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Palladium-catalyzed Cross-coupling Reactions of Arylmetal Compounds with β-Substituted α-Iodoenones and a Cyclohexyl Triflate

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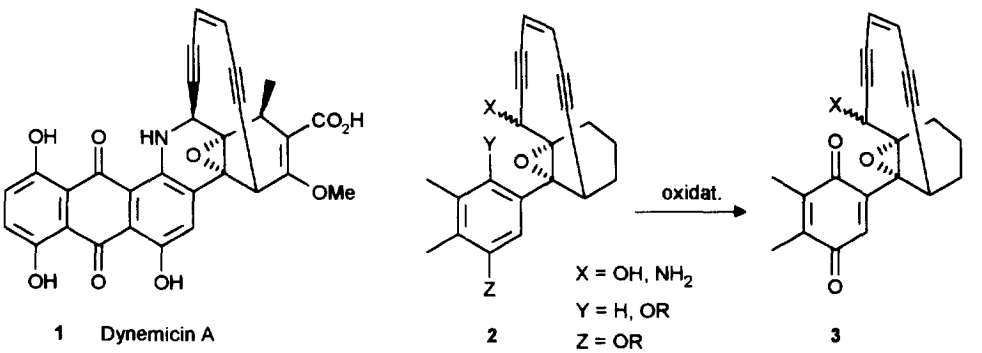
Abstract: Electron-rich arylstannanes were found to couple with α-iodoenones in the presence of $Pd_2(dba)_3 \cdot CHCl_3$, a weak-coordinating ligand [$AsPh_3$ or $Pd(o\text{-tol})_3$] and CuI (0.75-1.0 equiv) to give sterically hindered α-arylcyclohexenones **15-20**. In addition, compounds **19**, **22** and **23** were prepared by Suzuki coupling reactions of the cyclohexyl derivatives **7c,f** and **11**, respectively, with the arylboronic acid **21**. Copyright © 1996 Elsevier Science Ltd

The potent antitumor activity of the enediyne antibiotics ultimately arises from the cycloaromatization of the enediyne substructure to an aromatic diradical.[1] This radical in turn is able to induce double strand cleavage of cellular DNA. Because the lethal cycloaromatization is only possible after an activation step, these compounds represent natural prodrugs. For this reason the enediynes are interesting lead compounds for the development of novel antitumor compounds with a high therapeutic index.[2] Among the known members of this family of natural products, dynemicin A[3,4] (**1**) is unique in that it comprises the essential functional elements in a rather small molecule. Thus, besides the enediyne a device for molecular recognition of DNA (the anthraquinone) as well as a trigger mechanism (the anthraquinone plus the epoxide) are present. To reach structurally simple dynemicin A analogs, we designed compounds that lack the nitrogen heterocycle (Scheme 1). Yet, these analogs of type **3** should undergo activation upon reduction of the quinone ring and subsequent epoxide opening. This sequence would parallel the mode of activation of dynemicin A and that of many other quinone containing antibiotics.

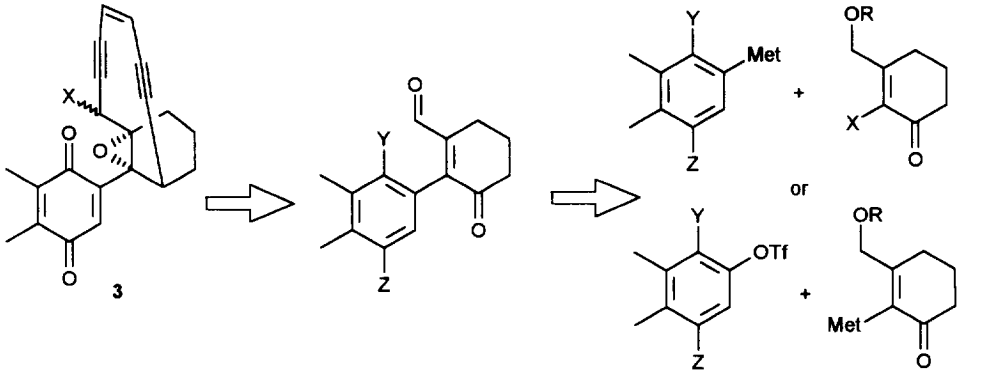


1 Dynemicin A **2** **3**

Scheme 1

These designed analogs should be available from functionalized cyclohexenone derivatives through attachment of the enediyne bow (Scheme 2). In our initial approach, the cyclohexenone ring was constructed through a Dieckmann condensation of a substrate that already contained an electron-rich aromatic ring.[5] However, in order to prepare cyclohexenones with different aryl groups in the 2-position, a more flexible and

convergent approach was sought. In this regard metal-catalyzed cross-coupling reactions appeared particularly promising. Thus, the crucial aryl-cyclohexene bond might be constructed from an arylmetal compound and a cyclohexene with a halide or triflate at the vinylic position. Alternatively, an aryl triflate could be reacted with suitable metallated cyclohexene derivatives. In this paper we demonstrate the application of the first approach towards the preparation of several functionalized cyclohexenes with an one-carbon function and an electron-rich aryl group attached to the double bond.



Scheme 2

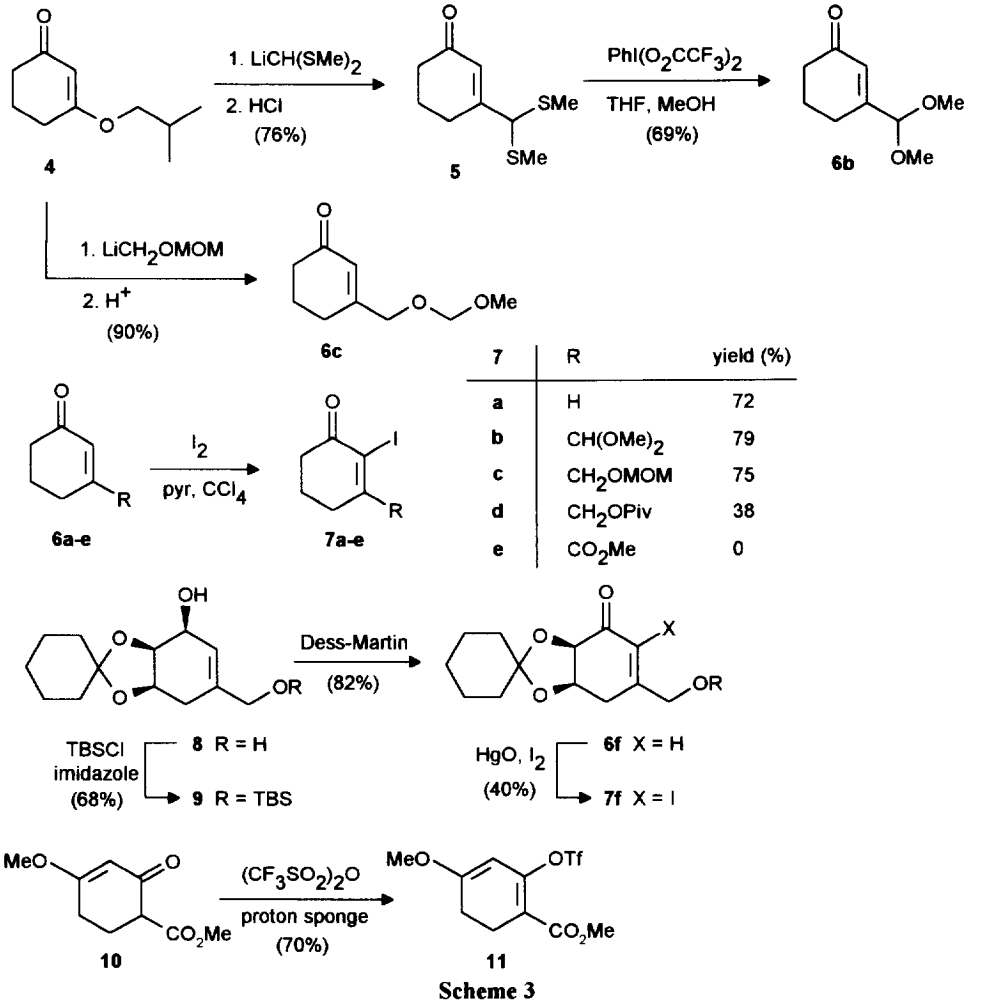
Cyclohexene Derivatives

This study required cyclohexene derivatives with a leaving group (halide, triflate) and a C-1 functional group at the vinylic positions. Next to the leaving group, a carbonyl function or a suitable precursor thereof was needed. In order to assess possible steric and electronic effects of a substituent next to the leaving group, the iodinated cyclohexenes **7a-f** were targeted. These in turn should be available by an iodination reaction from the corresponding β-substituted cyclohexenes **6a-f**. To reach the acetal **6b** the vinologous ester **4**[6] was first converted to the dithioacetal **5** by reaction with the formaldehyde dimethyldithioacetal anion[7] and subsequent acid treatment. Next, the dimethyldithioacetal was converted to the corresponding dimethylacetal through the action of bis(trifluoroacetoxyiodo)benzene.[8] In a similar manner, reaction of **4** with $MOMOCH_2Li$, generated from the corresponding stannane[9] provided the enone **6c**. Additionally, the two cyclohexenones **6d**[10] and **6e**[11] were included in this study. Finally, with a view toward the preparation of optically active dynemicin analogues, the cyclohexenone **6f** was prepared. This compound could be obtained from the diol **8**, which itself is available from (-)-quinic acid in four steps.[12] Selective silylation of the primary hydroxy group of **8** furnished the alcohol **9** which then was oxidized to the enone **6f** using the Dess-Martin periodinane.[13] Treatment of the cyclohexenones **6a-d** with I_2 in a mixture of CCl_4/pyridine[14] provided the α-iodocyclohexenones **7a-d**. As compared to cyclohexenone itself, longer reaction times and an excess of iodine were necessary in order to achieve good yields. The iodination failed with the cyclohexenone **6e**, probably due to the electron-poor double bond. To our disappointment, treatment of the enone **6f** with I_2/pyridine did not give any of the desired α-iodoenone **7f**. Our attention was then drawn to a recent communication which described the iodination of alkoxybenzenes.[15] Applying these conditions, that is HgO/I_2 in CH_2Cl_2, provided the enone **7f** in 40% yield. For the introduction of a triflate leaving group the functionalized β-ketoester **10**[16] was treated with triflic anhydride in the presence of proton sponge[17] to provide the coupling substrate **11** (Scheme 3). A similar triflate has recently been used by Myers et al. in the context of the synthesis of a quinolone that has been used for the synthesis of dynemicin analogs.[18]

Modified Stille Coupling Reactions

Prior to this study only a few palladium-catalyzed cross coupling reactions of arylmetal compounds with α-haloenones were known. In a report by Negishi et al. the low reactivity of α-haloenones in the oxidative addition of Pd(0) was pointed out.[19] Additional difficulties could be expected from the presence of a substituent

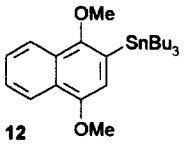
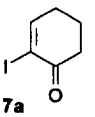
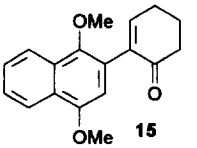
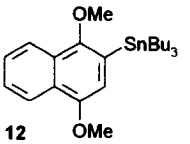
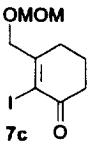
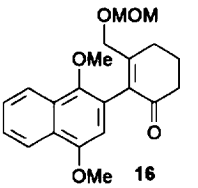
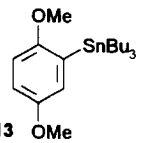
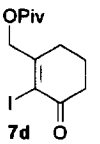
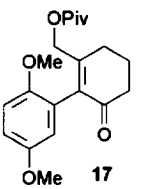
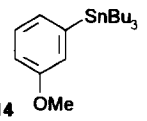
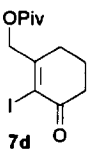
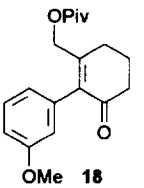
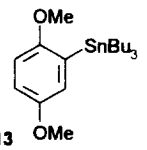
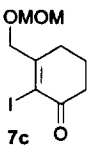
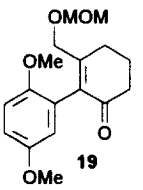
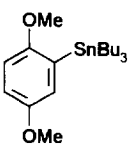
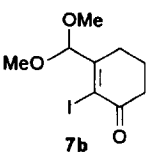
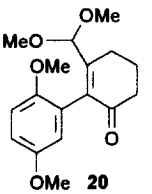
in the β-position of the enone. However, Johnson et al. recently reported the successful coupling of α-iodoenones with aryltin compounds in the presence of Pd(II), CuI, and triphenylarsine.[20] While this study was underway, Isobe and coworkers described the extension of palladium-catalyzed coupling reactions to ß-substituted α-bromoenones with aryltins.[21] Because the aryltin compounds carried a *N*-Boc group in the *ortho*-position, these couplings might represent special cases due to a possible intramolecular activation of the trialkyltin by the nitrogen.[22] For the coupling of the arylstannanes, the relatively stable catalyst $Pd_2(dba)_3 \cdot CHCl_3$[23] was chosen. As solvent, the polar *N*-methylpyrrolidinone (NMP) proved to be useful. The results are depicted in Table 1. However, in comparison to published conditions, some modifications were necessary that particularly emphasize the effect of added CuI on the yield. For example, entry 1 without CuI gave none of the coupled product **15**. With 0.1 equiv of CuI a yield of only 28% was observed. A similar dramatic effect of added CuI was seen with the coupling of entry 6. Thus, omitting CuI [$P(o\text{-tol})_3$ as ligand], provided only 12% of **20**. Performing this reaction in toluene gave no coupling. The results in Table 1 also demonstrate the influence of substituents at the β-position of the enone. It appears that an electron-withdrawing substituent, such as a pivaloyloxy group facilitates the coupling reaction. Comparing entry 3 and 4 shows a detrimental effect of the methoxy group *ortho* to the tin substituent on the coupling efficiency.



7	R	yield (%)
a	H	72
b	$CH(OMe)_2$	79
c	CH_2OMOM	75
d	CH_2OPiv	38
e	CO_2Me	0

Scheme 3

Table 1. Palladium Catalyzed Coupling of α-Iodoenones with Aryltin Compounds

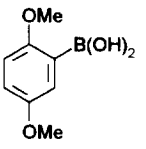
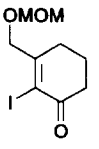
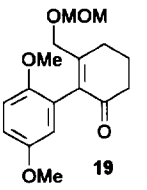
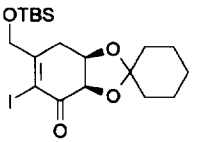
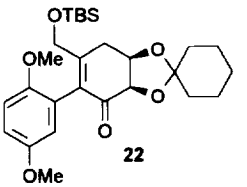
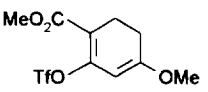
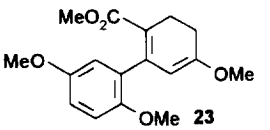
entry	stannane	vinyl halide	ligand (equiv)	CuI (equiv)	conditions (solvent, temp., time)	product	yield (%)
1	 **12**	 **7a**	$AsPh_3$ (0.20)	0.75	NMP, 70 °C, 24 h	 **15**	80
2	 **12**	 **7c**	$AsPh_3$ (0.20)	0.75	NMP, 70 °C, 27 h	 **16**	75
3	 **13**	 **7d**	$AsPh_3$ (0.20)	1.00	NMP, 75 °C, 24 h	 **17**	66
4	 **14**	 **7d**	$AsPh_3$ (0.20)	1.00	NMP, 75 °C, 18 h	 **18**	82
5	 **13**	 **7c**	$P(o\text{-tol})_3$ (0.20)	0.75	NMP, 65 °C, 23 h	 **19**	46
			$AsPh_3$ (0.20)	0.75	NMP, 65 °C, 23 h		51
6	 **13**	 **7b**	$P(o\text{-tol})_3$ (0.28)	1.00	NMP, 60 °C, 24 h	 **20**	43
			$AsPh_3$ (0.20)	1.00	NMP, 75 °C, 24 h		34

The effect of CuI as a co-catalyst in Stille-type coupling reactions has been mentioned by other authors. However, the fact that with our substrates practically stochiometric amounts (0.75-1.0 equiv) are necessary, points to an essential role of CuI in the catalytic cycle. Detailed mechanistic studies by Farina and Liebeskind identified two possible functions of CuI depending on the catalyst, solvent, and ligand.[24] In polar solvents and with soft or weak coordinating ligands, such as $AsPh_3$ or $P(o\text{-tol})_3$[25], the arylstannanes presumably react with CuI to an organocopper species or an aryltin-copper ate complex. This organocopper intermediate then transmetalates to the Pd(II)-vinyl species.

Suzuki Coupling Reactions

The above results underscore the importance of the metal that mediates the transmetalation step of the aryl group to the palladium. For this reason, the cross-couplings were also studied with the arylboronic acid **21**. As can be seen from Table 2, conditions could be found that delivered the desired compounds **19** and **22** in reasonable to good chemical yield. For the coupling of **21** with **7c**, the weak coordinating ligand $AsPh_3$ seems to facilitate the coupling reaction (entry 2). The coupling reaction of the highly substituted iodoenone **7f** shows the limits of the cross-coupling approach. It is not yet clear whether the difficulties in entry 3 stem from steric hindrance (TBS group) or lower conformational flexibility of the enone ring. Nevertheless, compound **22** was obtained in 33% yield. On the other hand, coupling of the triflate **11** with the boronic acid **21** provided the corresponding coupling product **23** in excellent yield (entry 4).

Table 2. Palladium Catalyzed Coupling of Arylboronic Acid **21** with α-Iodoenones **7c,f** and Triflate **11**

entry	boronic acid	vinyl halide/triflate	conditions	product	yield (%)
1	 **21**	 **7c**	$Pd[P(Ph)_3]_4$, benzene, 2 M Na_2CO_3, reflux, 65 h	 **19**	58
2	**21**	**7c**	$Pd_2(dba)_3 \cdot CHCl_3$, dioxane, $AsPh_3$, 85 °C, 21 h, 2 M Na_2CO_3	**19**	80
3	 **21**	**7f**	$Pd[P(Ph)_3]_4$, dioxane, K_2CO_3, 80 °C, 48 h	 **22**	33
4	 **21**	**11**	$Pd[P(Ph)_3]_4$, dioxane, 2 M Na_2CO_3, reflux, 5 h	 **23**	88

NMR Spectra

Due to the presence of a methoxy group *ortho* to the aryl-cyclohexenyl bond, the rotation around this bond in compounds **16**, **17**, **19**, **20**, **22**, and **23** is severely hindered. The non-planarity of the coupling product and the rotational barrier are evident from the diastereotopic nature of the geminal hydrogens of the one-carbon side chain of **16**, **17**, and **19**. In compound **20** the two aliphatic methoxy groups are diastereotopic. They appear at δ 3.20 and 3.31. Force-field calculations (PC-Model) for compound **16** indicate a rotational barrier of about 80 kJ mol^{-1}. Due to the stereo centers and the hindered rotation, compound **22** exists as an unseparable mixture of diastereomers.

To sum up, we have developed conditions that allow the efficient cross-coupling of electron-rich aryltin compounds with β-substituted α-iodoenones. It turned out that weak coordinating ligands and almost stochiometric amounts of CuI are necessary to allow the carbon-carbon bond formation in high yield. In addition, we could show that the arylboronic acid **21** can also be coupled with the enones **7c,f** and the

cyclohexyl triflate **11**. The syntheses of dynemicin analogs from the resulting cross-coupling products are currently being pursued in our laboratories.

EXPERIMENTAL

General

^{1}H NMR: VARIAN UNITY 500 (500 MHz), VARIAN GEMINI 200 (200 MHz), Bruker AM 400 (400 MHz) and AC 200 (200 MHz). - ^{13}C NMR: VARIAN UNITY 500 (125 MHz), VARIAN GEMINI 200 (50 MHz), Bruker AM 400 (100 MHz) and AC 200 (50 MHz); all spectra were recorded in $CDCl_3$ as solvent with TMS as internal standard. - The signal multiplicities were determined by means of the DEPT and APT technique; + for CH or CH_3, - for CH_2, × for C. - IR: Carl Zeiss Jena SPECORD IR 75. - Melting points: Dr. Tottoli melting point apparatus. - EI-MS: AMD Intectra GmbH AMD 402. - Optical rotations were measured on a Polartronic D, Haesch and Schmidt. - Flash chromatography: J. T. Baker silica gel 30-60 µm. - TLC: Merck Si 60 F_{254}. - Solvents were distilled prior to use; petroleum ether with a boiling range of 35-65 °C was used; THF was distilled from sodium diphenyl ketyl immediately before use. - The pH-7 buffer solution used in the workup procedures was prepared by dissolving potassium dihydrogen phosphate (85.0 g) and sodium hydroxide (14.5 g) in water (1 l). The following reagents and compounds were prepared according to literature procedures: 2-bromo-1,4-dimethoxy-naphthalene[26], 2-bromo-1,4-dimethoxybenzene[27], $Pd_2(dba)_3{\cdot}CHCl_3$[23], P(*o*-tol)$_3$[25], **4**[6], **6d**[10], **6e**[11], **7a**[14] (2 equiv of I_2 were used), **8**[12], **10**[16], **13**[28], **14**[28].

3-(Bis-methylsulfanyl-methyl)-cyclohex-2-enone (**5**): Under an atmosphere of nitrogen a solution of bis-methylsulfanyl-methane[7] (18.1 g, 0.167 mol) in 300 ml of anydrous THF was cooled to 0 °C and *n*-BuLi (2.5 M in hexane, 67 ml, 0.17 mol) was added dropwise. The mixture was stirred at 0 °C for 1 h. After the mixture was cooled to -60 °C, the vinylogous ester **4** (26.9 g, 0.160 mol) in THF (200 ml) was added over 30 min. After stirring for 1.5 h, during which time the temperature was allowed to warm to 0 °C and stirring for 1.5 h at 0 °C, the reaction was quenched by the addition of 10% HCl. The mixture was poured into CH_2Cl_2 (280 ml) and the aqueous layer was extracted with CH_2Cl_2 (3 x 130 ml). The combined organic layers were washed with brine (130 ml) and then dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by column chromatography (petroleum ether/ethyl acetate, 5:1) to give the title enone (24.7 g, 0.122 mol, 76%) as a slightly yellow solid of m.p. 34 °C. - TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.33. - ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.00-2.09 (m, 2 H, CH_2), 2.09 (s, 6 H, CH_3), 2.40-2.44 (m, 2 H, CH_2), 2.50-2.53 (m, 2 H, CH_2), 4.20 [s, 1 H, C*H*(SCH$_3$)$_2$], 5.97 (s, 1 H, vinyl-H). - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.39 (+, CH_3), 22.76, 27.01, 37.59 (3 -, CH_2), 58.10 [+, *C*H(SCH$_3$)$_2$], 126.02 (+, vinyl-CH), 159.89 (×, vinyl-C), 199.39 (×, C=O). - MS (EI), *m/z* (%): 202 (20) [M^+], 155 (100), 127 (38), 79 (48).

3-Dimethoxymethyl-cyclohex-2-enone (**6b**): Under an atmosphere of nitrogen a solution of compound **5** (16.8 g, 83.1 mmol) in anhydrous THF (120 ml) and anhydrous methanol (250 ml) was cooled to 0 °C and bis(trifluoroacetoxy)iodobenzene (50.0 g, 0.16 mol) in anhydrous methanol (120 ml) was added. After 10 min the mixture was poured into saturated aqueous $NaHCO_3$ (500 ml) followed by the addition of ether (670 ml) and water (340 ml). The aqueous layer was extracted with ether (5 x 250 ml). The combined organic layers were washed with brine (170 ml) and then dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by column chromatography (petroleum ether/ethyl acetate, 5:1) to give the title enone (9.7 g, 57 mmol, 69%) as a colorless oil. - TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.20. - ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.98-2.08 (m, 2 H, CH_2), 2.32-2.35 (m, 2 H, CH_2), 2.40-2.43 (m, 2 H, CH_2), 3.33 (s, 6 H, CH_3), 4.75 [s, 1 H, C*H*(OCH$_3$)$_2$], 6.13 (d, *J* = 0.9 Hz, 1 H, vinyl-H). - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.43, 24.58, 37.85 (3 -, CH_2), 53.52 (+, CH_3), 103.69 [+, *C*H(OCH$_3$)$_2$], 126.82 (+, vinyl-CH), 158.66 (×, vinyl-C), 199.88 (×, C=O). - MS (EI), *m/z* (%): 170 (4) [M^+], 142 (4), 139 (20), 111 (20), 75 (100).

3-(Methoxymethoxy-methyl)-cyclohex-2-enone (**6c**): Under an atmosphere of nitrogen a solution of (methoxymethoxy-methyl)tributylstannane[9] (8.49 g, 23.2 mmol) in 110 ml of anhydrous THF was cooled to -80 °C and *n*-BuLi (2.5 M in hexanes, 8.9 ml, 22 mmol) was added dropwise. The mixture was stirred for 5 min followed by the addition of the vinologous ester **4** (3.55 g, 21.1 mmol). After stirring for 24 h during which

time the temperature was allowed to warm to room temperature, the reaction was quenched by the addition of 100 ml of saturated aqueous NH_4Cl. The aqueous layer was extracted with ethyl acetate (100 ml), and the combined organic layers were washed with water (100 ml), brine (100 ml) and then dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by flash chromatography (gradient elution from petroleum ether to petroleum ether/ethyl acetate, 1:1) to give the title enone (3.24 g, 19.0 mmol, 90%) as a colorless oil. - TLC (petroleum ether/ethyl acetate, 1:2): R_f = 0.43. - IR (film): $\tilde{\nu}_{max}$ = 3037 cm^{-1}, 1674. - ^1H NMR (400 MHz, $CDCl_3$): δ = 2.00-2.07 (m, 2 H, CH_2), 2.27-2.30 (m, 2 H, CH_2), 2.40-2.43 (m, 2 H, CH_2), 3.39 (s, 3 H, CH_3), 4.17 (s, 2 H, CH_2OMOM), 4.67 (s, 2 H, OCH_2OCH_3), 6.13 (t, J = 1.5 Hz, 1 H, vinyl-H). - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.38, 26.34, 37.71 (3 -, CH_2), 55.49 (+, CH_3), 68.86 (-, CH_2OMOM), 96.05 (-, OCH_2OCH_3), 124.45 (+, vinyl-CH), 160.90 (×, vinyl-C), 199.44 (×, C=O). - MS (EI), *m/z* (%): 170 (2) [M^+], 141 (38), 125 (2), 111 (22), 45 (100). - HRMS for $C_9H_{14}O_3$ (M^+): calcd. 170.094, found 170.094.

3-tert-Butyldimethylsilyloxymethyl-5,6-O-cyclohexylidene-cyclohex-2-enone (**6f**): A solution of **9** (2.23 g, 6.29 mmol) in CH_2Cl_2 (6 ml) was added to a stirred solution of the Dess-Martin periodinane[13] (3.05 g, 7.19 mmol) in CH_2Cl_2 (20 ml) over 2 min. The solution started to boil. After 20 min, the reaction mixture was diluted with diethyl ether (40 ml) and poured into saturated aqueous $NaHCO_3$ (40 ml) containing 12 g of $Na_2S_2O_3$. The mixture was stirred for 5 min, 40 ml of diethyl ether were added, and the layers separated. The aqueous layer was extracted with diethyl ether (2 x 40 ml). The combined extracts were dried ($MgSO_4$) and filtered. Removal of the solvent followed by flash chromatography (petroleum ether/ethyl acetate, 4:1) gave the enone **6f** as a white solid; yield 1.81 g (82%). - m.p. 88-89 °C. - TLC (petroleum ether/diethyl ether, 1:1): R_f = 0.50. - $[\alpha]_D^{20}$ = -39.2 (*c* = 1.0 in MeOH). - IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 1680 cm^{-1} (C=O). - ^1H NMR (200 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, $SiCH_3$), 0.88 [s, 9 H, $C(CH_3)_3$], 1.32-1.66 (m, 10 H, cyclohexylidene), 2.64 (s, 2 H, 4-H), 4.21 (s, 2 H, CH_2OTBS), 4.26 (d, J = 5.1 Hz, 1 H, 5-H), 4.59-4.65 (m, 1 H, 6-H), 6.22 (m, 1 H, olefinic). - ^{13}C NMR (125 MHz, $CDCl_3$): δ = -5.48 (+, $SiCH_3$), 18.26 [×, $C(CH_3)_3$], 23.75, 23.79, 24.94, 27.92, 37.04 (5 -, cyclohexylidene CH_2), 25.77 [+, $C(CH_3)_3$], 35.52 (-, 4-C), 65.11 (-, CH_2OTBS), 72.31 (+, 5-C), 75.15 (+, 6-C), 110.04 (×, ketal), 121.74 (+, C=CH), 160.10 (×, C=CH), 196.06 (×, C=O). - MS (EI), *m/z* (%): 352 (25) [M^+], 309 (65), 295 (85), 197 (100), 169 (40). - $C_{19}H_{32}O_4Si$ (352.5): calcd. C 64.73, H 9.15; found C 64.62, H 9.14.

3-Dimethoxymethyl-2-iodo-cyclohex-2-enone (**7b**): A solution of iodine (29.8 g, 118 mmol) in 170 ml of anhydrous CCl_4/pyridine (1:1) was added dropwise, under an atmosphere of nitrogen, to a solution of enone **6b** (5.03 g, 29.4 mmol) in 170 ml of CCl_4/pyridine (1:1) at 0 °C. After stirring for 2 d at room temperature, more iodine (14.9 g, 58.8 mmol) was added and the mixture was stirred for additional 4 d. The mixture was diluted with ether (510 ml), washed with water (2 x 230 ml), 20% aqueous $Na_2S_2O_3$ (2 x 230 ml), and dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1) to give the title iodoenone (6.94 g, 23.4 mmol, 79%) as a yellow oil. - TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.35. - IR (film): $\tilde{\nu}_{max}$ = 1687 cm^{-1}. - ^1H NMR (400 MHz, $CDCl_3$): δ = 1.95-2.02 (m, 2 H, CH_2), 2.54-2.57 (m, 2 H, CH_2), 2.66-2.69 (m, 2 H, CH_2), 3.48 (s, 6 H, CH_3), 5.26 [s, 1 H, $CH(OCH_3)_2$]. - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.12, 27.21, 37.63 (3 -, CH_2), 55.78 (+, CH_3), 107.55 (×, vinyl-CI), 110.88 [+, $CH(OCH_3)_2$], 162.81 (×, vinyl-C), 192.59 (×, C=O). - MS (EI), *m/z* (%): 296 (4) [M^+], 265 (18), 237 (2), 169 (58), 138 (12), 75 (100). - $C_9H_{13}IO_3$ (296.1) calcd. C 36.51, H 4.43; found C 36.04, H 4.42.

2-Iodo-3-(methoxymethoxy-methyl)-cyclohex-2-enone (**7c**): A solution of iodine (35.8 g, 141 mmol) dissolved in 180 ml anhydrous CCl_4/pyridine (1:1) was added dropwise, under an atmosphere of nitrogen, to a solution of enone **6c** (6.00 g, 35.3 mmol) in 150 ml of CCl_4/pyridine (1:1) at 0 °C. The mixture was stirred for 2 d at room temperature, diluted with ether (700 ml), washed with water (2 x 250 ml), 20% aqueous $Na_2S_2O_3$ (2 x 250 ml), and dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by column chromatography (Al_2O_3, petrolether/ethyl acetate 7:1) to give the title iodoenone (7.80 g, 26.3 mmol, 75%) as a yellow oil. - TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.23. - IR (film): $\tilde{\nu}_{max}$ = 1683 cm^{-1}. - ^1H NMR (400 MHz, $CDCl_3$): δ = 2.00-2.06 (m, 2 H, CH_2), 2.62-2.67 (m, 4 H, CH_2), 3.24 (s, 3

H, CH_3), 4.40 (s, 2 H, CH_2OMOM), 4.71 (s, 2 H, CH_2OCH_3). - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.19, 30.07, 37.07 (3 -, CH_2), 55.72 (+, CH_3), 76.05 (-, CH_2OMOM), 96.60 (-, $CH_2O\ CH_3$), 104.95 (×, vinyl-CI), 165.47 (×, vinyl-C), 191.80 (×, C=O). - MS (EI), *m/z* (%): 296 (15) [M^+], 267 (20), 264 (42), 43 (100). - $C_9H_{13}IO_3$ (296.1) calcd. C 36.51, H 4.43; found C 36.21, H 4.39.

(2-Iodo-3-oxo-cyclohex-1-enyl)methyl pivalate (**7d**): Iodine (14.5 g, 57.1 mmol) dissolved in 120 ml anhydrous CCl_4/pyridine (1:1) was added dropwise, under an atmosphere of nitrogen to a solution of enone **6d** (3.00 g, 14.3 mmol) in 120 ml of CCl_4/pyridine (1:1) at 0 °C. The mixture was stirred for 7 d at room temperature. The mixture was diluted with ether (600 ml), washed with water (2 x 240 ml), 20% aqueous $Na_2S_2O_3$ (2 x 240 ml), and dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by flash chromatography (petrolether/ethyl acetate, 5:1) to give the title iodoenone (2.37 g, 7.05 mmol, 49%) as a colorless solid of m.p. 46-47 °C. - TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.34. - IR (KBr): $\tilde{\nu}_{max}$ = 1727 cm^{-1}, 1682. - ^1H NMR (400 MHz, $CDCl_3$): δ = 1.16 (s, 9 H, CH_3), 1.91-1.98 (m, 2 H, CH_2), 2.38-2.41 (m, 2 H, CH_2), 2.55-2.58 (m, 2 H, CH_2), 4.80 (s, 2 H, CH_2OPiv). - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.04 (-, CH_2), 27.12 (+, CH_3), 29.50, 36.69 (2 -, CH_2), 38.86 [×, $C(CH_3)_3$], 79.93 (-, CH_2OPiv), 105.29 (×, vinyl-CI), 162.88 (×, vinyl-C), 177.63 [×, $OC(O)tBu$], 191.26 (×, C=O). - MS (EI), *m/z* (%): 336 (10) [M^+], 252 (14), 234 (50), 209 (10), 57 (100). - $C_{12}H_{17}IO_3$ (336.2): calcd. C 42.85, H 5.10; found C 42.91, H 5.19.

3-tert-Butyldimethylsilyloxymethyl-5,6-O-cyclohexylidene-cyclohex-2-iodo-2-enone (**7f**): A suspension of enone **6f** (1.05 g, 2.98 mmol), dry pyridine (0.94 g, 12 mmol), HgO (1.94 g, 8.96 mmol), iodine (2.27 g, 8.94 mmol), ZnI_2 (0.3 g, 0.9 mmol) in CH_2Cl_2 (20 ml) was stirred for 7 h at room temperature. After filtration, the filtrate was washed with 20 % aqueous $Na_2S_2O_3$ (25 ml), 10 % aqueous KI (25 ml) and water (25 ml), dried ($MgSO_4$) and filtered. Solvent removal gave an oil which was purified by flash chromatography (petroleum ether/ethyl acetate, 6:1) to give the α-iodoenone **7f** (0.56 g, 40%) as a yellow solid of m.p. 86-88 °C, and recovered starting material (0.37 g, 36%). - TLC (petroleum ether/diethyl ether, 1:1): R_f = 0.80. - $[\alpha]_D^{20}$ = -37.8 (*c* = 1.3 in $CHCl_3$). - IR (CH_2Cl_2): $\tilde{\nu}_{max}$ = 1720 cm^{-1} (C=O). - ^1H NMR (200 MHz, $CDCl_3$): δ = 0.11 (s, 6 H, $SiCH_3$), 0.92 [s, 9 H, $C(CH_3)_3$], 1.23-1.66 (m, 10 H, cyclohexylidene), 2.80 (dd, *J* = 20.7 and 4.7 Hz, 1 H, 4-H), 3.25 (d, *J* = 20.7 Hz, 1 H, 4-H), 4.40-4.44 (m, 1 H, 5-H), 4.45 (s, 2 H, CH_2OTBS), 4.59, (m, 1 H, 6-H). - ^{13}C NMR (50 MHz, $CDCl_3$): δ = -5.44 (+, $SiCH_3$), 18.17 [×, $C(CH_3)_3$], 23.67, 24.84, 31.18, 35.39, 36.89 (5 -, cyclohexylidene CH_2), 25.76 [+, $C(CH_3)_3$], 31.18 (-, 4-C), 71.82 (+, 5-C), 72.32 (-, CH_2OTBS), 74.80 (+, 6-C), 99.62 (×, C=C-I), 110.24 (×, ketal), 164.45 (×, C=C-I), 189.62 (×, C=O). - MS (EI), *m/z* (%): 478 (2) [M^+], 323 (45), 305 (100), 254 (45), 55 (65). - $C_{19}H_{31}IO_4Si$ (478.4): calcd. C 47.70, H 6.53; found C 47.83, H 6.54.

(1R,2R,3S)-5-tert-Butyldimethylsilyloxymethyl-1,2-O-cyclohexylidene-4-cyclohexene-1,2,3-triol (**9**): To a cooled solution (0 °C) of the diol **8**[12] (480 mg, 2.00 mmol) and imidazole (290 mg, 4.26 mmol) in dry CH_2Cl_2 (15 ml) was added *tert*-butyldimethylsilyl chloride (310 mg, 2.05 mmol). The reaction mixture was stirred for 3 days at 10 °C and then poured into saturated aqueous NH_4Cl (20 ml). The aqueous phase was extracted with CH_2Cl_2 (3 x 30 ml). The combined extracts were washed with brine (2 x 10 ml), dried ($MgSO_4$) and filtered. Concentration of the filtrate followed by flash chromatography (petroleum ether/ethyl acetate, 5:1) afforded compound **9** (480 mg, 68%) as a white solid of m.p. 40-41 °C. - TLC (petroleum ether/diethyl ether, 1:1): R_f = 0.45. - $[\alpha]_D^{20}$ = +3.58 (*c* = 2.05 in $CHCl_3$), - IR (CH_2Cl_2): $\tilde{\nu}$ = 3550 cm^{-1} (OH). - ^1H NMR (500 MHz, $CDCl_3$): δ = 0.05 (s, 6 H, $SiCH_3$), 0.89 [s, 9 H, $C(CH_3)_3$], 1.36-1.62 (m, 10 H, cyclohexylidene), 1.99 (d, br., *J* = 16.1 Hz, 1 H, 6-H), 2.24 (dd, *J* = 16.1, 3.3 Hz, 1 H, 6-H), 4.05 (s, 2 H, CH_2OTBS), 4.07-4.09 (m, 1 H, CHOH), 4.41-4.43 (m, 1 H, 1-H), 4.50-4.53 (m, 1 H, 2-H), 5.71 (s, 1 H, olefinic). - ^{13}C NMR (125 MHz, $CDCl_3$): δ = -5.43 (+, $SiCH_3$), 18.26 [×, $C(CH_3)_3$], 23.76, 24.01, 28.61, 29.46, 36.93 (5 -, cyclohexylidene CH_2), 25.80 [+, $C(CH_3)_3$], 35.52 (-, CH_2CH), 65.81 (-, CH_2OTBS), 66.70 (+, CHOH), 72.71 (+, 1-C), 75.33 (+, 2-C), 109.79 (×, ketal), 118.76 (+, C=CH), 137.96 (×, C=CH). - MS (EI), *m/z* (%): 354 (32) [M^+], 311 (34), 239 (35), 199 (100), 181 (82), 107 (70). - $C_{19}H_{34}O_4Si$ (354.6): calcd. C 64.36, H 9.67; found C 64.34, H 9.80.

Methyl 2-trifluoromethanesulfonate-4-methoxy-1,3-cyclohexadiene carboxylate (**11**): Methyl-4-methoxy-2-oxo-3-cyclohexene carboxylate (2.69 g, 14.7 mmol) and 1,8-bis-(*N,N*-dimethylamino)-naphthalene (proton sponge) (3.76 g, 17.8 mmol) were dissolved in dry CH_2Cl_2 (160 ml). After being stirred for 30 min at room temperature, the solution was cooled to 0 °C in an ice bath and trifluoromethanesulfonic anhydride (4.54 g, 3.43 ml, 16.1 mmol) was added dropwise over 20 min. The mixture was stirred for 5 h and allowed to warm to room temperature. The mixture was washed with aqueous $NaHCO_3$ (2 x 25 ml), brine (30 ml), dried over Na_2SO_4, and concentrated under reduced pressure (40 °C). The crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 9:1), yield 3.35 g (70%). The colorless solid is unstable at room temperature and moisture sensitive. However, it can be kept at -20 °C. Because of the somewhat unstable nature of this triflate no elemental analysis was performed. - TLC (petroleum ether/ethyl acetate, 9:1): R_f = 0.44. - m.p. 42 °C. - IR (KBr): $\tilde{\nu}$ = 1703 cm^{-1}, 1641, 1577. - ^1H NMR (500 MHz, $CDCl_3$): δ = 2.39 (t, *J* = 9.4 Hz, 2 H, CH_2), 2.71 (t, *J* = 9.4 Hz, 2 H, CH_2), 3.68 (s, 3 H, OCH_3), 3.76 (s, 3 H, $COOCH_3$), 4.91 (s, 1 H, olefinic). - ^{13}C NMR (500 MHz, $CDCl_3$): δ = 23.26, 26.81 (2 -, CH_2), 51.66, 55.90 (2 +, CH_3), 91.27 (+, CF_3), 108.83 (-, CH), 114.65 (×, C-OMe), 151.18 (×, *C*-CO_2Me), 164.70 (×, *C*-OSO_2CF_3), 168.72 (×, CO_2Me). - MS (EI), *m/z* (%): 316 (100) [M^+], 285 (40), 151 (80).

1,4-Dimethoxy-2-(tributyl-stannyl)-naphthalene (**12**): To a cooled (-80 °C) solution of 2-bromo-1,4-dimethoxy-naphthalene[26] (7.60 g, 28.5 mmol) in anhydrous THF (400 ml) was added *n*-BuLi (2.5 M in hexane, 12.5 ml, 31.5 mmol). After stirring for 5 min *n*-Bu_3SnCl (10.2 g, 31.3 mmol) was added and the solution was stirred for 2 h during which time it was allowed to warm to -15 °C. The mixture was poured into pH-7 buffer solution (200 ml), the organic layer was washed with brine (2 x 200 ml), dried over Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by flash chromatography (silica 100 g, petroleum ether and 2% triethylamine) to give stannane **12** (12.7 g, 26.6 mmol, 94%) as a colourless oil. - TLC (petroleum ether/ethyl acetate, 3:1): R_f = 0.82. - IR (film): $\tilde{\nu}_{max}$ = 3069 cm^{-1}. - ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.3 Hz, 9 H, CH_3) 1.14-1.61 (m, 18 H, CH_2) 3.87, 3.98 (2 s, 3 H each, OCH_3), 6.76 (s, 1 H, aryl-H), 7.43-7.52 (m, 2 H, aryl-H), 7.98-8.00 (m, 1 H, aryl-H), 8.22-8.24 (m, 1 H, aryl-H). - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.16 [-, $Sn(CH_2R)_3$], 13.66 (+, CH_3), 27.36, 29.16 (2 -, CH_2), 55.56, 62.95 (2 +, OCH_3), 109.81, 121.89, 122.48, 125.21, 126.05 (5 +, CH), 127.22, 127.43, 128.91 (3 ×, aryl-C), 151.43, 155.39 (×, aryl-$COCH_3$). - MS (EI), *m/z* (%): 478 (5) [M^+, ^{120}Sn], 463 (2), 421 (100), 307 (22), 188 (20). - $C_{24}H_{38}O_2Sn$ (477.3): calcd. C 60.40, H 8.03; found C 60.41, H 8.14.

2-(1,4-Dimethoxy-naphthalene-2-yl)-cyclohex-2-enone (**15**): In a nitrogen flushed flask 2-iodo-cyclohex-2-enone[14] (**7a**) (222 mg, 1.00 mmol), CuI (143 mg, 0.751 mmol), $AsPh_3$ (61 mg, 0.20 mmol) and $Pd_2(dba)_3 \cdot CHCl_3$ (26 mg, 0.025 mmol) were placed and NMP (3 ml) was added. The mixture was degassed and stirred for 15 min. The flask was lowered into an oil-bath (85 °C) and stannane **12** (524 mg, 1.10 mmol) was added. The solution was stirred for 24 h at 70-80 °C. After cooling, the mixture was treated with saturated KF solution (4 ml), stirred for 30 min, poured into ethyl acetate (150 ml), filtered and washed with water (2 x 50 ml). The aqueous layers were combined and then back-extracted with ethyl acetate (40 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1) to give the enone **15** (227 mg, 0.804 mmol, 80%) as a yellow oil. - TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.22. - IR (film): $\tilde{\nu}_{max}$ = 1675 cm^{-1}. - ^1H NMR (400 MHz, $CDCl_3$): δ = 2.16-2.22 (m, 2 H, CH_2), 2.57-2.61 (m, 2 H, CH_2), 2.65-2.69 (m, 2 H, CH_2), 3.72, 3.95 (2 s, 3 H each, OCH_3), 6.50 (s, 1 H, aryl-CH), 7.14 (t, *J* = 4.2 Hz, 1 H, vinyl-H), 7.44-7.54 (m, 2 H, aryl-H), 8.04-8.07 (m, 1 H, aryl-H), 8.20-8.23 (m, 1 H, aryl-H). - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.06, 26.50, 38.90 (3 -, CH_2), 55.57, 61.62 (2 +, OCH_3), 105.93, 122.06, 122.24 (3 +, aryl-CH), 125.26 (×, aryl-C), 125.45 (+, aryl-C), 126.31 (×, aryl-C), 126.43 (+, aryl-C), 128.51 (×, aryl-C), 138.09 (×, vinyl-CAr), 147.17 (×, aryl-$COCH_3$), 149.92 (+, vinyl-*C*H), 151.20 (×, aryl-$COCH_3$), 198.18 (×, C=O). - MS (EI), *m/z* (%): 282 (100) [M^+], 267 (70), 252 (10). - $C_{18}H_{18}O_3$ (282.3): calcd. C 76.57, H 6.43; found C 75.97, H 6.40.

2-(1,4-Dimethoxy-naphthalene-2-yl)-3-(methoxymethoxy-methyl)-cyclohex-2-enone (**16**): In a nitrogen flushed flask iodoenone **7c** (7.80 g, 26.3 mmol), CuI (3.76 g, 19.8 mmol), $AsPh_3$ (1.61 g, 5.27 mmol) and

$Pd_2(dba)_3 \cdot CHCl_3$ (0.682 g, 0.659 mmol) were placed and NMP (200 ml) was added. The mixture was degassed and stirred for 30 min. The flask was lowered into an oil-bath (70 °C) and stannane **12** (13.8 g, 29.0 mmol) was added. The solution was stirred for 27 h at 65-70 °C. After cooling, the mixture was treated with saturated KF solution (50 ml), stirred for 30 min, poured into ethyl acetate (700 ml), filtered, and washed with water (2 x 175 ml). The aqueous layers were combined and then back-extracted with ethyl acetate (150 ml). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution from petroleum ether/ethyl acetate 20:1 to petroleum ether/ethyl acetate 2:1) to give the enone **16** (7.02 g, 19.7 mmol, 75%) as a yellow oil. - TLC (petroleum ether/ethyl acetate, 2:1): R_f = 0.23. - IR (film): $\tilde{\nu}_{max}$ = 1672 cm^{-1}. - ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.16-2.22 (m, 2 H, CH_2), 2.63-2.80 (m, 4 H, CH_2), 3.27 (s, 3 H, CH_2OCH_3), 3.67, 3.91 (2 s, 3 H each, aryl-OCH_3), 4.03 (d, J = 13.3 Hz, 1 H, CH_2OMOM), 4.14 (d, J = 13.3 Hz, 1 H, CH_2OMOM), 4.51 (d, J = 6.8 Hz, 1 H, CH_2OCH_3), 4.53 (d, J = 6.8 Hz, 1 H, CH_2OCH_3), 6.39 (s, 1 H, aryl-H), 7.26-7.54 (m, 2 H, aryl-H), 8.03-8.05 (m, 1 H, aryl-H), 8.22-8.24 (m, 1 H, aryl-H). - ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 22.37, 27.37, 38.45 (3 -, CH_2), 55.36 (+, CH_2OCH_3), 55.56, 61.62 (2 +, aryl-OCH_3), 68.52 (-, CH_2OMOM), 98.49 (-, CH_2OCH_3), 105.74, 122.07, 122.27 (3 +, aryl-CH), 123.04 (×), 125.55, 126.41 (2 +, aryl-CH), 126.50, 128.39, 134.38, 147.26, 151.35, 157.47 (6 ×), 198.53 (×, C=O). - MS (EI), *m/z* (%): 356 (100) [M^+], 311 (35), 295 (8), 279 (40). - $C_{21}H_{24}O_5$ (356.4): calcd. C 70.77, H 6.79; found C 70.39, H 6.89.

[2-(2,5-Dimethoxy-phenyl)-3-oxocyclohex-1-enyl]methyl pivalate (**17**): In a nitrogen flushed flask iodoenone **7d** (873 mg, 2.60 mmol), CuI (495 mg, 2.60 mmol), $AsPh_3$ (159 mg, 0.519 mmol) and $Pd_2(dba)_3 \cdot CHCl_3$ (67 mg, 0.064 mmol) were placed and NMP (10 ml) was added. The mixture was degassed and stirred for 30 min. The stannane **13** (1.22 g, 2.86 mmol) was added and the flask was lowered into an oil-bath (70 °C). The solution was stirred for 24 h at 85 °C. After cooling, the mixture was treated with saturated KF solution (13 ml), stirred for 30 min, dissolved into ethyl acetate (250 ml), filtered and washed with water (2 x 100 ml). The aqueous layers were combined and then back-extracted with ethyl acetate (130 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petoleum ether/ethyl acetate, 3:1) to give the enone **17** (574 mg, 1.66 mmol, 66%) as a yellow oil. - TLC (petroleum ether/ethyl acetate, 3:1): R_f = 0.29. - IR (film): $\tilde{\nu}_{max}$ = 1731 cm^{-1}, 1678. - ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 [s, 9 H, $C(CH_3)_3$], 2.07-2.16 (m, 2 H, CH_2), 2.49-2.60 (m, 4 H, CH_2), 3.68, 3.78 (2 s, 3 H each, aryl-OCH_3), 4.51-4.61 (m, 2 H, CH_2OPiv), 6.57-6.60 (m, 1 H, aryl-CH), 6.82-86 (m, 2 H, aryl-H). - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.10, 26.86 (2 -, CH_2), 27.12 [+, $C(CH_3)_3$], 37.93 (-, CH_2), 38.81 [×, $C(CH_3)_3$], 55.58, 56.16 (2 +, aryl-OCH_3), 64.77 (-, CH_2OPiv), 112.09, 114.10, 116.68 (3 +, aryl-C), 124.16, 134.39, 151.14, 153.26, 153.70 (5 ×), 177.92 [×, OC(O)*t*Bu], 197.33 (×, C=O). - MS (EI), *m/z* (%): 346 (2) [M^+], 209 (10), 183 (94), 73 (100). $C_{20}H_{26}O_5$ (346.2): calcd. C 69.33, H 7.57; found: C 69.61, H 7.64.

[2-(3-Methoxy-phenyl)-3-oxo-cyclohex-1-enyl]methyl pivalate (**18**): In a nitrogen flushed flask iodoenone **7d** (274 mg, 0.815 mmol), CuI (155 mg, 0.814 mmol), $AsPh_3$ (50 mg, 0.16 mmol) and $Pd_2(dba)_3 \cdot CHCl_3$ (21 mg, 20 µmol) were placed and NMP (3 ml) was added. The mixture was degassed and stirred for 30 min. The stannane **14** (356 mg, 0.834 mmol) was added and the flask was lowered into an oil-bath (70 °C). The solution was stirred for 18 h at 85 °C. After cooling, the mixture was treated with saturated KF solution (4 ml), stirred for 30 min, dissolved into ethyl acetate (80 ml), filtered and washed with water (2 x 30 ml). The aqueous layers were combined and then back-extracted with ethyl acetate (40 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1) to give the enone **18** (212 mg, 0.670 mmol, 82%) as a yellow oil. - TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.23. - IR (film): $\tilde{\nu}_{max}$ = 1731 cm^{-1}, 1678. - ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21 [s, 9 H, $C(CH_3)_3$], 2.08-2.14 (m, 2 H, CH_2), 2.47-2.58 (m, 4 H, CH_2), 3.78 (s, 3 H, OCH_3), 4.59 (s, 2 H, CH_2OPiv), 6.60-6.65 (m, 2 H, aryl-H), 6.85 (ddd, J = 8.4, 2.5, 0.9 Hz, 1 H, aryl-H), 7.25-7.27 (m, 1 H, aryl-H). - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.07, 27.01 (2 -, CH_2), 27.11 [+, $C(CH_3)_3$], 38.02 (-, CH_2), 38.80 [×, $C(CH_3)_3$], 55.09 (-, CH_2OPiv), 64.69 (+, aryl-OCH_3), 113.39, 115.17, 121.90, 126.16 (4 +, aryl-CH), 135.50, 138.61, 153.33, 159.30 (4 ×), 177.88 [×, OC(O)*t*Bu],

197.62 (×, C=O). - MS (EI), *m/z* (%): 316 (52) [M^+], 232 (100), 214 (56), 56 (52). - $C_{19}H_{23}O_4$ (316.4): C 72.11, H 7.65; found: C 71.67, H 7.90.

2-(2,5-Dimethoxy-phenyl)-3-(methoxymethoxy-methyl)-cyclohex-2-enone (**19**): a) *Stille Coupling*: In a nitrogen flushed flask iodoenone **7c** (307 mg, 1.04 mmol), CuI (148 mg, 0.777 mmol), $AsPh_3$ (64 mg, 0.21 mmol) and $Pd_2(dba)_3 \cdot CHCl_3$ (27 mg, 26 μmol) were placed and NMP (3 ml) was added. The mixture was degassed and stirred for 10 min. The stannane **13** (487 mg, 1.14 mmol) was added and the flask was lowered into an oil-bath (65 °C). The solution was stirred for 23 h at 65-70 °C. After cooling, the mixture was poured into ethyl acetate (50 ml) and washed with water (10 ml) and brine (10 ml). The aqueous layers were combined and then back-extracted with ethyl acetate (10 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution from petroleum ether/ethyl acetate, 4:1 to petroleum ether/ethyl acetate, 2:1) to give the enone **19** (162 mg, 0.535 mmol, 51%) as a yellow oil. - TLC (petroleum ether/ethyl acetate, 2:1): R_f = 0.19. - IR (film): $\tilde{\nu}_{max}$ = 1666 cm^{-1}. - ^1H NMR (500 MHz, $CDCl_3$): δ = 2.03-2.15 (m, 2 H, CH_2), 2.48-2.66 (m, 4 H, CH_2), 3.27 (s, 3 H, CH_2OCH_3), 3.64, 3.72 (2 s, 3 H each, aryl-OCH_3), 3.96 (d, J = 13.0 Hz, 1 H, CH_2OMOM), 4.00 (d, J = 13.0 Hz, 1 H, CH_2OMOM), 4.52 (s, 2 H, CH_2OCH_3), 6.49-6.54 (m, 1 H, aryl-H), 6.74-6.81 (m, 2 H, aryl-H). - ^{13}C NMR (125 MHz, $CDCl_3$): δ = 22.24, 27.36, 38.15 (3 -, CH_2), 55.33, 55.65, 56.31 (3 +, CH_2OCH_3, aryl-OCH_3), 68.34 (-, CH_2OMOM), 96.39 (-, CH_2OCH_3), 112.20, 113.96, 116.83 (3 +, aryl-C), 124.95, 134.92, 151.31, 153.33, 155.72 (5 ×), 197.71 (×, C=O). - MS (EI), *m/z* (%): 307 (20) [M^+ + H], 306 (100), 261 (40), 245 (23). - $C_{17}H_{22}O_5$ (306.4): calcd. C 66.64, H 7.24; found C 66.71, H 7.25.

b) *Suzuki Coupling*: In a nitrogen flushed flask iodoenone **7c** (278 mg, 0.939 mmol), $AsPh_3$ (58 mg, 0.19 mmol) and $Pd_2(dba)_3 \cdot CHCl_3$ (24 mg, 23 μmol) were placed and dioxane (10 ml) was added. The mixture was stirred for 10 min and boronic acid **21** (188 mg, 1.03 mmol) and 2 ml 2 M Na_2CO_3 solution were added. The flask was lowered into an oil-bath (65 °C) and the solution was stirred for 21 h at 85 °C. After cooling, the mixture was treated with 30% H_2O_2 (3 drops), stirred for 30 min, dissolved into ethyl acetate (75 ml), and washed with water (2 x 10 ml) and brine (10 ml). The aqueous layers were combined and then back-extracted with ethyl acetate (25 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution from petroleum ether/ethyl acetate, 3:1 to petroleum ether/ethyl acetate, 2:1) to give the enone **19** (230 mg, 0.751 mmol, 80%).

3-Dimethoxymethyl-2-(2,5-dimethoxy-phenyl)-cyclohex-2-enone (**20**): In a nitrogen flushed flask iodoenone **7b** (6.40 g, 21.6 mmol), CuI (4.11 g, 21.6 mmol), P(*o*-tol)$_3$ (1.84 g, 6.05 mmol) and $Pd_2(dba)_3 \cdot CHCl_3$ (782 mg, 0.755 mmol) were placed and NMP (65 ml) was added. The mixture was degassed and stirred for 30 min. The stannane **13** (10.2 g, 23.8 mmol) in NMP (100 ml) was added and the flask was lowered into an oil-bath (50 °C). The solution was stirred for 15 h at 60 °C. After cooling, the mixture was poured into saturated $NaHCO_3$ solution (150 ml) and ethyl acetate (350 ml), filtered and washed with water (2 x 150 ml). The aqueous layers were combined and then back-extracted with ethyl acetate (200 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 5:1) to give the enone **20** (2.85 g, 9.29 mmol, 43%) as a colorless oil. - TLC (petroleum ether/ethyl acetate, 5:1): R_f = 0.10. - IR (film): $\tilde{\nu}_{max}$ = 1681 cm^{-1}. - ^1H NMR (400 MHz, $CDCl_3$): δ = 2.01-2.15 (m, 2 H, CH_2), 2.49-2.63 (m, 4 H, CH_2), 3.20, 3.31 [2 s, 3 H each, $CH(OCH_3)_2$], 3.67, 3.74 (2 s, 3 H each, aryl-OCH_3), 4.52 [s, 1 H, $CH(OCH_3)_2$], 6.56 (dd, J = 2.4, 0.8 Hz, 1 H, aryl-H), 6.82-6.87 (m, 2 H, aryl-H). - ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.12, 23.00, 38.37 (3 -, CH_2), 55.02, 55.51, 55.62, 56.12 [4 +, $CH(OCH_3)_2$, aryl-OCH_3], 104.36 [+, $CH(OCH_3)_2$] 111.94, 114.12, 116.82 (3 +, aryl-CH), 124.54, 135.84, 151.30, 153.16, 154.05 (5 ×), 198.18 (×, C=O). - MS (EI), *m/z* (%): 306 (94) [M^+], 275 (10), 259 (100), 244 (28), 75 (48). - $C_{17}H_{22}O_5$ (306.4): calcd. C 66.65, H 7.24; found: C 66.69, H 7.40.

Dimethoxy boronic acid (**21**): A solution of 2-bromo-1,4-dimethoxybenzene[27] (3.65 g, 16.8 mmol) in THF (35 ml) was treated at -78 °C with *n*-butyllithium (1.6 M in hexanes, 12.6 ml, 20.2 mmol, 1.2 equiv). The mixture was stirred at -78 °C for 20 min, treated with trimethyl borate (5.64 ml, 50.5 mmol, 3 equiv) and allowed to warm to room temperature over a period of 3 h. Hydrolysis was performed at 0 °C with 12% HCl

(25 ml). The mixture was extracted with diethyl ether (3 x 25 ml). The combined organic layers were washed with water, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting crude product was purified by flash chromatography (petroleum ether/ethyl acetate, 3:7); yield 2.75 g (90%). - m.p. 87-89 °C - TLC (petroleum ether/ethyl acetate, 3:7): R_f = 0.64. - ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.78, 3.85 (2 s, 3 H each, OCH_3), 6.35 (s, br., 2 H, OH), 6.83 (d, J = 9.0 Hz, 1 H, aryl-H), 6.96 (dd, J = 3.2, 9.0, 1 H, aryl-H), 7.37 (d, J = 3.2 Hz, 1 H, aryl-H). - ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.72, 56.08 (2 +, aryl-OCH_3), 111.28, 118.62, 120.70 (3 +, aryl-CH), 153.86, 158.81 (2 ×, aryl-C). - MS (EI), *m/z* (%): 182 (100) [M^+], 180 (24), 167 (85) [M^+ - CH_3].

3-tert-Butyldimethylsilyloxymethyl-5,6-O-cyclohexylidene-cyclohex-2-[2,5-dimethoxyphenyl]2-enone (**22**): To a flame-dried flask were added **7f** (74 mg, 0.15 mmol), boronic acid **21** (31 mg, 0.17 mmol), $Pd(PPh_3)_4$ (9 mg, 9 µmol, 5 mol %), K_2CO_3 (43 mg, 0.31 mmol) and dioxane (4 ml). The whole mixture was degassed and covered with argon. The mixture was stirred at 80 °C for 2 d. After being cooled to room temperature, the mixture was diluted with ethyl acetate (10 ml) and washed with water (5 ml). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 4:1) gave 25 mg (33 %) of **22** as a red oil. - TLC (petroleum ether/diethyl ether, 1:2): R_f = 0.35. - $[\alpha]_D^{20}$ = -34.3 (c = 2.3 in $CHCl_3$). - IR (CH_2Cl_2): $\tilde{\nu}$ = 1680 cm^{-1} (C=O). - ^{1}H NMR (500 MHz, $CDCl_3$): δ = -0.04, -0.06 (2 s, 3 H each, $SiCH_3$), 0.84 [s, 9 H, $C(CH_3)_3$], 1.22-1.79 (m, 10 H, cyclohexylidene), 2.81-3.00 (m, 1 H, 4-H), 3.02-3.19 (m, 1 H, 4-H), 3.62 (s, br., 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 4.14 (s, 2 H, CH_2OTBS), 4.41-4.44 (m, 1 H, 5-H), 4.69-4.71 (m, 1 H, 6-H), 6.49 (s, 1 H, aryl-H), 6.80-6.81 (m, 2 H, aryl-H). - ^{13}C NMR (125 MHz, $CDCl_3$): δ = -5.53 (+, $SiCH_3$), 18.18 [×, $C(CH_3)_3$], 23.66, 24.91, 25.05, 35.60, 37.18 (5 -, cyclohexylidene CH_2), 25.78 [+, $C(CH_3)_3$], 27.97 (-, 4-C), 55.71, 56.11 (2 +, OCH_3), 64.70 (-, CH_2OSi), 75.15 (+, 5-C), 78.42 (+, 6-C), 110.83 (×, ketal), 112.11, 113.99, 116.63 (3 +, aryl-CH), 124.13 (×, 2-C), 153.33 (×, 3-C), 154.06, 159.41 (2 ×, aryl-C), 194.71 (×, C=O). - MS (EI), *m/z* (%): 488 (27) [M^+], 431 (100), 361 (18), 333 (24), 305 (30). - HRMS: calcd for $C_{27}H_{40}O_6Si$ 488.2594; found 488.2576.

Methyl 2-(2,5-dimethoxy-phenyl)-4-methoxy-1,3-cyclohexadiene carboxylate (**23**): A mixture of triflate **11** (437 mg, 1.38 mmol), $Pd(PPh_3)_4$ (61 mg, 53 µmol, 2.5 mol %), boronic acid **21** (300 mg, 1.66 mmol) and aqueous 2 M Na_2CO_3 (1.05 ml, 2.2 equiv) in dry dioxane (25 ml) was refluxed for 5 h under argon. The reaction mixture was cooled to room temperature, treated with 30% H_2O_2 (4 drops), and then extracted with Et_2O (3 x 25 ml). The combined organic extracts were washed with water (20 ml), brine (15 ml), and dried (Na_2SO_4). Filtration and removal of solvent furnished a crude yellow product which was purified by flash chromatography (petroleum ether/ethyl acetate, 6:4); yield 337 mg (80%). - m.p. 71-73 °C. - TLC (petroleum ether/ethyl acetate, 6:4): R_f = 0.38. - IR (KBr): $\tilde{\nu}$ = 1706 cm^{-1}, 1650, 1573. - ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.37 (t, J = 9.5 Hz, 2 H, CH_2), 2.72 (t, J = 9.5 Hz, 2 H, CH_2), 3.44 (s, 3 H, OCH_3), 3.60 (s, 3 H, CO_2CH_3), 3.68 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 4.99 (s, 1 H, olefinic H), 6.62 (d, J = 2.9 Hz, 1 H, aryl-H), 6.75-6.79 (m, 2 H, aryl-H). - ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.89, 27.12 (2 -, CH_2), 50.79, 55.10, 55.56, 56.30 (4 +, OCH_3), 98.65 (+, CH), 111.93 (×, C-OMe), 112.55, 114.51, 116.32 (3 +, aryl-CH), 132.75, 143.61, 150.08 (3 ×, aryl-C), 153.39 (×, C-2), 163.53 (×, C-1), 168.27 (CO_2Me). - MS (EI), *m/z* (%): 304 (42) [M^+], 273 (100%). - $C_{17}H_{20}O_5$ (304.3): calcd. C 67.09, H 6.62; found C 66.82, H 6.61.

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