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Formal total synthesis of the PKC inhibitor, balanol: preparation of the fully protected benzophenone fragment

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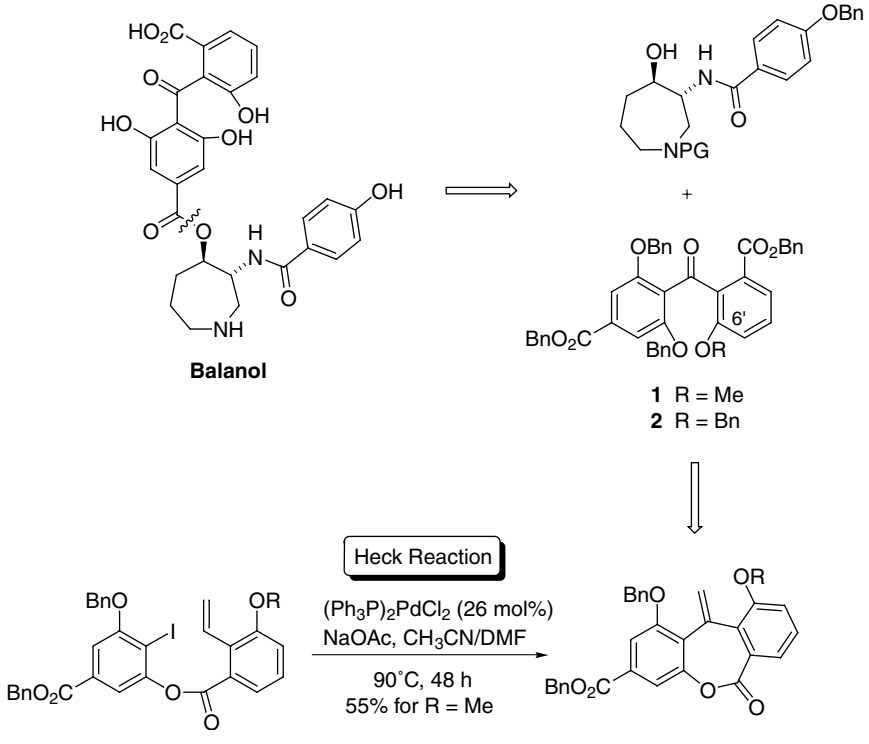
Abstract—The synthesis of a perbenzylated derivative of balanol's highly functionalized benzophenone fragment is reported employing a regioselective Heck reaction as the key step for the connection of the two aromatic rings. The intermediate 7-membered lactone obtained, is subsequently opened and then subjected to an oxidative degradation, resulting in a short synthesis of the benzophenone unit. As the benzophenone has previously been successfully carried through to the synthesis of balanol, our work constitutes a formal total synthesis of this natural product. Attempts were also made to provide other direct entries to this fragment via a Heck-like coupling onto an aryl aldehyde or a SmI_2-promoted ketyl radical cyclization.

1. Introduction

We have recently been interested in the total synthesis of one of the newest examples of protein kinase C (PKC) inhibitors, namely balanol (Scheme 1).[1] This natural product of fungal origin was isolated and reported independently by Kulanthaivel et al. at Sphinx Pharmaceuticals in 1993,[2] and by Ohshima et al. at Nippon Roche Research



Scheme 1.

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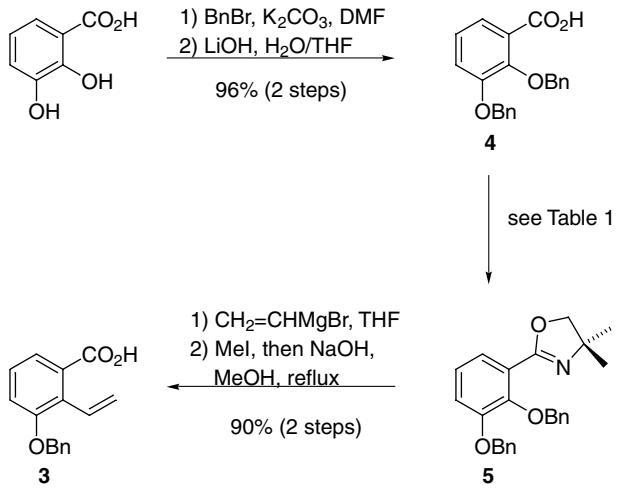
Center in 1994.[3] PKC is a large subclass of the protein kinases responsible for phosphate transfer from ATP to protein substrates involved in intracellular signalling pathways. Because activation of PKC enzymes has been implicated in a number of diseases, including AIDS, cancer, cardiovascular disorders, asthma, diabetes and central nervous system dysfunction, the identification of a suitable and specific inhibitor of this enzyme class would be of medicinal interest.[4] The structural difference of balanol compared to other known PKC inhibitors, makes balanol a new lead compound in the pursuit of more active and specific inhibitors of this enzyme.

In a recent paper, we reported a convergent route to the benzophenone fragment of balanol employing an intramolecular Heck reaction as the key step for connecting the two aromatic subunits (Scheme 1).[1a,c] Unlike the previously reported syntheses,[5,6] both aromatic coupling partners are fully functionalized with substituents in their correct oxidation state as in the benzophenone unit, making this route quite convergent. Unfortunately, the C6′-hydroxyl group of **1** was protected as its methyl ether, which did not make this compound suitable for the total synthesis of balanol. In support of this, attempted simultaneous debenzylation and demethylation under conditions reported by the Rhone–Poulenc Rorer group for a similar compound were unrewarding leading to multiple product formation.[5d] Hence, it was deemed necessary to replace the methyl group at the C6′-hydroxyl group with a benzyl group instead.

We therefore report our work on the synthesis of the fully benzylated benzophenone unit (**2**) of balanol. Contrary to our previous synthesis, the simple replacement of the C6′-methyl ether with a benzyl ether required several modifications in the synthesis in order to obtain the target molecule. As the fully benzylated benzophenone fragment has previously been synthesized and effectively carried through to balanol,[5d] our work represents a formal total synthesis of this novel PKC inhibitor. In addition to this work, we reveal several attempts to shorten the synthesis via either an intramolecular Heck-like reaction involving an aldehyde or an intramolecular ketyl radical cyclization approach.

2. Results and discussion

The synthesis of the highly functionalized aromatic fragment of balanol began with the preparation of the disubstituted benzoic acid **3** (Scheme 2). Hence, subsequent perbenzylation of 2,3-dihydroxy benzoic acid and basic hydrolysis afforded the dibenzyl ether **4**.[7] In our previous work,[1a,c] the corresponding oxazoline, necessary for carrying out the following nucleophilic aromatic substitution of



Scheme 2.

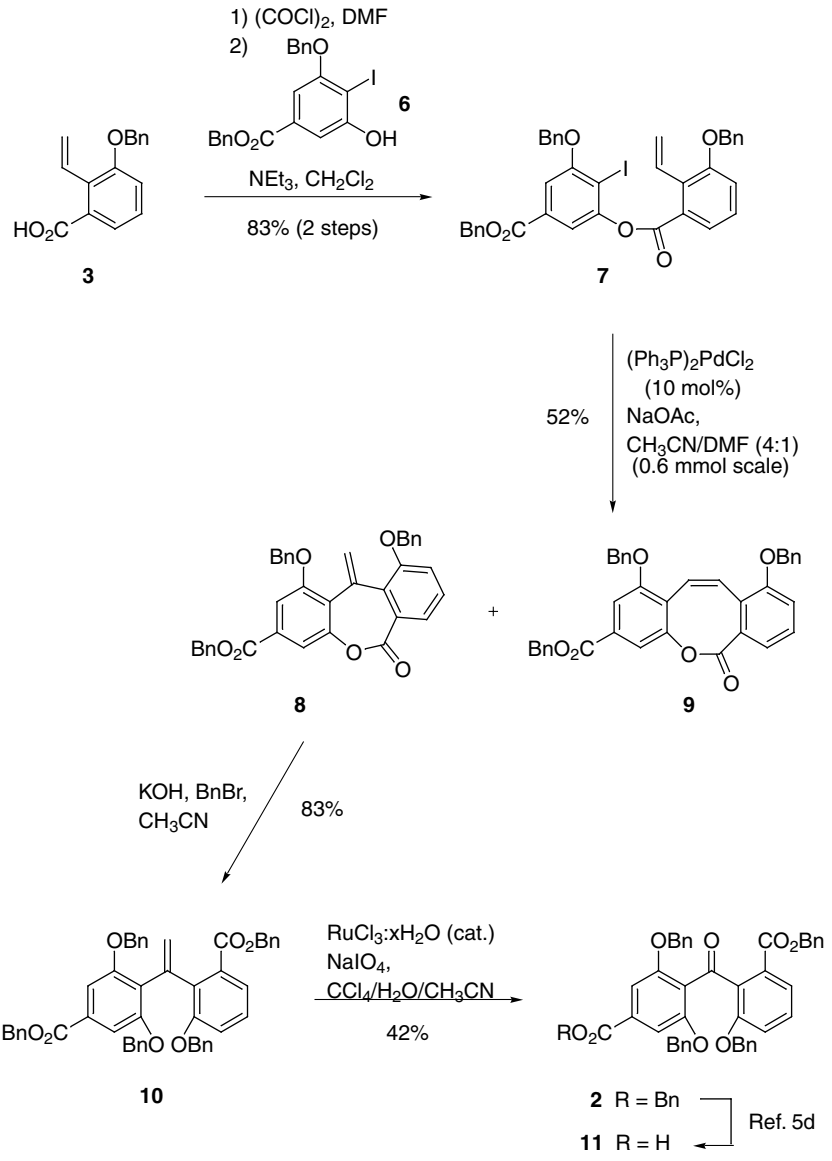
the *o*-methoxy group, was prepared in two steps by amide formation with 2-amino-3-methylpropanol followed by cyclization promoted by thionyl chloride, according to the procedure described by Meyers et al.[8] However, this protocol proved incompatible with the benzoic acid **4** leading to significant cleavage of the etheral linkages (Table 1, entry 1).

Hence, the corresponding amide was prepared in quantitative yield via the acid chloride generated from oxalyl chloride and DMF. Cyclization was thereafter attempted by activation of the primary alcohol with tosyl chloride in the presence of triethylamine and DMAP. Reaction times of 11 days were needed to give a 60% yield of the oxazoline **5** (entry 2).[9] Whereas the procedure reported by Vorbrüggen et al. for the one step cyclization of a carboxylic acid and an aminoalcohol to an oxazoline employing the $PPh_3/C_2Cl_6/NEt_3$ combination proved disappointing (entry 3),[10] applying the same protocol to the above amide in acetonitrile led to a rapid ring closure (15–30 min) affording an 86% overall yield of the desired oxazoline **5** from the carboxylic acid **4** (entry 4). If the solvent of this reaction was replaced with dichloromethane simple exchange of the primary alcohol to its chloride was the major event. Substitution of the *o*-benzyloxy group in **5** proved highly effective with vinyl magnesium bromide[8] at 25°C affording after a two step hydrolysis sequence the desired carboxylic acid **3** in a high overall yield of 90%.

Coupling of **3** with the phenol **6** employing Furukawa's conditions[11] as reported in our earlier work led to yields of the ester **7** no higher than 64% after repeated attempts (Scheme 3), in contrast to the 95% yield obtained for corresponding compound containing a methoxy substituent. This

Table 1. Conditions attempted for conversion of carboxylic acid **4** to oxazoline **5**

Entry	Conditions	Yield (%)
1	$SOCl_2$ then 2-amino 3-methylpropanol; $SOCl_2$	45
2	$(COCl_2)$, DMF, then 2-amino-3-methylpropanol; TsCl, NEt_3, DMAP, CH_2Cl_2, 50°C, 11 days	60
3	Ph_3P, C_2Cl_6, NEt_3, CH_3CN	Mixture of products
4	$(COCl_2)$, DMF, then 2-amino-3-methylpropanol; Ph_3P, C_2Cl_6, NEt_3, CH_3CN, 15 min	86

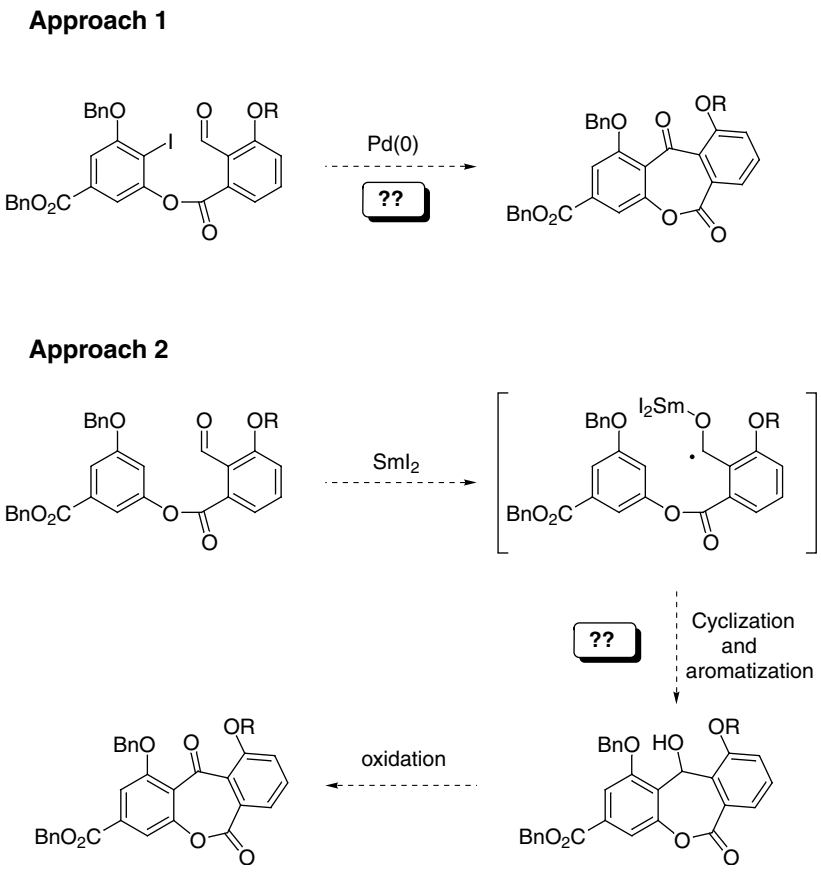


Scheme 3.

could be remedied by transforming **3** first to its acid chloride and then condensing it with phenol **6** in the presence of triethylamine affording **7** in 83% yield after recrystallization.

It was interesting to examine how the increased steric bulk on the C6 hydroxyl group in **7** would effect both the yields and the regioselectivity of the palladium(0) catalyzed ring closing event. In the previous study, best results and regioselectivities (7-*exo* vs 8-*endo*, 4.2:1) were attained by the use of $(PPh_3)_2PdCl_2$ as the catalyst in a solvent mixture of CH_3CN/DMF.[1c] Quite pleasingly, when **7** (0.6 mmol scale) was subjected to 10 mol% of the catalyst under similar conditions at 85°C, a 52% cyclization yield of the 7-*exo* and 8-*endo* products **8** and **9** as a 6.4:1 mixture was obtained.[12] These isomeric compounds could not be separated by column chromatography. Further opening of the lactone and in situ benzylation then led to a separable mixture affording alkene **10** in 83% yield. Finally, oxidative cleavage of **10** with ruthenium tetraoxide gave the desired benzophenone moiety of balanol as its perbenzylated derivative **2**, though in a modest yield of 42%. Vicker and coworkers have previously demonstrated the ability to selectively hydrolyze the sterically less hindered benzyl ester in **2** to the carboxylic acid **11** necessary for the completion of their total synthesis of balanol.[5d] Therefore, our synthetic approach to **2** constitutes a formal total synthesis of this natural product.

In an effort to overcome the final, problematic oxidative cleavage step encountered with the alkenes such as **10** and with the methoxy counterpart, an attempt was made to perform an intramolecular Pd(0) catalyzed arylation of a C=O double bond in order to directly generate the required benzophenone (Scheme 4, Approach 1). Precedence for this unorthodox Heck reaction comes from the work of Satoh et al. demonstrating the ability of substituted *o*-hydroxybenzaldehydes to undergo an intermolecular Heck-type arylation with aryl iodides.[13] The positioning of the hydroxyl group is essential for the C–C bond formation as the coupling reaction becomes intramolecular through the

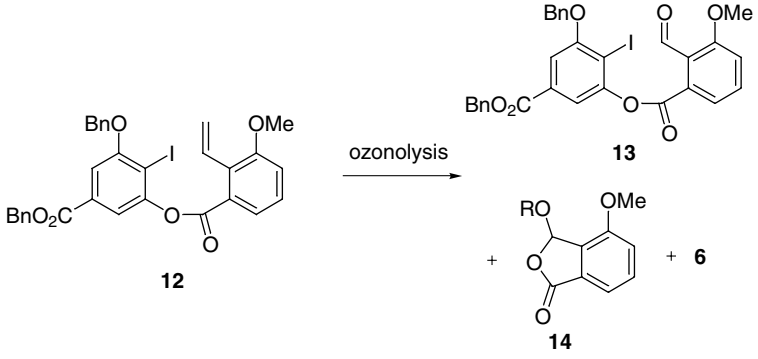


Scheme 4.

generation of a Pd–O species. Larock has likewise reported the intramolecular addition of a vinylpalladium intermediate to a C=O bond resulting in the synthesis of indenols.[14]

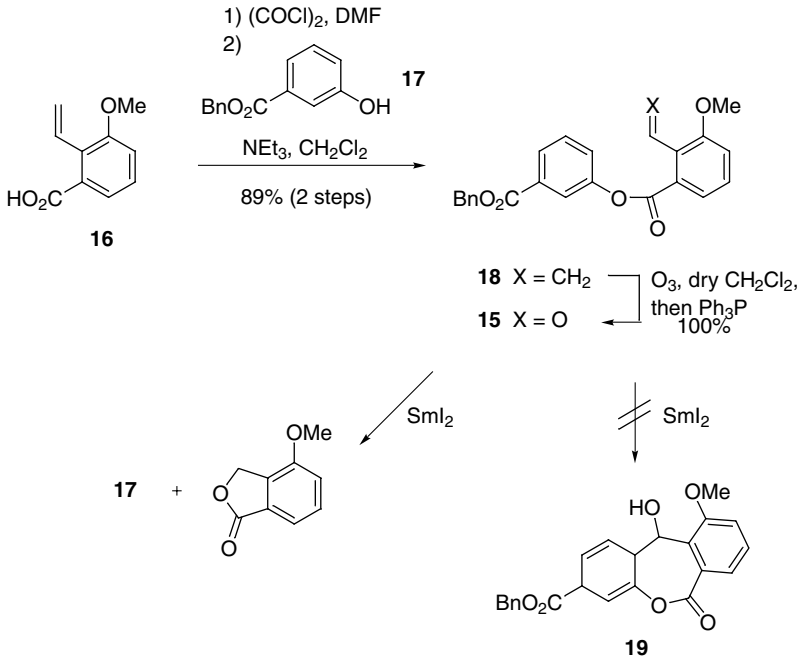
To study this route, we prepared the labile aldehyde **13** from the alkene **12**.[1c] Ozonolysis of the vinyl substituent in a typical solvent mixture CH_2Cl_2/MeOH did not lead to the required aldehyde **13** after treatment with Ph_3P, but rather phenol **6** and the monomethyl acetal of 6-methoxy-2-carboxybenzaldehyde **14** (R=Me) (Table 2, entry 1). This latter compound most likely arose from the transesterifcation of a hemiacetal intermediate. On the other hand, if the oxidation reaction was run under strictly anhydrous

Table 2. Ozonolysis studies of the alkene **13**



Entry	Conditions	Yield (%)		
		13	**14**	**6**
1	O_3, CH_2Cl_2/MeOH, then Ph_3P	–	56 (R=Me)	56
2[a]	O_3, CH_2Cl_2, then Ph_3P	67	33 (R=H)	33
3[a]	O_3, dry CH_2Cl_2, then Ph_3P	100	–	–

[a] Yields based on ^1H NMR spectrum of crude product mixture.



Scheme 5.

conditions in dichloromethane, the crude ^{1}H NMR spectrum in dry C_6D_6 revealed quantitative conversion to the aldehyde **13** (entry 3). Use of solvents which were not dried prior to the ozonolysis led to a considerable amount of cleavage products such as **6** and in this case the hemiacetal **14** (R=H) (entry 2). Without further purification this aldehyde was thus subjected to the conditions reported by Satoh for Pd(0) catalyzed C–C bond formation ($PdCl_2$, Na_2CO_3, LiCl, DMF).[13] However, both these conditions as well as others only led to multiple product mixtures according to both TLC and ^{1}H NMR analysis and hence further investigation in this line were discontinued.

Finally, inspired by a recent report from Dinesh and Reissig demonstrating the high tendency of alkyl ketones to undergo SmI_2-promoted intramolecular 6-*exo* radical cyclizations on to arenes,[15] we considered a similar type of reaction as illustrated in Scheme 4, Approach 2, for the construction of balanol's aryl fragment. Successful cyclization would then only require a simple oxidation step of the secondary benzylic alcohol formed. Although, a slower 7-*exo* ring closure of the intermediate ketyl would be implicated in this case, the correct placement of the electron withdrawing benzylcarboxy group could make this cyclization step competitive with the potential, but undesirable *trans*-esterification step involving the ketyl oxygen in a similar process as described above.

To study this reaction the model compound **15** was synthesized. Preparation of the aldehyde **15** began with the selective benzylation of *m*-hydroxybenzoic acid to **17** followed by its esterification in near quantitative yield with the acid chloride of the previously described **16**[1c] (Scheme 5). Oxidative cleavage of the alkene **18** proceeded as expected though only if dry dichloromethane was used, providing the aldehyde **15** in quantitative yield. Without further purification, the aldehyde was dissolved in THF and cooled to −78°C, after which a 0.1 M solution of SmI_2 in THF was added dropwise. An instantaneous reaction ensued and the reaction was worked up after completed addition of the reducing agent and stirring for 30 min. Disappointingly, only the product from ester cleavage, the phenol **17**, was identified, possibly originating from a *trans*-esterification pathway. The slow cyclization rate for the 7-*exo* ring closure and the requirement for a higher energy rotamer of the ester linkage for cyclization to take place both possible contribute to the unsuccessful preparation of the desired alcohol **19**.

3. Conclusion

In conclusion, we have successfully prepared the perbenzylated derivative of balanol's benzophenone fragment employing our previously described intramolecular Heck reaction as the key step. The described work therefore represents a formal total synthesis of this naturally occurring PKC inhibitor. Attempts were also made to improve the synthesis by either an intramolecular Heck-like reaction with a carbon–oxygen double bond or a SmI_2-mediated radical cyclization event involving a ketyl radical intermediate.

4. Experimental

4.1. General

Unless otherwise stated, all reactions were carried out under argon. THF was dried and freshly distilled over sodium/benzophenone. Dichloromethane and acetonitrile were freshly distilled over P_2O_5 and CaH_2, respectively. Reactions were monitored by thin-layer chromatography (TLC) analysis. Melting points are uncorrected.

3-Benzyloxy-5-hydroxy-4-iodobenzoic acid, benzyl ester (**6**) was prepared as previously described.[1c] Samarium diiodide was prepared according to the literature.[16]

4.1.1. 2-((2,3-Dibenzyloxy)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (5). To a solution of 2,3-dibenzyloxybenzoic acid **4** (3.46 g, 10.4 mmol) in CH_2Cl_2 (50 mL) was added oxalyl chloride (12 mL, 137 mmol) and DMF (10 μL, 129 μmol), followed by stirring for 1 h under nitrogen. The solvent and excess of oxalyl chloride were removed under reduced pressure yielding the acid chloride. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.57–7.10 (m, 13H), 5.15 (s, 2H), 5.08 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 164.7, 152.5, 147.7, 136.4, 135.8, 129.4, 128.7 (2C), 128.6, 128.3 (2C), 128.2, 128.2, 127.5 (2C), 124.3, 124.0, 119.7, 75.5, 71.3.

The acid chloride was redissolved in CH_2Cl_2 (50 mL) whereafter NEt_3 (8.7 mL, 62 mmol) and 2-amino-2-methylpropanol (1.0 mL, 11 mmol) were added. After stirring for 6.5 h under nitrogen, water was added to the solution followed by extraction with CH_2Cl_2 (3 times). The combined organic phases were dried over $MgSO_4$, and evaporated under reduced pressure. The residue which contains almost pure amide yielded by crystallization *(pentane/ethyl acetate) 2,3-dibenzyloxy-N-(2-hydroxy-1,1-dimethylethyl)benzamide* (4.22 g, 100%) as colorless crystals. Mp. 111–114°C; IR (KBr) 3431, 3376, 2928, 2872, 1648, 1572, 1545 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (bs, 1H), 7.69 (dd, *J*=5.4, 4.4 Hz, 1H), 7.33–7.85 (m, 10H), 7.15 (d, *J*=4.4 Hz, 1H), 7.15 (d, *J*=5.4 Hz, 1H), 5.15 (s, 2H), 5.09 (s, 2H), 3.52 (s, 2H), 1.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.7, 151.6, 146.7, 136.3, 136.2, 128.9 (2C), 128.8, 128.7 (2C), 128.3, 127.7 (2C), 127.2, 124.5, 123.2, 117.2, 76.6, 71.4, 71.1, 56.2, 24.5 (2C); HR-MS (ES) calcd for $C_{25}H_{27}NO_4Na$ 428.1838 (M+Na), found 428.1839.

The amide (2.57 g, 6.33 mmol), Ph_3P (2.50 g, 9.53 mmol), C_2Cl_6 (2.25 g, 9.50 mmol), and Et_3N (8.8 mL, 63 mmol) in CH_3CN (100 mL) were stirred for 25 min under nitrogen. As amide was still present after this time according to TLC analysis, additional Ph_3P (1.0 g, 3.8 mmol) and C_2Cl_6 (1.0 g, 4.2 mmol) were added, and the reaction was completed after an additional 20 min. The reaction mixture was concentrated under reduced pressure. Flash-chromatography (EtOAc/petane 1:4) gave the *oxazoline* **5** (2.10 g, 86%) as colorless crystals. Mp. 67.2–67.6°C; IR (KBr) 3064, 3032, 3966, 1952, 1812, 1648 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.00–7.43 (m, 13H), 5.13 (s, 2H), 5.10 (s, 2H), 4.05 (s, 2H), 1.36 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 161.3, 152.7, 148.1, 137.8, 136.9, 128.7, 128.6, 128.3, 128.1, 127.9, 127.6, 124.3, 124.1, 123.2, 117.5, 79.2, 75.7, 71.5, 67.5, 28.5 (2C); HR-MS (ES) calcd for $C_{25}H_{25}NO_3Na$ 410.1732 (M+Na), found 410.1732.

4.1.2. 3-Benzyloxy-2-vinylbenzoic acid (3). To a solution of the oxazoline **5** (2.04 g, 5.26 mmol) in THF (20 mL) was added a 0.1 M solution of vinylmagnesiumbromide (17 mL, 17 mmol). After being stirred under nitrogen for 18.5 h, saturated aqueous NH_4Cl was added. The aqueous phase was extracted 5 times with ether, and the combined organic phases were dried over $MgSO_4$, and concentrated under reduced pressure. The residue afforded *2-(3-benzyloxy-2-vinylphenyl)-4,4-dimethyl-4,5-dihydrooxazole* (1.89 g, 100%) as a pale yellow solid. Further purification through crystallization from ethyl acetate/pentane gave the pure oxazoline as colorless crystals. Mp. 68–69°C; IR (KBr) 2970, 1845, 1648, 1626, 1570 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.28–7.43 (m, 5H), 7.23 (dd, *J*=8.0, 1.6 Hz, 1H), 7.19 (t, *J*=8.0, 8.0 Hz, 1H), 7.02 (dd, *J*=18.0, 11.6 Hz, 1H), 7.00 (dd, *J*=8.0, 1.6 Hz, 1H), 5.80 (dd, *J*=18.0, 2.0 Hz, 1H), 5.46 (dd, *J*=11.6, 2.0 Hz, 1H), 5.11 (s, 2H), 4.06 (s, 2H), 1.38 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 163.1, 156.6, 136.7, 130.9, 129.3, 128.5 (2C), 127.8, 127.7, 127.2 (2C), 127.1, 122.5, 119.7, 114.4, 79.3, 70.5, 67.9, 28.2 (2C); HR-MS (ES) calcd for $C_{20}H_{21}NO_2Na$ 308.1650 (M+Na), found 308.1651.

Freshly distilled methyl iodide (2 mL, 32 mmol) was added to the oxazoline (63 mg, 175 μmol) under nitrogen, and stirred overnight. After evaporation of the excess of methyl iodide, the ^{1}H NMR spectrum clearly indicated formation of the methyl salt. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.45–7.26 (m, 5H), 7.21 (t, *J*=7.9, 7.9 Hz, 1H), 6.84 (dd, *J*=7.9, 1.0 Hz, 1H), 6.84 (dd, *J*=17.8, 11.8 Hz, 1H), 6.79 (dd, *J*=7.9, 1.0 Hz, 1H), 5.78 (dd, *J*=17.8, 1.8 Hz, 1H), 5.42 (dd, *J*=11.8, 1.8 Hz, 1H), 5.08 (s, 2H), 3.82 (s, 1H), 3.81 (s, 1H), 2.71 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H).

The pale yellow methyl iodide salt was subjected to 2 M $NaOH_{(aq)}$ (1 mL) and MeOH (1 mL) and stirred for 4 days under reflux. After cooling the reaction to room temperature, followed by an etheral wash, the aqueous phase was acidified to pH 1 with 6 M HCl resulting in a white participate, which was extracted into the organic phase with ether (4 times). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The product **3** was afforded as colorless crystals through crystallization in CH_2Cl_2/pentane (39 mg, 90%). Mp. 123–123.5°C; IR (KBr) 2873, 1690, 1576, 1453, 1413, 1263 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 11.22 (bs, 1H), 7.49 (dd, *J*=8.0, 1.1 Hz, 1H), 7.31–7.45 (m, 5H), 7.26 (t, *J*=8.0, 8.0 Hz, 1H), 7.12 (dd, *J*=8.0, 1.1 Hz, 1H), 7.10 (dd, *J*=17.8, 11.6 Hz, 1H), 5.76 (dd, *J*=17.8, 1.8 Hz, 1H), 5.55 (dd, *J*=11.6, 1.8 Hz, 1H), 5.13 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 174.3, 156.8, 136.7, 131.2, 131.1, 128.7 (2C), 128.7, 128.2, 127.4 (2C), 122.9, 120.9 (2C), 116.6, 71.0; MS (ES) calcd for $C_{16}H_{13}O_3$ 253.1, found 253.1.

4.1.3. 3-Benzyloxy-2-vinylbenzoic acid, 5-benzylcarboxyl-3-benzyloxy-2-iodophenyl ester (7). To a solution of the benzoic acid **3** (208 mg, 0.82 mmol) in CH_2Cl_2 (10 mL) was added oxalyl chloride (1.1 mL, 12 mmol) and DMF (10 μL, 0.13 mmol). The reaction mixture was stirred for 1 h under nitrogen. Solvent and excess of the oxalyl chloride were removed under reduced pressure, leaving the acid chloride as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.48–7.27 (m, 7H), 7.13 (dd, *J*=8.2, 1.0 Hz, 1H), 6.91 (dd, *J*=17.8, 11.6 Hz, 1H), 5.71 (dd, *J*=17.8, 1.6 Hz, 1H), 5.59 (dd, *J*=11.6, 1.6 Hz, 1H), 5.13 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.5, 156.6, 136.3, 135.9, 129.9, 128.7 (2C), 128.2, 128.1, 127.7, 127.2 (2C), 122.8, 122.3, 116.9, 70.9.

A solution of the acid chloride (0.82 mmol), Et_3N (150 μL,

1.08 mmol) and the phenol **6** (377 mg, 0.82 mmol) in CH_2Cl_2 (10 mL) was stirred under nitrogen for 17 h. After addition of water (5 mL), and extraction with ether (3 times), the combined organic phases were dried over $MgSO_4$ and evaporated to dryness. The solid residue consisting of **7** predominantly (556 mg, 99%) was recrystallized from CH_2Cl_2/pentane to give the product **7** as colorless crystals (462 mg, 83%). Mp. 84°C; IR (KBr) 3422, 2927, 1718, 1577, 1453, 1416, 1234 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.77 (dd, J=4.0, 0.2 Hz, 1H), 7.30–7.52 (m, 18H), 7.17 (d, J=8.4 Hz, 1H), 7.14 (dd, J=18.0, 12.0 Hz, 1H), 5.84 (dd, J=18.0, 0.8 Hz, 1H), 5.57 (dd, J=12.0, 0.8 Hz, 1H), 5.36 (s, 2H), 5.24 (s, 2H), 5.16 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.5, 165.3, 159.0, 159.0, 156.9, 153.0, 136.7, 135.9, 135.7, 132.1, 130.8, 130.5, 129.2, 128.8 (3C), 128.6, 128.4, 128.3, 128.1 (5C), 127.3 (4C), 123.0, 121.2, 116.8, 116.6, 110.3, 91.3, 71.6, 70.9, 67.4; HR-MS (ES) calcd for $C_{37}H_{29}IO_5Na$ 719.0908 (M+Na), found 719.0917.

4.1.4. 1,10-Dibenzyloxy-11-methylene-11-*H*-dibenzo-[*b*,*e*]oxepin-6-one-3-carboxylic acid, benzyl ester (8). A solution of the substrate **7** (380 mg, 0.55 mmol) with $(Ph_3P)_2PdCl_2$ (19.6 mg, 0.028 mmol) and anhydrous NaOAc (146 mg, 1.78 mmol) in freshly distilled CH_3CN (12 mL) and distilled DMF (3 mL) was stirred in a sealed tube at 85°C. After 21 h, an additional 5 mol% of $(Ph_3P)_2PdCl_2$ (19.6 mg, 0.028 μmol) was added and the reaction was continued for a further 22 h. 1 M AcOH (2 mL) was added and the mixture was extracted with ether (5 times). The combined organic phases were washed once with brine and dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography (CH_2Cl_2/pentane, 3:2) gave a an inseparable mixture (165 mg) of the 7-*exo* and 8-*endo* products **8** and **9** in the yields of 45 and 7%, respectively, the ratio of which was determined by ^1H NMR. For compound **8**: ^1H NMR ($CDCl_3$, 200 MHz) δ 7.57 (d, J=1.4 Hz, 1H), 7.53 (d, J=1.4 Hz, 1H), 7.50 (dd, J=7.8, 1.0 Hz, 1H), 7.17–7.43 (m, 16H), 7.12 (dd, J=8.2, 1.0 Hz, 1H), 5.99 (d, J=1.2 Hz, 1H), 5.93 (d, J=1.2 Hz, 1H), 5.32 (s, 2H), 5.14 (d, J=2.4 Hz, 2H), 5.10 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 165.1 (2C), 155.4, 153.9, 150.3, 136.6, 136.4, 135.6, 132.6, 130.6, 129.0, 128.6, 128.6, 128.5 (4C), 128.4, 128.1 (2C), 127.8 (2C), 126.8, 126.6, 124.4, 118.0, 114.6, 111.0, 70.7, 70.6, 67.1; HR-MS (ES) calcd for $C_{37}H_{28}O_6Na$ 591.1792 (M+Na), found 591.1784.

4.1.5. Diarylalkene (10). A mixture of the 7-*exo* and 8-*endo* products **8** and **9** in the ratio 6.4:1 (165 mg, 0.29 mmol), KOH (58 mg, 1.2 mmol) and benzyl bromide (400 μL, 2.89 mmol) in CH_3CN (6 mL) was stirred for 16.5 h under nitrogen. The reaction mixture was evaporated to dryness, and water was added, followed by extraction with CH_2Cl_2 (3 times). The combined organic phases were washed with brine and dried over $MgSO_4$ and concentrated in vacuo. Flash-chromatography afforded the diarylalkene **11** (152 mg, 83%) as well as the diarylalkene arising from the 8-*endo* cyclization product (23 mg, 78%). For compound **11**: ^1H NMR ($CDCl_3$, 200 MHz) δ 6.80–7.46 (m, 30H), 5.83 (d, J=1.6 Hz, 1H), 5.74 (d, J=1.6 Hz, 1H), 5.35 (s, 2H), 5.00 (s, 2H), 4.71 (s, 4H), 4.62 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 169.0, 166.3, 157.0 (2C), 156.2, 137.0 (2C), 136.6, 136.3, 136.0, 134.3, 133.8, 132.3, 129.2, 128.7 (2C), 128.4 (3C), 128.3 (5C), 128.2 (6C), 128.0, 127.7, 127.6 (2C), 127.5 (2C), 127.4 (4C), 127.2 (2C), 125.4, 121.6, 114.5, 107.1 (2C), 70.4 (2C), 66.8 (2C); HR-MS (ES) calcd for $C_{51}H_{42}O_7Na$ 789.2828 (M+Na), found 789.2871.

4.1.6. 6-Benzyloxy-2-benzyloxycarbonylphenyl-2,6-dibenzyloxy-4-benzyloxycarbonylphenylketone (2). The alkene **10** (21.9 mg, 0.029 mmol), $NaIO_4$ (205 mg, 0.285 mmol) and a catalytic amount of $RuCl_3{\cdot}xH_2O$ in a solvent mixture of CH_3CN, CCl_4 and water (0.5:0.5:0.75 mL, respectively) was rigorously stirred for 18 h at 20°C. An additional amount of $NaIO_4$ (60 mg) and a catalytic amount $RuCl_3{\cdot}xH_2O$ were added and TLC analysis indicated that the reaction was complete after another 18 h of stirring. Water was added and the reaction mixture was extracted with DCM (4 times). The combined organic phases were filtered through Celite and washed with brine and dried over $MgSO_4$, and then concentrated under reduced pressure. Flash chromatography (CH_2Cl_2/pentane 9:1) gave the benzophenone **2** (8.0 mg, 42%) as a colorless foam. ^1H NMR (d_6-Acetone, 200 MHz) δ 7.01–7.48 (m, 27H), 6.95 (d, J=8 Hz, 1H), 6.82 (m, 2H), 5.38 (s, 2H), 5.12 (s, 2H), 4.78 (s, 4H), 4.70 (2, 2H); HR-MS (ES) calcd for $C_{50}H_{40}O_8Na$ 791.2621 (M+Na), found 791.2620.

4.1.7. 3-Methoxy-2-formylbenzoic acid, 5-benzylcarboxyl-3-benzyloxy-2-iodophenyl ester (13). Ozone was bubbled through a solution of the alkene **12** (10 mg, 0.016 mmol) dissolved in dry CH_2Cl_2 (2 mL) at −78°C until a blue color was obtained. After removal of the excess ozone by bubbling nitrogen through the solution for 5–10 minutes at −78°C, triphenylphosphine (10 mg, 0.040 mmol) was added, and the reaction mixture was warmed to 20°C over a period of 15 min. Stirring was continued for an additional 30 min, and the solvents were removed by evaporation to dryness in vacuo to give the crude aldehyde **13** with excess triphenylphosphine, which was immediately used in the palladium-catalyzed coupling step. ^1H NMR (C_6D_6, 200 MHz) δ 10.28 (s, 1H), 8.35 (d, J=1.6 Hz, 1H), 6.73–7.28 (m, 14H), 4.95 (s, 2H), 4.31 (s, 2H), 2.95 (s, 3H).

4.1.8. 3-Hydroxybenzoic acid, benzyl ester (17). Benzyl bromide (861 μL, 7.24 mmol) was added to a mixture of 3-hydroxybenzoic acid (1.00 g, 7.24 mmol) and sodium carbonate (767 mg, 7.24 mmol) in dry DMF (10 mL). After stirring for 12 h at 20°C, water was added and the mixture was extracted 5 times with ether. The combined organic phases were first washed with water (5 times) and once with brine, and then dried over $MgSO_4$, and concentrated under reduced pressure, affording the benzyl ester **17** as a colorless solid (1.54 g, 93%). Mp. 68–69°C (lit.[17] 70°C); ^1H NMR ($CDCl_3$, 200 MHz) δ 7.65 (dt, J=7.8, 1.0 Hz, 1H), 7.59 (d, J=1.0, 0.9 Hz, 1H), 7.46–7.25 (m, 5H), 7.30 (t, J=7.8 Hz, 1H), 7.05 (ddt, J=7.8, 2.6, 0.9 Hz, 1H), 5.68 (broad s, 1H), 5.35 (s, 2H).

4.1.9. 3-Methoxy-2-vinylbenzoic acid, 3-benzylcarboxylphenyl ester (18). Oxalyl chloride (700 μL, 8.02 mmol) was added to a solution of the benzoic acid **16** (128 mg, 0.56 mmol) in CH_2Cl_2 (10 mL) and DMF (10 μL,

0.13 mmol). The reaction mixture was stirred for 1.5 h under nitrogen. Solvent and excess of the oxalyl chloride were removed under reduced pressure, leaving the acid chloride as a pale yellow solid.

A solution of the above acid chloride (0.56 mmol), Et_3N (100 μL, 0.71 mmol) and the phenol **17** (100 mg, 0.56 mmol) in CH_2Cl_2 (10 mL) was stirred under nitrogen for 2 h. After addition of water, and extraction with CH_2Cl_2 (3 times), the combined organic phases were dried over $MgSO_4$ and evaporated to dryness. Flash chromatography (CH_2Cl_2/pentane, 1:1 to 3:2) gave the ester **18** (198 mg, 89%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.02 (dt, J=7.4, 1.6 Hz, 1H), 7.92 (dt, J=1.6, 0.6 Hz, 1H), 7.32–7.56 (m, 9H), 7.10 (dd, J=15.8, 11.6 Hz, 1H), 5.70 (dd, J=15.8, 1.8 Hz, 1H), 5.59 (dd, J=11.6, 1.8 Hz, 1H), 5.40 (s, 2H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.8, 165.5, 157.6, 150.9, 135.8, 131.7, 131.0, 129.5, 128.7 (2C), 128.4, 128.3 (2C), 128.2, 127.3, 126.4, 122.9, 121.9, 120.4, 114.3, 67.0, 55.9; HR-MS (ES) calcd for $C_{24}H_{20}O_5Na$ 411.1207 (M+Na), found 411.1211.

4.1.10. Attempted cyclization of 3-methoxy-2-formylbenzoic acid, 3-benzylcarboxylphenyl ester (15) with samarium diiodide. Ozone was bubbled through a solution of the alkene **18** (59 mg, 0.15 mmol) dissolved in dry CH_2Cl_2 (5 mL) at −78°C until a blue color was obtained. After removal of the excess ozone by bubbling nitrogen through the solution for 5–10 minutes at −78°C, triphenylphosphine (100 mg, 0.38 mmol) was added, and the reaction mixture was warmed to 20°C over a period of 15 min. Stirring was continued for an additional 30 min, and the solvents were removed by evaporation to dryness in vacuo to give the crude aldehyde **15** with excess triphenylphosphine which was immediately used in the subsequent reaction with samarium diiodide. ^{1}H NMR (C_6D_6, 200 MHz) δ 10.16 (s, 1H), 8.20 (t, J=2.0 Hz, 1H), 7.74 (dt, J=7.8, 1.0 Hz, 1H), 6.77–7.25 (m, 9H), 6.19 (dt, J=9.4, 3.6 Hz, 1H), 4.94 (s, 2H), 2.95 (s, 3H).

The aldehyde was redissolved in THF (1 mL) under argon and then cooled to −78°C. A 0.1 M solution of SmI_2 in THF (3.4 mL, 0.34 mmol) was slowly added dropwise and the solution was stirred for 30 min and then quenched with saturated aqueous NH_4Cl. CH_2Cl_2 was added and the mixture was filtered through celite, whereafter the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was subjected to flash chromatography (CH_2Cl_2/pentane, 3:1 to 1:0) affording the phenol **17** (20 mg, 60% yield).

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