Synthesis of the Benzophenone Fragment of Balanol via an Intramolecular Cyclization Event

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Studies are reported on the use of either a 7-exo radical cyclization or an intramolecular Heck reaction as the key step for the construction of the benzophenone fragment of the PKC inhibitor, balanol. Whereas, the former approach was unsuccessful, the Heck reaction proved to be viable for the coupling of two fully functionalized aryl subunits affording regioselectively a biaryl seven-membered lactone with an exocyclic alkene as the major component, in contrast to the competing eight-membered ring lactone. Hydrolysis of the lactone followed by oxidative cleavage of the alkene with ruthenium tetraoxide completed this short synthesis of the benzophenone unit.

Introduction

The structurally unique fungal metabolite, balanol, isolated from *Verticillium balanoides*[1] and *Fusarium merismoides*,[2] has attracted much interest owing to its high inhibitory activity against protein kinase C (PKC) with IC_{50} values in the nanomolar range (Figure 1). Balanol therefore represents a new and potent lead compound for the deactivation of this important class of isoenzymes involved in intracellular signaling pathways and associated with a variety of disorders including cancer, cardiovascular disorders, asthma, diabetes, central nervous system dysfunction, and AIDS.[3] To provide further evaluation of this natural product, as well as opening up synthetic routes to analogues of balanol, several groups responded quickly to the synthesis of this fungal metabolite, with six total syntheses being published to date,[4] as well as numerous reports on the prepartion of key fragments.[5,6]

Whereas considerable modifications of the hexahydroazepine ring of balanol can be tolerated with even in certain cases such changes resulting in an increase in biological activity,[7] the benzophenone part represents a more sensitive structural element necessary for the inhibitory action of balanol against PKC. Hence, structural changes of this fragment lead to serious loss of activity against PKC. It is believed that this fragment mimics the triphosphate unit of ATP.[7m]

We have recently provided an approach to the hexahydroazepine ring of balanol via a samarium diiodide promoted 7-exo cyclization of an acyclic carbonylhydra-

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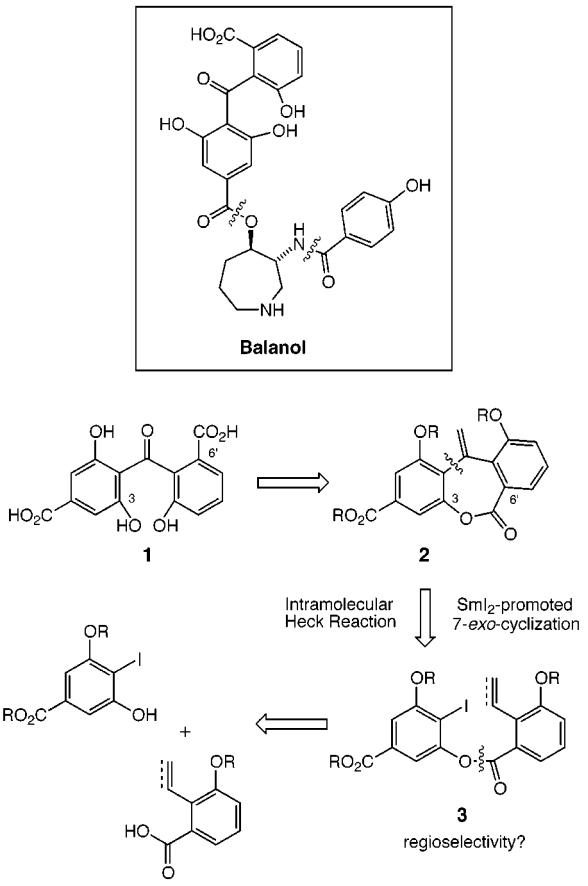


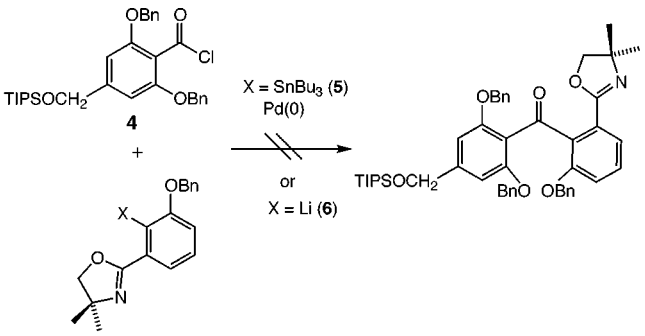
Figure 1. Retrosynthetic scheme for the synthesis of the benzophenone core structure of balanol.

zone.[8] In our continued endeavors for completing the synthesis of balanol, we now present our work concerning the preparation of the fully functionalized benzophenone moiety. Several routes to the benzophenone moiety have earlier been reported, with approaches involving key coupling steps of the two aryl units such as an anionic homo-Fries rearrangement,[4a−d] intermolecular carbonyl addition reactions,[4e,6a] and an iron-assisted S_NAr reaction followed by an intramolecular Friedel-Craft reaction.[6b,c] A possible biomimetic approach has also been published involving an oxidative ring cleavage of the naturally occurring anthraquinone, chrysophanic acid.[4h,i] In this work, we report on an alternative approach involving the application of an intramolecular Heck reaction as the key step for the coupling of two fully functionalized and readily available aryl subunits to the benzophenone fragment.[9]

Results and Discussions

Retrosynthetic Considerations. A retrosynthetic analysis of the benzophenone moiety **1** of balanol is illustrated in Figure 1. This aryl fragment could arise from the simple oxidative cleavage of the corresponding exocyclic alkene **2**, incorporated in a seven-membered lactone involving the C3-hydroxyl group and the C6′-carboxylic acid, and then lactone hydrolysis. Two possible routes for ring closure could then be envisaged. The first involves a 7-*exo-dig* radical cyclization with iodide **3** mediated by either SmI_2 or tributyltin hydride. Although 7-exo radical cyclizations have been reported to be slow,[10] we felt that because of the participation of a reactive aryl radical in combination with the conformational restrictions imparted by the two aryl groups, radical cyclization could nevertheless be competitive with simple reduction. In both cases, competing 8-endo ring closure would be a serious concern; however, a possible remedy in this respect would be to coax the reaction into favoring the seven-membered lactone formation via the introduction of an electron withdrawing group at the terminal position of the alkyne. Subsequent bond disconnection of the ester linkage then leads to two readily accessible tri- and tetra-functionalized aromatic rings.

Scheme 1



In the second approach, ring closure could potentially take place via an intramolecular Heck reaction[11,12] involving the participation of the iodide **3** possessing a vinyl-substituted aryl unit, although some concern was also made about the regioselectivity in this cyclization event. Again, two easily available aryl subunits would allow the preparation of the *δ*-lactone precursor. Whether an intramolecular version of Pd-catalyzed C−C bond forming reaction was indeed necessary to attain the diaryl core structure of balanol was supported by the preliminary synthetic studies reported by Nicolaou and co-workers (Scheme 1). Attempts to promote the Pd-catalyzed Stille coupling of the stannane **5** with the acid chloride **4** failed, possibly owing to the sterically congested environment at the carbonyl center of the product owing to the four ortho substituents.[4b] This was further substantiated by the lack of reactivity of the corresponding anion **6** with the acid chloride **4**,[4b,6a] known to perform well in simpler systems.[4e]

The Radical Cyclization Approach. To prepare the necessary cyclic precursor for the radical cyclization step, we first required the benzoic acid derivative **8** and the phenol **11** (Scheme 2). Methyl ester formation and triflation of commercially available 2-hydroxy-3-methoxybenzoic acid was followed by an efficient Sonogashira-

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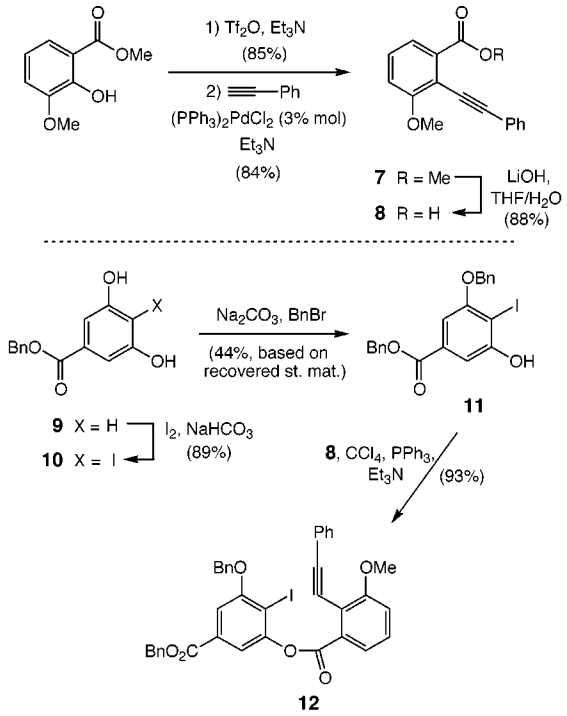
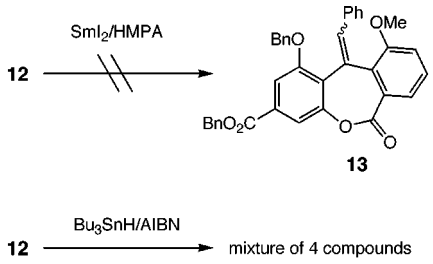
Scheme 2



type coupling with phenylacetylene according to that reported by Chen and Yang,[13] affording the diaryl substituted alkyne **7** in good yield. Subsequent hydrolysis of the methyl ester provided the acid **8** with an overall yield of 63% from the methyl ester of 2-hydroxy-3-methoxybenzoic acid. The corresponding phenol coupling partner could be prepared starting with a selective iodination of 3,5-dihydroxybenzoic acid under aqueous conditions in analogy to that reported for other systems.[14] Whereas some problems were encountered in the isolation of the iodide owing to its solubility in water, better results were obtained by converting the benzoic acid to its benzyl ester **9** prior to the iodination step. In this way, the iodide **10** was secured in 89% yield. Selective benzylation of one of the two alcohols proceeded only in a modest yield affording the phenol **11** in 44% yield (based on 36% recovered starting material), but considering the facility of the combined three steps required to prepare **11**, we still considered this a viable approach.[15] Subsequent ester formation of the two components employing the mild conditions developed by Furukawa performed well furnishing the cyclic precursor **12** in a 93% yield.[16]

Initial cyclization attempts were first performed with the SmI_2/HMPA combination, a well-known system previously exploited as a substitute to tributyltin hydride for promoting 5-*exo* cyclizations of aryl iodides (Scheme 3).[17] However, when SmI_2/HMPA in THF was slowly added to a solution of the iodide, a complex mixture of

Scheme 3



compounds arose according to TLC analysis. On the other hand, cyclization attempts with Bu_3SnH in benzene under conditions favoring ring closure (high dilution, slow addition of Bu_3SnH) produced a much cleaner reaction, but nevertheless gave rise to four chromatographically inseparable compounds as observed by ^1H NMR. Proper identification of these compounds as any of the three possible isomeric cyclization products (two 7-exo modes affording **13** and one 8-endo) was complicated by the overlap of the ^1H NMR signals from both the alkene and aryl protons. In any event, attempted ozonolysis of this mixture in order to determine its composition, as well as potentially getting hold of balanol's benzophenone fragment were thwarted by the extensive decomposition observed. This route was therefore abandoned and recourse was taken to investigate the intramolecular Heck reaction as an alternative approach for the cyclization step.

Application of the Heck Reaction. As indicated above with the radical cyclization approach, several potential problems were also anticipated in the adaptation of a Heck reaction for the formation of the seven-membered biaryl lactone as illustrated in Scheme 4. Again, we assumed that applying an intramolecular version of this Pd-catalyzed reaction would override any steric problems arising in the C−C bond forming step due to the four ortho-substituents. However, in the event of successful cyclization, 8-endo ring closure could also here become a serious competitor to the 7-exo cyclization as in the radical approach, and it was difficult to assess which of the two would be the most dominant. In addition, a third option involving cyclization onto the aromatic ring was also a contender leading to a benzopyranone derivative. As this pathway, nevertheless, requires dearomatization in the six-membered ring forming step, we assumed that the production of this compound would be less likely.

Synthesis of the cyclic precursor **20** only required modification of the right-hand fragment with respect to **12**, which was easily prepared from a two step procedure employing the readily available oxazoline **14** (Scheme 5). Nucleophilic aromatic substitution of **14**, as described by Meyers and co-workers,[18] with vinylmagnesium bromide, followed by a two step hydrolysis procedure (MeI, then NaOH) readily afforded the vinyl benzoic acid derivative **15** in 70% overall yield.[19] This material was then coupled to the phenol **11** as above, providing the diaryl ester **20**

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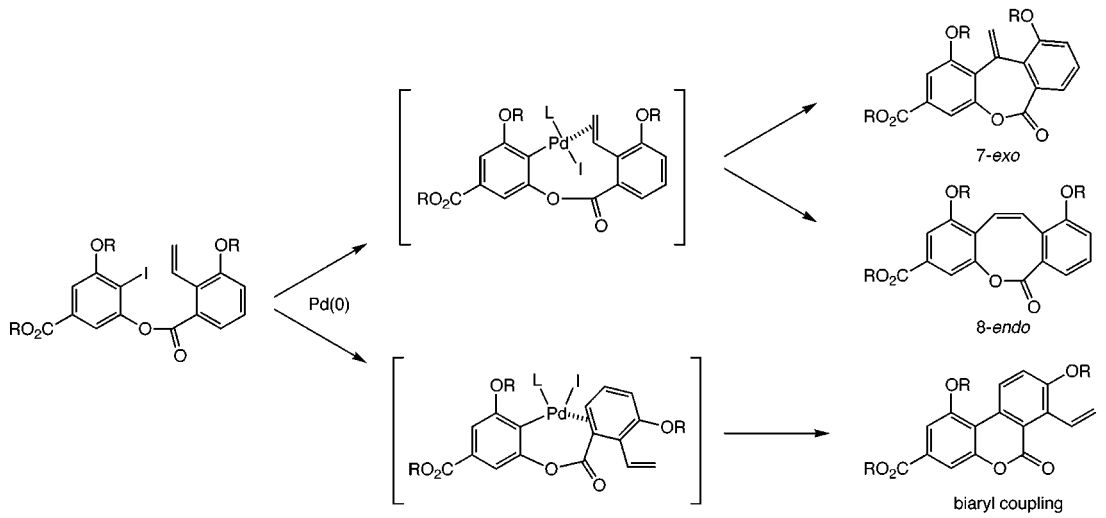
(19) Hydrolysis of 2-(3-methoxy-2-vinylphenyl)-4,4-dimethyl-2-oxazoline to the benzoic acid **15** was reported in ref 18 to proceed under acid conditions. However, in our hands hydrolysis of this oxazoline under identical conditions led to the formation of 4-methoxy-3-methylphthalide, and hence, the procedure for basic hydrolysis was employed.

Table 1. Intramolecular Heck Reaction of the Diaryl Ester 18[a]

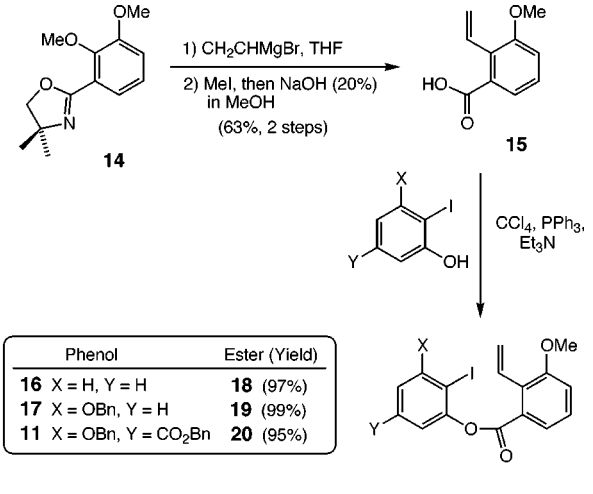
entry	catalyst (equiv)	base (equiv)	solvent	*T* (°C)	*t* (h)	yields (%) 21	22	23
1	$(Ph_3P)_2PdCl_2$ (0.26)	NaOAc (3)	DMA	125	0.5	48	11	8
2	$(Ph_3P)_2PdCl_2$ (0.26)	NaOAc (3)	DMF	85	0.75	58	13	2
3	$(Ph_3P)_2PdCl_2$ (0.52)	NaOAc (3)	CH_3CN	90	47	75	6	
4	$(Ph_3P)_2PdCl_2$ (0.52)	NaOAc (3)	CH_3CN	90	65	29	7	
5	$Pd(OAc)_2$ (0.025)	K_2CO_3 (4), Bu_4NBr (1)	DMF	95	0.25	58	10	4
6	$Pd(OAc)_2$ (0.10)	K_2CO_3 (4), Bu_4NCl (1)	CH_3CN	90	96		decomposition	
7	$Pd(OAc)_2$ (0.10), Ph_3P (0.26)	Et_3N (2)	CH_3CN	85	48	65	5	
8	$Pd(OAc)_2$ (0.10), Ph_3P (0.26)	Ag_2CO_3 (2)	CH_3CN	85	25		decomposition	

[a] Reaction was performed on the corresponding aryl bromide

Scheme 4. Possible Competing Cyclization Pathways

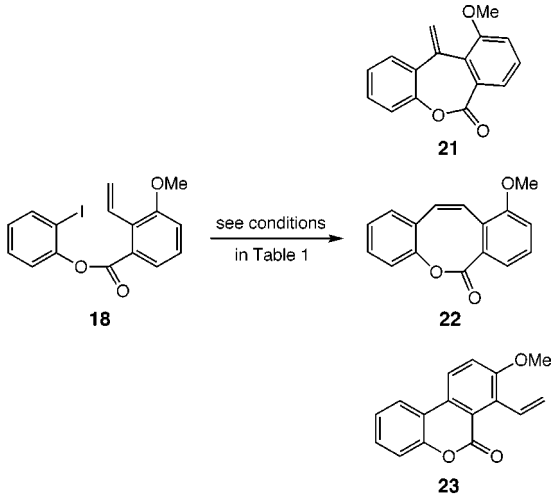


Scheme 5



Phenol	Ester (Yield)
16 X = H, Y = H	**18** (97%)
17 X = OBn, Y = H	**19** (99%)
11 X = OBn, Y = CO_2Bn	**20** (95%)

Scheme 6



in 95% yield.[17] To test the efficiency of the Heck reaction, two simpler systems **18** and **19** were also prepared from *o*-iodophenol (**16**) and the benzylated 2-iodoresorcinol **17**, the latter which was obtained as described for the phenol **11**.

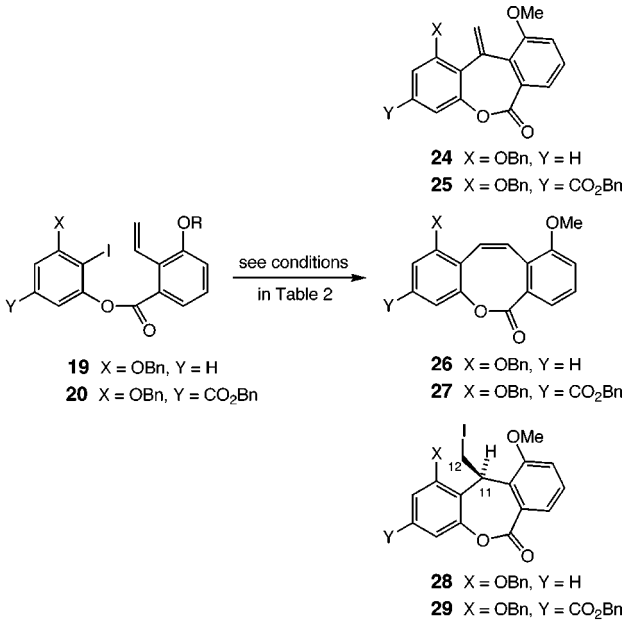
The feasibility of the 7-exo ring closure was initially carried out on the sterically less hindered model **18**, employing several conditions with the readily available palladium catalysts, $Pd(OAc)_2$ and $PdCl_2(PPh_3)_2$ (Scheme 6 and Table 1).[11] Cyclization with $PdCl_2(PPh_3)_2$ (26 mol %)/NaOAc (3 equiv) in a polar medium such as DMA proceeded fast (<1 h) and led to a 6:1.4:1 mixture of three isomeric cyclic compounds in 67% yield (entry 1). To our delight, the major compound did indeed correspond to the 7-exo product **21** as shown by ^1H NMR spectroscopy followed by the 8-endo product **22** and the pyrone **23**. With **21**, two doublets were found at 5.61 and 5.49 ppm with a small coupling constant ($J = 1.2$ Hz) conforming with the exocyclic methylene protons. On the other hand, in **22** the C=C protons, being bound to two different vicinal carbon atoms, and adjacent to an aromatic ring, are downfield shifted to 6.85 and 6.91 ppm and display a cis coupling of 11.2 Hz. The isomeric 6-exo product **23** is likewise easily identified by the presence in the ^1H NMR spectrum of the complete vinyl group, whereas only six aromatic protons could be identified.

Attempted cyclization in DMF was also rapid but did not improve greatly the ratio in favor of the 7-exo product (entry 2). In contrast, switching to acetonitrile dramati-

Table 2. Intramolecular Heck Reaction of the Diaryl Ester 19 and 20

entry	catalyst (equiv)	base (equiv)	solvent	*T* (°C)	*t* (h)	yields (%) 24, 25	26, 27	28, 29
1 (**19**)	$(Ph_3P)_2PdCl_2$ (0.26)	NaOAc (3)	CH_3CN	90	68	53	traces	13
2 (**19**)	$Pd(OAc)_2$ (0.10)	K_2CO_3 (4), Bu_4NCl (1)	DMF	100	2	decomposition		
3 (**20**)	$(Ph_3P)_2PdCl_2$ (0.26)	NaOAc (3)	CH_3CN	90	144	32	11	19
4 (**20**)	$(Ph_3P)_2PdCl_2$ (0.52)	NaOAc (3)	CH_3CN	90	79	70	13	5
5 (**20**)	$(Ph_3P)_2PdCl_2$ (0.26)	NaOAc (3)	CH_3CN/DMF (4:1)	90	48	55	13	4
6 (**20**)	$Pd(OAc)_2$ (0.10), Ph_3P (0.26)	$(iPr)_2NEt$ (2)	CH_3CN	90	10	44	20	
7 (**20**)	$Pd(OAc)_2$ (0.10), $(o\text{-Tol})_3P$ (0.26)	Et_3N (2)	CH_3CN	90	42	37	5	

Scheme 7



cally reduced the rate of cyclization being completed only after approximately 90 h (entry 3). Although the catalyst had to be replenished during the course of the reaction with a total of up to 52 mol % added in the end, the reaction was much cleaner affording **21** in 75% yield with only 6% of **22** and no traces of the pyrone product. The corresponding bromide was less reactive as expected but could not be forced to completion and only led to a low cyclization yield. Substituting the palladium catalyst with $Pd(OAc)_2$ did not improve the selectivity under various conditions (entries 5−8), although in one case, $Pd(OAc)_2/PPh_3/Et_3N$, a cyclization yield of 70% was obtained with a **21**:**22** ratio of 13:1, and with only 10% catalyst loading (entry 7).

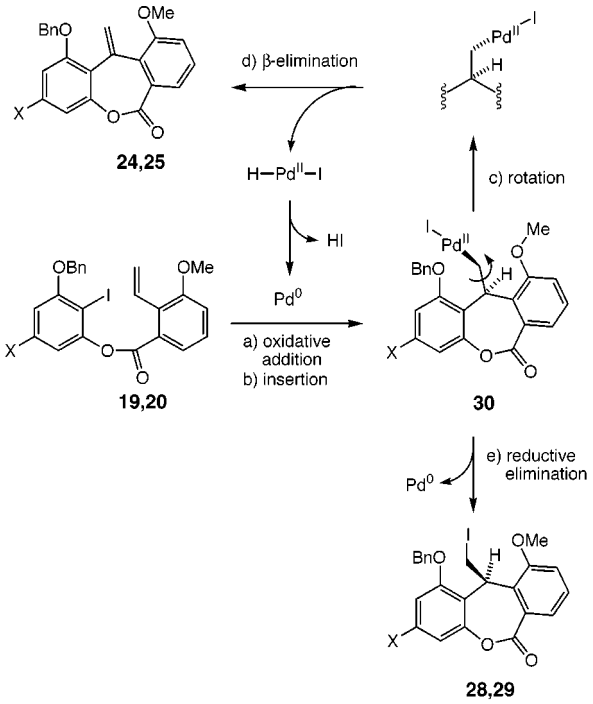
With these encouraging results, the more encumbered substrates **19** and **20** were then tested as shown in Scheme 7 and Table 2. As with the model compound **18**, best cyclization yields and regioselectivities were obtained with $PdCl_2(PPh_3)_2$ (entries 1,3−5). Again, high catalyst loading was necessary to bring about the completion of the reaction (26−52 mol %) particularly in the case of correct substrate **20**. Although a good yield (70%) of the 7-*exo* product **25** was obtained in one instance (entry 4), it was not reproducible and in general the yields were in the order of 50%. To try to reduce the reaction times, solvent mixtures of acetonitrile and DMF were also tested of which a 4:1 mixture, respectively, proved to give the best results (entry 5). Quite pleasing was it that the regioselectivity in the cyclization step was still in favor of the 7-exo product, implying that the sterical influence from the new ortho-substitutent was not a problem. On the other hand, employing $Pd(OAc)_2$ the regioselectivity with **20** had dropped somewhat (entry 6) compared to **18** (Table 1, entry 7). Confirmation of the structure of the 7-exo and 8-endo compounds, **25** and **27**, were made by single-crystal X-ray (see Figures S1 and S2, Supporting Information). It is interesting to note the approximately 60° torsional angle of the exocyclic C=C bond in **25** with respect to the planes of the aromatic rings, suggesting little conjugation between these chromophores.

Although, no sign of the pyrone derivative were detected in the reaction mixtures of these cyclizations as previously observed with **18**, we did detect a second minor component which was identified in the reaction of **25** as the primary iodide **29** by X-ray analysis (Scheme 7 and Figure S3, Supporting Information). As these products are themselves the result of an initial 7-exo cyclization event, implies that the ratio 7-exo/8-endo ring closures are even greater than initially observed. Nevertheless, this was of little use as attempts to convert the iodides **28** and **29** by simple elimination to either **24** or **25** with sterically hindered bases (DBU, KO-*t*-Bu) failed leading mainly to decomposition. Examination of the X-ray structure of **29** suggests an explanation for this observation. The C11−C12 bond is also approximately 60° to the planes of the aryl rings placing the C11 proton directly between the OMe and OBn substituents in the ortho-position. Hence, access by a base to this sterically encumbered proton becomes difficult.

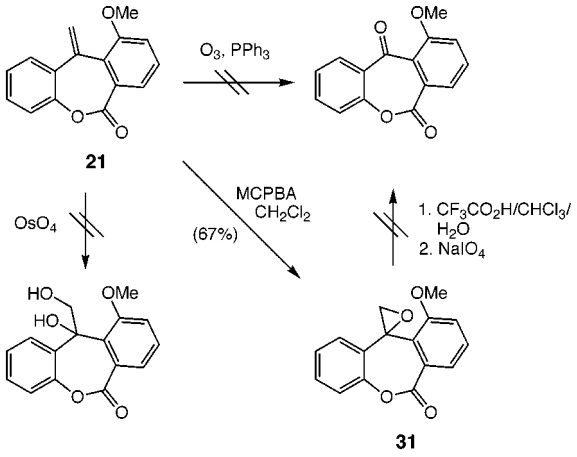
Although no mechanistic investigation was undertaken to examine the pathways leading to these iodides, the observation that a similar compound was not formed in the cyclization of **18**, suggests that these compounds do not originate from simple nucleophilic addition of iodide to the activated double bond. Instead, another mechanism is proposed as illustrated in Scheme 8. Oxidative addition of Pd(0) to the aryl iodides **19** and **20** and subsequent insertion of the adjacent alkene leads to the σ-alkyl Pd intermediate **30**. For the β-elimination step to the alkenes **24** and **25**, a rotation of the adjacent C−C bond is required in order to place the Pd and the β-H in a syn orientation. However, the sterical hindrance from the flanking alkoxy groups may prevent this step, resulting in reductive elimination and formation of the corresponding alkyl iodides **28** and **29**.

Oxidative Cleavage and Ring Opening. The final steps to balanol's benzophenone fragment now only required an oxidative cleavage step of the exocyclic alkene in **25** and a ring opening of the seven-membered lactone. However, these steps proved not to be so facile as first anticipated. In the model compound **21**, ozonolysis led only to degradation and cleavage of the two aryl units, while OsO_4 failed to react at all, even under stoichiometric conditions (Scheme 9). Epoxidation with *m*-CPBA did proceed to afford the labile epoxide **31**, however several attempts to hydrolyze this compound and then subjecting

Scheme 8



Scheme 9

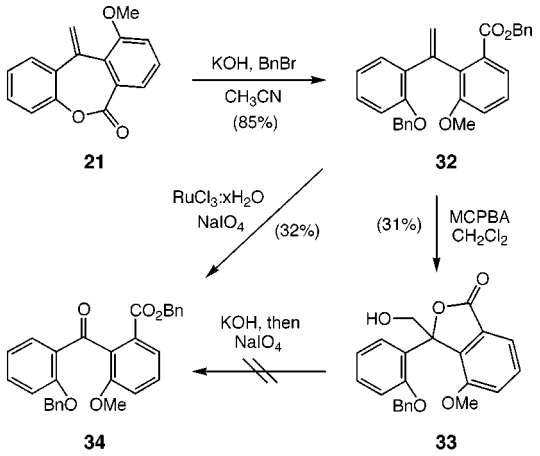


this material to a sodium periodate promoted cleavage were not successful.

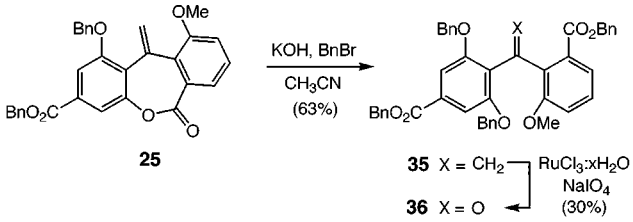
To examine whether the undesired reactivity of **21** was a result of the lactone ring, this compound was hydrolyzed and simulaneously benzylated to give **32** in 85% yield (Scheme 10).[20] Again, similar results as with **21** were obtained upon attempted ozonolysis or dihydroxylation with OsO_4 of this alkene. Treatment of **32** with *m*-CPBA did not lead to the corresponding epoxide in this case but instead led to the five-membered lactone **33** in low yield.

Efforts to hydrolyze this compound also proved futile and only led to migration and formation of the six-membered lactone. At last, treatment of alkene **32** with in situ generated ruthenium tetraoxide ($RuCl_3$:xH_2O/$NaIO_4$) did provide the desired benzophenone **34** in modest yield.[21] It is interesting to note, that best results

Scheme 10



Scheme 11



in this oxidation step were obtained with the opened substrate, whereas yields of less than 10% were characteristic of the same reaction performed with lactone **21**. Finally, it was gratifying to observe that the same sequence of reactions (ring opening and oxidative cleavage) could be carried out on the correct substrate **25** affording the protected benzophenone moiety **36** of balanol (Scheme 11).

Conclusions

The benzophenone fragment of the PKC inhibitor balanol has been synthesized using an intramolecular Heck reaction as the key step for assembling the two aryl units. In contrast to previous syntheses of the benzophenone moiety, the mild conditions of this approach allows the use of fully functionalized and readily available aryl units in the coupling step, though further studies are still required to improve the problematic alkene cleaving step. Previous reports have already shown that selective hydrolysis of the least encumbered ester of compounds analogous to **35** is a viable process,[4e] making it possible to couple this compound onto the hexahydroazepine unit of balanol and hence completing the synthesis of this natural product. This work is currently ongoing and will be reported in due course.

Experimental Procedure

General Considerations. THF was dried and freshly distilled over sodium/benzophenone. Dichloromethane was freshly distilled over P_2O_5, and acetonitrile from calcium hydride. Reactions were monitored by thin-layer chromatography (TLC) analysis. The following compounds were prepared according to literature procedures: 2-hydroxy-3-methoxybenzoic acid, methyl ester,[22] and oxazoline **14**.[18]

(20) Suau, R.; López-Romero, J. M.; Rico, R.; Alonso, F. J.; Lobo, C. *Tetrahedron* **1996**, *52*, 11307.

(21) Ghosh, S.; Karpha, A.; Saha, G.; Patra, D. *Tetrahedron Lett.* **1992**, *33*, 2363.

(22) Paulis, T.; Hewlett, W. A.; Schmidt, D. E.; Mason, N. S.; Trivedi, B. L.; Ebert, M. H. *Eur. J. Med. Chem.* **1997**, *32*, 385.

3,5-Dihydroxybenzoic Acid, Benzyl Ester (9). Benzyl bromide (3.9 mL, 32.8 mmol) was added to a solution of 3,5-dihydroxybenzoic acid (5.00 g, 32.4 mmol) and dry sodium carbonate (3.44 g, 32.5 mmol) in DMF (50 mL). The reaction was stirred overnight at room temperature under nitrogen. After addition of water, the solution was extracted five times with ether, and the combined organic phases were then washed three times with water and once with brine, dried over $MgSO_4$, and concentrated in vacuo. The solid residue was purified by crystallization in CH_2Cl_2/pentane affording the benzyl ester **9** as colorless crystals (6.03 g, 76% yield): mp 131−133 °C; ^{1}H NMR (200 MHz, acetone-d_6) δ 8.57 (s, 2H), 7.30−7.51 (m, 5H), 7.04 (d, 2H, J = 2.3 Hz), 6.59 (t, 1H, J = 2.3 Hz), 5.32 (s, 2H); ^{13}C NMR (50 MHz, acetone-d_6) δ 166.4, 159.4, 137.3, 132.9, 129.3, 128.8, 108.6, 108.0, 66.9; IR (KBr) ν 3380, 1696, 1611, 1337 cm^{-1}; HR-MS (ES) calcd for $C_{14}H_{12}O_4$ 267.0633 (M + Na), found 267.0622.

3,5-Dihydroxy-4-iodobenzoic Acid, Benzyl Ester (10). Iodine (1.44 g, 5.68 mmol) and $NaHCO_3$ (479 mg, 5.70 mmol) were added in small portions to a solution of the dihydroxybenzoate **9** (1.32 g, 5.40 mmol) in a 1:1 mixture of THF and H_2O (25 mL) at 0 °C. The reaction was stirred for 90 h at 20 °C. As **9** was still present, an additional 0.2 eq. of both $NaHCO_3$ and iodine were added and reaction mixture was left to react for an additional 50 h. After filtration through Celite, and extraction with ether (4 times), the combined organic phases were washed with a saturated solution of potassium thiosulfate, dried over $MgSO_4$, and finally evaporated to dryness in vacuo. The solid residue, consisting of predominantly **10**, was purified by crystallization in methanol to give **10** (1.78 g, 89% yield) as colorless crystals: mp 164 °C; ^{1}H NMR (200 MHz, acetone-d_6) δ 9.38 (s, 2H), 7.30−7.50 (m, 5H), 7.13 (s, 2H), 5.31 (s, 2H); ^{13}C NMR (50 MHz, acetone-d_6) δ 164.5, 157.5, 135.7, 131.0, 127.8, 127.5, 105.9, 80.1, 65.8; IR (KBr) ν 3474, 3392, 1698, 1584, 1498 cm^{-1}; HR-MS (ES) calcd for $C_{14}H_{11}IO_4$ 392.9600 (M + Na), found 392.9601.

3-Benzyloxy-5-hydroxy-4-iodobenzoic Acid, Benzyl Ester (11). Benzyl bromide (450 μL, 3.78 mmol) in DMF (5 mL) was slowly added to a solution of **10** (1.40 g, 3.78 mmol) and dry potassium carbonate (524 mg, 3.79 mmol) in DMF (20 mL). The reaction was stirred for 2 days at 20 °C under nitrogen. After addition of water, the solution was extracted six times with CH_2Cl_2 and once with ether. The combined organic phases were then washed five times with water, dried over $MgSO_4$, and concentrated in vacuo. The solid residue was purified by flash chromatography (CH_2Cl_2/pentane 1:1, 3:2, 9:1), affording compound **11** as a colorless solid (486 mg, 28% yield) along with the monobenzylated product **9** (733 mg, 36% yield) and the tribenzylated product 576 mg, 28% yield): mp 131−133 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30−7.60 (m, 11H), 7.01 (d, 1H, J = 1.8 Hz), 5.61 (s, 1H), 5.35 (s, 2H), 5.20 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.0, 158.0, 156.5, 136.0, 135.6, 132.0, 128.7, 128.6, 128.4, 128.2, 128.0, 127.1, 109.2, 105.0, 84.9, 71.2, 67.2; IR (KBr) ν 3392, 1692, 1592, 1423 cm^{-1}; HR-MS (ES) calcd for $C_{29}H_{24}O_5$ 483.0071 (M + Na), found 483.0072.

3-Methoxy-2-vinylbenzoic Acid (15). To a solution of oxazoline **14** (6.0 g, 25.5 mmol) in dry THF (50 mL) was added a 1.0 M solution of vinylmagnesiumbromide in THF (38 mL, 38 mmol). After being stirred overnight at room temperature under nitrogen, the reaction mixture was treated by addition of a solution of saturated aqueous NH_4Cl, and the aqueous phase was then extracted three times with ether. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (pentane:EtOAc, 1:1) affording 2-(3-methoxy-2-vinylphenyl)-4,4-dimethyl-2-oxazoline as a pale yellow solid (5.35 g, 91% yield): ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.23 (m, 2H), 6.97 (dd, 1H, J = 11.5, 17.8 Hz), 6.95 (m, 1H), 5.75 (dd, 1H, J = 2.0, 17.8 Hz), 5.46 (dd, 1H, J = 2.0, 11.5 Hz), 3.85 (s, 2H), 1.38 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 162.4, 156.9, 130.4, 128.6, 127.1, 125.9, 121.4, 118.8, 112.0, 78.5, 67.3, 55.0, 27.5; HR-MS (ES) calcd for $C_{14}H_{17}NO$ 254.1157 (M + Na), found 254.1158.

A solution of this oxazoline (5.23 g, 22.6 mmol) in an excess of methyl iodide (7 mL, 5 equiv) was stirred overnight at 20 °C. After removal of the methyl iodide under vacuum, 100 mL of a 1:1 solution MeOH/NaOH (20% aq) was added to the residue and the mixture was heated for 2 days to reflux. Cooling was followed by an etheral extraction. The aqueous phase was then acidified to pH 2 with 1 N HCl resulting in the formation of a white precipitate. The aqueous phase was extracted three times with Et_2O and the combined organic phases were then dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography (CH_2Cl_2) to give **15** as a solid (2.79 g, 69% yield) which was recrystallized from EtOAc/pentane: mp 123 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.48 (dd, 1H, J = 1.0, 7.8 Hz), 7.26 (t, 1H, J = 8.0 Hz), 7.08 (dd, J = 1.0, 8.3 Hz), 7.06 (dd, 1H, J = 11.6 and 17.8 Hz), 5.71 (dd, 1H, J = 1.8, 17.7 Hz), 5.55 (dd, 1H, J = 1.8, 11.6 Hz), 3.68 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 173.6, 157.0, 130.1, 127.5, 127.2, 121.7, 119.8, 114.1, 55.3; IR (KBr) ν 3003, 1683, 1590, 1457 cm^{-1}; HR-MS (ES) calcd for $C_{10}H_{10}O_3$ 201.0527 (M + Na), found 201.0525.

3-Methoxy-2-vinylbenzoic Acid 2-Iodophenyl Ester (18). General Procedure for the Preparation of the Arylbenzoates. A solution of 2-iodophenol (660 mg, 3.0 mmol), 3-methoxy-2-vinylbenzoic acid (**15**) (641 mg, 3.0 mmol), triphenylphosphine (944 mg, 3.6 mmol), Et_3N (502 μL, 3.6 mmol), and CCl_4 (347 μL, 3.6 mmol) in acetonitrile (12 mL) was heated overnight at 60 °C. After evaporation of the solvent, the residue was purified by silica gel column chromatography (pentane/EtOAc, 7:3) affording **18** as a colorless oil (1.11 g, 97% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.86 (dd, 1H, J = 1.6, 7.8 Hz), 7.72 (dd, 1H, 1.7, 10.0 Hz), 7.36 (t, J = 8.3 Hz), 7.11 (dd, 1H, J = 1.4, 9.3 Hz), 7.10 (dd, 1H, J = 11.6, 17.8 Hz), 7.01 (dt, J = 1.7, 7.8 Hz), 5.76 (dd, 1H, J = 1.8, 17.8 Hz), 5.57 (dd, 1H, J = 1,8, 11.6 Hz), 3.89 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.0, 157.1, 150.7, 138.9, 130.2, 130.0, 128.9, 127.7, 127.4, 127.1, 122.4, 121.7, 120.0, 113.9, 89.9, 55.3; IR (film) ν 1590, 1465 cm^{-1}; HR-MS (ES) calcd for $C_{29}H_{24}O_5$ 402.9809 (M + Na), found 402.9816.

3-Methoxy-2-vinylbenzoic Acid, 3-Benzyloxy-2-iodophenyl Ester (19). The aryl benzoic ester **19** was prepared according to the general procedure outlined for **18**, with the following quantities: 3-benzyloxy-2-iodophenol (326 mg, 1.00 mmol), benzoic acid **15** (214 mg, 1.20 mmol), PPh_3 (315 mg, 1.20 mmol), Et_3N (170 μL, 1.2 mmol), distilled CCl_4 (110 μL, 1.2 mmol) in acetonitrile (12 mL). Purification by column chromatography (pentane/Et_2O, 1:1) afforded **19** (480 mg, 99% yield) as a solid. Recrystallization frome EtOAc/pentane gave colorless crystals: mp 107−109 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76 (dd, 1H, J = 1.0, 7.7 Hz), 7.54−7.02 (m, 8H), 6.85 (dd, 1H, J = 1.0, 8.1 Hz), 6.76 (dd, 1H, J = 1.0, 8.1 Hz), 5.77 (dd, 1H, J = 1.8, 17.2 Hz), 5.56 (dd, 1H, J = 1.8, 11.8 Hz), 5.17 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.0, 158.2, 157.0, 152.1, 135.6, 130.2, 129.1, 127.9, 127.3, 126.4, 121.7, 120.0, 115.0, 113.8, 109.3, 70.6, 55.3; IR (KBr) ν 1732, 1587, 1469, 1449 cm^{-1}; HR-MS (ES) calcd for $C_{23}H_{19}IO_4$ 509.0227 (M + Na), found 509.0221.

3-Methoxy-2-vinylbenzoic Acid, 4-Benzylcarboxyl-3-benzyloxy-2-iodophenyl Ester (20). The aryl benzoic ester **20** was prepared according to the general procedure outlined for **18**, with the following quantities: 3-benzyloxy-3-hydroxy-2-iodobenzoic acid, benzyl ester **11** (1.93 g, 4.18 mmol), benzoic acid **15** (896 mg, 5.02 mmol), PPh_3 (1.32 g, 5.02 mmol), distilled NEt_3 (700 μL, 5.0 mmol), distilled CCl_4 (485 μL, 5.0 mmol) in acetonitrile (50 mL). Purification by column chromatography (pentane:Et_2O, 3:2) followed by recrystallization (pentane/CH_2Cl_2) afforded compound **20** as colorless crystals (2.46 g, 95% yield): mp 149−150 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.62 (dd, 1H, J = 1.2, 8.0 Hz), 7.19−7.40 (m, 12H), 7.00 (dd, 1H, J = 0.6, 8.0 Hz), 6.98 (dd, 1H, J = 11.4, 17.8 Hz), 5.65 (dd, 1H, J = 2.2, 17.8 Hz), 5.45 (dd, 1H, J = 2.2, 11.4 Hz), 5.23 (s, 2H), 5.09 (s, 2H), 3.74 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 164.7, 164.5, 158.2, 152.3, 135.1, 135.0, 131.4, 130.1, 129.7, 128.0, 127.8, 127.7, 127.5, 127.4, 126.5, 121.8, 120.2, 116.1, 114.1,

90.1, 70.9, 66.7, 55.3; IR (KBr) ν 1745, 1723, 1414 cm^{-1}; HR-MS (ES) calcd for $C_{31}H_{25}IO_6$ 643.0594 (M + Na), found 643.0594.

10-Methoxy-11-methylene-11*H*-dibenzo[*b*,*e*]oxepin-6-one (21). General Procedure for the Intramolecular Heck Reaction. A solution of iodide **18** (152 mg, 0.40 mmol), anhydrous NaOAc (98 mg, 1.2 mmol), and 0.26 equiv of bis-(triphenylphosphine)palladium(II) dichloride (73 mg, 0.10 mmol) in fresh distilled CH_3CN (12 mL) was heated at 85−90 °C under argon in a sealed tube. After 20 h, another portion of the catalyst (73 mg, 0.10 mmol) was added, and the reaction mixture was left stirring for another 26 h at 90 °C. CH_2Cl_2 was then added, and the reaction mixture was washed once with 1 N AcOH, two times with water, and then brine. The organic phase was dried over $MgSO_4$ and then concentrated under vacuum. Purification by flash chromatography afforded the lactone **21** (76 mg, 75% yield) together with **22** (6 mg, 6% yield) and the starting iodide **18** (18 mg, 12% yield) was also recovered. For **21**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36 (dd, 1H, J = 1.6, 7.6 Hz), 7.10−7.24 (m, 3H), 6.93−7.06 (m, 3H), 5.61 (d, 1H, J = 1.2 Hz), 5.49 (d, 1H, J = 1.2 Hz), 3.69 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.8, 148.3, 136.0, 134.3, 128.5, 128.1, 125.0, 123.4, 121.9, 119.4, 115.0, 55.6; HR-MS (ES) calcd for $C_{16}H_{12}O_3$ 275.0684 (M + Na), found 275.0684.

For **22**: 7.40−7.02 (m, 7H), 6.91 (d, 1H, J = 11.2 Hz), 6.85 (d, 1H, J = 11.2 Hz), 3.79 (3H, s).

1-Benzyloxy-10-methoxy-11-methylene-11*H*-dibenzo-[*b*,*e*]oxepin-6-one (24). The biaryl lactone **24** was prepared according to the general procedure outlined for **21**, starting from **19** (95 mg, 0.19 mmol), bis(triphenylphosphine)palladium(II) dichloride (36 mg, 0.049 mmol), NaOAc (48 mg, 0.58 mmol) in CH_3CN (6 mL). Another 18 mg (0.13 eq) of the catalyst was added after 45 h and the reaction was stopped after 68 h. Purification by chromatography (pentane/CH_2Cl_2, 2:3 to 3:2) afforded the alkene **24** (37 mg, 53% yield), iodide **28** (13 mg, 13% yield) and **19** (17 mg, 18% yield). For **24**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.08−7.55 (m, 9H), 6.85 (dt, 2H, J = 1.2, 8.4 Hz), 5.86 (d, 1H, J = 1.4 Hz), 5.85 (d, 1H, J = 1.4 Hz), 5.08 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.8, 136.5, 128.9, 127.9, 127.7, 127.0, 125.9, 124.7, 123.2, 115.2 112.5, 109.6, 69.8, 55.6; IR (film) ν 1733, 1448 cm^{-1}; HR-MS (ES) calcd for $C_{23}H_{18}O_4$ 381.1103 (M + Na), found 381.1112.

For **28**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68 (, 1H), 7.27−7.56 (m, 6H), 7.18 (t, 1H, J = 8.2 Hz), 7.06 (dd, 1H, J = 1.1, 8.2 Hz), 6.83 (m, 1H), 5.95 (dd, 1H, J = 7.9, 9.7 Hz), 5.15 (d, 1H, J = 11.6 Hz), 5.08 (d, 1H, J = 11.6 Hz), 3.81 (s, 3H), 3.72 (t, 1H, J = 9.7 Hz), 3.54 (dd, 1H, J = 7.9, 9.6 Hz); HR-MS (ES) calcd for $C_{23}H_{19}IO_4$ 509.0227, found 509.0231.

1-Benzyloxy-10-methoxy-11-methylene-11*H*-dibenzo-[*b*,*e*]oxepin-6-one-3-carboxylic Acid, Benzyl Ester (25). The biaryl lactone **25** was prepared according to the general procedure outlined for **21**, starting from **20** (100 mg, 0.16 mmol), bis(triphenylphosphine)palladium(II) dichloride (29 mg, 0.042 mmol), NaOAc (40 mg, 0.48 mmol) in CH_3CN/DMF (4:1, 8 mL). The reaction was completed after 48 h at 100 °C. Purification by chromatography (pentane:acetone, 4:1) afforded the alkene **25** (43 mg, 55% yield), the eight-membered lactone **27** (10 mg, 13% yield) and iodide **29** (4 mg, 4% yield). The three compounds were recrystallized from pentane:EtOAc. For **25**: mp 148−150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 1H, J = 1.3 Hz); 7.53 (m, 3H), 7.49 (dd, 1H, J = 0.8, 7.8 Hz), 7.31−7.43 (m, 9H), 7.12 (dd, 1H, J = 1.3, 8.0 Hz), 5.90 (d, 1H, J = 0.8 Hz), 5.87 (d, 1H, J = 0.8 Hz), 5.35 (s, 2H), 5.17 (d, 1H, J = 12.1 Hz), 5.11 (d, 1H, J = 12.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.3, 155.5, 155.1, 150.3, 136.7, 135.7, 132.2, 130.6, 129.1, 129.0, 128.8, 128.7, 128.5, 128.4, 128.2, 127.8, 126.7, 126.1, 124.0, 116.0, 114.8, 110.9, 70.5, 67.2, 56.3; IR (film) ν 1734, 1718, 1577, 1466 cm^{-1}; HR-MS (ES) calcd for $C_{31}H_{24}O_6$ 515.1470 (M + Na), found 515.1480.

For **27**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, 1H, J = 1.0 Hz), 7.25−7.33 (m, 12 H), 6.98 (dd, 1H, J = 0.8, 7.8 Hz), 6.89 (d, 1H, J = 11.5 Hz), 6.80 (dd, 1H, J = 0.8, 7.6 Hz), 6.77 (d, 1H, J = 11.5 Hz), 5.23 (s, 2H), 5.03 (s, 2H), 3.73 (s, 3H); HR-MS (ES) calcd for $C_{31}H_{24}O_6$ 515.1470 (M + Na), found 515.1442.

For **29**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (m, 3H), 7.51 (m, 2H), 7.32−7.46 (m, 9H), 7.08 (dd, 1H, J = 0.8, 8.2 Hz), 5.98 (dd, 1H, J = 7.4, 10.1 Hz), 5.34 (s, 2H), 5.20 (d, 1H, J = 11.7 Hz), 5.16 (d, 1H, J = 11.7 Hz), 3.82 (s, 3H), 3.74 (dd, 1H, J = 9.7, 10.1 Hz), 3.52 (dd, 1H, J = 7.4, 9.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.2, 164.6, 156.2, 151.8, 136.4, 135.7, 132.9, 131.0, 130.8, 128.7, 128.6, 128.5, 128.3, 128.2, 128.0, 127.8, 127.2, 125.3, 115.7, 115.5, 110.3, 71.0, 67.2, 56.4, 32.8; IR (KBr) 1732, 1716, 1584, 1422 cm^{-1}; mp 147−149 °C; HR-MS (ES) calcd for $C_{31}H_{25}IO_6$ 643.0595 (M + Na), found 643.0596.

2-[1-(3-Benzyloxyphenyl)vinyl]-3-methoxybenzoic Acid, Benzyl Ester (32). To a solution of seven-membered ring lactone **21** (237 mg, 0.94 mmol) in CH_3CN (12 mL) was added powdered KOH (232 mg, 4.13 mmol) and benzylbromide (1.12 mL, 9.39 mmol). The reaction mixture was then stirred overnight at 20 °C. After evaporation of the solvent, water was added to the residue and the mixture was extracted two times with chloroform. The organic phase was then washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Purification by column chromatography (pentane/CH_2Cl_2, 3:2) afforded compound **32** as a colorless oil (361 mg, 85% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.10−7.28 (m, 14H), 6.79−6.91 (m, 3H), 5.94 (d, 1H, J = 1.6 Hz), 5.34 (d, 1H, J = 1.6 Hz), 5.05 (s, 2H), 4.91 (s, 2H), 3.57 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.8, 156.5, 155.5, 140.2, 136.5, 135.1, 132.4, 131.8, 130.3, 129.5, 128.4, 127.9, 127.8, 127.6, 127.4, 127.2, 127.1, 126.9, 126.8, 126.6, 126.1, 123.5, 121.5, 120.4, 119.9, 119.5, 113.3, 112.2, 66.6, 66.1, 55.3; IR (film) ν 3032, 2937, 1725, 1595, 1576, 1489 cm^{-1}; HR-MS (ES) calcd for $C_{30}H_{26}O_4$ 473.1729 (M + Na), found 473.1750.

Diarylalkene 35. To a solution of **25** (22 mg, 0.045 mmol) in CH_3CN (3 mL) was added powdered KOH (11 mg, 0.20 mmol) and benzylbromide (53 μL, 0.44 mmol). The reaction mixture was then stirred for 4 h at 20 °C. After evaporation of the solvent, water was added to the residue and the mixture was extracted three times with CH_2Cl_2. The organic phase was then washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Purification by column chromatography (pentane:EtOAc, 19:1) afforded compound **35** as a colorless oil (19 mg, 63% yield): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33−7.41 (m, 6H), 7.09−7.26 (m, 18H), 6.78 (dd, J = 1.6, 7.8 Hz), 5.93 (d, 1H, J = 1.7 Hz), 5.80 (d, 1H, J = 1.7 Hz), 5.30 (s, 2H), 5.24 (s, 4H), 4.93 (s, 2H), 3.42 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.5, 166.2, 157.3, 157.1, 136.9, 136.1, 136.0, 133.1, 133.0, 132.0, 129.5, 128.7, 128.3, 128.2, 128.1, 127.9, 127.6, 127.5, 127.2, 126.1, 121.0, 113.8, 106.9, 70.6, 66.8, 66.6, 55.9; IR (film) ν 3064, 3032, 2936, 1715, 1574, 1454 cm^{-1}; HR-MS (ES) calcd for $C_{45}H_{38}O_7$ 713.2515 (M + Na), found 713.2501.

2-(2-(Benzyloxy)benzoyl)-3-methoxybenzoic Acid, Benzyl Ester (34). To a solution of alkene **32** (28 mg, 0.062 mmol) in a mixture of CH_3CN/CCl_4/H_2O (1.5:1.5:2.3 mL, respectively) was added $NaIO_4$ (140 mg, 0.65 mmol) and ruthenium(III) chloride hydrate (approximately 2 mg). After the mixture was stirred overnight at 20 °C, water was added and the reaction mixture was extracted three times with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. Purification by column chromatography (CH_2Cl_2/pentane, 7:3) afforded the benzophenone **32** as a colorless oil (9 mg, 32% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (dd, 1H, J = 1.8, 7.8 Hz), 7.37−7.47 (m, 3H), 7.16−7.28 (m, 7H), 7.14 (t, 1H, J = 8.0 Hz), 7.02 (dt, J = 1.0, 6.6 Hz), 6.87 (m, 4H), 5.12 (s, 2H), 4.70 (s, 2H), 3.63 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 193.8, 191.6, 165.6, 158.6, 155.9, 135.8, 135.5, 135.4, 134.2, 131.4, 129.7, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.4, 127.0, 122.1, 120.7, 115.1, 112.8, 70.2, 66.8, 56.0; IR ($CHCl_3$) ν 1717, 1656, 1596, 1468 cm^{-1}; HR-MS (ES) calcd for $C_{29}H_{24}O_5$ 475.1521 (M + Na), found 475.1514.

4-((2-Benzyloxycarbonyl-6-methoxy)benzoyl)-3,5-dibenzyloxybenzoic Acid, Benzyl Ester (36). To a solution of the methylene compound **35** (18 mg, 0.026 mmol) in a mixture of CH_3CN/CCl_4/H_2O (0.5:0.5:0.8 mL, respectively) was added

$NaIO_4$ (44 mg, 0.21 mmol) and ruthenium(III) chloride hydrate (approximately 1 mg). After stirring for 2 h at 20 °C, water was added and the reaction mixture was extracted three times with CH_2Cl_2. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Purification by column chromatography (ether:pentane, 2:3) afforded the benzophenone **36** as a colorless oil (5.4 mg, 30% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.42 (m, 6H), 7.26 (m, 4H), 7.23 (m, 6H), 7.17 (m, 4H), 7.13 (m, 4H), 6.82 (m, 1H), 5.35 (s, 2H), 5.09 (s, 2H), 4.94 (s, 4H), 3.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.6, 167.1, 165.7, 158.2, 157.4, 136.2, 135.8, 132.9, 136.2, 135.8, 132.9, 132.6, 131.7, 130.4, 128.7, 128.5, 128.4, 128.3, 128.0, 127.4, 127.0, 123.7, 121.8, 114.9, 107.0, 79.7, 67.1, 67.0, 56.1; IR ($CHCl_3$) 1718, 1670, 1582, 1455 cm^{-1}; HR-MS (ES) calcd for $C_{44}H_{36}O_8$ 715.2308 (M + Na), found 715.2310.

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Supporting Information Available: Copies of ^{1}H NMR spectra for all new compounds, ORTEP diagrams and tables of crystallographic data for the seven-membered lactone **25**, the eight-membered lactone **27** and the iodide **29**, and Figures S1−S3. This material is available free of charge via the Internet at http//pubs.acs.org.

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