Synthesis of *o*-brominated diaryl ethers using symmetrical iodonium salts: application to the synthesis of Bastadin precursors

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Dedicated to Professor Anastasios Varvoglis on the occasion of his 65th birthday
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Abstract
The coupling of *o*-brominated phenols with symmetrical iodonium salts for the construction of the corresponding diaryl ethers was studied. Bis-(2-benzyloxy-5-formyl-phenyl)-iodonium bromide **6b**, only once mentioned in the literature, was fully characterized and tested for the synthesis of Bastadin related diaryl ethers.

Keywords: Bastadins, iodonium salt, synthesis, natural products

Introduction

Diaryl ether is the common structural feature of many natural products with significant biological activity. Vancomycin is the most prominent example, since it is a very potent antibiotic and constitutes the last defense of science against the penicillin resistant *Staphylococcus aureus*.[1] Bastadins, a family of linear or macrocyclic bis-diaryl ether tetrapeptides possessing brominated aryl units and unique α-oximinino amide bonds, are yet another example.[2]

Despite recent advances in the synthesis of diaryl ethers,[3] the efficient preparation of *o*-halogenated derivatives continues to constitute a synthetic challenge with which we were faced in the course of ongoing research towards the synthesis of Bastadins. We would like to report herein results related to our studies on the construction of the *o*-brominated diaryl ether moiety of these natural products, based on the coupling of phenols with triazenes or iodonium salts.

	Y^1	Y^2	Y^3	W–Z
Bastadin-4	H	Br	Br	
Bastadin-7	H	Br	H	
Bastadin-11	H	H	Br	
Bastadin-14	Br	Br	H	
Bastadin-8	H	Br	Br	
Bastadin-10	H	Br	H	
Bastadin-12	Br	Br	H	OH
Bastadin-17	H	H	Br	
Bastadin-5	H	Br	Br	
Bastadin-6	Br	Br	Br	
Bastadin-9	H	H	Br	
Bastadin-15	Br	Br	H	
Bastadin-16	Br	H	Br	

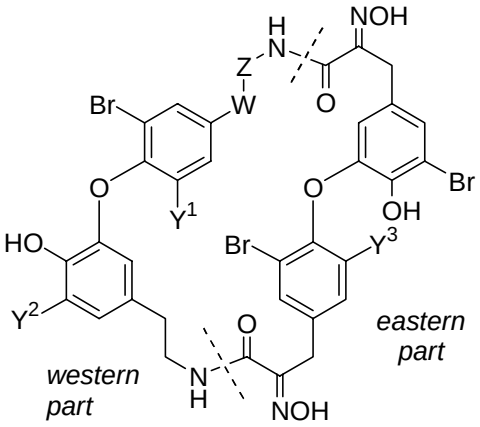
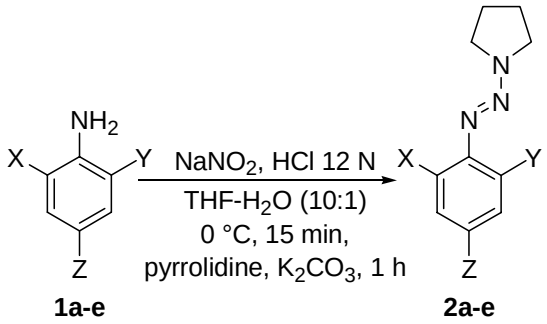


Figure 1. Bastadins isolated from the marine sponge *Ianthella basta*.

Results and Discussion

According to the first method, the triazene functionality of an appropriately substituted aryl can be used to facilitate its coupling to phenols.[4] Subsequent to diaryl ether formation, this directing group could be reductively or hydrolytically removed.

In order to investigate the utility of this method for the construction of diaryl ethers related to Bastadins, we opted to use as models triazenes of aniline, p-toluidine and its *o*-brominated analogs. These substrates were conveniently obtained from the corresponding diazonium salts by treatment with pyrrolidine (Scheme 1).

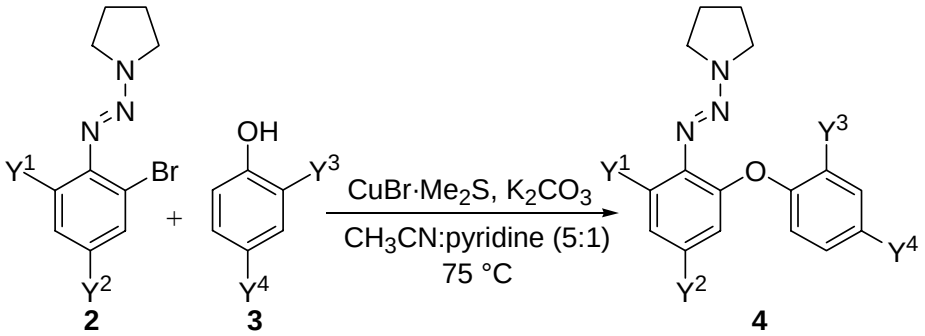


1a-e **2a-e**

Cmpnd	X	Y	Z	Yield (%)
a	H	H	H	91
b	H	H	CH_3	88
c	H	Br	CH_3	87
d	Br	Br	CH_3	87
e	Br	Br	$CH_2CH_2CH_2OH$	94

Scheme 1. Synthesis of triazenes.

Although their coupling with simple phenols proceeded in good yields (Scheme 2) subsequent hydrolysis of the triazene group proved to be problematic (Scheme 3).



2 **3** **4**

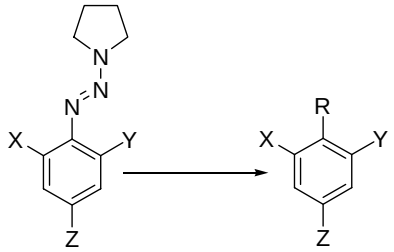
Entry	Y^1	Y^2	Y^3	Y^4	Time (h)	Product (Yield, %)
1	H	CH_3	H	CH_3	5	**4a** (52)
2	H	CH_3	H	CH_2CH_2COOEt	16	**4b** (56)
3	Br	$CH_2CH_2CH_2OH$	Br	CH_2CH_2COOEt	15	**4c** (59)

Scheme 2. Synthesis of diaryl ethers utilizing the triazene method.

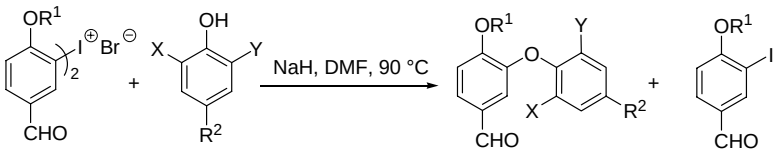
Entry	Triazene	X	Y	Z	R	Conditions[a]	Yield (%)
1	**2a**	H	H	H	OH	1 - 4	80-87
2	**2b**	H	H	CH_3	OH	1, 2	87
3	**2c**	H	Br	CH_3	OH	5	60
4	**2d**	Br	Br	CH_3	OH	1 - 4, 6	–
5	**4b**	H	OC_6H_4-*p*-CH_2CH_2COOEt	CH_3	OH	1 - 4	–
6	**4a**	H	OC_6H_4-*p*-CH_3	CH_3	OH	1 - 4, 7	–
7	**2c**	H	Br	CH_3	H	8	56
8	**4a**	H	OC_6H_4-*p*-CH_3	CH_3	H	8	44
9	**4a**	H	OC_6H_4-*p*-CH_3	CH_3	H	9	37
10	**2c**	H	Br	CH_3	OCH_3	10	–
11	**2b**	H	H	CH_3	$OCOCH_3$	11	56
12	**2c**	H	Br	CH_3	$OCOCH_3$	11, 12	~5

Scheme 3. Hydrolysis of triazenes. [a]Reagents and conditions: 1. 10 % HCl, THF, sat.aq.$CuSO_4$, r.t., 1 h; 2. HCOOH:$CuSO_4$ 1:10(v/v), r.t., 12 h; 3. 10 % HCl, THF, $Cu(NO_3)_2$, Cu_2O, 0 °C; 4. H^+-resin, THF, 75 °C, 1 h; 5. 12 N HCl, $Cu(NO_3)_2$, Cu_2O, 0 °C → r.t.; 6. TMS-Cl, $Cu(OH)_2$, CH_3CN, 60 °C; 7. EtOH 95 %, TFA, 0 °C → reflux; 8. TMS-Cl, NaI, CH_3CN, 60 °C; MeMgBr, *i*PrMgBr, $B(OMe)_3$; H_2O_2; 9. TMS-Cl, NaBr, CH_3CN, 60 °C; MeMgBr, *i*PrMgBr, $B(OMe)_3$;

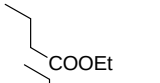
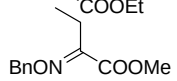
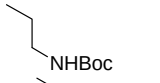
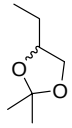
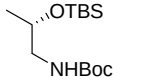
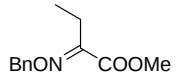
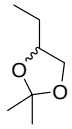
H_2O_2; 10. TMS-Cl, NaOMe, CH_3CN, 60 °C; 11. AcOH, $Cu(OAc)_2$, 60 °C, 2 h; 12. TMS-Cl, AgOAg, CH_3CN, 60 °C.



Although the non-halogenated triazenes were easily converted to the corresponding phenols under acidic conditions (Scheme 3; entries 1,2), substituted substrates required more vigorous conditions or failed all together to provide the desired products (Scheme 3; entries 3-6). Even the reported alternative indirect hydrolysis procedure,[5] through the intermediacy of the corresponding aryl iodides or bromides, was unsuccessful in our hands resulting mainly to competing reduction byproducts (Scheme 3, entries 7-9). Finally, we tested the conversion of triazenes to protected phenols, which also proved to be low yielding or totally unsuccessful (Scheme 3, entries 10-12).



6a or **6b** **7** **8** **9**

Entry	R^1	X	Y	R^2	Product (Yield, %)
1	Me	H	Br		**8a** (43)
2	Me	H	Br		**8b** (35)
3	Me	H	Br		**8c** (70)
4	Bn				**8d** (66)
5	Me	H	Br		**8e** (76)
6	Bn				**8f** (65)
7	Me	Br	Br		**8g** (68)
8	Bn	Br	Br		**8h** (67)
9	Bn	Br	Br		**8i** (58)
10	Bn	H	H		**8j** (41)
11	Bn	Br	Br		**8k** (67)

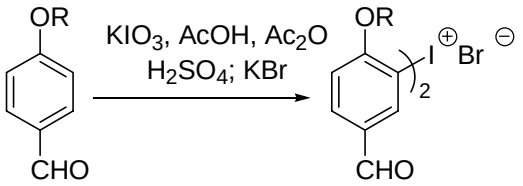
Scheme 4. Synthesis of diaryl ethers utilizing iodonium salts.

On the contrary, the iodonium salt method for the construction of diaryl ethers proved to be more fruitful.[6] Coupling of the known symmetrical iodonium salt **6a** (R^1 = Me) with *o*-brominated phenols proceeds in good to fair yields (Scheme 4) and allowed us to develop an efficient and general synthetic strategy towards Bastadins.

Employing this strategy we were able to construct for the first time an unsymetrically brominated member of this class of natural products, Bastadin 12, albeit in fully protected form.[7] Attempts to achieve its final deprotection failed, presumably due to the methyl ether protected phenol groups originating from the iodonium salt used.

Thus, we were forced to investigate alternatively protected iodonium salts. Although the most straightforward method for their construction requires cheap and either commercially available or easily prepared *p*-benzaldehyde derivatives, the conditions employed are harsh and seriously limit the repertoire of compatible protective groups for the phenol moiety. Thus, from the derivatives tested only the benzyloxy and *o*-nitrobenzyloxy *p*-benzaldehydes furnished the corresponding iodonium salts and only the former in synthetically useful yield (Scheme 5).

It is noteworthy that, although the benzyl-protected iodonium salt (**6b**) has been previously utilized, no detailed experimental procedure for its preparation has been reported.[8] Considerable experimentation was required to optimize the reaction conditions and yields reported herein. Gratifyingly, coupling of this iodonium salt with phenols was equally effective as its methyl protected counterpart (Scheme 4, entries 4, 6, 8 - 11).



5 **6**

TPS = triphenylsilyl
PMB = *p*-methoxybenzyl

Cmpnd	R	Yield (%)
a	Me	56
b	Bn	42
c	Bn(*o*-NO_2)	13
d	H	0
e	TPS	0
f	PMB	0
g	Allyl	0

Scheme 5. Synthesis of modified iodonium salts.

Conclusions

In conclusion, the coupling of phenols with symmetrical iodonium salts provides an efficient method for the construction of densely functionalized diaryl ethers, even *ortho*-brominated ones. Indeed, elaboration of the diaryl ethers thus obtained to free Bastadin 12 has been successful and its total synthesis as well as that of other members of this family of natural products will be soon reported elsewhere.

Experimental Section

General Procedures. All reactions were carried out under a dry argon atmosphere with anhydrous, freshly distilled solvents under anhydrous conditions unless otherwise noted. All reactions were magnetically stirred with Teflon stir bars, and temperatures were measured externally. Reactions requiring anhydrous conditions were carried out in oven dried (120 °C, 24 h) or flame dried (vacuum < 0.5 Torr) glassware. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials. All reagents were obtained from Aldrich Chemical Co. Inc. and used without further purification. All reactions were monitored by thin layer chromatography (TLC) carried out on 0.25-mm E.Merck silica gel plates (60F-254). E.Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash column chromatography. Infrared spectra (IR) were recorded on Nicolet, Magna FT-IR 550, mass

spectra were recorded using a VG ZAB ZSE instrument, optical rotations were recorded using a Perkin-Elmer 241 polarimeter. Samples were analysed as neat films on sodium chloride plates. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM-250 instrument. Chemical shifts are measured in parts per million (δ) relative to the deuterated solvent used in the experiment. Multiplicities are designated as singlet (s), doublet (d), triplet (t), or multiplet (m).

3-[3,5-Dibromo-4-(pyrrolidin-1-ylazo)-phenyl]-propan-1-ol (2e). To a solution of 3.0 g 3-(4-amino-3,5-dibromo-phenyl)-propan-1-ol **1e** (9.7 mmol) in THF (50 mL) at ambient temperature were added 4 mL of concentrated HCl. To this stirred mixture was added dropwise at 0 °C a solution of $NaNO_2$ (870 mg, 12.62 mmol) in 1 mL of water followed, after 15 min, by pyrrolidine (6.4 mL, 77.7 mmol). Upon completion of the reaction the mixture was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried ($MgSO_4$), concentrated and purified by flash column chromatography (30% ethyl acetate in hexane) to give 3.6 g (94%) of the corresponding dibromotriazene **2e** as white amorphous solid; ν_{max}/cm^{-1} 3350, 2935, 2860, 1525, 1405, 1310, 1220, 1155, 1050, 755, 730, 670; δ_H (250 MHz, $CDCl_3$) 7.30 (s, 2H, Ar), 4.00-3.60 (br d, 4H, CH_2NCH_2), 3.55 (t, *J* = 5.7 Hz, 2H, CH_2OH), 2.60 (t, *J* = 7.6 Hz, 2H, $ArCH_2$), 2.20-1.90 (br s, 4H, $CH_2CH_2NCH_2CH_2$), 1.70-1.60 (m, 2H, $ArCH_2CH_2$); FAB HRMS (NBA) *m/e* 389.9824/392/394, $(M+H)^+$ for $C_{13}H_{17}Br_2N_3O$ requires 389.9817/392/394.

3-{3-Bromo-4-[3-bromo-5-(3-hydroxy-propyl)-2-(pyrrolidin-1-ylazo)-phenoxy]-phenyl}-propionic acid ethyl ester (4c). To a solution of dibromotriazene **2e** (770 mg, 1.97 mmol) and bromophenol **3c** (538 mg, 1.97 mmol) in 3 mL of CH_3CN/pyridine 5:1 (v/v) was added K_2CO_3 (680 mg, 4.92 mmol) and $CuBr{\cdot}Me_2S$ (1.0 g, 4.92 mmol). The mixture was heated with stirring at 75 °C for 15 h. Upon completion of the reaction the mixture was partitioned between a saturated aqueous solution of $CuSO_4$ and ethyl acetate. The organic layer was washed with water and brine, dried ($MgSO_4$), concentrated and purified by flash column chromatography (30% ethyl acetate in hexane) to give 678 mg (59%) of diaryl ether **4c** as white amorphous solid; ν_{max}/cm^{-1} 3440, 3035, 2975, 2940, 2870, 1730, 1600, 1550, 1485, 1410, 1340, 1320, 1270, 1235, 1160, 1040, 680; δ_H (250 MHz, $CDCl_3$) 7.37 (d, *J* = 2.0 Hz, 1H, Ar), 7.30 + 7.11 (2 x d, *J* = 1.8 Hz, 1H, Ar), 6.95 (dd, *J* = 8.5, 2.0 Hz, 1H, Ar), 6.88 + 6.85 (2 x d, *J* = 1.8 Hz, 1H, Ar), 6.59 + 6.58 (2 x d, *J* = 8.5 Hz, 1H, Ar), 4.15 (q, *J* = 7.1 Hz, 2H, $COOCH_2CH_3$), 3.75-3.30 (br d, 4H, CH_2NCH_2), 3.65 (t, *J* = 6.1 Hz, 2H, CH_2OH), 2.85 (t, *J* = 7.3 Hz, 2H, $ArCH_2CH_2COOEt$), 2.65 (t, *J* = 7.3 Hz, 2H, CH_2COOEt), 2.55 (t, *J* = 7.6 Hz, 2H, $ArCH_2CH_2CH_2OH$), 1.95-1.85 (br s, 4H, $CH_2CH_2NCH_2CH_2$), 1.85 (m, 2H, $ArCH_2CH_2CH_2OH$), 1.25 (t, *J* = 7.1 Hz, 3H, $COOCH_2CH_3$); FAB HRMS (NBA) *m/e* 582.0589/584/586, $(M+H)^+$ for $C_{24}H_{29}Br_2N_3O_4$ requires 582.0603/584/586.

3-[2-Bromo-4-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-phenoxy]-4-methoxy-benzaldehyde (8e). A stirred solution of the appropriate bromophenol (6.0 g, 21 mmol) in 115 mL DMF was cooled at 0 °C. Sodium hydride (550 mg, 23 mmol) was added in small portions followed by a catalytic amount of imidazole. The mixture was allowed to warm to ambient temperature and was stirred at this temperature for 30 min. Subsequently iodonium salt **6a**[6a] (11.0 g, 23 mmol) was added and the mixture was heated at 90 °C for 3 h. Upon completion of the reaction the

mixture was partitioned between water and ethyl acetate. The organic layer was washed with water and brine, dried ($MgSO_4$), concentrated and purified by flash column chromatography (20% ethyl acetate in hexane) to give 6.7 g (76%) of diaryl ether **8e** as white amorphous solid; ν_{max}/cm^{-1} 2994, 2938, 1698, 1603, 1513, 1496, 1440, 1293, 1242, 1121, 1065, 1048, 1022, 816; δ_H (250 MHz, $CDCl_3$) 9.75 (s, 1H, CHO), 7.55 (dd, *J* = 8.2, 1.9 Hz, 1H, Ar), 7.42 (d, *J* = 1.9 Hz, 1H, Ar), 7.22 (d, *J* = 1.9 Hz, 1H, Ar), 7.02 (dd, *J* = 8.6, 1.9 Hz, 1H, Ar), 7.01 (d, *J* = 8.2 Hz, 1H, Ar), 6.72 (d, *J* = 8.6 Hz, 1H, Ar), 4.25 (m, 1H, $ArCH_2CHCH_2$), 3.93 (dd, *J* = 7.8, 6.0 Hz, 1H, $ArCH_2CHCHH$), 3.53 (dd, *J* = 7.8, 7.1 Hz, 1H, $ArCH_2CHCHH$), 3.85 (s, 3H, $ArOCH_3$), 2.84 (dd, *J* = 13.8, 6.3 Hz, 1H, ArCHH), 2.67 (dd, *J* = 13.8, 6.3 Hz, 1H, ArCHH), 1.35 (s, 3H, CH_3CCH_3), 1.25 (s, 3H, CH_3CCH_3); δ_C (62.5 MHz, $CDCl_3$) 190.0, 155.5, 151.6, 145.9, 134.9, 134.2, 129.9, 129.4, 128.1, 119.1, 118.0, 113.8, 112.0, 109.1, 75.9, 68.6, 56.1, 38.7, 26.8, 25.5; FAB HRMS (NBA) *m/e* 421.0640/423, $(M+H)^+$ for $C_{20}H_{21}BrO_5$ requires 421.0651/423.

2(S)-{2-(*tert*-Butyl-dimethyl-silanyloxy)-2-[3,5-dibromo-4-(5-formyl-2-methoxy-phenoxy)-phenyl]-ethyl}-carbamic acid *tert*-butyl ester (8g). In analogy to the above procedure 4.3 g (68%) of diaryl ether **8g** were obtained as white amorphous solid; $[\alpha]_D$ +10.7 (CH_2Cl_2, *c* = 0.14); ν_{max}/cm^{-1} 3600 – 3100, 2956, 2931, 2857, 1713, 1696, 1601, 1512, 1453, 1277, 1252, 1171, 1114, 837, 779, 737; δ_H (250 MHz, $CDCl_3$) 9.70 (s, 1H, CHO), 7.50 (br s, 2H, Ar), 7.48 (dd, *J* = 8.6, 1.9 Hz, 1H, Ar), 7.02 (d, *J* = 8.6 Hz, 1H, Ar), 6.80 (d, *J* = 1.9 Hz, 1H, Ar), 4.80-4.60 (m, 2H, ArCHOTBS + NHBoc), 3.95 (s, 3H, $ArOCH_3$), 3.32 (m, 1H, CHHNHBoc), 3.00 (m, 1H, CHHNHBoc), 1.35 (s, 9H, ^tBuOCO), 0.85 (s, 9H, ^tBuSi), 0.00 (s, 3H, CH_3Si), -0.15 (s, 3H, CH_3Si); δ_C (62.5 MHz, $CDCl_3$) 190.4, 155.8, 154.2, 147.8, 146.2, 143.0, 130.7, 129.8, 127.5, 118.1, 112.9, 111.9, 79.6, 72.3, 56.5, 48.9, 28.4, 25.8, 18.2, 3.3, 3.1; FAB HRMS (NBA/CsI) *m/e* 791.9812/794, $(M+Cs)^+$ for $C_{27}H_{37}Br_2NO_6Si$ requires 791.9791/794.

Bis-(2-benzyloxy-5-formyl-phenyl)-iodonium bromide (6b). To a 250 mL round bottom flask equipped with an efficient mechanical stirrer were added successively KIO_3 (6.74 g, 31.5 mmol), AcOH (10 mL) and Ac_2O (15 mL). The reaction was placed in an ice bath and concentrated H_2SO_4 (6.74 mL) was added dropwise. *p*-Benzyloxybenzaldehyde (20 g, 94.3 mmol) was dissolved with gentle heating and stirring in 30 mL AcOH. This solution was allowed to cool to ambient temperature and added dropwise to the reaction mixture. During the addition, when the aldehyde was crystallizing out of the added solution it was redissolved with gentle heating and stirring and the solution was allowed to cool to ambient temperature before resuming its addition to the reaction mixure. The vessel containing the aldehyde was washed with AcOH (10 mL) and the washings were added to the reaction mixture. The reaction mixture was protected from light and stirring was continued for 2 h at 0 °C and then for 24 h at ambient temperature. During the course of the reaction the initially formed thick light orange suspension turned to a dark brown solution. This solution was poured into a vigorously stirred solution of KBr (4.6 g, 37 mmol) in 84 mL of water. A gummy precipitate formed. The supernatant was decanted and the precipitate was washed successively with diethyl ether (3 × 40 mL), water (3 × 50 mL) and acetone (2 × 20 mL). The final off-white amorphous solid was air-dried on a Büchner funnel and then further dried in a descicator over $CaCl_2$ under reduced pressure for 2 days to provide 12.4g (42%) of iodonium salt **6b**; ν_{max}/cm^{-1} 1768, 1695, 1590, 1484, 1197, 747, 699; δ_H (250 MHz, $CDCl_3$) 9.76

(s, 1H, CHO), 8.50 (d, *J* = 1.9 Hz, 1H, Ar), 8.08 (dd, *J* = 8.8, 1.9 Hz, 1H, Ar), 7.43 (d, *J* = 8.8 Hz, 1H, Ar), 7.40-7.28 (bant, 5H, Ar), 5.31 (s, 2H, CH_2Ph); δ_C (62.5 MHz, DMSO-d_6) 189.9, 159.6, 138.5, 135.2, 135.0, 130.9, 128.5, 128.3, 127.6, 113.8, 110.6, 71.1; FAB HRMS (NBA) *m/e* 549.0561, M^+ for $C_{28}H_{22}IO_4$ requires 549.0557.

2(S)-{2-[4-(2-Benzyloxy-5-formyl-phenoxy)-3,5-dibromo-phenyl]-2-(*tert*-butyl-dimethyl-silanyloxy)-ethyl}-carbamic acid *tert*-butyl ester (8h). A stirred solution of the appropriate phenol (1.5 g, 2.9 mmol) in 16 mL DMF was cooled at 0 °C. Sodium hydride (76 mg, 3.2 mmol) was added in small portions followed by a catalytic amount of imidazole. The mixture was allowed to warm to ambient temperature and was stirred at this temperature for 30 min. Subsequently iodonium salt **6b** (2.0 g, 3.2 mmol) was added and the mixture was heated at 90 °C for 3.5 h. Upon completion of the reaction the mixture was partitioned between water and ethyl acetate. The organic layer was washed with water and brine, dried ($MgSO_4$), concentrated and purified by flash column chromatography (20% ethyl acetate in hexane) to give 1.4 g (67%) of diaryl ether **8h** as white amorphous solid; $[\alpha]_D$ +7.0 (CH_2Cl_2, *c* = 0.97); ν_{max}/cm^{-1} 3600 – 3100, 2957, 2932, 2857, 1716, 1696, 1602, 1510, 1454, 1280, 1256, 1169, 1118, 839, 780, 740; δ_H (250 MHz, $CDCl_3$) 9.70 (s, 1H, CHO), 7.59 (br s, 2H, Ar), 7.47 (dd, *J* = 8.2, 1.9 Hz, 1H, Ar), 7.40-7.25 (bant, 5 H, Ar), 7.08 (d, *J* = 8.2 Hz, 1H, Ar), 6.92 (d, *J* = 1.9 Hz, 1H, Ar), 5.32 (s, 2H, CH_2Ph), 4.92-4.74 (m, 2H, Ar*CH*OTBS + *NH*Boc), 3.39 (m, 1H, C*H*HNHBoc), 3.07 (m, 1H, CH*H*NHBoc), 1.43 (s, 9H, ^tBuOCO), 0.90 (s, 9H, ^tBuSi), 0.07 (s, 3H, CH_3Si), -0.03 (s, 3H, CH_3Si); δ_C (62.5 MHz, $CDCl_3$) 190.3, 155.7, 153.0, 147.8, 146.6, 142.8, 135.9, 130.5, 129.9, 128.6, 128.1, 127.2, 127.1, 118.0, 113.9, 113.1, 79.5, 72.1, 70.9, 48.9, 28.3, 25.7, 18.1, 3.2, 3.0; FAB HRMS (NBA/NaI) *m/e* 756.0966/758/760, $(M+Na)^+$ for $C_{33}H_{41}Br_2NO_6Si$ requires 756.0962/758/760.

4-Benzyloxy-3-[2-bromo-4-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-phenoxy]-benzaldehyde (8f). In analogy to the above procedure 7.6 g (65%) of diaryl ether **8f** were obtained as colorless oil; δ_H (250 MHz, $CDCl_3$) 9.71 (s, 1H, CHO), 7.51 (dd, *J* = 8.6, 2.2 Hz, 1H, Ar), 7.40 (d, *J* = 2.2 Hz, 1H, Ar), 7.32 (d, *J* = 1.9 Hz, 1H, Ar), 7.25-7.15 (m, 5H, Ar), 7.02 (d, *J* = 8.6 Hz, 1H, Ar), 6.99 (dd, *J* = 8.6, 1.9 Hz, 1H, Ar), 6.69 (d, *J* = 8.6 Hz, 1H, Ar), 5.13 (s, 2H, OCH_2Ph), 4.20 (p, *J* = 6.3 Hz, 1H, $ArCH_2CHCH_2$), 3.90 (dd, *J* = 8.2, 6.0 Hz, 1H, $ArCH_2CHCHH$), 3.52 (dd, *J* = 8.2, 7.1 Hz, 1H, $ArCH_2CHCHH$), 2.83 (dd, *J* = 13.8, 6.3 Hz, 1H, ArC*H*H), 2.66 (dd, *J* = 13.8, 6.3 Hz, 1H, ArC*H*H), 1.33 (s, 3H, CH_3CCH_3), 1.26 (s, 3H, CH_3CCH_3); δ_C (62.5 MHz, $CDCl_3$) 190.2, 154.8, 152.2, 146.3, 135.7, 134.7, 134.4, 130.4, 129.4, 128.6, 128.2, 128.1, 126.9, 119.3, 118.9, 114.1, 113.8, 109.3, 76.2, 70.8, 68.8, 38.9, 27.0, 25.7; FAB HRMS (NBA/NaI) *m/e* 519.0792/521, $(M+Na)^+$ for $C_{26}H_{25}BrO_5$ requires 519.0777/521.

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