slowly warmed to r.t. and stirred until complete by TLC. The reaction was quenched at –78 ºC through the addition of saturated aqueous NH_4Cl and extracted with Et_2O. The layers were separated, the organic phase washed with H_2O, brine, and dried over Na_2SO_4. The mixture was filtered and the solvent was removed in vacuo to provide the crude product.

General procedure B: To a solution of *n*-butyllithium (1.1 equiv.) in tetrahydrofuran (15 mL) at –78 ºC under N_2 atmosphere was added ethynyltrimethylsilane (1.1 equiv.). After 15 minutes of stirring the 3-aryl-2-propynal[30,31] (1.0 equiv.) was added dropwise and the reaction was slowly warmed to r.t. and stirred until complete by TLC. The reaction was quenched at –78 ºC through the addition of saturated aqueous NH_4Cl and extracted with Et_2O. The layers were separated, the organic phase washed with H_2O, brine, and dried over Na_2SO_4. The mixture was filtered and the solvent was removed in vacuo to provide the crude product.

4.2.1. 1-(4-methoxyphenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-ol (**S1**). This reaction was performed according to general procedure A.[29] 4-Ethynylanisole (954 mg, 7.20 mmol) in THF (20 mL). Crude alcohol **S1** was isolated (1.51 g, 81%) as a light brown oil and was used without purification: R_f = 0.3 (EtOAc:hexanes, 1:10); ^1H NMR (400 MHz, C_6D_6): δ = 7.25 – 7.19 (m, 2H), 6.48 – 6.42 (m, 2H), 5.18 (d, J = 6.6 Hz, 1H), 3.07 (s, 3H), 1.72 (d, J = 6.8 Hz, 1H), 0.07 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6): δ = 160.4, 133.7, 114.7, 114.3, 103.5, 89.0, 85.8, 84.8, 54.7, 53.5, –0.3; IR (film): 3414, 2961, 2224, 1610, 1511, 1252 cm^{-1}; HRMS (APCI-TOF) *m*/*z* calcd for $[C_{15}H_{18}O_2Si - OH)]^+$ 241.1043; found 241.1034.

4.2.2. 1-(2-methoxyphenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-ol (**S2**). This reaction was performed according to general procedure A.[29] 2-Ethynylanisole (954 mg, 7.20 mmol) in THF (20 mL). Crude alcohol **S2** was purified by column chromatography [pH 7 buffered phosphate silica gel; EtOAc/ CH_2Cl_2/hexanes (1:29:70)] to yield **S2** (1.53 g, 82 %) as a yellow-orange oil: R_f = 0.2 (CH_2Cl_2:hexanes, 2:3); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 – 7.39 (m, 1H), 7.34 – 7.25 (m, 1H), 6.94 – 6.79 (m, 2H), 5.41 (d, J = 5.2 Hz, 1H), 3.87 (s, 3H), 2.88 (d, J = 6.1 Hz, 1H), 0.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3 133.9, 130.4, 120.5, 111.3, 110.8,

102.1, 90.2, 89.5, 80.9, 55.9, 53.3, –0.2; IR (film): 3411, 2952, 2236, 1594, 1492, 1261 cm^{-1}; HRMS (APCI-TOF) *m/z* calcd for $[C_{15}H_{18}O_2Si - OH]^+$ 241.1043; found 241.1034.

4.2.3. 1-(4-bromophenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-ol (**S3**). This reaction was performed according to general procedure B. 3-(4-Bromophenyl)-2-propynal[30,31] (553 mg, 2.65 mmol) in THF (30 mL). Crude alcohol **S3** was isolated (770 mg, 95%) as a light brown oil and was used without purification: R_f = 0.4 (EtOAc:hexanes, 1:10); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 – 7.42 (m, 2H), 7.32 – 7.29 (m, 2H), 5.34 (s, 1H), 2.67 (s, 1H), 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.4, 131.7, 123.3, 121.0, 101.6, 90.1, 87.1, 83.5, 53.1, –0.2; IR (film): 3294, 2955, 2236, 2179, 1483, 1245 cm^{-1}; HRMS (APCI-TOF) *m/z* calcd for $[C_{14}H_{15}BrOSi - OH]^+$ 289.0043; found 289.0033.

4.2.4. 1-(2-bromophenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-ol (**S4**). This reaction was performed according to general procedure B. 3-(2-Bromophenyl)-2-propynal[29,30] (986 mg, 4.72 mmol) in THF (20 mL). Crude alcohol **S4** was isolated (1.51 g, 81%) as a brown oil and was used without purification: R_f = 0.4 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 – 7.54 (m, 1H), 7.51 – 7.44 (m, 1H), 7.27 – 7.21 (m, 1H), 7.19 – 7.13 (m, 1H), 5.39 (s, 1H), 2.68 (s, 1H), 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.7, 132.5, 130.1, 127.1, 125.9, 124.2, 101.5, 90.4, 90.1, 83.1, 53.2, –0.2; IR (film): 3348, 2961, 2895, 2173, 2097, 1632, 1470 cm^{-1}; HRMS (ESI-TOF) *m/z* calcd for $[C_{14}H_{15}BrOSi - OH]^+$ 289.0043; found 289.0036.

4.2.5. 1-phenyl-5-(trimethylsilyl)-1,4-pentadiyn-3-ol (**S5**). This compound was synthesized following a known procedure.[32] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 – 7.42 (m, 2H), 7.37 – 7.26 (m, 3H), 5.37 (d, *J* = 5.5 Hz, 1H), 2.73 (s, 1H), 0.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.9, 128.9, 128.4, 122.0, 101.9, 89.8, 86.0, 84.5, 53.1, –0.2.

4.2.6. 1-(4-fluorophenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-ol (**S6**). This reaction was performed according to general procedure B. 3-(4-Fluorophenyl)-2-propynal[29,31] (1.08 g, 7.30 mmol) in THF (20 mL). Crude alcohol **S6** was isolated (1.49 g, 83%) as a yellow oil and was used without purification: R_f = 0.4 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 – 7.39 (m, 2H), 7.02 – 6.92 (m, 2H), 5.35 (s, 1H), 2.86 (s, 1H), 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8 (d, *J* = 250.2 Hz), 133.9 (d, *J* = 8.7 Hz), 118.1 (d, *J* = 3.6 Hz), 115.7 (d, *J* = 22.3 Hz), 101.8, 89.9, 85.8 (d, *J* = 1.6 Hz), 83.5, 53.0, –0.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ = –110.0; IR (film): 3335, 2961, 2901, 2230, 2179, 1600, 1505 cm^{-1}; HRMS (APCI-TOF) *m/z* calcd for $[C_{14}H_{15}FOSi+H]^+$ 247.0949; found 247.0942.

4.2.7. 1-(2-fluorophenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-ol (**S7**). This reaction was performed according to general procedure A.[29] 2-fluorophenylacetylene (239 mg, 1.99 mmol) in THF (10 mL). Crude alcohol **S7** was isolated (188 mg, 38%) as a yellow oil by fractional distillation: R_f = 0.4 (EtOAc:hexanes, 1:10); ^{1}H NMR (100 MHz, C_6D_6): δ = 7.16 – 7.10 (m, 1H), 6.77 – 6.68 (m, 1H), 6.67 – 6.61 (m, 1H), 6.60 – 6.53 (m, 1H), 5.22 (s, 1H), 2.29 (s, 1H), 0.10 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6): δ = 163.3 (d, *J* = 251.7 Hz), 133.9 (d, *J* = 1.2 Hz), 130.6 (d, *J* = 7.9 Hz), 124.0 (d, *J* = 3.9 Hz), 115.6 (d, *J* = 20.9 Hz), 111.2 (d, *J* = 15.6 Hz), 102.8, 92.3 (d, *J* = 3.0 Hz), 89.5, 78.1, 53.3, –0.3; ^{19}F NMR (376 MHz, C_6D_6) δ = –109.6; IR (film): 3408, 2961, 2278, 1689, 1644, 1492 cm^{-1}; HRMS (APCI-TOF) *m/z* calcd for $[C_{14}H_{15}FOSi+H]^+$ 247.0949; found 247.0945.

4.2.8. 1-*tert*-butyl-5-(trimethylsilyl)-1,4-pentadiyn-3-ol (**S8**).[29] To a solution of *n*-butyllithium (4.00 mL, 10.0 mmol, 2.50 M in hexanes) in tetrahydrofuran (15 mL) at –78 ºC under N_2 atmosphere was added ethynyltrimethylsilane (1.10 g, 11.2 mmol). After 45 minutes of stirring **S8** (1.0 g, 9.0 mmol) was added dropwise and the reaction was slowly warmed to r.t. and stirred until complete by TLC. The reaction was quenched at –78 ºC through the addition of saturated aqueous NH_4Cl and extracted with Et_2O. The layers were separated, the organic phase washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed in vacuo to yield **S8** (88%) as a light yellow solid: M.p.: 39–41 ˚C; R_f = 0.5, (EtOAc:hexanes, 1:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.01 (s, 1H), 3.02 (s, 1H), 1.14 (s, 9H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 103.2, 93.0, 88.2, 76.2, 52.4, 30.6, 27.2, –0.3; IR (film): 3326, 2965, 2243, 2173 cm^{-1}; HRMS (APCI-TOF) *m*/*z* calcd for $[C_{12}H_{20}OSi - OH]^+$ 191.1251; found 191.1253.

4.2.9. 1-(trimethylsilyl)-1,4-hexadiyn-3-ol (**S9**). This compound was synthesized following a known procedure.[33]

4.3. General experimental procedure for 1,4-pentadiyn-3-one (4a-i)

Dichloromethane was added to a mixture of sieves (2 wt. equiv.), celite (2 wt. equiv.), and pyridinium chlorochromate (2 equiv.). A dilute solution of 1,4-pentadiyn-3-ol (**4a**, **4c**, **4e**, **4h**) (1 equiv.) in dichloromethane was added slowly to the reaction mixture and stirred overnight or until complete by TLC. The resulting mixture was filtered through a celite/silica gel plug. The solvent was removed in vacuo and the crude product used without further purification. $BaMnO_4$ (4 equiv.) in dichloromethane was used for 1,4-pentadiyn-3-ol (**4b**, **4d**, **4f**, **4g**, and **4i**) (1 equiv.) and stirred overnight or until complete by TLC. The resulting mixture was purified by filtering through a celite/silica gel plug.

4.3.1 1-*tert*-butyl-5-(trimethylsilyl)-1,4-pentadiyn-3-one (**4a**). Alcohol **S8** (5.24 g, 25.2 mmol). The crude product used without further purification, **4a** (59%) as a pale brown solid: M.p.: 37–40 ˚C; R_f = 0.6, (EtOAc:hexanes, 1:10); ^{1}H NMR (500 MHz, $CDCl_3$): 1.25 (s, 9H), 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 102.9, 102.5, 97.6, 80.8, 29.8, 27.9, –0.9; IR (film): 2975, 2219, 1614 cm^{-1}; HRMS (APCI-TOF) *m*/*z* calcd for $[C_{12}H_{18}SiO+H]^+$ 207.1200; found 207.1198.

4.3.2 1-(trimethylsilyl)-1,4-hexadiyn-3-one (**4b**). This compound was synthesized from **S9** following a known procedure.[33]

4.3.3 1-phenyl-5-(trimethylsilyl)-1,4-pentadiyn-3-one (**4c**).[32] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 – 7.60 (m, 2H), 7.51 – 7.46 (m, 1H), 7.44 – 7.36 (m, 2H), 0.29 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 133.5, 131.4, 128.8, 119.5, 102.8, 99.4, 91.8, 89.4, –0.7.

4.3.4 1-(2-methoxyphenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-one (**4d**). Alcohol **S2** (1.53 g, 5.90 mmol). Crude ketone **4d** was isolated (860 mg, 57 %) as a yellow oil and was used without purification: R_f = 0.3 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 – 7.47 (m, 1H), 7.41 (ddd, *J* = 9.1, 7.6, 1.8 Hz, 1H), 6.96 – 6.85 (m, 2H), 3.86 (s, 3H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0, 160.5, 135.2, 133.2, 120.6, 111.0, 108.5, 102.8, 98.8, 93.5,

89.5, 55.9, –0.8; IR (film): 2968, 2202, 1616, 1489, 1464, 1277, 1245 cm^{-1}; HRMS (APCI-TOF) *m*/*z* calcd for $[C_{15}H_{16}O_2Si+H]^+$ 257.0992; found 257.0986.

4.3.5 1-(4-methoxyphenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-one (**4e**). Alcohol **S1** (1.51 g, 5.84 mmol). Crude ketone **4e** was isolated (308 mg, 21%) as a yellow solid and was used without purification: R_f = 0.3 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55 – 7.49 (m, 2H), 6.89 – 6.83 (m, 2H), 3.80 (s, 3H), 0.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 160.4, 135.5, 114.5, 110.9, 102.8, 98.4, 93.2, 89.6, 55.4, –0.8; IR (film): 2968, 2838, 2195, 1619, 1596, 1515 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $[C_{15}H_{16}O_2Si+H]^+$ 257.0992; found 257.0989.

4.3.6 1-(2-bromophenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-one (**4f**). Alcohol **S4** (1.34 g, 4.36 mmol). Crude alcohol **4f** was isolated (1.01 g, 76%) as a burnt orange oil and was used without purification: R_f = 0.5 (EtOAc:hexanes, 1:10); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63 – 7.53 (m, 2H), 7.35 – 7.22 (m, 2H), 0.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 135.0, 132.9, 132.3, 127.4, 127.2, 121.9, 102.6, 100.1, 92.2, 89.6, –0.9; IR (film): 2958, 2202, 2145, 1625, 1461, 1426, 1255 cm^{-1}; HRMS (APCI-TOF) *m*/*z* calcd for $[C_{14}H_{13}BrOSi+H]^+$ 304.9992; found 304.9986.

4.3.7 1-(4-bromophenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-one (**4g**). Alcohol **S3** (770 mg, 2.51 mmol). Crude ketone **4g** was isolated (598 mg, 78%) as a yellow oil and was used without purification: R_f = 0.4 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (dd, *J* = 8.6, 1.9 Hz, 2H), 7.46 (dd, *J* = 8.5, 2.0 Hz, 2H), 0.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3, 134.7, 132.2, 126.3, 118.4, 102.6, 99.8, 90.1, 90.0, –0.8; IR (film): 2965, 2208, 2145, 1616, 1584, 1480, 1274 cm^{-1}; HRMS (APCI-TOF) *m*/*z* calcd for $[C_{14}H_{13}BrOSi+H]^+$ 304.9992; found 304.9981.

4.3.8 1-(2-fluorophenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-one (**4h**). Alcohol **S7** (188 mg, 0.763 mmol). Crude ketone **4h** was isolated (126 mg, 68%) as a yellow oil and was used without purification: R_f = 0.5 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, C_6D_6): δ = 6.97 – 6.93 (m, 1H), 6.76 – 6.70 (m, 1H), 6.57 – 6.41 (m, 2H), 0.00 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6): δ = 164.02 (d, *J* = 256.3 Hz), 159.77, 134.9, 133.16 (d, *J* = 8.2 Hz), 124.3 (d, *J* = 4.0 Hz), 115.9 (d, *J* = 20.2 Hz), 108.6 (d, *J* = 15.2 Hz), 103.4, 99.0, 94.1 (d, *J* = 3.4 Hz), 84.3, –1.2; ^{19}F NMR (376 MHz, C_6D_6) δ = –107.0; IR (film): 2958, 2211, 1622, 1489, 1258, 1128 cm^{-1}; HRMS (APCI-TOF) *m*/*z* calcd for $[C_{14}H_{13}FOSi+H]^+$ 245.0792; found 245.0807.

4.3.9 1-(4-fluorophenyl)-5-(trimethylsilyl)-1,4-pentadiyn-3-one (**4i**). Alcohol **S6** (1.49 g, 6.05 mmol). Crude ketone **4i** was isolated (1.16 g, 78%) as a brown oil and was used without purification: R_f = 0.6 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 – 7.56 (m, 2H), 7.11 – 7.03 (m, 2H), 0.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3 (d, *J* = 254.9 Hz), 160.3, 135.8 (d, *J* = 9.0 Hz), 116.4 (d, *J* = 22.5 Hz), 115.6 (d, *J* = 3.5 Hz), 102.6, 99.4, 90.5, 89.2 (d, *J* = 1.5 Hz), –0.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ = –105.1; IR (film): 2965, 2211, 2148, 1622, 1594, 1502 cm^{-1}; HRMS (APCI-TOF) *m*/*z* calcd for $[C_{14}H_{13}FOSi+H]^+$ 245.0792; found 245.0788.

4.4. Experimental procedure for 9*H*-fluoren-9-ones (6a-i)

4.4.1. 1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(*tert*-butyl)-9*H*-fluoren-9-one (**6a**). To a solution of **4a** (124 mg, 0.600 mmol) in CH_2Cl_2 (9 mL) under N_2 at 0 ˚C was added boron trichloride (0.59 mL, 0.59 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (240 mg, 2.96 mmol). The reaction was stirred until complete by TLC (1.5 h). The reaction was quenched at 0 ˚C with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The layers were separated, the organic phase washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; EtOAc/hexanes (1:30)] to yield **6a** (76 mg, 43%) as a white solid. The isomeric ratio of the crude product was determined to be 15:2:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 200 ˚C for 5 min., ramp at 2 ˚C/min. to 250 ˚C and hold for 10 min.). The isomeric ratio of the purified product **6a** to all other isomers was determined to be >20:1 by ^{1}H NMR analysis: R_f = 0.4 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.93 (dd, J = 15.0, 7.5 Hz, 2H), 2.70 – 2.61 (m, 2H), 2.44 (dd, J = 5.7, 2.5 Hz, 1H), 2.37 (dd, J = 14.4, 2.6 Hz, 1H), 2.24 (dd, J = 13.9, 2.8 Hz, 1H), 2.11 – 1.97 (m, 2H), 1.69 (s, 3H), 1.67 (s, 3H), 1.54 (s, 3H), 1.49 (s, 3H), 0.95 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.6, 173.0, 139.5, 126.8, 125.8, 123.3, 121.7, 56.5, 49.8, 36.4, 35.1, 33.8, 32.9, 28.6, 27.3, 19.5, 19.2, 18.9, 18.6; IR (film): 2965, 2908, 1701, 1644, 1432, 1369 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $[C_{21}H_{30}O+H]^+$ 299.2369; found 299.2374.

4.4.2. 1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(methyl)-9*H*-fluoren-9-one (**6b**). To a solution of **4b** (72 mg, 0.44 mmol) in CH_2Cl_2 (8 mL) under N_2 at 0 °C was added boron trichloride (0.44 mL, 0.44 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (181 mg, 2.20 mmol). The reaction was stirred until complete by TLC (40 min). The reaction was quenched at 0 °C with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The layers were separated, the organic phase washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; EtOAc/hexanes (1:30)] to yield **6b** (19 mg, 17 %) as an off-white solid. The isomeric ratio of the crude product was determined to be 15:1:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 200 ˚C for 5 min., ramp at 1 ˚C/min. to 250 ˚C and hold for 10 min.). The isomeric ratio of the purified product **6b** to all other isomers was determined to be >20:1 by ^{1}H NMR analysis: R_f = 0.5 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, C_6D_6): δ = 2.81 – 2.72 (m, 2H), 2.56 – 2.50 (m, 3H), 2.13 (dd, J = 14.6, 6.4 Hz, 1H), 2.03 (dd, J = 6.6, 3.6 Hz, 1H), 1.80 – 1.70 (m, 2H), 1.63 (s, 3H), 1.52 (s, 3H), 1.45 (s, 3H), 1.43 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ = 206.7, 172.3, 137.3, 127.5, 126.1, 124.1, 121.4, 53.9, 45.6, 40.5, 31.9, 30.8, 29.3, 25.0, 19.4, 19.2, 18.8, 18.5; IR (film): 2908, 2851, 1701, 1654, 1442, 1378, 1302 cm^{-1}; HRMS (APCI-TOF) *m*/*z* calcd for $[C_{18}H_{24}O+H]^+$ 257.1900; found 257.1904.

4.4.3. 1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(phenyl)-9*H*-fluoren-9-one (**6c**). To a solution of **4c** (153 mg, 0.676 mmol) in CH_2Cl_2 (10 mL) at 0 ˚C under N_2 was added boron trichloride (0.68 mL, 0.68 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (276 mg, 3.36 mmol). The reaction was stirred until complete by TLC (2 h). The reaction was quenched at 0 ˚C with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The layers were separated, the organic phase washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product purified by recrystallization from hexanes at 0 ˚C to yield **4c** (68 mg, 32%) as an off-white solid. The diastereomeric ratio of the crude product was

determined to be >20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 220 ˚C for 5 min., ramp at 1 ˚C/min. to 260 ˚C and hold for 10 min.). The diastereomeric ratio of the purified product was determined to be >20:1 by GC analysis: R_f = 0.3 (EtOAc:hexanes, 1:20); ^{1}H NMR (400 MHz, C_6D_6): δ = 7.22 – 7.16 (m, 4H), 7.13 – 7.05 (m, 1H), 2.95 – 2.87 (m, 2H), 2.68 (dd, *J* = 6.7, 3.1 Hz, 1H), 2.64 – 2.49 (m, 3H), 2.44 – 2.30 (m, 1H), 2.21 (d, *J* = 14.6 Hz, 1H), 2.18 – 2.10 (m, 1H), 1.65 (s, 3H), 1.59 (s, 3H), 1.46 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ = 207.5, 172.0, 145.5, 138.6, 129.0, 127.7, 126.8, 126.7, 125.4, 123.6, 121.7, 57.0, 53.7, 36.2, 32.3, 31.6, 29.4, 19.4, 19.1, 18.6, 18.5; IR (film): 2984, 2917, 2854, 1698, 1651 cm^{-1}; HRMS (APCI-TOF) *m*/*z* calcd for $[C_{23}H_{26}O+H]^+$ 319.2056; found 319.2063.

4.4.4. 1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(2-methoxyphenyl)-9*H*-fluoren-9-one (**6d**). To a solution of **4d** (138 mg, 0.538 mmol) in CH_2Cl_2 (10 mL) under N_2 at 0 °C was added boron trichloride (0.54 mL, 0.54 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (222 mg, 2.70 mmol). The reaction was stirred until complete by TLC (2-2.5 h). The reaction was quenched at 0 °C with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The layers were separated, the organic phase washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; EtOAc/hexanes (1:20)] to yield **6d** (45 mg, 24%) as a white solid. The diastereomeric ratio of the crude product was determined to be >20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 220 ˚C for 5 min., ramp at 1 ˚C/min. to 250 ˚C and hold for 10 min.). The diastereomeric ratio of the purified product was determined to be >20:1 by ^{1}H NMR analysis: R_f = 0.4 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 – 7.20 (m, 2H), 6.97 – 6.93 (m, 1H), 6.85 – 6.83 (m, 1H), 3.65 (s, 3H), 2.87 (dd, *J* = 7.1, 3.0 Hz, 1H), 2.83 – 2.62 (m, 4H), 2.46 (dt, *J* = 22.8, 7.2 Hz, 1H), 2.35 (dd, *J* = 15.1, 3.1 Hz, 1H), 2.26 (d, *J* = 14.1 Hz, 1H), 2.28 – 2.20 (m, 1H), 1.71 (s, 3H), 1.67 (s, 3H), 1.63 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.8, 172.4, 158.2, 137.2, 132.1, 128.1, 128.0, 127.2, 124.9, 123.5, 121.8, 120.5, 111.8, 55.3, 53.2, 52.2, 37.4, 32.5, 32.1, 29.0, 19.5, 19.0, 18.8, 18.8; IR (film): 2984, 2917, 2854, 1689, 1654, 1486, 1426 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $[C_{24}H_{28}O_2+H]^+$ 349.2162; found 349.2159.

4.4.5. 1,4,4a,9a-tetrahydro-2,3,6,7-tetramethyl-4a-(2-methoxyphenyl)-9*H*-fluoren-9-one (**S10**). R_f = 0.4 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (s, 1H), 7.31 – 7.29 (m, 1H), 7.24 – 7.20 (m, 1H), 7.03 (s, 1H), 6.93 – 6.90 (m, 1H), 6.83 – 6.81 (m, 1H), 3.54 (s, 3H), 3.07 (t, *J* = 4.9 Hz, 1H), 2.98 (d, *J* = 14.0 Hz, 1H), 2.45 (d, *J* = 4.8 Hz, 2H), 2.37 (d, *J* = 13.9 Hz, 1H), 2.28 (s, 6H), 1.56 (s, 3H), 1.41 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.5, 158.9, 157.8, 144.0, 136.5, 135.8, 134.8, 128.0, 127.6, 127.0, 126.5, 125.6, 123.1, 120.3, 112.1, 55.7, 55.1, 50.3, 40.9, 33.5, 21.0, 19.9, 19.6, 19.2; IR (film): 2927, 2851, 1701, 1613, 1486, 1454, 1245 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $[C_{24}H_{26}O_2+H]^+$ 347.2006; found 347.2008.

4.4.6. 1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(4-methoxyphenyl)-9*H*-fluoren-9-one (**6e**). To a solution of **4e** (89 mg, 0.35 mmol) in CH_2Cl_2 (11 mL) under N_2 at r.t. was added boron trichloride (0.35 mL, 0.35 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (145 mg, 1.77 mmol). The reaction was stirred until complete by TLC (1.5 h). The reaction was quenched at r.t. with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The layers were separated, the organic phase washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered

phosphate silica gel; EtOAc/hexanes (1:20)] to yield **6e** (39 mg, 32%) as an off-white solid. The diastereomeric ratio of the crude product was determined to be >20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 220 ˚C for 35 min., ramp at 1 ˚C/min. to 260 ˚C and hold for 10 min.). The diastereomeric ratio of the purified product was determined to be >20:1 by ^{1}H NMR analysis: R_f = 0.3 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, C_6D_6): δ = 7.07 – 7.01 (m, 2H), 6.79 – 6.73 (m, 2H), 3.34 (s, 3H), 2.93 – 2.86 (m, 2H), 2.68 (dd, J = 6.6, 3.1 Hz, 1H), 2.61 – 2.50 (m, 3H), 2.46 – 2.33 (m, 1H), 2.23 – 2.11 (m, 2H), 1.63 (s, 3H), 1.57 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ = 207.7, 172.3, 158.8, 138.3, 137.2, 127.8, 127.7, 125.5, 123.7, 121.8, 114.4, 57.0, 54.9, 53.1, 36.5, 32.3, 31.6, 29.4, 19.4, 19.1, 18.6, 18.5; IR (film): 2984, 2923, 2857, 1692, 1651, 1515 cm^{-1}; HRMS (APCI-TOF) *m*/*z* calcd for $[C_{24}H_{28}O_2+H]^+$ 349.2162; found 349.2169.

4.4.7. 1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(2-bromophenyl)-9*H*-fluoren-9-one (**6f**). To a solution of **4f** (162 mg, 0.531 mmol) in CH_2Cl_2 (10 mL) under N_2 at 0 °C was added boron trichloride (0.53 mL, 0.53 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (218 mg, 2.70 mmol). The reaction was stirred until complete by TLC (2 h). The reaction was quenched at 0 °C with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The layers were separated, the organic phase washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; EtOAc/hexanes (1:25)] to yield **6f** (62 mg, 29 %) as an off-white solid. The diastereomeric ratio of the crude product was determined to be 12:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 220 ˚C for 5 min., ramp at 1 ˚C/min. to 260 ˚C and hold for 10 min.). The diastereomeric ratio of the purified product was determined to be >20:1 by ^{1}H NMR analysis: R_f = 0.4 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 – 7.54 (m, 1H), 7.37 – 7.27 (m, 2H), 7.12 – 7.08 (m, 1H), 3.12 (dd, J = 7.5, 2.5 Hz, 1H), 2.88 (d, J = 15.2 Hz, 1H), 2.81 – 2.77 (d, 2H), 2.78 – 2.51 (m, 2H), 2.50 (d, J = 16.5 Hz, 1H), 2.28 – 2.19 (m, 1H), 2.22 (d, J = 15.2 Hz, 1H), 1.73 (s, 3H), 1.68 (s, 3H), 1.66 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.4, 172.8, 141.4, 138.4, 135.8, 130.1, 128.5, 127.5, 127.2, 123.8, 123.5, 123.4, 121.5, 53.7, 52.5, 39.4, 32.5, 31.1, 29.0, 19.3, 19.0, 18.8, 18.8; IR (film): 2909, 2847, 1701, 1416 cm^{-1}; HRMS (APCI-TOF) *m*/*z* calcd for $[C_{23}H_{25}BrO+H]^+$ 397.1162; found 397.1139.

4.4.8. 1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(4-bromophenyl)-9*H*-fluoren-9-one (**6g**). To a solution of **4g** (154 mg, 0.505 mmol) in CH_2Cl_2 (10 mL) at 0 ˚C under N_2 was added boron trichloride (0.50 mL, 0.50 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (203 mg, 2.47 mmol). The reaction was stirred until complete by TLC (1.5 h). The reaction was quenched at 0 ˚C with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The layers were separated, the organic phase washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product purified by recrystallization from hexanes to yield **6g** (83 mg, 42%) as an off-white solid. The diastereomeric ratio of the crude product was determined to be >20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 230 ˚C for 5 min., ramp at 1 ˚C/min. to 260 ˚C and hold for 10 min.). The diastereomeric ratio of the purified product was determined to be >20:1 by ^{1}H NMR analysis: R_f = 0.5 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 – 7.42 (m, 2H), 7.11 – 7.03 (m, 2H), 2.89 – 2.79 (m, 2H), 2.73 – 2.64 (m, 2H), 2.56 (dd, J = 6.7, 3.6 Hz, 1H), 2.46 – 2.17 (m, 4H), 1.71 (s, 3H), 1.70 (s, 3H), 1.64 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.2, 173.3, 144.0,

138.4, 131.8, 128.3, 127.4, 125.2, 123.4, 121.6, 120.5, 56.6, 53.5, 36.1, 32.2, 31.5, 28.8, 19.5, 19.0, 18.7, 18.7; IR (film): 2980, 2917, 2854, 2243, 1698, 1685, 1647, 1483, 1429 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $[C_{23}H_{25}BrO+H]^+$ 397.1162; found 397.1162.

4.4.9. 1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(2-fluorophenyl)-9*H*-fluoren-9-one (**6h**). To a solution of **4h** (95 mg, 0.39 mmol) in CH_2Cl_2 (7 mL) at 0 ˚C under N_2 was added boron trichloride (0.39 mL, 0.39 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (160 mg, 1.95 mmol). The reaction was stirred until complete by TLC (< 1 h). The reaction was quenched at 0 ˚C with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The layers were separated, the organic phase washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product purified by recrystallization from hexanes at 0 ˚C to yield **6h** (50 mg, 38%) as a white solid. The diastereomeric ratio of the crude product was determined to be >20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 220 ˚C for 5 min., ramp at 1 ˚C/min. to 260 ˚C and hold for 10 min.). The diastereomeric ratio of the purified product was determined to be >20:1 by GC analysis: R_f = 0.4 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, C_6D_6): δ = 7.15 – 7.09 (m, 1H), 6.89 – 6.82 (m, 2H), 6.78 – 6.70 (m, 1H), 2.94 – 2.83 (m, 3H), 2.65 – 2.49 (m, 3H), 2.49 – 2.35 (m, 1H), 2.11 (d, *J* = 14.3 Hz, 1H), 2.16 – 2.07 (m, 1H), 1.60 (s, 3H), 1.52 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ = 206.6, 169.2, 162.0 (d, *J* = 248.4 Hz), 138.6 (d, *J* = 2.3 Hz), 132.2 (d, *J* = 9.5 Hz), 128.8, 128.7 (d, *J* = 1.5 Hz), 128.7, 128.0, 124.3 (d, *J* = 59.3 Hz), 124.3 (d, *J* = 3.5 Hz), 121.4, 116.8 (d, *J* = 23.3 Hz), 54.3, 51.6, 37.0, 32.3, 31.9, 29.4, 19.3, 19.1, 18.6, 18.5; ^{19}F NMR (376 MHz, C_6D_6): δ = –109.3; IR (film): 2984, 2920, 2851, 1704, 1654 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $[C_{23}H_{25}FO+H]^+$ 337.1962; found 337.1960.

4.4.10. 1,4,4a,5,8,9a-hexahydro-2,3,6,7-tetramethyl-4a-(4-fluorophenyl)-9*H*-fluoren-9-one (**6i**). To a solution of **4i** (135 mg, 0.553 mmol) in CH_2Cl_2 (10 mL) at 0 ˚C under N_2 was added boron trichloride (0.55 mL, 0.55 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (225 mg, 2.74 mmol). The reaction was stirred until complete by TLC (2.5 h). The reaction was quenched at 0 ˚C with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The layers were separated, the organic phase washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product purified by recrystallization from hexanes to yield **6i** (79 mg, 43%) as an off-white solid. The diastereomeric ratio of the crude product was determined to be >20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 220 ˚C for 5 min., ramp at 1 ˚C/min. to 260 ˚C and hold for 10 min.). The diastereomeric ratio of the purified product was determined to be >20:1 by ^{1}H NMR analysis: R_f = 0.5 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, C_6D_6): δ = 6.91 – 6.83 (m, 2H), 6.83 – 6.75 (m, 2H), 2.86 (t, *J* = 7.3 Hz, 2H), 2.56 – 2.43 (m, 3H), 2.40 (d, *J* = 14.3 Hz, 1H), 2.25 (dt, *J* = 23.2, 7.3 Hz, 1H), 2.11 – 2.06 (m, 2H), 1.61 (s, 3H), 1.53 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ = 207.2, 171.6, 161.9 (d, *J* = 245.1 Hz), 141.1 (d, *J* = 3.2 Hz), 138.7, 128.4 (d, *J* = 7.7 Hz), 127.8, 125.3, 123.7, 121.7, 115.6 (d, *J* = 21.1 Hz), 56.9, 53.2, 36.4, 32.2, 31.5, 29.4, 19.4, 19.1, 18.6, 18.5; ^{19}F NMR (376 MHz, C_6D_6): δ = –116.5; IR (film): 2917, 2857, 1689, 1651, 1603, 1505, 1439, 1400 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $[C_{23}H_{25}FO+H]^+$ 337.1962; found 337.1969.

4.4.11. 1,4,4a,5,8,9a-hexahydro-6,7-dimethyl-4a-(*tert*-butyl)-9*H*-fluoren-9-one (**7a**). To a solution of **4a** (177 mg, 0.858 mmol) in CH_2Cl_2 (8 mL) at –40 ˚C under N_2 was added boron trichloride (0.86 mL, 0.86 mmol, 1.0 M in hexanes) followed by 2,3-dimethyl-1,3-butadiene (78 mg, 0.95 mmol). The reaction was kept between –40 ˚C and –10 ˚C until the ketone was fully converted to monocyclized (3 h) after which 1,3-butadiene was bubbled into the solution for 3 minutes. The reaction was warmed to r.t. and stirred until complete by TLC (5-6 h). The reaction was quenched at 0 ˚C with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The layers were separated, the organic phase washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; EtOAc/hexanes (1:30)] to yield **7a** (48 mg, 21%) as a pale yellow oil. The diastereomeric and regioisomeric ratio of the crude product were both determined to be >20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 190 ˚C for 5 min., ramp at 1 ˚C/min. to 260 ˚C and hold for 10 min.). The isomeric ratio of the purified product **7a** to all other isomers was determined to be >20:1 by ^{1}H NMR analysis: R_f = 0.4 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, C_6D_6): δ = 5.82 – 5.72 (m, 1H), 5.53 (ddt, *J* = 10.0, 7.3, 2.9 Hz, 1H), 2.93 – 2.59 (m, 5H), 2.42 (dd, *J* = 6.5, 2.1 Hz, 1H), 1.97 (dd, *J* = 15.1, 6.9 Hz, 1H), 1.93 – 1.83 (m, 2H), 1.49 (s, 3H), 1.42 (s, 3H), 0.74 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6): δ = 207.2, 171.0, 140.0, 128.7, 127.6, 123.7, 121.7, 55.9, 49.3, 36.6, 35.1, 29.2, 27.1, 26.6, 26.4, 18.8, 18.4; IR (film): 3044, 2965, 2892, 1695, 1644, 1435, 1366, 1302 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $[C_{19}H_{26}O+H]^+$ 271.2056; found 271.2057.

4.4.12. 1,4,4a,9a-tetrahydro-6,7-tetramethyl-4a-(*tert*-butyl)-9*H*-fluoren-9-one (**9a**). R_f = 0.5 (EtOAc:hexanes, 1:10); ^{1}H NMR (400 MHz, C_6D_6): δ = 7.61 (s, 1H), 7.15 (s, 1H), 5.70 (ddt, *J* = 9.6, 6.7, 3.3 Hz, 1H), 5.56 (ddt, *J* = 9.7, 6.7, 3.2 Hz, 1H), 2.86 – 2.74 (m, 2H), 2.32 (dd, *J* = 14.7, 6.8 Hz, 1H), 2.19 (dq, *J* = 14.6, 2.8 Hz, 1H), 2.11 – 2.00 (m, 1H), 1.92 (s, 3H), 1.84 (s, 3H), 0.78 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6): δ = 207.1, 158.3, 143.6, 138.0, 136.4, 129.0, 128.2, 126.8, 123.9, 53.8, 51.4, 37.6, 30.0, 27.5, 26.7, 20.8, 19.3; IR (film): 3037, 2965, 1704, 1613, 1454, 1407, 1363, 1302 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $[C_{19}H_{24}O+H]^+$ 269.1900; found 269.1900.

4.4.13. 1,4,4a,5,8,9a-hexahydro-2,3-dimethyl-4a-(*tert*-butyl)-9*H*-fluoren-9-one (7b). To a solution of **4a** (90 mg, 0.44 mmol) in CH_2Cl_2 (6 mL) at –78 ˚C under N_2 was added boron trichloride (0.48 mL, 0.48 mmol, 1.0 M in hexanes). 1,3-Butadiene was bubbled into the solution for 3 minutes. The reaction was kept at –78 ˚C until the ketone was fully converted to the monocyclized **5b** intermediate (3 h) after which 2,3-dimethyl-1,3-butadiene (excess) was added and the reaction warmed to 0 ˚C and stirred until complete by TLC (1 h). The reaction was quenched at 0 ˚C with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The layers were separated, the organic phase washed with H_2O, brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product purified by column chromatography [pH 7 buffered phosphate silica gel; EtOAc/hexanes (1:30)] to yield **7b** (27 mg, 23%) as a white solid. The diastereomeric and regioisomeric ratio of the crude product were both determined to be >20:1 by GC analysis (GC-MS method: flow = 1 mL/min.; inlet = 250 °C; 190 ˚C for 5 min., ramp at 1 ˚C/min. to 250 ˚C and hold for 10 min.). The isomeric ratio of the purified major product **7b** to all other isomers was determined to be >20:1 by ^{1}H NMR analysis: R_f = 0.3 (EtOAc:hexanes, 1:10); ^{1}H NMR (500 MHz, C_6D_6): δ = 5.56 – 5.50 (m, 1H), 5.48 – 5.43 (m, 1H), 2.97 – 2.88 (m, 1H), 2.78 – 2.72 (m, 1H), 2.72 – 2.64 (m, 2H), 2.62 (d, J = 2.6 Hz, 1H), 2.37 (dd, J = 5.6, 2.6 Hz,

1H), 2.05 – 1.98 (m, 1H), 1.95 (dddd, J = 15.8, 3.9, 2.6, 1.3 Hz, 1H), 1.77 (d, J = 14.5 Hz, 1H), 1.63 (dt, J = 2.3, 1.2 Hz, 3H), 1.44 (dt, J = 2.3, 1.2 Hz, 3H), 0.71 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6): δ = 207.4, 170.3, 139.3, 127.4, 125.7, 124.7, 122.9, 56.5, 49.5, 36.2, 33.8, 33.0, 28.2, 27.0, 22.7, 19.4, 19.3; IR (film): 3022, 2957, 2909, 1691, 1672, 1626, 1424, 1401, 1366 cm^{-1}; HRMS (APCI-TOF) *m*/*z* calcd for $[C_{19}H_{26}O+H]^+$ 271.2056; found 271.2061.

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra) associated with this article can be found in the online version, at…

References and notes

(1) National Research Council (US). *Health and Medicine: Challenges for the Chemical Sciences in the 21st Century*; The National Academies Collection: Reports funded by National Institutes of Health; National Academies Press (US): Washington (DC), 2004.
(2) Ardkhean, R.; Caputo, D. F. J.; Morrow, S. M.; Shi, H.; Xiong, Y.; Anderson, E. A. *Chem. Soc. Rev.* **2016**, *45*, 1557.
(3) Jin, T.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 3137.
(4) Wender, P. A.; Stemmler, R. T.; Sirois, L. E. *J. Am. Chem. Soc.* **2010**, *132*, 2532.
(5) Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443.
(6) Wender, P. A.; Fournogerakis, D. N.; Jeffreys, M. S.; Quiroz, R. V.; Inagaki, F.; Pfaffenbach, M. *Nat. Chem.* **2014**, *6*, 448.
(7) Theunissen, C.; Métayer, B.; Henry, N.; Compain, G.; Marrot, J.; Martin-Mingot, A.; Thibaudeau, S.; Evano, G. *J. Am. Chem. Soc.* **2014**, *136*, 12528.
(8) Carlsen, P. N.; Jiang, C.; Herrick, I. R.; Frontier, A. J. *Tetrahedron* **2015**, *71*, 5886.
(9) Diels, O.; Alder, K. *Justus Liebigs Ann. Chem.* **1928**, *460*, 98.
(10) Dai, M.; Sarlah, D.; Yu, M.; Danishefsky, S. J.; Jones, G. O.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 645.
(11) Hilt, G.; Danz, M. *Synthesis* **2008**, 2257.
(12) Lebœuf, D.; Theiste, E.; Gandon, V.; Daifuku, S. L.; Neidig, M. L.; Frontier, A. J. *Chem. Eur. J.* **2013**, *19*, 4842.
(13) Jacob, S. D.; Brooks, J. L.; Frontier, A. J. *J. Org. Chem.* **2014**, *79*, 10296.
(14) Santelli-Rouvier, C.; Santelli, M. *Synthesis* **1983**, 429.
(15) Shimada, N.; Stewart, C.; Tius, M. A. *Tetrahedron* **2011**, *67*, 5851.
(16) Vaidya, T.; Eisenberg, R.; Frontier, A. J. *ChemCatChem* **2011**, *3*, 1531.

(17) Carmichael, R. A.; Chalifoux, W. A. *Chem. Eur. J.* **2016**, *22*, 8781.
(18) Zheng, H.; Lejkowski, M.; Hall, D. G. *Tetrahedron Lett.* **2013**, *54*, 91.
(19) Nicolaou, K. C.; Sarlah, D.; Wu, T. R.; Zhan, W. *Angew. Chem. Int. Ed.* **2009,** *48*, 6870.
(20) Liao, X.; Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2088.
(21) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Siret, P.; Keck, G. E.; Gras, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 8031.
(22) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S.; Keck, G. E.; Gopalan, B.; Larsen, S. D.; Siret, P.; Gras, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 8034.
(23) Chang, C.-I.; Chang, J.-Y.; Kuo, C.-C.; Pan, W.-Y.; Kuo, Y.-H. *Planta Med.* **2005**, *71*, 72.
(24) Frontier, A. J.; Collison, C. *Tetrahedron* **2005**, *61*, 7577.
(25) Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642.
(26) Denmark, S. E.; Habermas, K. L.; Hite, G. A.; Jones, T. K. *Tetrahedron* **1986**, *42*, 2821.
(27) Denmark, S. E.; Klix, R. C. *Tetrahedron* **1988**, *44*, 4043.
(28) Corey, E. J.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 5755.
(29) Bowling, N. P.; Burrmann, N. J.; Halter, R. J.; Hodges, J. A.; McMahon, R. J. *J. Org. Chem.* **2010**, *75*, 6382.
(30) Paioti, P. H. S.; Abboud, K. A.; Aponick, A. *J. Am. Chem. Soc.* **2016**, *138*, 2150.
(31) Hack, D.; Chauhan, P.; Deckers, K.; Hermann, G. N.; Mertens, L.; Raabe, G.; Enders, D. *Org. Lett.* **2014**, *16*, 5188.
(32) Eisler, S.; Chahal, N.; McDonald, R.; Tykwinski, R. R. *Chem. Eur. J.* **2003**, *9*, 2542.
(33) Mukai, C.; Miyakoshi, N.; Hanaoka, M. *J. Org. Chem.* **2001**, *66*, 5875.