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Efficient Synthesis of the Structural Core of Tetracyclines by a Palladium-Catalyzed Domino Tsuji–Trost–Heck–Mizoroki Reaction

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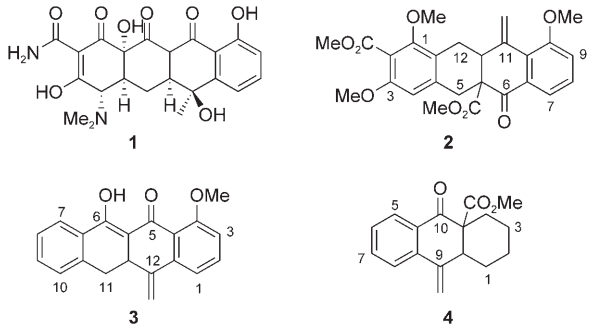
Dedicated to Professor Karl Heinz Dötz on the occasion of his 65th birthday

Abstract: The Pd-catalyzed domino Tsuji–Trost–Heck–Mizoroki reactions of compounds **18**, **27**, and **34**, respectively, each containing an allyl acetate and a halogen aryl moiety, lead to the formation of hexahydronaphthacenes **2** and **3** and octahydroanthracene **4** in 62–81 % yield. The octahydroanthracene and hexahydronaphthacene motifs are found in many natural products, for example, the tetracycline antibiotics.

Keywords: antibiotics · domino reactions · metathesis · palladium · tetracyclines

Introduction

Domino reactions[1–3] represent one of the most efficient and ecologically favorable methods for the formation of diverse complex scaffolds of carbon- and heteroatom-containing non-natural and natural compounds. Nearly all known chemical transformations can be used in domino processes, in which the combination of transition-metal-catalyzed reactions is of special interest. In particular, Pd-catalyzed transformations, such as the Heck–Mizoroki reaction,[4–6] the Tsuji–Trost reaction,[7–9] and the Wacker oxidation[10] have found wide application in synthesis. We have recently developed an enantioselective domino Wacker–Heck–Mizoroki reaction for the synthesis of vitamin E[11] and have used a combination of a Tsuji–Trost and a Heck–Mizoroki reaction for the enantioselective preparation of the antileukemic pentacyclic alkaloid cephalotaxine.[12–15] Herein we describe, as a new application of a domino Tsuji–Trost–Heck–Mizoroki reaction, the synthesis of **2**, which presents the structural core of tetracyclines such as **1**. These natural products represent a very important group of antibiotics.[16] In addition, we have also prepared hexahydronaphthacene **3** and octahydroanthracene **4** by using this method.



Results and Discussion

Domino reactions of two or more Pd-catalyzed reactions require careful adjustment of the reactivity of the different reactive functionalities to allow a successive process. We had already shown that an allyl acetate moiety is more reactive than an aryl iodide or aryl bromide containing an electron-donating substituent in the aromatic system.[17] In the synthesis of **2**, we, therefore, used compound **18** as the starting material for the domino process; this compound corresponds to the general compound **6** in the retrosynthesis depicted in Scheme 1. Substrate **18**, necessary for the preparation of **2** via **5**, can easily be obtained from the β-keto ester

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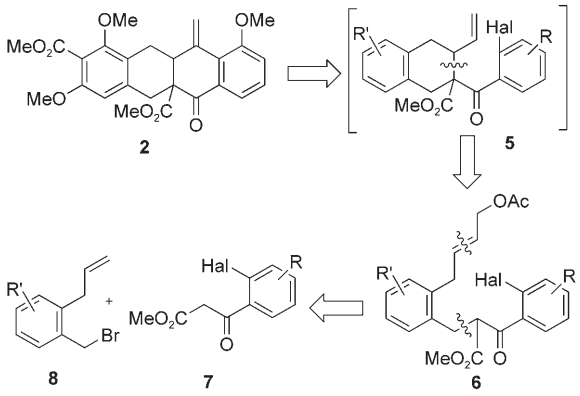
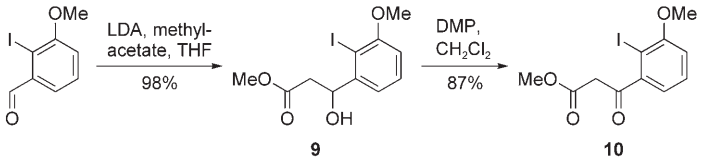


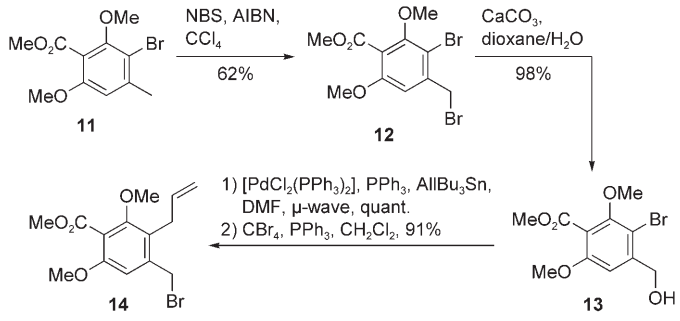
Scheme 1. Retrosynthetic analysis of hexahydronaphthacene **2**.

10 and the benzyl bromide **14**. The β-keto ester **10** (Scheme 2) was synthesized from the known 2-iodo-3-methoxybenzaldehyde[18] by an aldol reaction with acetic acid methyl ester by using LDA in THF at −78 °C to give **9** in 98 % yield followed by an oxidation of the secondary hydroxy group with Dess–Martin periodinane in 87 % yield.

For the synthesis of benzyl bromide **14** (Scheme 3), the known 3-bromo-2,6-dimethoxy-4-methyl benzoic acid methyl ester[19,20] (**11**) was treated with NBS and AIBN in CCl_4 to give **12** as the product of the radical bromination in 62 % yield.[21] As a benzylic bromide is more reactive than an aryl bromide in a Stille reaction, which we intended to use for the introduction of the allyl moiety, we had to transform the benzyl bromide into a benzyl alcohol; this was done by using $CaCO_3/H_2O$ under microwave irradiation at 150 °C to give **13** in 98 % yield within 30 min.[22] The Stille reaction could now be performed without protection of the



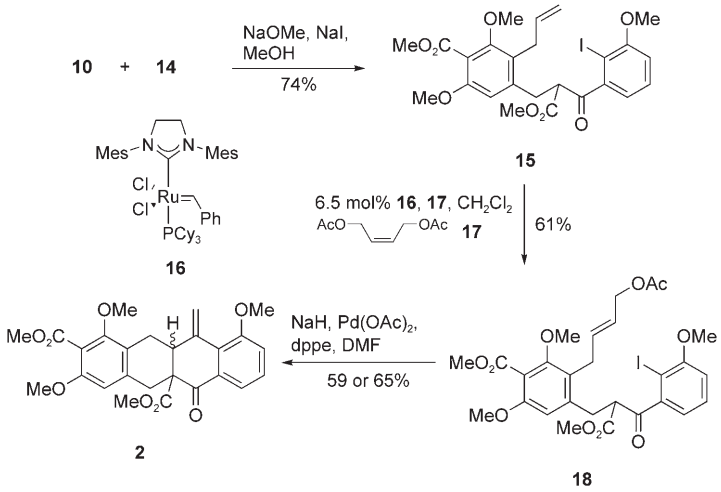
Scheme 2. Synthesis of β-keto ester **10**. LDA: lithium diisopropylamide; DMP: Dess–Martin periodinane.



Scheme 3. Synthesis of benzyl bromide **14**. NBS: *N*-bromosuccinimide; AIBN: 2,2′-azobis(2-methylpropionitrile); All: allyl.

hydroxy group, by using $[PdCl_2(PPh_3)_2]$, allyl tributyltin, and triphenylphosphine in DMF again under microwave conditions (150 °C, 15 min) to afford 3-allyl-4-hydroxymethyl-2,6-dimethoxybenzoic acid methyl ester in almost quantitative yield.[23] Higher temperatures led to readdition and elimination of the palladium species and resulted in isomerization of the allylic moiety into a vinylic moiety. To transform the hydroxy group back into the benzyl bromide group necessary for the subsequent S_N-coupling reaction with β-keto ester **10**, an Appel reaction[24] with tetrabromomethane and triphenylphosphine was used to afford 3-allyl-4-bromomethylbenzoate **14** in 91 % yield (Scheme 3).

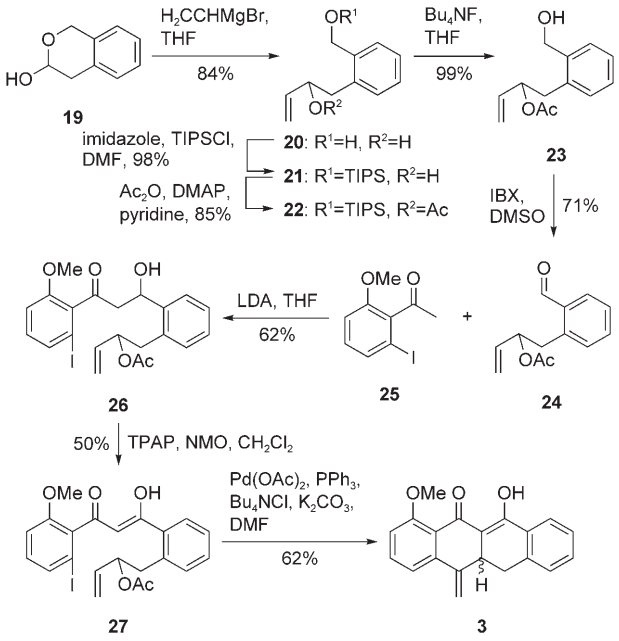
The S_N coupling between β-keto ester **10** and benzyl bromide **14** (Scheme 4) was accomplished in 74 % yield by



Scheme 4. Synthesis of hexahydronaphthacene **2**. Mes: mesityl; Cy: cyclohexyl; dppe: 1,2-bis(diphenylphosphino)ethane.

using sodium methoxide in MeOH as a base in the presence of NaI under microwave irradiation (130 °C, 10 min). The necessary allyl acetate moiety was finally introduced by a cross-metathesis of **15** and 1,4-diacetoxybutene (**17**) in the presence of the second-generation Grubbs catalyst **16** (6.5 mol %; Scheme 4). The desired product, **18**, containing an *E*-configured allyl acetate moiety was obtained in 61 % yield as the only product. We have also tried to prepare **18** by the reaction of **10** with a benzyl bromide of type **14** already containing the allyl acetate moiety. However, only decomposed material was obtained when the conditions described for the substitution reaction were used. The final reaction for the synthesis of tetracene **2** was the domino Tsuji–Trost–Heck–Mizoroki reaction, which was carried out in a preheated oil bath at 110 °C for 2 h with sodium hydride, $Pd(OAc)_2$, dppe, and K_2CO_3 to give the desired hexahydronaphthacene **2** in 65 % yield as a 1.6:1 mixture of isomers. The microwave-assisted transformation at 100 °C for 10 min, employing the same solvent and catalytic system, led to **2** in only 59 % yield, showing that microwave-assisted reactions are not always superior.

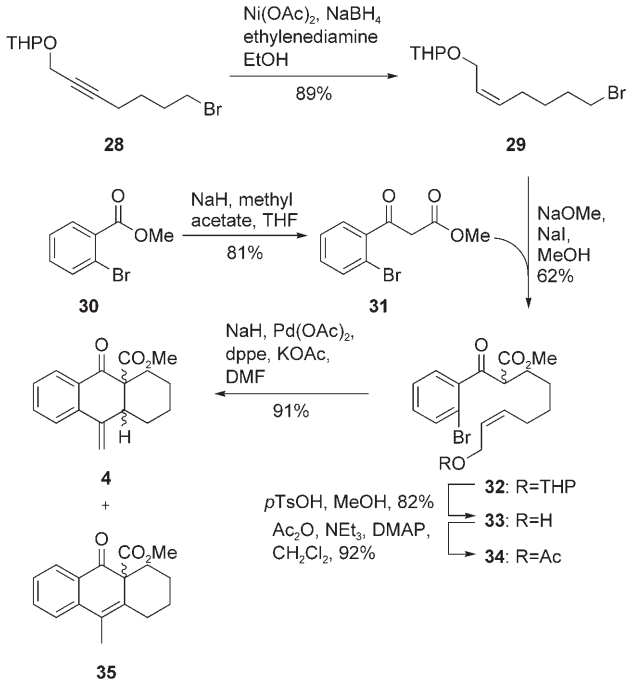
For the synthesis of the hexahydronaphthacene **3**, compound **27** was used as the substrate in the domino process to give the desired product in 62% yield by employing $Pd(OAc)_2$, triphenylphosphine, tetrabutylammonium chloride, and K_2CO_3 in DMF for 4 h at 80°C (Scheme 5). Compound **27** was prepared by an aldol reaction of **24** with **25** followed by an oxidation, with an overall yield of only 31%. The low yield is mainly due to difficulties in the oxidation of **26**. We have tried several different reagents and reaction conditions. However, the only oxidant which gave reasonable yields was TPAP in the presence of NMO.



Scheme 5. Synthesis of hexahydronaphthacene **3**. TIPS: triisopropylsilyl; DMAP: 4-dimethylaminopyridine; IBX: 2-iodoxybenzoic acid; DMSO: dimethylsulfoxide; TPAP: tetrapropylammonium perruthenate; NMO: 4-methylmorpholine *N*-oxide.

Compound **25** was prepared according to a published procedure[17] and **24** was obtained by the reaction of known compound **19**[25–29] with vinyl magnesium bromide, protection of the primary hydroxy group with TIPSCl, and formation of the allyl acetate by using acetic anhydride to give **22** via **20** and **21**. This is followed by cleavage of the TIPS ether and the oxidation of the formed primary hydroxy group to afford aldehyde **24** via **23**. The overall yield of the five-step synthesis of **24** from **19** is 49%.

Finally, we also prepared octahydroanthracenes **4** and **35** by the Pd-catalyzed domino process by using the procedure developed for the synthesis of **2**, which is more reliable and gives better yields than the method used for the preparation of **3** (Scheme 6). As starting materials we employed the *Z*-alkene **29**, obtained from the THP-protected bromoheptynyl alcohol[30,31] **28** by hydrogenation in the presence of P_2-nickel catalyst, and the β-keto ester **31**, which is accessible by a Claisen ester condensation from 2-bromobenzoate **30**



Scheme 6. Synthesis of octahydroanthracene **4**. THP: tetrahydropyranyl.

with acetic acid methyl ester. However, the S_N-coupling reaction of **29** and **31** with sodium hydride in DMF afforded the undesired *O*-alkylated product in 57% yield. Luckily, deprotonation of **31** with sodium methoxide in methanol for 1 h at room temperature followed by addition of heptenyl bromide **29** and an excess of sodium iodide yielded the desired alkylated β-keto ester **32** in a yield of 62%. The THP-acetal moiety in **32** was cleaved by using a catalytic amount of *p*-toluenesulfonic acid monohydrate to give alcohol **33**, and the necessary allylic acetate **34** was prepared from **33** by using Ac_2O and catalytic amounts of DMAP in dichloromethane, with 75% yield over the two steps. For the domino Tsuji–Trost–Heck–Mizoroki reaction, **34** was deprotonated by using sodium hydride in DMF and transformed into the octahydroanthracene **4** by employing the same reaction conditions as those described for the synthesis of **2**. Here, the use of a microwave reactor gave superior results; thus, **4** was obtained in 81% yield as a 8.1:1 mixture of diastereomers. In addition, 10% of the isomerized product, **35**, was formed.

Conclusion

The domino Tsuji–Trost–Heck–Mizoroki reaction is a powerful tool for the efficient preparation of substituted octahydroanthracenes and hexahydronaphthacenes. Further investigations will focus on the total synthesis of natural tetracyclines.

Experimental Section

General: Reactions were carried out under argon in flame-dried glassware. All solvents were dried according to standard laboratory methods. If indicated, solvents were degassed by argon being bubbled through the solvent for an appropriate period of time. All reagents obtained from commercial sources were used without further purification. Reactions under microwave irradiation were carried out in a SmithCreator microwave reactor from Personal Chemistry. Thin-layer chromatography (TLC) was performed on precoated (0.25 mm) silica gel SIL G/UV$_{254}$ plates from Machery–Nagel. UV/Vis spectra were recorded with a Perkin–Elmer Lambda 2 instrument. IR spectra were recorded with samples in KBr pellets or as films between NaCl plates by using a Bruker Vector 22 instrument. ^{1}H and ^{13}C NMR spectra were recorded with Varian Mercury 200, Mercury 300, Unity-300, Unity Inova-500, and Unity Inova-600 spectrometers with TMS or the indicated solvent as an internal standard. For NMR spectra of compounds exhibiting a keto–enol equilibrium, the assignment of the resonances to the keto or enol form of the compounds is based on the different integration of the peaks in the ^{1}H NMR spectra. MS were recorded by using a Finnigan MAT 95, TSQ 7000, LCQ instrument. HRMS were recorded with a Bruker APEX IV spectrometer equipped with a Bruker Apollo source and a Cole–Parmer syringe pump (74900 series). Melting points (m.p.) were determined with a Mettler FP61 instrument and are uncorrected.

3-Hydroxy-3-(2-iodo-3-methoxyphenyl)propionic acid methyl ester (9): *n*BuLi (40.4 mL, 101 mmol, 1.50 equiv) was added dropwise to a stirred solution of diisopropyl amine (14.3 mL, 10.2 g, 101 mmol, 1.50 equiv) in dry THF at −78 °C, and the mixture was stirred at room temperature for a further 30 min. The mixture was then recooled to −78 °C and a solution of acetic acid methyl ester (8.04 mL, 7.48 g, 101 mmol, 1.50 equiv) in dry THF (20.0 mL) was added dropwise. After the mixture had been stirred for 30 min, a solution of 2-iodo-3-methoxybenzaldehyde[18] (17.6 g, 67.3 mmol, 1.00 equiv) in dry THF (30.0 mL) was added, and the stirring was continued for 1 h at −78 °C. After addition of saturated aq. NH_4Cl (50 mL), the reaction mixture was warmed to room temperature, diluted with Et_2O (200 mL), and washed with water (2×300 mL). The aqueous phase was extracted with Et_2O (4×200 mL), the combined organic extracts were washed with brine (500 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure to give **9** as a white solid in 98% yield. R_f=0.23 (petroleum ether/EtOAc 8:2); ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.53 (dd, J=9.9, 16.6 Hz, 1H; 2-H$_A$), 2.89 (dd, J=2.6, 16.6 Hz, 1H; 2-H$_B$), 3.43 (d, J=3.2 Hz, 1H; OH), 3.76 (s, 3H; $COOCH_3$), 3.90 (s, 3H; OCH_3), 5.42 (dt, J=2.6, 9.9 Hz, 1H; C*H*OH), 6.77 (dd, J=1.4, 7.8 Hz, 1H; 4′-H), 7.21 (dd, J=1.4, 7.8 Hz, 1H; 6′-H), 7.34 ppm (t, J=7.8 Hz, 1H; 5′-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ= 41.33 (C-2), 52.00 ($COOCH_3$), 56.55 ((C-3′)OCH_3), 73.94 (C-3), 89.35 (C-2′), 110.1 (C-4′), 119.3 (C-6′), 129.6 (C-5′), 146.2 (C-1′), 157.6 (C-3′), 172.8 ppm (C-1); UV (MeOH): λ_{max} (lg ε)=205.0 (4.544), 278.0 (3.441), 285.0 nm (3.442); IR (KBr): $\tilde{\nu}$=3467, 2978, 2948, 2842, 1944, 1716, 1586, 1566, 1464, 1443, 1429, 1417, 1364, 1330, 1280, 1245, 1223, 1172, 1080, 1055, 1013, 984, 924, 891, 877, 786, 725, 712, 649, 598, 558, 518, 469 cm^{-1}; MS (EI, 70 eV): m/z (%): 336 (32) $[M]^+$, 263 (42) $[M-CH_2CO_2CH_3]^+$, 209 (100) $[M-I]^+$, 136 (29) $[M-CH_2CO_2CH_3-I]^+$, 135 (49) $[M-CH_2CO_2CH_3-I-H]^+$, 108 (32) $[PhOCH_3]^+$.

3-(2-Iodo-3-methoxyphenyl)-3-oxopropionic acid methyl ester (10): Dess–Martin periodinane (3.28 g, 7.74 mmol, 1.30 equiv) was added to a stirred solution of **9** (2.00 g, 5.95 mmol, 1.00 equiv) in CH_2Cl_2 (30.0 mL) at room temperature, and the mixture was stirred for a further 2.5 h. Saturated aq. $NaHCO_3$ (5 mL) and saturated aq. $Na_2S_2O_3$ (5 mL) were added simultaneously, and the mixture was stirred for an additional hour. The organic phase was washed with 1 N NaOH (50 mL); the aqueous phase was acidified with 2 N HCl and extracted with Et_2O (5×50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give **10** as a white solid in 87% yield after flash chromatography (EtOAc/pentane 1:99→5:95). R_f=0.45 (petroleum ether/EtOAc 7:3); ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.75 (s, 3H; $COOCH_3$, ketone), 3.82 (s, 3H; $COOCH_3$, enol), 3.91 (s, 3H; 3-OCH_3, enol), 3.92 (s, 3H; 3-OCH_3, ketone), 4.00 (s, 2H; CH_2, ketone), 5.32 (s, 1H; 2-H, enol), 6.88 (dd, J=1.4, 8.0 Hz, 1H; 6′-H, enol), 6.89 (dd, J=1.6, 8.4 Hz, 1H; 6′-H, ketone), 6.96 (dd, J=1.6, 8.4 Hz, 1H; 4′-H, ketone), 6.97 (dd, J=1.4, 8.0 Hz, 1H; 4′-H, enol), 7.31 (t, J=8.0 Hz, 1H; 5′-H, enol), 7.35 (t, J=8.4 Hz, 1H; 5′-H, ketone), 12.3 ppm (s, 1H; OH, enol); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=48.41 (C-2), 51.55 ($COOCH_3$, enol), 52.48 ($COOCH_3$, ketone), 56.71 (OCH_3, ketone, enol), 83.40 (C-2′, ketone), 92.61 (C-2, enol), 111.8 (C-4′, enol), 112.5 (C-4′, ketone), 120.1 (C-6′, enol), 121.9 (C-6′, ketone), 129.4 (C-5′, enol), 129.8 (C-5′, ketone), 141.9 (C-1′, enol), 146.1 (C-1′, ketone), 158.3 (C-3′, ketone), 167.0 (C-3′, enol), 172.8 (C-3, enol), 174.6 (C-1, ketone), 197.2 ppm (C-3, ketone); UV (MeOH): λ_{max} (lg ε)=203.0 (4.415), 223.0 nm (4.145); IR (KBr): $\tilde{\nu}$=2953, 1747, 1654, 1579, 1564, 1464, 1441, 1421, 1389, 1293, 1256, 1212, 1182, 1117, 1095, 1048, 1008, 943, 890, 817, 786, 741, 715, 608, 421 cm^{-1}; MS (EI, 70 eV): m/z (%): 334 (14) $[M]^+$, 261 (48) $[M-CH_2CO_2CH_3]^+$, 207 (100) $[M-I]^+$; HRMS: calcd for $[M+H^+]$, $[M+NH_4^+]$, and $[M+Na^+]$: 334.97748, 352.00403, 356.95942; found: 334.97748, 352.00395, 356.95930.

3-Bromo-4-bromomethyl-2,6-dimethoxybenzoic acid methyl ester (12): A catalytic amount of α,α′-bisazoisobutyronitrile was added several times to a stirred solution of **11** (8.14 g, 28.2 mmol, 1.00 equiv) and NBS (5.01 g, 28.2 mmol, 1.00 equiv) in CCl_4 (560 mL), and the reaction mixture was heated under reflux conditions for 18 h. The mixture was filtered, and the solvent was removed under reduced pressure to give **12** as a light-yellow solid in 62% yield after flash chromatography (EtOAc/petroleum ether 1:99→5:95→10:90). R_f=0.58 (petroleum ether/EtOAc 7:3); ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.85 (s, 3H; 6-OCH_3), 3.89 (s, 3H; $COOCH_3$), 3.92 (s, 3H; 2-OCH_3), 4.59 (s, 2H; CH_2), 6.83 ppm (s, 1H; 5-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=33.23 (CH_2), 52.75 ($COOCH_3$), 56.28 (6-OCH_3), 62.29 (2-OCH_3), 109.4 (C-5), 110.6 (C-4), 119.8 (C-3), 140.1 (C-6), 155.2 (C-2), 156.1 (C-1), 165.4 ppm ($COOCH_3$); UV (MeOH): λ_{max} (lg ε)=210.5 (4.462), 298.0 nm (3.362); IR (KBr): 2945, 2852, 1733, 1597, 1563, 1466, 1447, 1435, 1390, 1331, 1278, 1214, 1105, 1039, 976, 950, 921, 882, 852, 834, 779, 694, 663, 617, 579, 556 cm^{-1}; MS (EI, 70 eV): m/z (%): 370 (6) $[M]^+$, 368 (16) $[M]^+$, 366 (6) $[M]^+$, 290 (58) $[M-Br+H]^+$, 289 (32) $[M-Br]^+$, 288 (59) $[M-Br+H]^+$, 287 (25) $[M-Br]^+$, 259 (98) $[M-Br-2Me]^+$, 257 (100) $[M-Br-2Me]^+$, 244 (22) $[M-Br-3Me]^+$, 242 (22) $[M-Br-3Me]^+$; HRMS: calcd for $[M]^+$: 365.9102; found: 365.9111.

3-Bromo-4-hydroxymethyl-2,6-dimethoxybenzoic acid methyl ester (13): A microwave tube was charged with **12** (368 mg, 1.00 mmol, 1.00 equiv), calcium carbonate (300 mg, 3.00 mmol, 3.00 equiv), and a 1,4-dioxane/water mixture (1:1 v/v, 5 mL), then the tube was sealed and heated in the microwave reactor for 30 min at 150 °C. The reaction mixture was diluted with water (50 mL) and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed under reduced pressure to give **13** as a white solid in 98% yield after flash chromatography (EtOAc/petroleum ether 1:99→3:7). R_f=0.25 (petroleum ether/EtOAc 7:3); ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.45 (t, J=6.3 Hz, 1H; OH), 3.82 (s, 3H; 6-OCH_3), 3.87 (s, 3H; $COOCH_3$), 3.92 (s, 3H; 2-OCH_3), 4.71 (d, J=6.3 Hz, 2H; CH_2OH), 6.91 ppm (s, 1H; 5-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=52.69 (C(O)OCH_3), 56.19 (6-OCH_3), 62.21 (2-OCH_3), 64.75 (CH_2OH), 106.4 (C-5), 107.1 (C-3), 118.1 (C-1), 143.7 (C-4), 154.4 (C-6), 165.4 (C-2), 166.0 ppm (C(O)O); UV (MeOH): λ_{max} (lg ε)=202.5 (4.486), 204.5 (4.521), 286.0 nm (3.296); IR (KBr): $\tilde{\nu}$=3462, 3098, 2952, 2850, 1717, 1594, 1563, 1453, 1428, 1395, 1353, 1322, 1269, 1200, 1177, 1112, 1084, 1024, 982, 973, 942, 911, 845, 795, 757, 692, 676, 624, 592, 481 cm^{-1}; MS (ESI): m/z (%): 635 (20) $[2M+Na]^+$, 633 (46) $[2M+Na]^+$, 631 (22) $[2M+Na]^+$, 329 (64) $[M+Na]^+$, 327 (67) $[M+Na]^+$.

3-Allyl-4-bromomethyl-2,6-dimethoxybenzoic acid methyl ester (14):

3-Allyl-4-hydroxymethyl-2,6-dimethoxybenzoic acid methyl ester: In a microwave tube, **13** (420 mg, 1.14 mmol, 1.00 equiv), $[PdCl_2(PPh_3)_2]$ (42 mg, 60 μmol, 5.0 mol%), and triphenylphosphine (29 mg, 0.11 μmol, 10 mol%) were dissolved in degassed DMF (5.0 mL) under an argon atmosphere. Allyl tributyltin (387 μL, 414 mg, 1.25 mmol, 1.10 equiv) was added and the reaction mixture was heated to 160 °C for 10 min in the microwave reactor. The reaction mixture was cooled and diluted with water (20 mL). The aqueous phase was extracted with Et_2O (5×20 mL),

the combined organic fractions were dried over Na_2SO_4, and the solvent was removed under reduced pressure to give the title compound as a colorless oil in quantitative yield after flash chromatography (EtOAc/pentane 3:7→2:3). R_f=0.26 (pentane/EtOAc 1:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.10 (t, J=6.0 Hz, 1H; OH), 3.38 (dt, J=1.7, 5.4 Hz, 2H; CH_2CH=CH$_2$), 3.76 (s, 3H; 2-OCH$_3$), 3.82 (s, 3H; 6-OCH$_3$), 3.92 (s, 3H; COOCH$_3$), 4.65 (d, J=6.0 Hz, 2H; CH_2OH), 4.88 (dd, J=1.7, 18.2 Hz, 1H; CH=CHH_{trans}), 5.02 (dd, J=1.7, 10.3 Hz, 1H; CH=CHH_{cis}), 5.86–6.05 (ddt, J=5.4, 10.3, 18.2 Hz, 1H; CH$_2$CH=CH$_2$), 6.88 ppm (s, 1H; 5-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=29.08 (CH$_2$CH=CH$_2$), 52.47 (COOCH_3), 55.96 (6-OCH$_3$), 62.42 (CH$_2$OH), 62.76 (2-OCH$_3$), 106.0 (C-5), 115.2 (CH$_2$CH=CH_2), 116.9 (C-1), 122.1 (C-3), 137.0 (CH$_2$CH=CH$_2$), 143.4 (C-4), 155.7 (C-6), 156.2 (C-2), 167.1 ppm (COOCH$_3$).

3-Allyl-4-bromomethyl-2,6-dimethoxybenzoic acid methyl ester (**14**): A solution of triphenylphosphine (2.03 g, 7.73 mmol, 1.25 equiv) in CH_2Cl_2 (16.0 mL) was added to a solution of 3-allyl-4-hydroxymethyl-2,6-dimethoxybenzoic acid methyl ester (1.65 g, 6.18 mmol, 1.00 equiv) and tetrabromomethane (2.56 g, 7.73 mmol, 1.25 equiv) in CH_2Cl_2 (27.0 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 1.5 h. The solvent was removed under reduced pressure, the residue was taken up in Et_2O (50 mL), the solution was filtered, and the solids were washed in portions with Et_2O (150 mL). The combined organic filtrates were concentrated under reduced pressure to give **14** as a colorless oil in 91% yield after flash chromatography (EtOAc/petroleum ether 1:9). R_f=0.66 (pentane/EtOAc 4:1); ^{1}H NMR (200 MHz, $CDCl_3$): δ=3.51 (dt, J=1.7, 5.4 Hz, 2H; CH_2CH=CH$_2$), 3.77 (s, 3H; 6-OCH$_3$), 3.82 (s, 3H; 2-OCH$_3$), 3.92 (s, 3H; COOCH$_3$), 4.45 (s, 2H; CH$_2$Br), 4.89 (dd, J=1.6, 17.2 Hz, 1H; CH=CHH_{trans}), 5.04 (dd, J=1.6, 10.1 Hz, 1H; CH=CHH_{cis}), 5.91–6.10 (ddt, J=5.4, 10.1, 17.2 Hz, 1H; CH=CH$_2$), 6.72 ppm (s, 1H; 5-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ=29.29 ((C-3)CH$_2$), 30.91 (CH$_2$Br), 52.51 (COOCH_3), 56.04 (6-OCH$_3$), 62.78 (2-OCH$_3$), 109.8 (C-5), 115.4 (CH=CH_2), 118.5 (C-1), 124.3 (C-3), 136.6 (CH=CH$_2$), 139.8 (C-4), 155.6 (C-6), 156.7 (C-2), 166.6 ppm (COOCH$_3$); UV (MeOH): λ_{max} (lg ε)=212.0 (4.503), 244.5 (3.876), 296.5 nm (3.490); IR (neat): $\tilde{\nu}$=2948, 1733, 1637, 1604, 1575, 1484, 1462, 1433, 1404, 1327, 1273, 1195, 1157, 1103, 1011, 919, 845, 804 cm^{-1}; MS (EI, 70 eV): m/z (%): 330 (97) $[M]^+$, 328 (100) $[M]^+$, 299 (25) $[M-OCH_3]^+$, 297 (25) $[M-OCH_3]^+$, 249 (74) $[M-Br]^+$, 217 (65) $[C_{13}H_{13}O_3]^+$, 203 (43) $[M-Br-OCH_3-CH_3]^+$, 190 (32) $[M-Br-CO_2Me]^+$, 189 (22) $[M-Br-CO_2CH_3-H]^+$; HRMS: calcd for $[M+H^+]$: 329.03885; found: 329.03837.

3-Allyl-4-[3-(2-iodo-3-methoxyphenyl)-2-methoxycarbonyl-3-oxopropyl]-2,6-dimethoxybenzoic acid methyl ester (15): A solution of **10** (250 mg, 748 μmol, 1.00 equiv) in dry MeOH (0.8 mL) was added dropwise to a stirred solution of NaOMe (30% solution in MeOH, 148 mg, 823 μmol, 1.10 equiv) in dry MeOH (0.8 mL) at room temperature, and stirring of the mixture was continued for 1 h. After addition of NaI (123 mg, 823 μmol, 1.10 equiv) to the mixture, a solution of **14** (271 mg, 823 μmol, 1.10 equiv) in dry MeOH (0.8 mL) was added dropwise, and the resulting solution was heated in the microwave reactor at 130 °C for 10 min. The cooled reaction mixture was diluted with water (6.0 mL) and the aqueous phase was extracted with CH_2Cl_2 (5×6.0 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give **15** as an orange oil in 74% yield after flash chromatography (EtOAc/pentane 2:8). R_f=0.22–0.36 (pentane/EtOAc 7:3); ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.22 (dd, J=0.8, 5.3 Hz, 2H; CH_2CH=CH$_2$, enol), 3.31 (dd, J=6.3, 8.4 Hz, 2H; C1″-CH$_2$, ketone), 3.39 (m, 2H; CH_2CH=CH$_2$, ketone), 3.63, 3.70, 3.73, 3.75, 3.76, 3.81, 3.89, 3.91 (8×s, 10×3H; 2×COOCH$_3$, ketone, 3×OCH$_3$, ketone, 2×COOCH$_3$, enol, 3×OCH$_3$, enol), 4.46 (dd, J=6.3, 8.4 Hz, 1H, 2-H; ketone), 4.61 (dd, J=1.9, 17.1 Hz, 1H; CH=CHH_{trans}, enol), 4.77 (dd, J=1.9, 10.3 Hz, 1H; CH=CHH_{cis}, enol), 4.82 (dd, J=1.9, 17.1 Hz, 1H; CH=CHH_{trans}, ketone), 5.00 (dd, J=1.9, 10.1 Hz, 1H; CH=CHH_{cis}, ketone), 5.68–5.81 (ddt, J=5.3, 10.0, 17.1 Hz, 1H; CH=CH$_2$, enol), 5.85–5.98 (ddt, J=5.7, 9.9, 17.1 Hz, 1H; CH=CH$_2$, ketone), 6.52 (s, 1H, 6″-H, enol), 6.61 (s, 1H; 6″-H, ketone), 6.74 (dd, J=1.3, 7.4 Hz, 1H; 6′-H, enol), 6.75 (dd, J=1.3, 7.6 Hz, 1H; 6′-H, ketone), 6.79 (dd, J=1.5, 8.4 Hz, 1H; 4′-H, enol), 6.89 (dd, J=1.2, 8.4 Hz, 1H; 4′-H, ketone), 7.24 (dd, J=7.6, 8.4 Hz, 1H; 5′-H, enol), 7.33 (dd, J=7.8, 8.4 Hz, 1H; 5′-H, ketone), 12.92 ppm (s, 1H; OH, enol); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=29.11 ((C-1″)-CH_2, enol), 29.34 (CH_2CH=CH$_2$, enol), 29.64 (CH_2CH=CH$_2$, ketone), 31.26 ((C-1″)-CH_2, ketone), 52.03 ((C-4″)-OCH_3, enol), 52.50 ((C-4″)-OCH_3, ketone), 52.47 ((C-1)-OCH_3, enol), 52.61 ((C-1)-OCH_3, ketone), 55.99 ((C-5″)-OCH_3, ketone), 56.20 ((C-5″)-OCH_3, enol), 56.60 ((C-3″)-OCH_3, enol), 56.68 ((C-3″)-OCH_3, ketone), 58.84 (C-2, ketone), 62.67 ((C-3′)-OCH_3, ketone), 62.76 ((C-3′)-OCH_3, enol), 83.96 (C-2′, ketone), 88.10 (C-2′, enol), 99.70 (C-2, enol), 106.1 (C-6″, enol), 108.8 (C-6″, ketone), 111.2 (C-4′, enol), 112.4 (C-4′, ketone), 114.7 (CH=CH_2, enol), 115.3 (CH=CH_2, ketone), 115.6 (C-4″, enol), 116.6 (C4″, ketone), 119.9 (C-6′, ketone), 121.1 (C-6′, enol), 122.8 (C-2″, enol), 123.6 (C-2″, ketone), 129.6 (C-5′), 135.9 (CH=CH$_2$, enol), 136.8 (CH=CH$_2$, ketone), 140.9 (C-1″, ketone), 140.9 (C-1″, enol), 141.3 (C-1′, enol), 146.0 (C-1′, ketone), 155.2 (C-3′, enol), 155.3 (C-5″, ketone), 156.0 (C-5″, enol), 156.4 (C-3″, ketone), 158.4 (C-3″, enol), 158.5 (C-3′, ketone), 167.1 (C-1, enol), 168.8 (COOCH$_3$, ketone), 171.3 (C-3, enol), 173.1 (COOCH$_3$, enol), 173.7 (C-1, ketone), 198.4 ppm (C-3, ketone); UV (MeOH): λ_{max} (lg ε)=202.0 (4.733), 204.0 nm (4.730); IR (MeOH): $\tilde{\nu}$=2950, 1733, 1650, 1604, 1577, 1464, 1435, 1420, 1404, 1352, 1268, 1203, 1149, 1107, 1002, 916, 850, 788, 732 cm^{-1}; MS (ESI): m/z (%): 582 (14) $[M+H]^+$, 541 (10) $[M-CH_2CH=CH_2+H]^+$, 261 (31) $[C_8H_6IO_2+H]^+$, 248 (100) $[C_{14}H_{17}O_4-H]^+$, 217 (14) $[C_{13}H_{13}O_3]^+$, 135 (16) $[C_8H_6O_2+H]^+$; HRMS: calcd for $[M+H]^+$: 583.082; found: 583.082.

3-(4-Acetoxybut-2-enyl)-4-[3-(2-iodo-3-methoxyphenyl)-2-methoxycarbonyl-3-oxopropyl)-2,6-dimethoxybenzoic acid methyl ester (18): A round-bottomed flask was charged with second-generation Grubbs catalyst **16** (11 mg, 13 μmol, 6.5 mol%), a solution of **15** (117 mg, 201 μmol, 1.00 equiv) in dry CH_2Cl_2 (2.5 mL), and (*Z*)-acetic acid 4-acetoxy-but-2-enyl ester (**17**) (116 mg, 673 μmol, 3.35 equiv). The flask was sealed and heated to 50 °C for 25 h. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure to give **16** as a gray oil in 61% yield after flash chromatography (EtOAc/petroleum ether 3:7). R_f=0.08–0.22 (pentane/EtOAc 7:3). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.99 (s, 3H; CH$_3$, ketone), 2.01 (s, 3H; CH$_3$, enol), 3.22 (d, J=5.4 Hz, 2H; CH_2CH=CH$_2$, enol), 3.29 (dd, J=6.4, 8.6 Hz, 2H; (C-1″)-CH$_2$, ketone), 3.62, 3.69, 3.73, 3.75, 3.80, 3.89, 3.91 (7×s, 10×3H; 2×COOCH$_3$, ketone, 3×OCH$_3$, ketone, 2×COOCH$_3$, enol, 3×OCH$_3$, enol), 4.32 (d, J=6.4 Hz, 2H; OCH_2CH=CH$_2$, enol), 4.43 (d, J=6.7 Hz, 1H; 2-H, ketone), 4.45 (d, J=6.0 Hz, 2H; OCH_2CH=CH$_2$, ketone), 5.21 (dt, J=6.4, 15.3 Hz, 1H; OCH$_2$CH=CH, enol), 5.33 (dt, J=6.0, 15.6 Hz, 1H; OCH$_2$CH=CH, ketone), 5.67 (dt, J=5.1, 15.3 Hz, 1H; OCH$_2$CH=CH, enol), 5.84 (dt, J=5.1, 15.6 Hz, 1H; OCH$_2$CH=CH, ketone), 6.52 (s, 1H; 6″-H, enol), 6.60 (s, 1H; 6″-H, ketone), 6.74 (d, J=7.6 Hz, 1H; 4′-H, enol), 6.75 (d, J=7.6 Hz, 1H; 4′-H, ketone), 6.80 (d, J=8.3 Hz, 1H; 6′-H, enol), 6.88 (d, J=8.3 Hz, 1H; 6′-H, ketone), 7.24 (t, J=7.6 Hz, 1H; 5′-H, enol), 7.33 (t, J=7.6 Hz, 1H; 5′-H, ketone), 12.92 ppm (s, 1H; OH, enol); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=20.90 (CH$_3$, ketone), 20.93 (CH$_3$, enol), 27.77 (ArCH_2CH=CHCH$_2$, enol), 28.31 (ArCH_2CH=CHCH$_2$, ketone), 29.52 (ArCH_2, enol), 31.25 (ArCH_2, ketone), 52.06, 52.48, 52.50, 52.60 (4×COOCH_3), 55.98 ((C-5″)-OCH_3, ketone), 56.18 ((C-5″)-OCH_3, enol), 56.54 ((C-3′)-OCH_3, enol), 56.65 ((C-3′)-OCH_3, ketone), 58.76 (C-2, ketone), 62.54 ((C-3″)-OCH_3, enol), 62.65 ((C-3″)-OCH_3, ketone), 64.64 (OCH_2CH=CH, enol), 64.70 (OCH_2CH=CH, ketone), 83.89 (C-2′, ketone), 87.99 (C-2′, enol), 99.52 (C-2, enol), 106.1 (C-6″, enol), 108.8 (C-6″, ketone), 111.2 (C-6′, enol), 112.4 (C-6′, ketone), 115.6 (C-2″, enol), 116.6 (C-2″, ketone), 119.9 (C-4′, ketone), 121.9 (C-4′, enol), 122.6 (C-4″, enol), 123.4 (C-4″, ketone), 124.2 (OCH$_2$CH=CH, enol), 124.7 (OCH$_2$CH=CH, ketone), 129.5 (C-5′, enol), 129.6 (C-5′, ketone), 133.2 (ArCH$_2$CH=CH, enol), 133.9 (ArCH$_2$CH=CH, ketone), 140.7 (C-1″, ketone), 141.2 (C-1″, enol), 143.2 (C-1′, ketone), 146.0 (C-1′, enol), 155.4, 155.4, 155.9, 156.5, 158.4, 158.4 (C-3′, C-3″, C-5″, keto, enol), 167.0 (CH$_3$C(O), ketone), 167.2 (CH$_3$C(O), enol), 168.7 ((C-1)-COOCH$_3$, ketone), 171.0 (C-3, enol), 170.7 ((C-1)-COOCH$_3$, enol), 173.3 ((C-4″)-COOCH$_3$, ketone), 173.6 ((C-4″)-COOCH$_3$, enol), 198.4 ppm (C-3, ketone); UV (MeOH): λ_{max} (lg ε)=204.0 (4.730), 279.0 nm (3.882); IR (neat): $\tilde{\nu}$=3425, 2950, 1735, 1651, 1604, 1577, 1464, 1437, 1421, 1406, 1362, 1267, 1201, 1149, 1106, 1023, 966, 789, 736, 702, 605 cm^{-1}; MS (ESI): m/z (%): 677 (52) $[M+Na]^+$, 653 (100) $[M-H]^-$; HRMS: calcd for

$[M+NH_4]^+$ and $[M+Na]^+$: 672.13002, 677.08541; found: 672.13002, 677.08541.

1,3,10-Trimethoxy-11-methylene-6-oxo-(5,5a,6,11,11a,12-hexahydronaphthacene)-2,5a-dicarboxylic acid dimethyl ester (2):

Conventional heating: NaH (60% in mineral oil, 7 mg, 0.16 mmol, 1.1 equiv) was added in one portion to a solution of **18** (95 mg, 0.14 mmol, 1.0 equiv) in degassed DMF (0.9 mL) at 0°C, and the mixture was warmed to room temperature and stirred for 20 min (solution A). In a separate flask, a solution of $Pd(OAc)_2$ (7 mg, 14 μmol, 0.10 equiv) and dppe (12 mg, 29 μmol, 0.20 equiv) in degassed DMF (0.58 mL) was stirred for 30 min at room temperature (solution B). Solution A was added dropwise through a syringe to solution B, and the combined mixture was stirred for 10 min at room temperature. KOAc (28 mg, 0.29 mmol, 2.00 equiv) was then added, and the reaction mixture was stirred for 2 h in a preheated oil bath at 110°C. The reaction mixture was cooled to room temperature and concentrated to give **2** as a yellow oil in 65% yield after flash chromatography (EtOAc/petroleum ether 2:8).

Microwave heating: NaH (60% in mineral oil, 10 mg, 0.26 mmol, 1.1 equiv) was added in one portion to a solution of **18** (152 mg, 0.232 mmol, 1.00 equiv) in degassed DMF (0.93 mL) at 0°C, and the mixture was warmed to room temperature and stirred for 20 min (solution A). In a separate flask, a solution of $Pd(OAc)_2$ (11 mg, 23 μmol, 0.10 equiv) and dppe (19 mg, 47 μmol, 0.20 equiv) in degassed DMF (0.58 mL) was stirred for 30 min at room temperature (solution B). Solution A was added dropwise through a syringe to solution B, and the combined mixture was stirred for 10 min at room temperature. KOAc (46 mg, 0.47 mmol, 2.00 equiv) was added, and the reaction mixture was stirred in the microwave reactor for 10 min at 100°C. The reaction mixture was cooled to room temperature and concentrated to give **2** as a yellow oil in 59% yield after flash chromatography (EtOAc/petroleum ether 2:8).

*Compound **2***: As the assignment of the NMR peaks to the *cis* and *trans* isomers is not possible, the isomers are distinguished by h for the major isomer and m for the minor isomer. $R_f=0.58$ (pentane/EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=2.70$ (dd, $J=9.0$, 18.0 Hz, 1H; 12-H_a, m), 2.85 (dd, $J=12.8$, 15.8 Hz, 1H; 12-H_a, h), 2.92 (dd, $J=6.3$, 18.0 Hz, 1H; 12-H_b, m), 3.00 (d, $J=4.2$, 12.8 Hz, 1H; 11a-H, h), 3.07 (d, $J=17.9$ Hz, 1H; 5-H_a, h), 3.19 (dd, $J=4.2$, 16.0 Hz, 1H; 12-H_b, h), 3.20 (d, $J=16.9$ Hz, 1H; 5-H_a, m), 2.51, 3.81, 3.83, 3.92, 3.93 (5×s, 5×3H, OCH_3 or CO_2CH_3, h), 3.55 (dd, $J=6.3$, 8.9 Hz, 1H; 11a-H, m), 3.65, 3.67, 3.79, 3.89, 3.91 (5×s, 5×3H, OCH_3 or CO_2CH_3, m), 3.69 (d, $J=17.9$ Hz, 1H; 5-H_b, h), 5.56 (s, 1H; 11-C$H H_b$, h), 5.69 (d, $J=0.9$ Hz, 1H; 11-C$H H_b$, h), 6.19 (d, $J=1.4$ Hz, 1H; 11-C$H H_a$, m), 6.29 (d, $J=0.9$ Hz, 1H; 11-C$H H_a$, h), 6.49 (s, 1H; 4-H, m), 6.55 (s, 1H; 4-H, h), 7.17 (dd, $J=1$,0, 8.2 Hz, 1H; 9-H, m), 7.20 (dd, $J=1.1$, 8.2 Hz, 1H; 9-H, h), 7.33 (dd, $J=8.0$ Hz, 1H; 8-H, m), 7.37 (dd, $J=8.0$ Hz, 1H; 8-H, m), 7.70 (dd, $J=1.0$, 7.8 Hz, 1H; 7-H, m), 7.79 ppm (dd, $J=1.1$, 7.8 Hz, 1H; 7-H, h); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta=23.60$ (C-12, h), 24.85 (C-12, m), 32.49 (C-5, m), 35.64 (C-5, h), 43.42 (C-11a, h), 46.25 (C-11a, m), 52.02, 52.41 ((C-5a)-COOCH_3, (C-2)-COOCH_3, h), 52.39, 52.70 ((C-5a)-COOCH_3, (C-2)-COOCH_3, m), 55.84, 55.91 ((C-3)-OCH_3, (C-10)-OCH_3, m), 55.92, 55.96 ((C-3)-OCH_3, (C-10)-OCH_3, h), 57.71 (C-5a, h), 58.63 (C-5a, m), 61.16 ((C-1)-OCH_3, m), 61.49 ((C-1)-OCH_3, h), 106.5 (C-4, m), 106.62 (C-4, h), 115.4 (C-2, h), 115.6 (C-2, m), 116.5 (C-9, h), 116.6 (C-9, m), 117.1 ((C-11)-CH_2, h), 119.1 (C-12a, m), 119.7 (C-12a, h), 120.0 ((C-11)-CH_2, m), 120.0 (C-7, m), 120.4 (C-7, h), 127.1 (C-10a, m), 128.3 (C-8, m), 128.5 (C-8, h), 130.8 (C-10a, h), 131.6 (C-6a, m), 131.7 (C-6a, h), 137.1 (C-4a, m), 137.4 (C-4a, h), 137.7 (C-11, m), 137.9 (C-11, h), 155.2, 155.3, 155.4 (C-1, C-3, h, m), 156.5 (C-10, h), 157.5 (C-10, m), 167.0 ((C-2)-$COOCH_3$, m), 167.1 ((C-2)-$COOCH_3$, h), 170.0 ((C-5a)-$COOCH_3$, h), 172.1 ((C-5a)-$COOCH_3$, m), 194.1 (C-6, m), 195.4 ppm (C-6; h); UV (MeOH): λ_{max} (lg ε) = 204.0 (4.730), 279.0 nm (3.882); IR (neat): $\tilde{\nu}=2950$, 1735, 1684, 1608, 1589, 1465, 1411, 1270, 1212, 1157, 1105, 764 cm^{-1}; MS (ESI): *m*/*z* (%): 950 (55) $[2M+NH_4]^+$, 467 (100) $[M+H]^+$, 435 (60) $[M-OCH_3]^+$; HRMS: calcd for $[M+H]^+$, $[M-OCH_3]^+$: 467.17004, 435.14438; found: 467.17027, 435.14396.

1-(2-Hydroxymethylphenyl)but-3-en-2-ol (20): Vinyl magnesium bromide (1M solution in THF, 20.0 mL, 20.0 mmol, 3.00 equiv) was added dropwise to a stirred solution of lactol **19** (1.00 g, 6.66 mmol, 1.00 equiv) in dry THF (40 mL) at −78°C. Stirring of the mixture was continued for 2 h, then the reaction mixture was warmed to room temperature. The mixture was washed with saturated aq. NH_4Cl (50 mL) and 2M HCl (50 mL), then the aqueous phase was extracted with Et_2O (5×60 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4, and the solvent was removed under reduced pressure to give **20** as a colorless oil in 84% yield after flash chromatography (EtOAc/pentane 1:2). $R_f=0.13$ (pentane/EtOAc 3:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=2.91$ (d, $J=6.4$ Hz, 2H; 1-H_2), 3.27 (s, 2H; 2×OH), 4.33 (ddd, $J=6.4$ Hz, 1H; 2-H), 4.51 (d, $J=12.0$ Hz, 1H; CH_2OH), 4.75 (d, $J=12.0$ Hz, 1H; CH_2OH), 5.17 (d, $J=10.4$ Hz, 1H; 4-H_{cis}), 5.30 (d, $J=17.2$ Hz, 1H; 4-H_{trans}), 5.99 (ddd, $J=6.4$, 10.4, 17.2 Hz, 1H; 3-H), 7.18–7.38 ppm (m, 4H; Ar-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=39.7$ (C-1), 63.0 (*C*H_2OH), 73.7 (C-2), 114.8 (C-4), 126.8, 128.3, 130.0, 130.5 (C-3′, C-4′, C-5′, C-6′), 137.1, 139.3 (C-1′, C-2′), 140.5 ppm (C-3); IR (neat): $\tilde{\nu}=3315$, 2920, 2876, 1452, 1425, 1002, 750 cm^{-1}; MS (200 eV, DCI): *m*/*z* (%): 196 (100) $[M+NH_4]^+$, 374 (12) $[2M+NH_4]^+$.

1-(2-Triisopropylsilanyloxymethylphenyl)-but-3-en-2-ol (21): TIPSCl (1.21 mL, 1.10 g, 5.72 mmol, 1.20 equiv) was added dropwise to a stirred solution of **20** (0.850 g, 4.77 mmol, 1.00 equiv) and imidazole (0.820 g, 11.9 mmol, 2.50 equiv) in DMF (27 mL) at −10°C. The solution was stirred for 3 h at −10°C and then allowed to warm to room temperature. The reaction mixture was diluted with water (100 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. After removal of the volatiles and flash chromatography (EtOAc/pentane 1:9), **21** was obtained as a colorless oil in 98% yield. $R_f=0.30$ (pentane/EtOAc 10:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=1.05$–1.25 (m, 21H; Si(*i*Pr)$_3$), 2.71–2.99 (m, 3H; 1-H_2, OH), 4.35 (m, 1H; 2-H), 4.78 (d, $J=12.3$ Hz, 1H; CH_2OTIPS), 4.91 (d, $J=12.3$ Hz, 1H; CH_2OTIPS), 5.13 (d, $J=10.4$ Hz, 1H; 4-H_{cis}), 5.29 (d, $J=17.2$ Hz, 1H; 4-H_{trans}), 5.97 (ddd, $J=17.0$, 10.3, 5.6 Hz, 1H; 3-H), 7.18–7.38 ppm (m, 4H; Ar-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=11.9$ (3×Si*C*H(CH$_3$)$_2$), 18.0 (3×SiCH(*C*H$_3$)$_2$), 39.9 (C-1), 63.7 (*C*H_2OTIPS), 73.2 (C-2), 114.3 (C-4), 126.5, 127.5, 127.9, 130.2 (C-3′, C-4′, C-5′, C-6′), 135.9, 139.0 (C-1′, C-2′), 140.7 ppm (C-3); IR (neat): $\tilde{\nu}=3406$, 2943, 2866, 1463, 1067, 883, 682 cm^{-1}; MS (200 eV, DCI): *m*/*z* (%): 335 (80) $[M+H]^+$, 352 (100) $[M+NH_4]^+$, 687 (28) $[2M+NH_4]^+$.

Acetic acid 1-(2-triisopropylsilanylmethylphenyl)allyl ester (22): Ac_2O (10.2 g, 9.43 mL, 99.8 mmol, 5.00 equiv) was added dropwise to a stirred solution of **21** (6.67 g, 20.0 mmol, 1.00 equiv) and a catalytic amount of DMAP in pyridine (19 mL). After the reaction had been stirred for 4 h, MeOH (40 mL) was added and the mixture was stirred again for 1 h. The reaction mixture was diluted with water (20 mL) and extracted with Et_2O (3×40 mL). The combined organic fractions were washed with brine and dried over Na_2SO_4, then the solvent was evaporated under reduced pressure to give **22** as a colorless oil in 85% yield after flash chromatography (EtOAc/pentane 1:19). $R_f=0.59$ (pentane/EtOAc 10:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=1.06$–1.27 (m, 21H; Si(*i*Pr)$_3$), 2.01 (s, 3H; $COCH_3$), 2.95 (m, 2H; 1-H_2), 4.90 (s, 2H; CH_2OTIPS), 5.16 (d, $J=10.5$ Hz, 1H; 4-H_{cis}), 5.21 (d, $J=17.2$ Hz, 1H; 4-H_{trans}), 5.50 (q, $J=6.7$ Hz, 1H; 2-H), 5.84 (ddd, $J=17.2$, 10.5, 6.2 Hz, 1H; 3-H), 7.12–7.30, 7.48–7.56 ppm (m, 4H; Ar-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=12.0$ (3×Si*C*H(CH$_3$)$_2$), 18.0 (3×SiCH(*C*H$_3$)$_2$), 21.1 (CO*C*H$_3$), 36.9 (C-1), 63.1 (*C*H_2OTIPS), 74.6 (C-2), 116.7 (C-4), 126.7, 126.8, 130.1, 133.7 (C-3′, C-4′, C-5′, C-6′), 135.9, 139.6 (C-1′, C-2′), 139.6 (C-3), 169.1 ppm (*C*OCH_3); IR (neat): $\tilde{\nu}=2943$, 2866, 1743, 1463, 1236, 1083, 1066, 882, 683 cm^{-1}; MS (200 eV, DCI): *m*/*z* (%): 377 (50) $[M+H]^+$, 394 (100) $[M+NH_4]^+$, 771 (6) $[2M+NH_4]^+$.

Acetic acid 1-(2-hydroxymethylphenyl)allyl ester (23): Bu_4NF (16.1 g, 51.0 mmol, 3.00 equiv) was added to a stirred solution of **22** (6.40 g, 17.0 mmol, 1.00 equiv) in THF at 0°C, and stirring of the mixture was continued for 20 min. The reaction mixture was then diluted with water (100 mL) and extracted with Et_2O (5×70 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4, then the solvent was evaporated under reduced pressure to give **23** as a colorless oil in 99% yield after flash chromatography (EtOAc/pentane 1:3). $R_f=0.43$ (pentane/EtOAc 3:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=1.96$ (s, 3H; $COCH_3$), 2.78 (br s, 1H; OH), 2.99 (m, 2H; 1-H_2), 4.90 (d, $J=5$ Hz, 2H;

CH_2OH), 5.16 (d, $J=10.5$ Hz, 1H; 4-H_{cis}), 5.21 (d, $J=17.2$ Hz, 1H; 4-H_{trans}), 5.48 (q, $J=6.7$ Hz, 1H; 2-H), 5.85 (ddd, $J=17.2$, 10.5, 6.2 Hz, 1H; 3-H), 7.13–7.38 ppm (m, 4H; Ar-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=$ 20.8 ($COCH_3$), 37.1 (C-1), 62.6 (CH_2OH), 75.0 (C-2), 116.8 (C-4), 126.8, 127.4, 128.6, 130.6 (C-3′, C-4′, C-5′, C-6′), 134.8, 139.1 (C-1′, C-2′), 135.5 (C-3), 170.2 ppm ($COCH_3$); IR (neat): $\tilde{\nu}=3419$, 2933, 1737, 1373, 1240, 1022 cm^{-1}; MS (200 eV, DCI): m/z (%): 238 (29) $[M+NH_4]^+$, 458 (100) $[2M+NH_4]^+$.

Acetic acid 1-(2-formylbenzyl)allyl ester (24): Molecular sieves (4 Å, 5.0 g) and IBX (9.90 g, 35.4 mmol, 2.00 equiv) were added to a stirred solution of **23** (3.90 g, 17.7 mmol, 1.00 equiv) in DMSO (400 mL), and the reaction mixture was shaken at room temperature for 3 h, before being diluted at −10 °C with cold brine (−10 °C) and filtered. The filtrate was extracted with Et_2O (5×80 mL) and the solids were extracted by using a Soxhlet apparatus (100 mL Et_2O, 10 h). The combined organic extracts were washed with brine and dried over Na_2SO_4, then the solvents were evaporated under reduced pressure to give **24** as a colorless oil in 71% yield after flash chromatography (EtOAc/pentane 1:3). $R_f=0.63$ (pentane/EtOAc 3:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=1.94$ (s, 3H; $COCH_3$), 3.23 (dd, $J=13.5$, 8.5 Hz, 1H; 1-H_a), 3.49 (dd, $J=13.5$, 5.2 Hz, 1H; 1-H_b), 5.17 (d, $J=10.5$ Hz, 1H; 4-H_{cis}), 5.23 (d, $J=17.3$ Hz, 1H; 4-H_{trans}), 5.46 (m, 1H; 2-H), 5.87 (ddd, $J=17.3$, 10.5, 6.1 Hz, 1H; 3-H), 7.28 (dd, $J=$ 7.4, 1.5 Hz, 1H; 3′-H), 7.41 (dt, $J=7.4$, 1.5 Hz, 1H; 5′-H), 7.51 (dt, $J=$ 7.4, 1.5 Hz, 1H; 4′-H), 7.83 (dd, $J=7.4$, 1.5 Hz, 1H; 6′-H), 10.23 ppm (s, 1H; CHO); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=20.8$ ($COCH_3$), 37.0 (C-1), 74.6 (C-2), 116.8 (C-4), 127.2, 132.1, 132.4, 133.3 (C-3′, C-4′, C-5′, C-6′), 134.2, 139.1 (C-1′, C-2′), 135.5 (C-3), 169.7 ($COCH_3$), 192.5 ppm (CHO); IR (neat): $\tilde{\nu}=3073$, 3021, 2989, 2934, 2866, 2839, 2744, 1739, 1697, 1600, 1372, 1237, 1022, 759 cm^{-1}; MS (200 eV, DCI): m/z (%): 236 (100) $[M+NH_4]^+$, 454 (9) $[2M+NH_4]^+$.

Acetic acid 1-{2-[1-hydroxy-3-(2-iodo-6-methoxyphenyl)-3-oxopropyl]-benzyl}allyl ester (26): *n*BuLi (1.6 M solution in hexane, 2.99 mL, 4.72 mmol, 1.00 equiv) was added dropwise to a stirred solution of diisopropylamine (573 mg, 0.800 mL, 5.66 mmol, 1.20 equiv) in dry THF (10 mL) at 0 °C. After the mixture had been stirred for 1 h, a solution of **25** (1.30 g, 4.72 mmol, 1.00 equiv) was added dropwise. After stirring for another hour at 0 °C, the reaction mixture was cooled to −78 °C and a solution of **24** (1.03 g, 4.72 mmol, 1.00 equiv) in dry THF (5.0 mL) was added dropwise. Stirring was continued at −78 °C for 1 h and at −20 °C for an additional 30 min, after which the mixture was diluted with saturated aq. $NaHCO_3$ (25 mL) and allowed to warm to room temperature. The aqueous phase was extracted with CH_2Cl_2 (4×100 mL), the combined organic extracts were washed with brine and dried over Na_2SO_4, and the solvents were evaporated under reduced pressure to give **26** as a yellow oil in 62% yield after flash chromatography (EtOAc/pentane 1:3). $R_f=0.24$ (pentane/EtOAc 3:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=1.93$, 1.98 (2×s, 3H; $COCH_3$), 2.91–3.28 (m, 4H; 4-H_2, 8-H_2), 3.41, 3.46 (2×d, $J=2.2$ Hz, 1H; OH), 3.78, 3.80 (2×s, 3H; OCH_3), 5.20 (d, $J=10.5$ Hz, 1H; 1-H_{cis}), 5.29 (d, $J=16.9$ Hz, 1H; 1-H_{trans}), 5.36, 5.46 (2×m, 1H; 3-H), 5.53 (dd, $J=7.3$, 4.9 Hz, 0.5H; 7-H), 5.58 (dd, $J=7.5$, 4.3 Hz, 0.5H; 7-H), 5.88 (ddd, $J=16.9$, 10.5, 6.2 Hz, 1H; 2-H), 6.77 (dd, $J=8.4$, 5.5 Hz, 1H; 12′-H), 6.92 (dt, $J=8.1$, 1.5 Hz, 1H; 13′-H), 7.02–7.18 (m, 3H; 6′, 7′, 8′-H), 7.28 (dd, $J=7.9$, 1.5 Hz, 1H; 9′-H), 7.43 ppm (br d, $J=7.7$ Hz, 1H; 14′-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=20.9$ ($OCOCH_3$), 37.1 (C-4), 51.3 (C-8), 55.8 (OCH_3), 65.8 (C-7), 74.8 (C-3), 90.5 (C-15′), 110.6 (C-12′), 116.9 (C-1), 126.2, 127.2, 127.3, 130.6, 131.1, 131.4 (C-6′, C-7′, C-8′, C-9′, C-13′, C-14′), 133.6 (C-10′), 135.7, 141.0 (C-5, C-6), 135.9 (C-2), 156.1 (C-11′), 170.0 ($OCOCH_3$), 206.5 ppm (C-9); IR (neat): $\tilde{\nu}=3508$, 2940, 1731, 1582, 1565, 1456, 1429, 1258, 1027, 776 cm^{-1}; MS (70 eV, EI): m/z (%): 261 (100) [**25**−CH_3]$^+$, 434 (4) $[M-OAc]^+$, 476 (9) $[M-H_2O]^+$, 494 (1) $[M]^+$.

Acetic acid 1-{2-[1-hydroxy-3-(2-iodo-6-methoxyphenyl)-3-oxopropenyl]-benzyl}allyl ester (27): TPAP (80.0 mg, 0.200 mmol, 0.100 equiv) and NMO (702 mg, 6.06 mmol, 3.00 equiv) were added to a solution of **26** (1.00 g, 2.02 mmol, 1.00 equiv) in CH_2Cl_2 (20 mL) at room temperature. The reaction mixture was stirred for 24 h before the solvents were removed under reduced pressure and the residue was purified by preparative TLC (acetone/pentane 1:10) to give **27** as a yellow oil in 50% yield. $R_f=0.37$ (pentane/EtOAc 3:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=1.98$ (s, 3H; $COCH_3$), 3.17 (dd, $J=13.7$, 8.3 Hz, 1H; 4-H_a), 3.41 (dd, $J=13.7$, 5.0 Hz, 1H; 4-H_b), 3.64 (s, 0.6H; 8-H_2 ketone), 3.82 (s, 3H; OCH_3), 5.16 (br d, $J=10.4$ Hz, 1H; 1-H_{cis}), 5.22 (br d, $J=17.1$ Hz, 1H; 1-H_{trans}), 5.63 (m, 1H; 3-H), 5.87 (ddd, $J=16.9$, 10.5, 6.1 Hz, 1H; 2-H), 6.04 (s, 0.7H; 8-H enol), 6.72–7.88 (m, 7H; Ar-H), 15.8 ppm (br s, 0.7H; OH enol); UV (CH_3CN): λ_{max} (lg ε) = 308.5 nm (2.16); IR (neat): $\tilde{\nu}=2938$, 1739, 1565, 1461, 1424, 1025 cm^{-1}; MS (70 eV, EI): m/z (%): 261 (100) [**25**−CH_3]$^+$, 432 (17) $[M-OAc]^+$, 492 (1) $[M]^+$.

6-Hydroxy-4-methoxy-12-methylene-(5,5a,6,11,11a,12-hexahydronaphthacene)-5-one (3): Bu_4NCl (11.1 mg, 40.6 μmol, 2.00 equiv), K_2CO_3 (5.50 mg, 40.6 μmol, 2.00 equiv), $Pd(OAc)_2$ (4.50 mg, 20.3 μmol, 1.00 equiv), and PPh_3 (10.5 mg, 40.6 μmol, 2.00 equiv) were added to a solution of **27** (10.0 mg, 20.3 μmol, 1.00 equiv) in DMF (2.0 mL), and the mixture was stirred for 4 h at 80 °C. The reaction was then quenched by the addition of saturated aq. NH_4Cl (5.0 mL), and the aqueous phase was extracted with Et_2O (3×25 mL). The combined organic fractions were washed with brine and dried over Na_2SO_4, then the solvents were evaporated under reduced pressure to give **3** as a yellow oil in 62% yield after flash chromatography (acetone/pentane 1:10). $R_f=0.33$ (pentane/EtOAc 3:1); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=2.63$ (d, $J=8.9$ Hz, 2H; 11-H_2), 3.22–3.31 (m, 1H; 11a-H), 3.38 (s, 3H; OCH_3), 4.88 (d, $J=2.7$ Hz, 1H; 13-H_a), 5.28 (s, $J=2.7$ Hz, 1H; 13-H_b), 6.80–7.40 (m, 7H; Ar-H), 17.99 ppm (s, 1H; OH); MS (70 eV, EI): m/z (%): 304 (100) $[M]^+$, 289 (27) $[M-CH_3]^+$.

2-(7-Bromo-hept-2-enyloxy)tetrahydropyran (29): A suspension of Ni(OAc)$_2$ (220 mg, 1.25 mmol, 0.125 eq) in dry EtOH (2.0 mL) was treated with a solution of $NaBH_4$ (95 mg, 2.5 mmol, 0.25 equiv) in dry EtOH (4.0 mL) and stirred until gas evolution had ceased. Ethylenediamine (150 mg, 2.50 mmol, 0.250 equiv) and, after 10 min of stirring at room temperature, 2-(7-bromohept-2-ynyloxy)tetrahydropyran (2.75 g, 10.0 mmol, 1.00 equiv) were added. The reaction mixture was stirred at room temperature under an H_2 atmosphere until complete conversion (as determined by TLC). After the mixture had been stirred with charcoal for 15 min, the obtained suspension was filtered through a pad of silica gel and the solvent was removed under reduced pressure to give **29** as a colorless oil in 89% yield. $R_f=0.48$ (EtOAc/pentane 1:9); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=1.45$–1.95 (m, 10H; 5-H_2, 6-H_2, 3′-H_2, 4′-H_2, 5′-H_2), 2.12 (td, $J=7.1$, 6.1 Hz, 2H; 4-H_2), 3.40 (t, $J=6.6$ Hz, 2H; 7-H_2), 3.44–3.57 (m, 1H; 6′-H_A), 3.80–3.94 (m, 1H; 6′-H_B), 3.99–4.10 (m, 1H; 1-H_A), 4.19–4.30 (m, 1H; 1-H_B), 4.62 (m, 1H; 2′-H), 5.57 ppm (m, 2H; 2-H, 3-H); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=19.47$ (C4′), 25.41 (C4), 25.94 (C5′), 30.61 (C3′), 32.32 (C5), 33.08 (C6), 62.23 (C1), 62.68 (C6′), 97.98 (C2′), 127.6 (C2), 131.2 ppm (C3); IR (neat): $\tilde{\nu}=3017$, 2941, 2870, 2851, 1658, 1453, 1440, 1388, 1352, 1339, 1320, 1298, 1271, 1249, 1201, 1183, 1158, 134, 1118, 1077, 1057, 1026, 973, 905, 870, 815, 677, 647 cm^{-1}; MS (200 eV, DCI/NH_3): m/z (%): 296/294 (21/19), 136 (4), 119 (21), 102 (100).

3-(2-Bromophenyl)-3-oxopropionic acid methyl ester (31): Acetic acid methyl ester (161 μL, 2.33 mmol, 1.00 equiv) in dry THF (4 mL) was added dropwise to a suspension of 2-bromobenzoic acid methyl ester (**30**; 1.00 g, 4.65 mmol, 2.00 equiv) and sodium hydride (139 mg, 4.65 mmol, 2.00 equiv) in dry THF (4 mL). The reaction mixture was stirred for 2 h at room temperature and then heated under reflux conditions for 24 h. The solvent was removed under reduced pressure, and the residue taken up in toluene. This solution was washed with 2 N HCl (7 mL) and saturated aq. $NaHCO_3$ (7 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Compound **31** was obtained as a yellowish oil in 81% yield after flash chromatography (EtOAc/pentane 1:9). $R_f=0.40$ (EtOAc/pentane 1:4); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=3.74$ (s, 3H; CO_2CH_3, ketone), 3.81 (s, 3H; CO_2CH_3, enol), 4.03 (s, 2H; 2-H_2, ketone), 5.47 (s, 1H; 2-H, enol), 7.32 (ddd, $J=7.5$, 7.5, 1.0 Hz, 1H; 5′-H), 7.42 (dd, $J=8.6$, 1.0 Hz, 1H; 3′-H), 7.50 (ddd, $J=7.5$, 7.5, 1.0 Hz, 1H; 4′-H), 7.63 (dd, $J=8.0$, 1.1 Hz, 1H; 6′-H), 12.33 ppm (s, 1H; OH, enol); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta=48.48$ (C-2, ketone), 51.54 (OCH_3, enol), 52.44 (OCH_3, ketone), 92.85 (C-2, enol), 119.1 (C-2′, ketone), 120.9 (C-2′, enol), 127.3 (C-5′, enol), 127.5 (C-5′, ketone), 129.5 (C-6′, enol), 130.2 (C-6′, enol), 131.2 (C-3′, enol), 132.4

(C-3′, ketone), 133.7 (C-4′, enol), 133.9 (C-4′, ketone), 135.6 (C-1′, enol), 139.8 (C-1′, ketone), 167.2 (C-1, enol), 171.9 (C-3, enol), 172.8 (C-1, ketone), 195.4 ppm (C-3, ketone); UV (CH_3CN): λ_{max} (lg ε) = 208.0 (4.160), 244.0 nm (3.685); IR (neat): $\tilde{\nu}$ = 1746, 1704, 1651, 1633, 1587, 1564, 1536, 1468, 1446, 1435, 1390, 1326, 1286, 1272, 1249, 1205, 761, 729 cm^{-1}; MS (70 eV, EI): *m/z* (%): 258/256 (3/3), 225/227 (2/2), 183/185 (38/38), 177 (100), 155/157 (8/8), 69 (8), 50 (4); HRMS: calcd for $[M]^+$: 255.9735; found: 255.9735.

2-(2-Bromobenzoyl)-9-(tetrahydropyran-2-yloxy)non-7-enoic acid methyl ester (32): A solution of the β-keto ester **31** (2.42 g, 9.41 mmol, 1.00 equiv) in MeOH (20 mL) was added dropwise to a stirred solution of NaOMe (5.4 M solution in dry MeOH, 1.74 mL, 9.41 mmol, 1.00 equiv) in MeOH (20 mL) at 0 °C, and stirring was continued for 1 h at room temperature. Compound **29** (3.26 g, 11.8 mmol, 1.25 equiv) and NaI (1.77 g, 11.8 mmol, 1.25 equiv) were added and the mixture was heated under reflux conditions for 12 h before being diluted with water (30 mL). The aqueous phase was extracted with CH_2Cl_2 (4 × 20 mL), the combined organic phases were washed with brine (40 mL), and the volatiles were removed under reduced pressure to give **32** as a colorless oil in 62% yield after flash chromatography (EtOAc/pentane 1:9). R_f = 0.64 (EtOAc/pentane 1:4); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.09–2.14 (m, 14H; 3-H_2, 4-H_2, 5-H_2, 6-H_2, 3″-H_2, 4″-H_2, 5″-H_2), 3.41–3.58 (m, 1H; 6″-H_A), 3.68 (s; CO_2CH_3, ketone), 3.79–3.95 (m, 1H; 6″-H_B), 3.84 (s; CO_2CH_3, enol), 3.98–4.09 (m, 1H; 9-H_A), 4.16–4.28 (m, 1H; 9-H_B), 4.23 (t, J = 7.1 Hz, 1H; 3-H, ketone), 4.61 (m, 1H; 2″-H), 5.40–5.63 (m, 2H; 7-H, 8-H), 7.20–7.45 (m, 3H; 4′-H, 5′-H, 6′-H), 7.56–7.65 (m, 1H; 3′-H), 12.65 ppm (s, 1H; OH, enol); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 19.50 (C-4″), 25.43 (C-5″), 26.70 (C-3″, enol), 27.09 (C-6), 27.18 (C-4), 28.38 (C-3, ketone), 29.26 (C-5), 30.64 (C-3″), 51.84 (C-2, ketone), 52.38 (CO_2CH_3, ketone), 57.60 (CO_2CH_3, enol), 62.22 (C-9), 62.66 (C-6″), 97.88 (C-2″), 103.3 (C-2, enol), 119.0 (C-2′, ketone), 121.4 (C-2′), 125.8 (C-8, enol), 126.2 (C-8, ketone), 127.2 (C-5′, enol), 127.3 (C-5′, ketone), 128.9 (C-6′, ketone), 129.8 (C-6′, enol), 130.5 (C-7, enol), 131.9 (C-7, ketone), 132.9 (C-3′, enol), 133.1 (C-3′, ketone), 133.3 (C-4′, enol), 133.8 (C-4′, ketone), 136.0 (C-1′, enol), 140.4 (C-1′, ketone), 169.4 (C-1, enol), 169.7 (C-1 ketone), 198.5 ppm (Ar*C*O, ketone).

2-(2-Bromobenzoyl)-9-hydroxynon-7-enoic acid methyl ester (33): A solution of **32** (1.60 g, 3.54 mmol, 1.00 equiv) and *p*-toluenesulfonic acid monohydrate (66 mg, 0.35 mmol, 0.10 equiv) in MeOH (7.0 mL) was stirred at room temperature until the starting material had been completely consumed (as determined by TLC). The reaction mixture was diluted with saturated aq. $NaHCO_3$ (11 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with brine and dried over $MgSO_4$, then the solvents were removed under reduced pressure to give **33** as a colorless oil in 82% yield after flash chromatography (EtOAc/pentane 3:7). R_f = 0.31 (EtOAc/pentane 3:7); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.05–1.79 (m, 5H; 4-H_2, 5-H_2, OH), 1.84–2.18 (m, 4H; 3-H_2, 6-H_2), 3.68 (s, 3H; OCH_3, ketone), 3.85 (s, 3H; OCH_3, enol), 4.17 (d, 6.5 Hz, 2H; 9-H_2), 4.24 (t, J = 7.3 Hz, 1H; 2-H, ketone), 5.32–5.68 (m, 2H; 7-H, 8-H), 7.21–7.45 (m, 3H; 4′-H, 5′-H, 6′-H), 7.57–7.66 (m, 1H; 3′-H), 12.64 ppm (s, 1H; OH, enol); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 26.81 (C-3), 26.85 (C-6), 28.24 (C-4), 29.07 (C-5), 52.47 (OCH_3), 57.59 (C-2), 58.53 (C-9), 119.8 (C-2′), 127.4 (C-5′), 128.9 (C-8), 129.0 (C-7), 132.0 (C-6′), 132.4 (C-3′), 133.9 (C-4′), 140.0 (C-1′), 169.8 (C-1), 179.2 ppm (Ar*C*O).

9-Acetoxy-(2-bromobenzoyl)non-7-enoic acid methyl ester (34): A solution of **33** (1.05 g, 2.85 mmol, 1.00 equiv), Ac_2O (335 mg, 3.28 mmol, 1.15 equiv), NEt_3 (433 mg, 4.28 mmol, 1.50 equiv), and DMAP (35 mg, 0.29 mmol, 0.10 equiv) in CH_2Cl_2 (4.3 mL) was stirred until the starting material had been completely consumed (as determined by TLC). The volatiles were removed under reduced pressure to give **34** as a colorless oil in 92% yield after flash chromatography (EtOAc/pentane 1:9→1:4). R_f = 0.61 (EtOAc/pentane 1:4); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.21–1.85 (m, 4H; 4-H_2, 5-H_2), 1.97–2.23 (m, 4H; 6-H_2, 3-H_2), 2.03 (s, 3H; $C(O)CH_3$), 3.71 (s, 3H; OCH_3), 4.57 (d, J = 6.5 Hz; 9-H_2), 5.56 (m, 2H; 7-H, 8-H), 7.20–7.41 (m, 3H; 4′-H, 5′-H, 6′-H), 7.55–7.65 (m, 1H; 3′-H), 12.64 ppm (s, 1H; OH, enol).

9-Methylene-10-oxo-(1,2,3,4,4a,9,9a,10-octahydroanthracene)-4a-carboxylic acid methyl ester (4) and 9-methyl-10-oxo-(1,2,3,4,4a,10-hexahydroanthracene)-4a-carboxylic acid methyl ester (35): NaH (60% in mineral oil, 11 mg, 0.27 mmol, 1.2 equiv) was added in one portion to a solution of **34** (92 mg, 0.22 mmol, 1.0 equiv) in DMF (1.6 mL) at 0 °C, and the mixture was stirred for 20 min at room temperature (solution A). In a separate flask, a solution of $Pd(OAc)_2$ (5.4 mg, 24 μmol, 11 mol%) and dppe (20 mg, 49 μmol, 22 mol%) in DMF (0.8 mL) was stirred for 20 min at room temperature (solution B). KOAc (48 mg, 0.49 mmol, 2.2 equiv) was added to solution B, then solution A was added dropwise through a syringe to solution B. The reaction mixture was heated for 10 min at 90 °C in the microwave reactor and then diluted with saturated aq. NH_4Cl solution. The aqueous phase was extracted with Et_2O (3 × 3 mL). After removal of all volatiles and chromatography (EtOAc/pentane 1:9), **4** was obtained as a colorless oil (8.1:1 mixture of diastereomers) in 81% yield; in addition, **35** was isolated in 10% yield.

Compound **4**: R_f = 0.44, 0.40 (EtOAc/pentane 1:9); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.34 (m, 1H; 2-H_A), 1.68 (m, 1H; 2-H_B), 1.77 (m, 2H; 1-H_A, 3-H_A), 1.93 (m, 2H; 3-H_B, 4-H_A), 2.23 (m, 1H; 4-H_B), 2.54 (m, 1H; 1-H_B), 2.67 (m, 1H; 9a-H), 3.50 (s, 3H; CO_2CH_3), 5.25 (d, J = 2.1 Hz, 1H; C=CHH_A), 5.80 (d, J = 2.1 Hz, 1H; C=CHH_B), 7.37 (td, J = 7.7, 1.2 Hz, 1H; 6-H), 7.52 (td, J = 7.3, 1.5 Hz, 1H; 7-H), 7.66 (d, J = 7.9 Hz, 1H; 8-H), 8.03 ppm (dd, J = 8.0, 1.3 Hz, 1H; 5-H); ^{13}C NMR (150.8 MHz, $CDCl_3$): δ = 21.87 (C-3), 25.08 (C-1), 25.26 (C-2), 31.08 (C-4), 46.40 (C-9a), 51.90 (CO_2CH_3), 58.67 (C-4a), 110.8 (C=CH_2), 124.4 (C-8), 127.9 (C-6), 128.3 (C-5), 130.3 (C-10a), 133.5 (C-7), 141.1 (C-8a), 143.6 (C-9), 170.1 (CO_2CH_3), 195.5 ppm (C-10); MS (ESI): *m/z* (%): 563 (37) [2M^++Na], 425 (13), 271 (100) [M^+], 211 (25).

Compound **35**: R_f = 0.36 (EtOAc/pentane 1:9); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.21–2.09 (m, 6H; 2-H_2, 3-H_2, 4-H_2), 2.21 (s, 3H; 9-CH_3), 2.76 (ddt, J = 13.7, 3.8, 2.2 Hz, 1H; 1-H_A), 3.01 (ddt, J = 13.3, 3.1, 1.5 Hz, 1H; 1-H_B), 3.64 (s, 3H; CO_2CH_3), 7.35 (ddd, J = 7.1, 7.1, 1.4 Hz, 1H; 6-H), 7.55 (dd, J = 7.9, 1.2 Hz, 1H; 8-H), 7.66 (ddd, J = 7.1, 7.1, 1.7 Hz, 1H; 7-H), 8.09 ppm (ddd, J = 7.6, 1.5, 0.5 Hz, 1H; 5-H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.08 (9-CH_3), 22.93 (C-3), 28.60 (C-2), 29.90 (C-1), 36.41 (C-4), 52.76 (CO_2CH_3), 61.48 (C-4a), 122.0 (C-9), 124.6 (C-5), 126.9 (C-8), 127.2 (C-10a), 127.5 (C-6), 135.0 (C-7), 139.4 (C-9a), 140.4 (C-8a), 169.9 (CO_2CH_3), 196.4 ppm (C-10).

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[1] L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.
[2] L. F. Tietze, F. Haunert in *Stimulating Concepts in Chemistry* (Eds.: M. Shibasaki, J. F. Stoddart, F. Vögtle), Wiley-VCH, Weinheim, **2000**, pp. 39–64.
[3] L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136.
[4] I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066.
[5] M. Beller, T. H. Riermeier, G. Stark in *Transition Metals for Organic Synthesis* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**, pp. 208–240.
[6] S. Bräse, A. de Meijere in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, pp. 99–166.
[7] B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395–422.
[8] B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921–2944.
[9] J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, New York, **1996**.
[10] B. L. Feringa in *Transition Metals for Organic Synthesis* (Eds.: M. Beller, C. Bolm), *Vol. 2*, Wiley-VCH, Weinheim, **1998**, pp. 307–315.

[11] L. F. Tietze, K. M. Sommer, J. Zinngrebe, F. Stecker, *Angew. Chem.* **2005**, *117*, 262–264; *Angew. Chem. Int. Ed.* **2005**, *44*, 257–259.
[12] L. F. Tietze, H. Schirok, M. Wöhrmann, *Chem. Eur. J.* **2000**, *6*, 510–518.
[13] L. F. Tietze, H. Schirok, M. Wöhrmann, K. Schrader, *Eur. J. Org. Chem.* **2000**, 2433–2444.
[14] L. F. Tietze, H. Schirok, *J. Am. Chem. Soc.* **1999**, *121*, 10264–10269.
[15] L. F. Tietze, H. Schirok, *Angew. Chem.* **1997**, *109*, 1159–1160; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1124–1125.
[16] J. J. Hlavka, J. H. Boothe (Eds.), *The Tetracyclines*, Springer, Berlin, **1985**.
[17] L. F. Tietze, G. Nordmann, *Eur. J. Org. Chem.* **2001**, 3247–3253.
[18] L. F. Tietze, S. G. Stewart, M. E. Polomska, A. Modi, A. Zeeck, *Chem. Eur. J.* **2004**, *10*, 5233–5242.
[19] L. Crombie, D. E. Games, A. W. G. James, *J. Chem. Soc. Perkin Trans. 1* **1996**, *22*, 2715–2742.
[20] F. P. Doyle, J. H. C. Nayler, H. R. J. Waddington, J. C. Hanson, G. R. Thomas, *J. Chem. Soc.* **1963**, 497–506.
[21] J. L. Bloomer, C. S. Brosz, *Tetrahedron* **1985**, *41*, 3241–3252.
[22] G. Bringmann, D. Menche, J. Kraus, J. Mühlbacher, K. Peters, E.-M. Peters, R. Brun, M. Bezabih, B. M. Abegaz, *J. Org. Chem.* **2002**, *67*, 5595–5610.
[23] G. Martorell, A. García-Raso, J. M. Saá, *Tetrahedron Lett.* **1990**, *31*, 2357–2360.
[24] X. Fang, D. L. Larson, P. S. Portoghese, *J. Med. Chem.* **1997**, *40*, 3064–3070.
[25] J. E. Horan, R. W. Schiessler, *Org. Synth.* **1961**, *41*, 53–55.
[26] W. Spaleck, M. Antberg, J. Rohrmann, A. Winter, B. Bachmann, P. Kiprof, J. Behm, W. A. Herrmann, *Angew. Chem.* **1992**, *104*, 1373–1376; *Angew. Chem. Int. Ed.* **1992**, *31*, 1347–1350.
[27] F. Cottet, L. Cottier, G. Descotes, *Synthesis* **1987**, 497–498.
[28] N. Philippe, V. Levacher, G. Dupas, J. Duflos, G. Quéguiner, J. Bourguignon, *Tetrahedron: Asymmetry* **1996**, *7*, 417–420.
[29] R. Gabriella, S. Riva, B. Danieli, *Tetrahedron: Asymmetry* **1999**, *10*, 3939–3949.
[30] D. F. Harvey, K. P. Lund, D. A. Neil, *J. Am. Chem. Soc.* **1992**, *114*, 8424–8434.
[31] M. Buck, J. M. Chong, *Tetrahedron Lett.* **2001**, *42*, 5825–5827.

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