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Citation for the original published paper (version of record):

Jalalian, N., Olofsson, B. (2010)

Design and asymmetric synthesis of chiral diaryliodonium salts.

*Tetrahedron*, 66(31): 5793-5800

<http://dx.doi.org/10.1016/j.tet.2010.05.004>

Access to the published version may require subscription.

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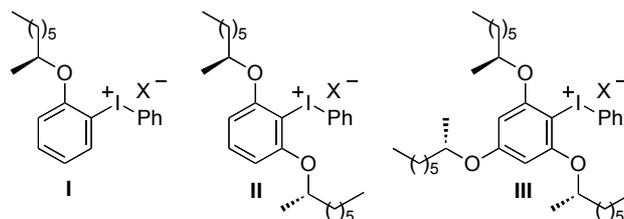
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## Graphical Abstract

### Design and asymmetric synthesis of chiral diaryliodonium salts

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# Design and asymmetric synthesis of chiral diaryliodonium salts

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## ARTICLE INFO

### Article history:

Received  
Received in revised form  
Accepted  
Available online

### Keywords:

Hypervalent iodine  
Diaryl- $\lambda^3$ -iodanes  
Asymmetric synthesis  
Oxidation  
Arylation reagents

## ABSTRACT

The application of chiral hypervalent iodine reagents in asymmetric synthesis is highly desirable, as the reagents are metal-free, environmentally benign and employed under mild conditions. Three chiral diaryliodonium salts have been designed to provide chemoselectivity and asymmetric induction in asymmetric  $\alpha$ -phenylation of carbonyl compounds. The synthetic routes to the selected targets are detailed herein, together with a structural investigation into the diastereoselectivity of the alkylation process.

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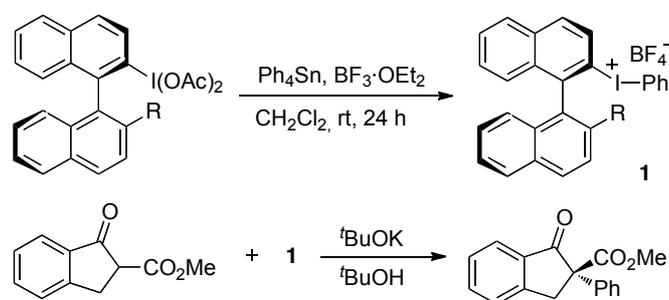
## 1. Introduction

Hypervalent iodine compounds have emerged as selective and environmentally benign reagents in many areas of organic synthesis.<sup>1-3</sup> Iodine(III) reagents with two heteroatom ligands are employed in  $\alpha$ -oxidations of carbonyl compounds, oxidations of alcohols, carbon-carbon bond formation and many other transformations.<sup>1-3</sup>

Diaryliodonium salts, also named diaryl- $\lambda^3$ -iodanes, are iodine(III) reagents with two aryl ligands. They are efficient electrophilic arylation reagents for a number of nucleophiles, including enolates, phenols and amines.<sup>4</sup> Furthermore, they can be employed in a wide range of cross-coupling reactions under metal-catalyzed or metal-free conditions.<sup>4-6</sup>

Recent progress in hypervalent iodine chemistry has focused on the development of catalytic methodology<sup>7-9</sup> and asymmetric applications using chiral reagents.<sup>10</sup> The first chiral hypervalent iodine compound ever reported, diphenyliodonium tartrate, was published already in 1907.<sup>11</sup> Surprisingly few chiral diaryliodonium salts have since then appeared in the literature.<sup>12</sup> In 1999, Ochiai and coworkers reported the synthesis of 1,1'-binaphthyl-2-yl(phenyl)iodonium salts **1** (Scheme 1).<sup>13</sup> The efficiency of the salts was evaluated in arylations of  $\beta$ -keto esters, and gave  $\alpha$ -phenylated products in moderate yields and

enantioselectivities.<sup>13</sup> In a similar fashion, Zhdankin *et al.* prepared chiral benzimidazole structures, where the *N*-functionalized amide moiety acted as internal anion.<sup>14</sup>



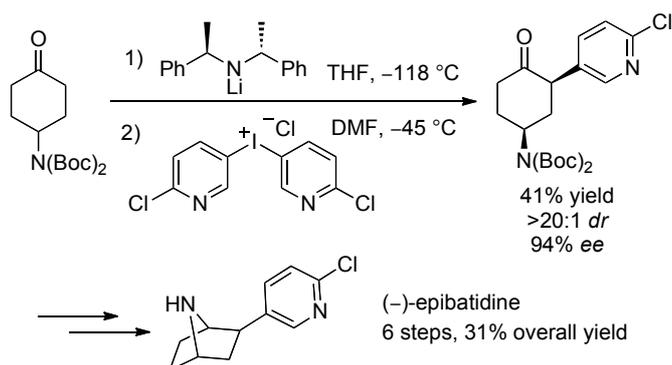
R = H	63% yield, 40% ee
R = <sup>t</sup> Ph	51% yield, 37% ee
R = Me	68% yield, 34% ee
R = Bn	37% yield, 53% ee

**Scheme 1.** Asymmetric phenylation with chiral diaryliodonium salts.

Aggarwal and Olofsson used a different strategy to realize enantioselective  $\alpha$ -arylation of carbonyl compounds with diaryliodonium salts. Asymmetric induction was obtained by the use of a chiral base, followed by treatment with an achiral

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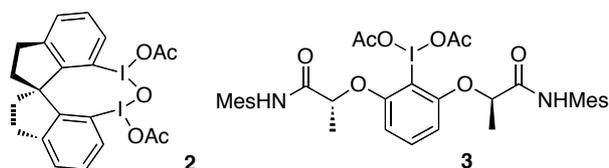
diaryliodonium salt. This methodology was applied in an efficient total synthesis of (–)-epibatidine (Scheme 2).<sup>15</sup> Although this arylation protocol is highly enantioselective, it can only be applied to a limited set of cyclic, prochiral substrates.



**Scheme 2.** Asymmetric synthesis of (–)-epibatidine.

We have recently performed a theoretical study on the mechanism of  $\alpha$ -arylation of carbonyl compounds with diaryliodonium salts, which together with experimental results led to the conclusion that asymmetric induction cannot be achieved by use of chiral anions or chiral PTC.<sup>16</sup> Thus, the design of chiral diaryliodonium salts, where one of the aryl moieties have substituents with stereogenic elements, remains as one of few possibilities to obtain enantioenriched  $\alpha$ -arylated carbonyl compounds using hypervalent iodine reagents.

The development of chiral hypervalent iodine(III) compounds with two heteroatom ligands has been more successful.<sup>17</sup> Catalytic reactions involving chiral iodine(III) reagents have also resulted in high enantioselectivities.<sup>18, 19</sup> In 2008, Kita and coworkers employed chiral reagent **2**, with a rigid 1,1-spiroindanone backbone, in oxidative spirocyclizations (Figure 1).<sup>20</sup> Very recently, Ishihara's group reported the use of  $C_2$ -symmetric chiral iodane **3** in the same reaction.<sup>21</sup> Both reagents could be formed in situ from the corresponding aryl iodide with a stoichiometric amount of *m*-chloroperbenzoic acid (*m*CPBA).



**Figure 1.** Chiral iodine(III) reagents used in oxidative spirocyclization.

The synthesis of chiral diaryliodonium salts has been an ongoing project in our laboratory for some time. The similarity between Ishihara's chiral iodane **3** and our chiral salts prompted us to report our results in the synthesis of chiral, enantiopure diaryliodonium salts.

## 2. Results and discussion

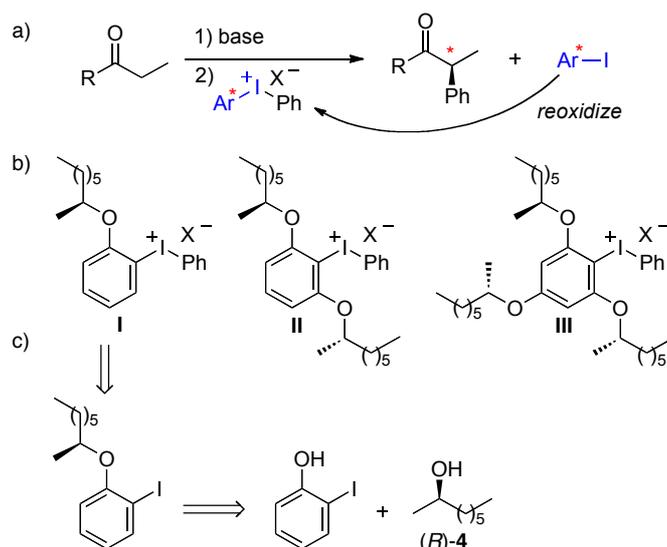
### 2.1. Design and synthetic strategy

The design of chiral diaryliodonium salts is limited by the often harsh conditions used in the synthetic routes. Therefore, the use of acid- or base-labile substituents should be avoided. The absence of catalytic arylation protocols, where the diaryliodonium salt is formed in situ from the corresponding iodoarene, makes stability issues of the target compounds a difficult problem. The recent success in applications of chiral iodine(III) reagents with two heteroatom ligands has indeed often depended on catalytic formation of the chiral iodine(III) species, thus avoiding stability issues in the isolation.

When unsymmetric diaryliodonium salts are employed in enolate and heteroatom arylations, the aryl groups can often be differentiated. Generally, the more electron-deficient aryl moiety is selectively transferred, although aryl moieties bearing *ortho*-substituents are sometimes transferred despite being more electron-rich (the so-called *ortho*-effect).<sup>22, 23</sup>

We envisioned the use of diaryliodonium salts where one of the aryl groups is more electron-rich and has substituents bearing stereocenters. This aryl moiety should behave as a chiral ligand and promote asymmetric induction in the transfer of the other, more electron-deficient, aryl group to the nucleophile (Scheme 3a). The resulting chiral iodoarene could be recovered and reoxidized into the chiral salt to provide good atom economy.

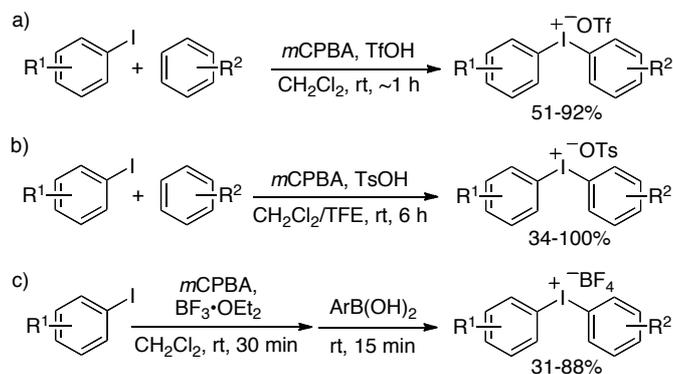
Three target structures (**I-III**) were designed to fulfill these demands, having one, two or three substituents (Scheme 3b). *Ortho*-substituents with stereocenters were selected to deliver asymmetric induction by close proximity to the iodine. Furthermore, the oxygen-based substituents should make the aryl moiety electron-rich enough to give chemoselective phenyl transfer. The steric bulk of the substituents was given careful consideration, as too small substituents were likely to cause little induction, while too large substituents could give rise to undesired chemoselectivity by the *ortho*-effect. The long aliphatic chains were selected to improve the solubility and thus allow arylation reactions in a variety of solvents.



**Scheme 3.** a) Expected chemoselectivity in the arylation. b) Target structures. c) Retrosynthetic analysis.

The number of substituents was expected to influence the reactivity, asymmetric induction and chemoselectivity in arylation reactions. In the synthesis of mono- and disubstituted targets **I** and **II**, regioselectivity issues must be controlled, which limits the number of possible synthetic routes. The diaryliodonium salts would be derived from the corresponding substituted iodoarenes, which could be prepared from the iodophenol and enantiomerically pure alcohol (*R*)-**4**, as shown for target **I** (Scheme 3c).

The synthesis of the diaryliodonium salts was envisioned using the methodology recently developed in our laboratory (Scheme 4). Symmetrical and unsymmetrical diaryliodonium triflates can be obtained in high yields and short reaction times employing *m*CPBA and trifluoromethanesulfonic acid (TfOH), as depicted in Scheme 4a.<sup>24, 25</sup> The protocol can be extended to the direct formation of diaryliodonium triflates from iodine and arenes.<sup>24-26</sup>



**Scheme 4.** Some of our one-pot routes to diaryliodonium salts.

A variation of this synthesis, employing *p*-toluenesulfonic acid (TsOH), gives access to electron-rich diaryliodonium tosylates (Scheme 4b). If necessary, the corresponding triflate salts are conveniently obtained via an *in situ* anion exchange.<sup>27</sup>

A regioselective one-pot reaction utilizing arylboronic acids has also been developed, giving diaryliodonium tetrafluoroborates in high yields (Scheme 4c).<sup>28</sup> Also this protocol allows an *in situ* anion exchange to triflate, which is beneficial when isolation or stability issues are noticed. An alternative one-pot preparation of diaryliodonium triflates employs hydrogen peroxide instead of *m*CPBA as the oxidant.<sup>29</sup>

## 2.2. Synthesis of target I

Alcohol (*R*)-4 was synthesized in 42% yield and >99% *ee* by enzymatic kinetic resolution of racemic 2-octanol (Scheme 5a).<sup>30</sup> The alcohol was mesylated to (*R*)-6 in 99% yield and used in alkylation of 2-iodophenol, to deliver the desired iodoarene 7 without loss of enantiomeric excess (Scheme 5b). Unfortunately, all attempts to synthesize the target I from 7 using the TsOH protocol (see Scheme 4b) were unsuccessful, possibly due to sluggish oxidation caused by steric hindrance from the *ortho*-substituent.

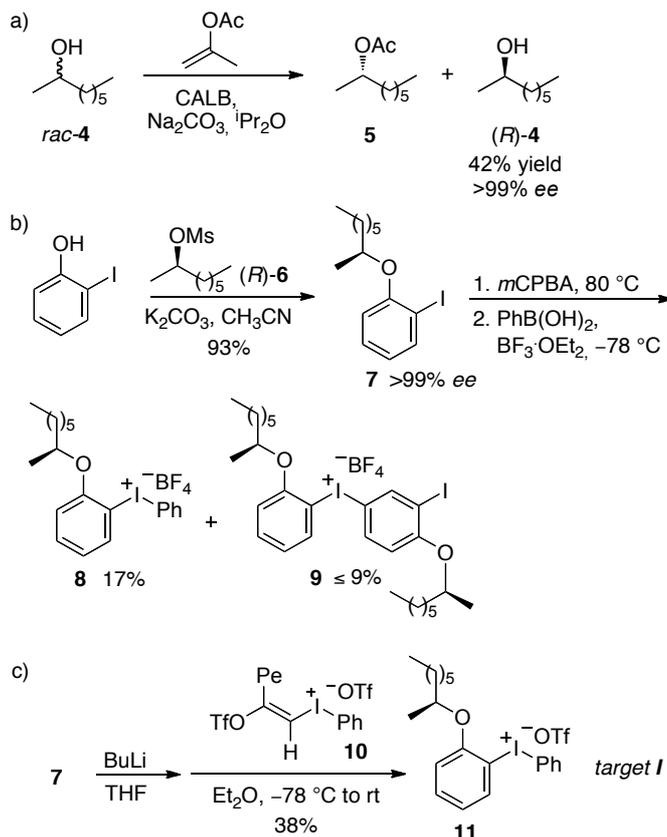
The synthesis of target I was instead accomplished using the boronic acid method (see Scheme 4c). Attempts to oxidize 7 at ambient temperature in the presence of BF<sub>3</sub>·OEt<sub>2</sub> led to decomposition. Thus, the procedure was modified to oxidation of 7 with *m*CPBA at elevated temperature, followed by cooling to -78 °C and addition of phenylboronic acid and BF<sub>3</sub>·OEt<sub>2</sub>. Diaryliodonium salt 8 could then be isolated in modest yield (Scheme 5b).

This synthesis, however, also led to another chiral diaryliodonium salt 9, which was obtained in various amounts depending on small changes in the experimental procedure. The formation of this compound can be explained by incomplete oxidation of iodoarene 7, which leads to an undesired EAS reaction of 7 onto the formed iodine(III) intermediate, upon addition of BF<sub>3</sub>·OEt<sub>2</sub>.

Due to the difficulties in oxidation of iodoarene 7, we turned to the use of basic reaction conditions. Fortunately, treatment of 7 with BuLi followed by reaction with vinylidonium triflate 10<sup>31</sup> delivered diaryliodonium triflate 11 (Scheme 5c).

## 2.3. Synthesis of target II

The synthesis of the disubstituted target compound was investigated using racemic 2-octanol (*rac*-4). Difficulties were predicted due to the desired 1,2,3-substitution pattern, which restricted the synthetic possibilities and was likely to cause problems related to steric hindrance.



**Scheme 5.** Synthesis of the monosubstituted target I. CALB = *Candida Antarctica* Lipase B.

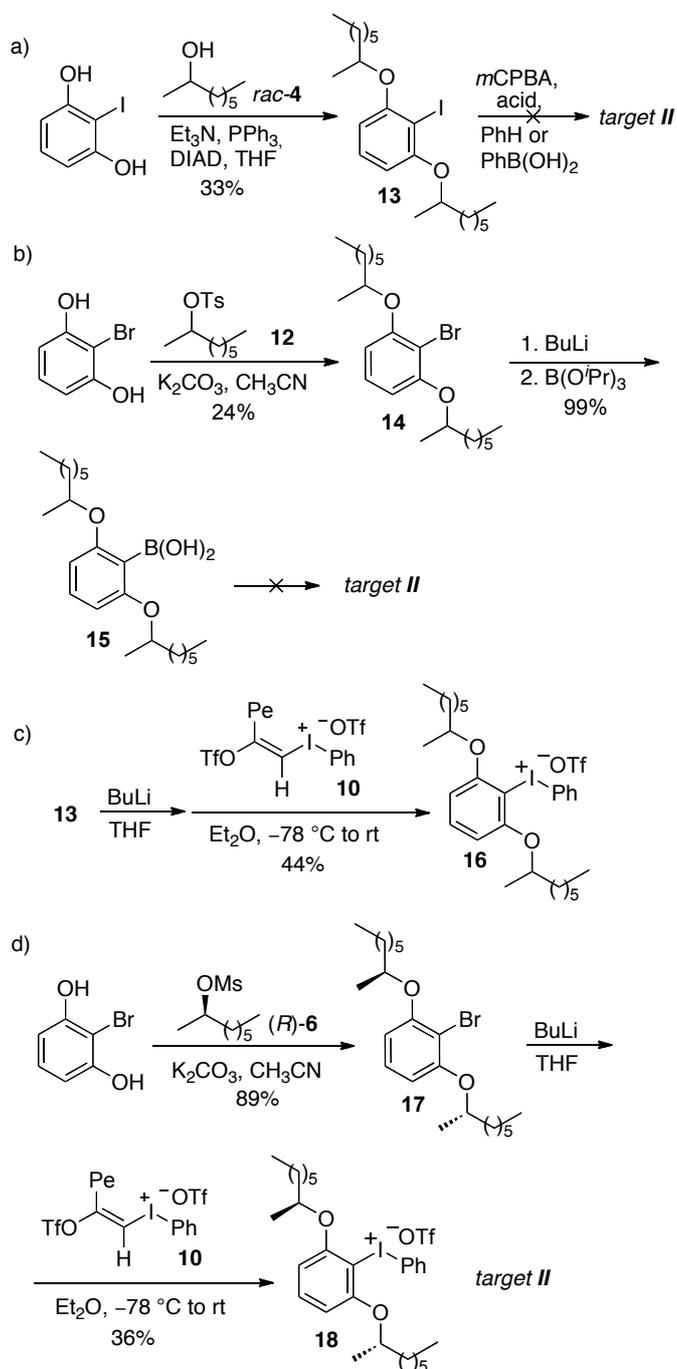
Indeed, dialkylation of 2-iodoresorcinol<sup>32</sup> with either mesylate *rac*-6 or the corresponding tosylate 12 was unproductive. The starting materials were recovered under normal reaction conditions, whereas forcing conditions led to decomposition of the alkylating reagent.

Dialkylated iodoarene 13 was instead obtained by a Mitsunobu reaction with *rac*-4 (Scheme 6a). Conversion of compound 13 to the desired diaryliodonium target II was attempted with the TsOH protocol (see Scheme 4b), but resulted in decomposition of 13 also at low temperatures. Similar discouraging results were obtained using BF<sub>3</sub>·OEt<sub>2</sub> and phenylboronic acid.

As both the synthesis of 13 and further transformation to a diaryliodonium salt proved problematic, we turned to alternative approaches toward target II. Alkylation of 2-bromoresorcinol<sup>33</sup> with tosylate 12 afforded disubstituted bromoarene 14, which was smoothly converted to arylboronic acid 15 (Scheme 6b). Unfortunately, all attempts at converting 15 into target II also failed, both when using the one-pot method depicted in Scheme 4c and when applying preformed iodine(III) reagents such as (diacetoxyiodo)benzene or Koser's reagent.<sup>34</sup>

Clearly, the substituents did not tolerate acidic conditions even at low temperatures. Milder methods, such as reaction of Koser's reagent with the 1,3-disubstituted arene,<sup>35</sup> were not applicable due to the desired regiochemistry with coupling in the 2-position.

Having screened the available acidic methods for synthesis of target II, we again turned to the use of basic conditions. Iodoarene 13 was lithiated and treated with vinylidonium salt 10, which indeed furnished disubstituted diaryliodonium salt 16 (Scheme 6c).



**Scheme 6.** Synthesis of the disubstituted target **II**. DIAD = diisopropyl azodicarboxylate; Pe = pentyl.

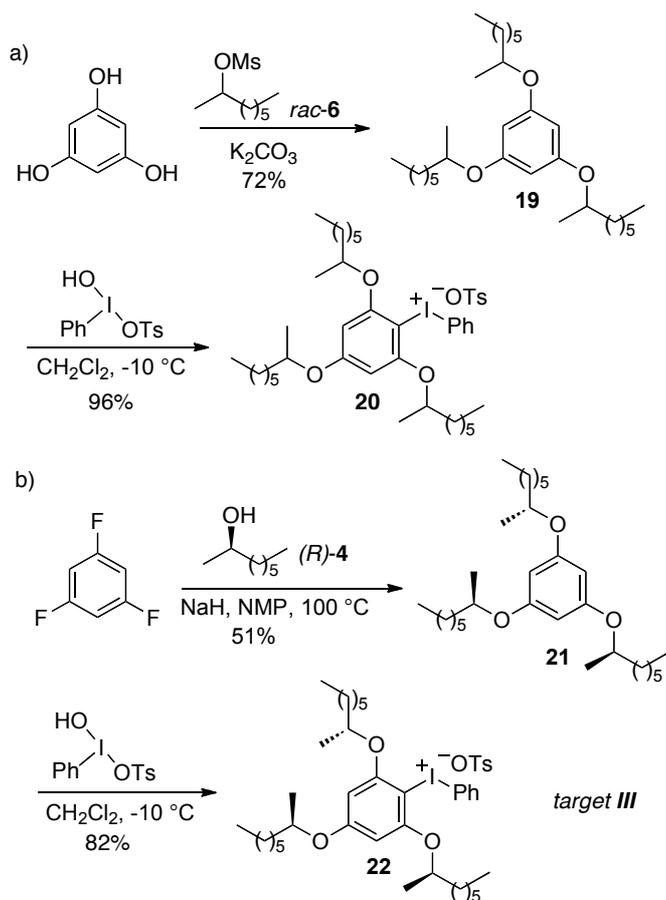
This methodology was subsequently repeated with enantiomerically pure material. Dialkylation of 2-bromoresorcinol with mesylate (*R*)-**6** proved to be the most efficient way to reach the required dialkylated haloarene, and **17** was obtained in 89% yield (Scheme 6d). Bromoarene **17** was subsequently treated with BuLi and vinyliodonium salt **10**, providing the disubstituted target compound **18**.

#### 2.4. Synthesis of target **III**

As expected, synthesis of the trisubstituted salt proved to be more straightforward, as regioselectivity issues were avoided. Having experienced the difficulties discussed above with synthesis of target **II**, we directly turned to methods avoiding acidic conditions in formation of target **III**.

Thus, trisubstituted arene **19** was synthesized in 72% yield by alkylation of 1,3,5-trihydroxybenzene with mesylate *rac*-**6**

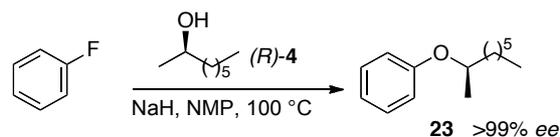
(Scheme 7a). Arene **19** was treated with Koser's reagent<sup>35</sup> at low temperature to afford the desired trisubstituted diaryliodonium tosylate **20** in excellent yield.



**Scheme 7.** Synthesis of the trisubstituted target **III**.

The racemic synthesis was next to be repeated with enantiomerically pure material. Surprisingly, the alkylation of trihydroxybenzene with mesylate (*R*)-**6** proved difficult under all conditions, providing mainly the mono- and dialkylated arene. The route was therefore revised to a nucleophilic aromatic substitution on 1,3,5-trifluorobenzene<sup>36</sup> with alcohol (*R*)-**4**, which delivered **21** in moderate yield (Scheme 7b). Arene **21** was subsequently converted to target structure **III** with Koser's reagent, giving tosylate salt **22** in good yield.

Due to the apolar nature of arene **21**, the enantiopurity of this compound could not be determined by chiral GC or HPLC. Thus, the nucleophilic aromatic substitution was repeated using fluorobenzene and alcohol (*R*)-**4**, yielding monosubstituted arene **23** (Scheme 8). As expected, the nucleophilic aromatic substitution took place without loss of enantiomeric excess, which was verified by chiral HPLC analysis of arene **23**. By analogy, we anticipate formation of compound **21** in >99% *ee*.

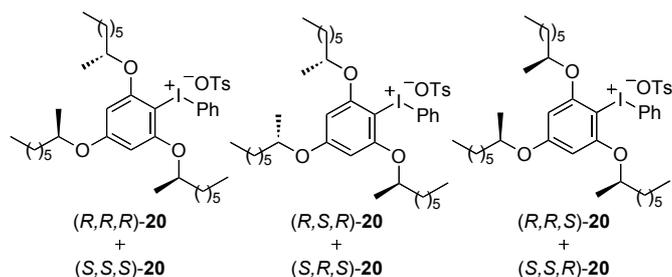


**Scheme 8.** Synthesis of monosubstituted arene **23** for *ee* determination.

#### 2.5. Structural investigations

The unforeseen difference in alkylation rate of 1,3,5-trihydroxybenzene with racemic and enantiomerically pure mesylate **6** was intriguing, and necessitated a deeper

investigation. When employing *rac*-**6** in the synthesis of diaryliodonium salt **20**, three diastereomeric pairs of enantiomers can be formed, as depicted in Figure 2.



**Figure 2.** Possible diastereomers of diaryliodonium salt **20**.

Close examination of the NMR spectra of diaryliodonium salts **20** and **22** revealed small shift differences between the two compounds in both  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR. The analysis was complicated by the different shifts observed for the *ortho*- and *para*-substituents. These peaks were identified by the 2:1 ratio observed in compound **22**. Figure 3 depicts a selection of the non-identical peaks seen in  $^{13}\text{C}$ -NMR, where the *ortho*- and *para*-substituents are clearly differentiated. For remaining parts of the combined spectra, see the Supplementary Information. The NMR data of compounds **20** and **22** are listed in Table 1, with the *ortho*- and *para*-substituents assigned.

This data indicate that two diastereomers of **20** are formed, namely (*R,S,R/S,R,S*)-**20** and (*R,R,S/S,S,R*)-**20**. Unfortunately, all attempts to verify these results by X-ray crystallography failed, as **20** remained an oil under all recrystallization conditions tested.

Formation of only the two unsymmetric diastereomers of **20** would correspond to diastereoselective synthesis of only the (*R,S,R/S,R,S*) diastereomer of arene **19**. Indeed, the  $^{13}\text{C}$ -NMR of this compound shows only one diastereomer, which is slightly different from (*R,R,R*)-**21**. Preferential formation of one of the two possible diastereomers can be explained by rate differences in the third alkylation caused by steric hindrance. This conclusion is supported by the different reactivity observed in alkylations with racemic and enantiopure mesylate **6**.

Diaryliodonium salt **16** is also formed as two diastereomeric pairs of enantiomers; (*R,R/S,S*)-**16** and (*R,S/S,R*)-**16**. Comparison with the NMR data of diaryliodonium salt **18** suggests that (*R,S/S,R*)-**16** is the major diastereomer (Table 1).

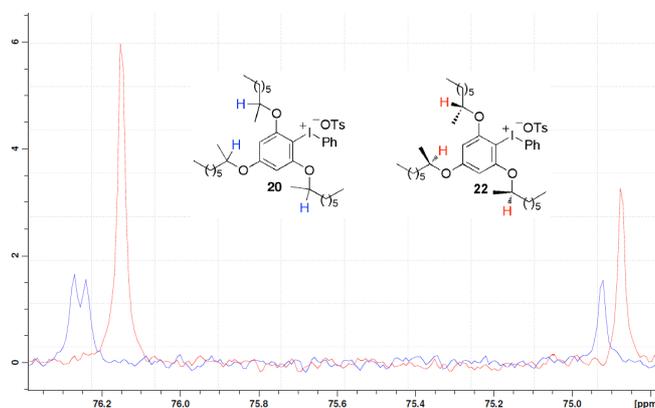
## 2.6. Conclusions

Compared to chiral iodine(III) reagents with two heteroatom ligands, chiral diaryliodonium salts are difficult to prepare and few reports on the synthesis and applications of these compounds exist. Herein, we have presented our synthetic routes towards three enantiopure diaryliodonium salts, targets **I-III**. Monosubstituted target **I** was synthesized from the corresponding iodoarene, either by a one-pot reaction with *m*CPBA and phenylboronic acid, or by lithiation and treatment with a vinylidonium salt. Furthermore, an unexpected chiral salt was obtained, with stereocenters on both aryl moieties.

Due to acid-lability of the substituents under all tested conditions, the synthesis of the *ortho*-disubstituted target **II** was

accomplished by lithiation of the corresponding bromoarene and treatment with a vinylidonium salt.

The trisubstituted target **III** was formed by reaction of the trisubstituted arene with Koser's reagent. Remarkable reactivity differences were noted in the racemic and enantiopure route, which was explained by preferential formation of two of the three possible diastereomers of the diaryliodonium salt in the racemic synthesis.



**Figure 3.** Characteristic peaks in  $^{13}\text{C}$ -NMRs of **20** (blue) and **22** (red).

The synthesized chiral diaryliodonium salts are anticipated to show interesting differences in reactivity, asymmetric induction and chemoselectivity in arylation reactions. They are currently being investigated in the asymmetric  $\alpha$ -arylation of carbonyl compounds, the results of which will be reported in due time.

## 3. Experimental section

### 3.1. General experimental conditions

Commercial *m*CPBA was dried under vacuum at room temperature for 1 h, the percentage of active oxidizing agent was determined by iodometric titration after drying.<sup>37</sup>  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  was stored under an argon atmosphere. THF and  $\text{Et}_2\text{O}$  were dried on a VAC Solvent Purifier. Acetonitrile was distilled from  $\text{CaH}_2$ . NMP was distilled from  $\text{P}_2\text{O}_5$ . All other chemicals were used as received without further purification. Kinetic resolution was performed using Novozyme 435 (immobilized CALB). Air- and moisture sensitive reactions were carried out in flame-dried, septum-capped flasks under an atmospheric pressure of argon. All liquid reagents were transferred via oven-dried syringes. Sealed tubes were used in reactions that were carried out above the boiling point of the solvent NMR spectra were recorded using  $\text{CDCl}_3$  or  $\text{DMSO}-d_6$  as solvent. Chemical shifts are given in ppm relative to the residual peak of  $\text{CDCl}_3$  ( $^1\text{H}$  NMR  $\delta$  7.26,  $^{13}\text{C}$  NMR  $\delta$  77.16) or  $\text{DMSO}-d_6$  ( $^1\text{H}$  NMR  $\delta$  2.50) with integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, sex=sextet, m=multiplet, app=apparent) and coupling constants (Hz). Chiral GC was run on a Varian 3800 Gas Chromatograph equipped with a CP-Chiralsil-Dex-CB (25 m x 0.32 mm x 0.25  $\mu\text{m}$ ) column. Chiral HPLC was run on HPLC Waters 2695 with an auto sampler, UV detection at 230 nm, Chiralcel OB (0.46 cm i.d. x 25 cm).

**Table 1.** NMR data of diaryliodonium salts in CDCl<sub>3</sub> (ppm) with *J* couplings (Hz).<sup>a</sup>

Compound	<sup>1</sup> H NMR (400 MHz)
<b>16 major</b>	7.85 (2 H, m), 7.53 (1 H, tt, <i>J</i> =7.4, 1.1), 7.47 (1 H, td, <i>J</i> =8.4, 0.9), 7.38 (2 H, ddt, <i>J</i> =8.2, 7.4, 1.5), 6.57 (2 H, dd, <i>J</i> =8.4, 1.3), 4.50 (2 H, app sex, <i>J</i> =6.1), 1.73 (2 H, m), 1.59 (2 H, m), 1.34–1.20 (16 H, m), 1.28 (6H, d, <i>J</i> =6.1), 0.87 (6 H, t, <i>J</i> =7.0).
<b>16 minor<sup>c</sup></b>	7.85 (2 H, m), 7.53 (1 H, tt, <i>J</i> =7.4, 1.1), 7.47 (1 H, td, <i>J</i> =8.4, 0.9), 7.38 (2 H, ddt, <i>J</i> =8.2, 7.4, 1.5), 6.57 (2 H, dd, <i>J</i> =8.4, 1.3), 4.50 (2 H, app sex, <i>J</i> =6.1), 1.73 (2 H, m), 1.59 (2 H, m), 1.34–1.20 (16 H, m), 1.27 (6H, d, <i>J</i> =6.1), 0.88 (6 H, t, <i>J</i> =7.0).
<b>18</b>	7.85 (2 H, m), 7.53 (1 H, tt, <i>J</i> =7.4, 1.1), 7.47 (1 H, t, <i>J</i> =8.4), 7.37 (2 H, ddt, <i>J</i> =8.2, 7.4, 1.6), 6.57 (2 H, d, <i>J</i> =8.4), 4.50 (2 H, app sex, <i>J</i> =6.1), 1.74 (2 H, m), 1.59 (2 H, m), 1.36–1.20 (16 H, m), 1.27 (6H, d, <i>J</i> =6.1), 0.88 (6 H, t, <i>J</i> =7.0).
<b>20<sup>b</sup></b>	7.85 (2 H, m), 7.76 (2 H, d, <i>J</i> =8.1), 7.46 (1 H, t, <i>J</i> =7.4), 7.30 (2 H, dd, <i>J</i> =8.1, 7.4), 7.12 (2 H, d, <i>J</i> =7.9), 6.07 (2 H, s), 4.40 (2 H, app sex, <i>J</i> =6.1) ( <u>o</u> ), 4.36 (1 H, app sex, <i>J</i> =6.1) ( <u>p</u> ), 2.34 (3 H, s), 1.78–1.67 (3H, m), 1.65–1.50 (3H, m), 1.47–1.18 (24 H, m), 1.33 (3 H, d, <i>J</i> =6.0) ( <u>p</u> ), 1.26 (6 H, d, <i>J</i> =6.1) ( <u>o</u> ), 1.25 (3 H, d, <i>J</i> =6.1) ( <u>o</u> ), 0.89 (3 H, t, <i>J</i> =6.9) ( <u>p</u> ); 0.89 (3 H, t, <i>J</i> =7.1) ( <u>o</u> ), 0.88 (3 H, t, <i>J</i> =7.1) ( <u>o</u> ).
<b>22</b>	7.85 (2 H, m), 7.77 (2 H, app dt, <i>J</i> =8.2, 1.8), 7.45 (1 H, tt, <i>J</i> =7.4, 1.1), 7.30 (2 H, ddt, <i>J</i> =8.2, 7.4, 1.7), 7.12 (2 H, m), 6.08 (2 H, s), 4.40 (2 H, app sex, <i>J</i> =6.1) ( <u>o</u> ), 4.37 (1 H, app sex, <i>J</i> =6.1) ( <u>p</u> ), 2.34 (3 H, s), 1.80–1.67 (3 H, m), 1.65–1.50 (3 H, m), 1.49–1.19 (24 H, m), 1.34 (3H, dd, <i>J</i> =6.1, 0.6) ( <u>p</u> ), 1.24 (6H, dd, <i>J</i> =6.1, 0.6) ( <u>o</u> ), 0.89 (3 H, t, <i>J</i> =6.9) ( <u>p</u> ); 0.89 (6 H, t, <i>J</i> =6.9) ( <u>o</u> ).
Compound	<sup>13</sup> C NMR (100 MHz)
<b>16 major</b>	158.33, 136.54, 134.29, 131.89, 120.62 (CF <sub>3</sub> , <i>J</i> =320), 119.03, 113.99, 105.84, 95.14, 77.35, 36.10, 31.82, 29.22, 25.58, 22.70, 19.56, 14.19.
<b>16 minor<sup>c</sup></b>	158.31, 136.54, 134.33, 131.89, 128.33, 120.62 (CF <sub>3</sub> , <i>J</i> =320), 119.03, 114.04, 105.80, 95.14, 77.35, 36.10, 31.82, 29.22, 25.58, 22.70, 19.54, 14.19.
<b>18</b>	158.31, 136.51, 134.33, 131.87, 129.35, 120.62 (CF <sub>3</sub> , <i>J</i> =320), 119.03, 114.14, 105.79, 95.14, 77.35, 36.10, 31.82, 29.22, 25.59, 22.71, 19.54, 14.19.
<b>20 major</b>	165.51, 159.38, 143.22, 139.31, 133.61, 131.33, 131.00, 128.58, 126.19, 116.14, 93.58, 85.59, 76.26 ( <u>o</u> ), 74.91 ( <u>p</u> ), 36.38 ( <u>p</u> ), 36.02 ( <u>o</u> ), 31.83 ( <u>p</u> ), 31.79 ( <u>o</u> ), 29.30 ( <u>p</u> ), 29.18 ( <u>o</u> ), 25.54, 22.67, 21.40, 19.78 ( <u>p</u> ), 19.55 ( <u>o</u> ), 14.15.
<b>20 minor<sup>c</sup></b>	165.48, 159.41, 143.22, 139.31, 133.68, 131.33, 131.00, 128.58, 126.19, 116.06, 93.63, 85.59, 76.23 ( <u>o</u> ), 74.91 ( <u>p</u> ), 36.38 ( <u>p</u> ), 36.02 ( <u>o</u> ), 31.83 ( <u>p</u> ), 31.79 ( <u>o</u> ), 29.30 ( <u>p</u> ), 29.18 ( <u>o</u> ), 25.54, 22.67, 21.40, 19.80 ( <u>p</u> ), 19.51 ( <u>o</u> ), 14.15.
<b>22</b>	165.44, 159.31, 143.41, 139.10, 133.55, 131.27, 130.97, 128.48, 126.13, 116.18, 93.53, 85.57, 76.14 ( <u>o</u> ), 74.87 ( <u>p</u> ), 36.30 ( <u>p</u> ), 35.96 ( <u>o</u> ), 31.76 ( <u>p</u> ), 31.72 ( <u>o</u> ), 29.23 ( <u>p</u> ), 29.13 ( <u>o</u> ), 25.49 ( <u>o</u> ), 25.47 ( <u>p</u> ), 22.61 ( <u>o</u> ), 22.59 ( <u>p</u> ), 21.33, 19.74 ( <u>p</u> ), 19.47 ( <u>o</u> ), 14.09.

<sup>a</sup> The *ortho/para* pairs are marked (o) and (p) and appear in a 2:1 ratio.

<sup>b</sup> Peaks of major and minor diastereomers overlap.

<sup>c</sup> Peaks in italics overlap with the major diastereomer.

### 3.2. Synthesis of monosubstituted target **1**

#### 3.2.1. (*R*)-2-Octanol ((*R*)-**4**):

Prepared by kinetic resolution of *rac*-**4** following a modified literature procedure:<sup>30</sup> To a flame dried 250 mL round bottom flask was loaded racemic 2-octanol (12.21 mL, 76.79 mmol), isopropenyl acetate (10.0 mL, 92.14 mmol), Na<sub>2</sub>CO<sub>3</sub> (1.59 g, 15.0 mmol) and *i*-Pr<sub>2</sub>O (120 mL). The flask was purged with argon and CALB (300 mg) was added. The reaction was monitored by GC and when > 50% of the starting material was consumed the reaction was stopped by filtering the crude reaction mixture through a silica plug. H<sub>2</sub>O (15 mL) was added to the filtrate, which was extracted with ether (3×10 mL). The combined organic phases were washed with H<sub>2</sub>O (3×10 mL) and brine (3×10 mL), dried with MgSO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane:Et<sub>2</sub>O, 20:1) to give (*R*)-**4** (4.20 g, 42%, >99% *ee*) as a clear liquid. The enantiomeric excess was analyzed by chiral GC on the corresponding acetylated compound, using a gradient from 70 to 86 °C over 9 min. Analytical data were in agreement with the literature.<sup>38</sup>

#### 3.2.2. (*R*)-Octan-2-yl methanesulfonate ((*R*)-**6**):

To a solution of (*R*)-**4** (5.0 mL, 31.79 mmol) and Et<sub>3</sub>N (1.6 mL, 11.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (40 mL) at ≤-5 °C was added MsCl (0.65 mL, 8.5 mmol) drop-wise while maintaining a temperature below 0 °C. The reaction was stirred at room temperature for an additional 20 min and then quenched by addition of H<sub>2</sub>O. The water phase was extracted with Et<sub>2</sub>O (3×20 mL) and the combined organic phases were washed with H<sub>2</sub>O (3×20 mL), 10% aq. HCl (3×20 mL), brine (3×20 mL), dried with Na<sub>2</sub>CO<sub>3</sub>,

filtered and concentrated under reduced pressure to give (*R*)-**6** (1.56 g, 97%) as a colorless oil. The product was used without further purification. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ 4.39 (1 H, dqd, *J*=7.1, 6.3, 5.6 Hz), 2.98 (3 H, s), 1.71 (1 H, m), 1.59 (1 H, m Hz), 1.44–1.22 (8 H, m), 1.40 (3 H, d, *J*= 6.3 Hz), 0.88 (3 H, t, *J*= 6.9 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 80.6, 38.8, 36.8, 31.7, 29.0, 25.2, 22.7, 21.3, 14.2; [α]<sub>D</sub><sup>20</sup> +9.0 (c 1.04 in CH<sub>2</sub>Cl<sub>2</sub>); HRMS (ESI): calcd for C<sub>18</sub>H<sub>40</sub>NaO<sub>6</sub>S<sub>2</sub> ([2M+Na]<sup>+</sup>): 439.2159, found 439.2142.

#### 3.2.3. (*S*)-1-Iodo-2-(octan-2-yloxy)benzene (**7**):

To a suspension of anhydrous K<sub>2</sub>CO<sub>3</sub> (1.38 g, 10.0 mmol) in anhydrous acetonitrile (10 mL) was added 2-iodophenol (440 mg, 2.00 mmol) and (*R*)-**6** (630 mg, 3.00 mmol) and the reaction was refluxed for 18 hours. The solvent was evaporated under reduced pressure and H<sub>2</sub>O was added to the crude product. The crude mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×15 mL), washed with brine (3×15 mL), dried with Na<sub>2</sub>CO<sub>3</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (pentane:Et<sub>2</sub>O, 25:1) to give compound **7** (692 mg, 97%, >99% *ee*) as a colorless oil. The enantiomeric excess was analyzed by chiral HPLC using OB 99.9:0.1 to 98:2 gradient over 30 min *iso*-hexane:*i*-PrOH. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.78 (1 H, dd, *J*=7.8, 1.6 Hz), 7.26 (1 H, ddd, *J*=8.3, 7.3, 1.6 Hz), 6.80 (1 H, dd, *J*=8.3, 1.3 Hz), 6.67 (1 H, app td, *J*=7.5, 1.3 Hz), 4.39 (1 H, app sex, *J*=6.1 Hz), 1.80 (1 H, dddd, *J*=13.6, 10.3, 6.5, 5.2 Hz), 1.62 (1 H, ddt, *J*= 13.6, 10.5, 5.3 Hz), 1.52–1.36 (2 H, m), 1.34 (3 H, d, *J*= 6.1 Hz), 1.32–1.26 (6 H, m), 0.88 (3 H, t, *J*= 6.9 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 157.1, 139.7, 129.4, 122.3, 113.9, 88.4, 75.9, 36.6, 31.9, 29.4, 25.6, 22.7, 19.9, 14.2; [α]<sub>D</sub><sup>20</sup> -39.3 (c 0.72 in CH<sub>2</sub>Cl<sub>2</sub>); HRMS (ESI): calcd for C<sub>14</sub>H<sub>21</sub>INaO ([M+Na]<sup>+</sup>): 355.0529, found 355.0543.

#### 3.2.4. (*S*)-(2-(Octan-2-yloxy)phenyl)(phenyl)-iodonium tetrafluoroborate (**8**):

Iodoarene **7** (50 mg, 0.15 mmol) was pre-oxidized during 40 min with *m*CPBA (35.7 mg, 0.17 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) at 80 °C. Phenylboronic acid (20.7 mg, 0.17 mmol) and BF<sub>3</sub>·OEt<sub>2</sub> (47 μL, 0.38 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and added to the reaction at -78 °C. The reaction was stirred at -78 °C for 30 min and then brought to room temperature and applied to a silica plug. Elution with a CH<sub>2</sub>Cl<sub>2</sub>:MeOH gradient gave **8** (12.9 mg, 17%) as an oil. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 8.29 (1 H, dd, *J*=7.9, 1.6 Hz), 8.02 (2 H, m), 7.62 (1 H, tt, *J*=7.4, 1.1 Hz), 7.61 (1 H, ddd, *J*=8.8, 7.4, 1.6 Hz), 7.49 (2 H, m), 7.29 (1 H, dd, *J*=8.8, 1.2 Hz), 7.06 (1 H, ddd, *J*=7.9, 7.4, 1.2 Hz), 4.67 (1 H, app sex, *J*=6.0 Hz), 1.65 (1 H, m), 1.54 (1 H, m), 1.32–1.17 (8 H, m), 1.15 (3 H, d, *J*=6.0 Hz), 0.86 (3 H, t, *J*=7.0 Hz).

### 3.2.5. (*S,S*)-(2-(*Octan-2-yloxy*)phenyl)(3-iodo-[4-(*octan-2-yloxy*)]phenyl)iodonium tetrafluoroborate (**9**):

Formed as a byproduct in the synthesis of iodonium salt **8**, isolated by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>:MeOH 100:0→100:1) in 9% as a yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.25 (1 H, d, *J*=2.4 Hz), 8.03 (1 H, dd, *J*=9.0, 2.4 Hz), 7.76 (2 H, dd, *J*=8.4, 1.5 Hz), 7.56 (1 H, ddd, *J*=8.2, 7.4, 1.5 Hz), 7.02 (2 H, m), 6.83 (1 H, d, *J*=9.4 Hz), 4.56 (1 H, app sex, *J*=6.1 Hz), 4.45 (1 H, app sex, *J*=6.1 Hz), 1.87–1.74 (2 H, m), 1.71–1.58 (2 H, m), 1.50–1.29 (16 H, m), 1.36 (3 H, d, *J*=6.1 Hz), 1.35 (6 H, d, *J*=6.1 Hz), 0.89 (3 H, t, *J*=6.9 Hz); 0.87 (3 H, t, *J*=6.9 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 160.9, 155.2, 145.8, 138.1, 135.7, 135.0, 124.1, 115.6, 114.3, 103.9, 98.2, 90.5, 76.9, 70.7, 36.3, 36.1, 31.8, 29.3, 29.3, 25.6, 25.4, 22.7, 22.7, 19.6, 19.5, 14.2; [α]<sub>D</sub><sup>20</sup> +52.0 (*c* 0.10 in CH<sub>2</sub>Cl<sub>2</sub>); HRMS (ESI): calcd for C<sub>28</sub>H<sub>41</sub>I<sub>2</sub>O<sub>2</sub> ([M-BF<sub>4</sub>]<sup>+</sup>): 663.1190, found 663.1160.

### 3.2.6. (*E*)-[2-[(Trifluoromethanesulfonyl)oxy]-1-heptenyl](phenyl)iodonium triflate (**10**):

To a solution of (diacetoxyiodo)benzene (2.30 g, 7.28 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added TfOH (1.30 mL, 14.56 mmol) at 0 °C. The mixture was allowed to reach rt and stirred for 2 h. Then 1-heptyne (0.68 mL, 5.20 mmol) was added drop-wise at 0 °C, and the reaction was stirred at rt for another 2 h. The solvent was evaporated under reduced pressure to yield dark solids. Ether was added to cause precipitation and the resulting solid was filtered, washed with ether, and dried *in vacuo* to give **10** (2.55 mg, 56%) as a white solid. mp 126–128 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.97 (2 H, dd, *J*=8.4, 1.0 Hz), 7.64 (1 H, tt, *J*=7.5, 1.0 Hz), 7.49 (2 H, dd, *J*=8.4, 7.5 Hz), 7.11 (1 H, s), 2.79 (2 H, t, *J*=7.7 Hz), 1.53 (2 H, m), 1.28 (4 H, m), 0.86 (3 H, t, *J*=6.9 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 162.7, 134.9, 132.7, 132.4, 120.0 (CF<sub>3</sub>, q, *J*=319 Hz), 118.4 (CF<sub>3</sub>, q, *J*=320 Hz), 114.0, 92.8, 34.9, 31.0, 25.8, 22.3, 13.8; HRMS (ESI): calcd for C<sub>14</sub>H<sub>17</sub>F<sub>3</sub>IO<sub>3</sub>S ([M-OTf]<sup>+</sup>): 448.9890, found 448.9888.

### 3.2.7. (*S*)-(2-(*Octan-2-yloxy*)phenyl)(phenyl)iodonium triflate (**11**):

Iodoarene **7** (100 mg, 0.31 mmol) was dissolved in anhydrous Et<sub>2</sub>O (1.25 mL) and cooled to -78 °C before addition of *n*-BuLi (1.6 M, 194 μL, 0.31 mmol). The mixture was stirred for 1 hour at rt, cooled again to -78 °C and vinyliodonium salt **10** (169 mg, 0.26 mmol) was added from a solid addition tube. The mixture was stirred for 2 hours 40 min at -78 °C and was then allowed to reach rt over 2 hours. The crude mixture was evaporated under reduced pressure and purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:MeOH 100:0→100:1) to give **11** (55 mg, 38%) as a pale yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.93 (2 H, dd, *J*=8.5, 1.1 Hz), 7.75 (1 H, dd, *J*=8.0, 1.5 Hz), 7.61 (1 H, tt, *J*=7.5, 1.3 Hz), 7.56 (1 H, ddd, *J*=8.5, 7.4, 1.5 Hz), 7.45 (2 H, m), 7.01 (2 H, m), 4.52 (1 H, app sex, *J*=6.1 Hz), 1.72 (1 H, m), 1.56 (1 H, m), 1.34–1.24 (8 H, m), 1.25 (3 H, d, *J*=6.1 Hz), 0.87 (3 H, t, *J*=6.9

Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 155.3, 136.2, 135.4, 135.1, 132.6, 132.3, 123.9, 120.4 (CF<sub>3</sub>, q, *J*=320 Hz), 114.3, 112.1, 103.7, 77.1, 36.0, 31.8, 29.2, 25.5, 22.7, 19.4, 14.1; [α]<sub>D</sub><sup>20</sup> -10.3 (*c* 0.32 in CH<sub>2</sub>Cl<sub>2</sub>); HRMS (ESI): calcd for C<sub>20</sub>H<sub>26</sub>IO ([M-OTf]<sup>+</sup>): 409.1023, found 409.1042.

## 3.3. Synthesis of disubstituted target **II**

### 3.3.1. *Octan-2-yl toluenesulfonate (12)*:

To a solution of racemic 2-octanol (5.00 mL, 31.8 mmol) and DMAP (200 mg, 0.05 mmol) in pyridine (20 mL) at -5 °C was added TsCl (6.00 g, 31.5 mmol) portion-wise so that the temperature was kept below 0 °C. This temperature was kept for 1 hour, and then the reaction was left to stir at rt for 24 hours. The precipitate was filtered off and the filtrate was pored into ice-diluted HCl (40 mL, 4 M) and stirred for 20 min. The organic phase was separated and the water phase was extracted with Et<sub>2</sub>O (3×40 mL). The combined organic phases were washed H<sub>2</sub>O (3×20 mL), 10% aq. HCl (3×20 mL), brine (3×20 mL), and dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give **12** (6.24 g, 94%) as a colorless oil, that was used without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.78 (2 H, dt, *J*=8.3, 1.7 Hz), 7.32 (2 H, m), 4.59 (1 H, dqd, *J*=7.1, 6.3, 5.5 Hz), 2.43 (3 H, s), 1.64–1.54 (1 H, m), 1.50–1.40 (1 H, m), 1.25 (3 H, d, *J*=6.3 Hz), 1.25–1.10 (8 H, m), 0.85 (3 H, t, *J*=7.1 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 144.5, 134.7, 129.8, 127.8, 80.8, 36.6, 31.7, 28.9, 24.9, 22.6, 21.7, 21.0, 14.1; HRMS (ESI): calcd for C<sub>30</sub>H<sub>48</sub>NaO<sub>6</sub>S<sub>2</sub> ([2M+Na]<sup>+</sup>): 591.2785, found 591.2804.

### 3.3.2. 2-Iodo-1,3-bis(*octan-2-yloxy*)benzene (**13**):

To a solution of PPh<sub>3</sub> (233 mg, 0.89 mmol), 2-iodobenzene-1,3-diol<sup>32</sup> (100 mg, 0.42 mmol), 2-octanol (141 μL, 0.89 mmol) and Et<sub>3</sub>N (124 μL, 0.89 mmol) in anhydrous THF (2 mL) at 0 °C was added DIAD (175 μL, 0.89 mmol). The reaction was left to stir at room temperature during 2 hours and quenched with 5 % HCl. The reaction was extracted with ether (3×5 mL), dried with MgSO<sub>4</sub>, filtrated and the solvent was evaporated at reduced pressure. The crude material was purified by column chromatography (pentane: EtOAc 250:1) to afford compound **13** (64 mg, 33%) as a colorless oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.16 (1 H, t, *J*=8.2 Hz), 6.42 (2 H, d, *J*=8.2 Hz), 4.38 (2 H, app sex, *J*=6.1 Hz), 1.80 (2 H, dddd, *J*=13.5, 10.4, 6.5, 5.2 Hz), 1.62 (2 H, ddt, *J*=13.5, 10.8, 5.5 Hz), 1.49 (2 H, m), 1.40 (2 H, m), 1.36–1.25 (12 H, m), 1.34 (6H, dd, *J*=6.1, 0.6 Hz), 0.88 (6 H, t, *J*=6.9 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 158.7, 129.3, 106.4, 82.3, 75.9, 36.6, 31.9, 29.4, 25.6, 22.7, 20.0, 14.2; HRMS (ESI): calcd for C<sub>44</sub>H<sub>74</sub>I<sub>2</sub>O<sub>4</sub> ([2M+Na]<sup>+</sup>): 943.3569, found 943.3585.

### 3.3.3. 2-Bromo-1,3-bis(*octan-2-yloxy*)benzene (**14**):

To a suspension of anhydrous K<sub>2</sub>CO<sub>3</sub> (2.70 g, 19.6 mmol) in anhydrous MeCN (15 mL) was added 2-bromobenzene-1,3-diol<sup>33</sup> (1.00 g, 5.30 mmol) and tosylate **12** (3.30 g, 11.6 mmol) and the reaction was refluxed for 18 hours. The solvent was concentrated under reduced pressure and H<sub>2</sub>O was added to the crude product. The crude mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×15 mL), washed with brine (3×15 mL), dried with Na<sub>2</sub>CO<sub>3</sub>, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (pentane:Et<sub>2</sub>O, 25:1) to give compound **14** (527 mg, 24%) as a yellow oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.13 (1 H, t, *J*=8.3 Hz), 6.52 (2 H, d, *J*=8.3 Hz), 4.37 (2 H, app sex, *J*=6.1 Hz), 1.80 (2 H, dddd, *J*=13.5, 10.3, 6.5, 5.2 Hz), 1.61 (2 H, ddt, *J*=13.5, 10.5, 5.3 Hz), 1.51–1.37 (4 H, m), 1.33 (6 H, d, *J*=6.1 Hz), 1.32–1.26 (12 H, m), 0.88 (6 H, t, *J*=6.9 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 156.5, 127.8, 107.5, 105.0, 76.0, 36.6, 31.9, 29.4, 25.6, 22.7, 20.0, 14.2; HRMS (ESI): calcd for C<sub>22</sub>H<sub>37</sub>BrNaO<sub>2</sub> ([M+Na]<sup>+</sup>): 435.1869, found 435.1884.

### 3.3.4. (2,6-Bis(octan-2-yloxy)phenyl)boronic acid (**15**):

Anhydrous THF (4 mL) was added to a round bottom flask containing **14** (200 mg, 0.48 mmol) under argon. The solution was cooled to -78 °C and *n*-BuLi (0.6 M, 0.90 mL, 0.54 mmol) was added drop-wise. The reaction was brought to rt and stirred for 1 hour followed by addition of B(O<sup>i</sup>Pr)<sub>3</sub> (391 μL, 1.70 mmol) at -78 °C. After another 16 hours, the reaction was quenched by addition of 1 M HCl (aq) (10 mL) and the mixture was refluxed for 18 hours. The organic phase was separated and H<sub>2</sub>O phase was extracted with ether (3×10 mL). The combined organic phases were washed with brine (1×50 mL), dried with MgSO<sub>4</sub> and concentrated under reduced pressure to afford **15** (195 mg, >99%) as a slightly yellow oil, which was used without further purification. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.51 (2 H, s), 7.31 (1 H, t, *J*=8.4 Hz), 6.56 (2 H, d, *J*=8.4 Hz), 4.51 (2 H, app sex, *J*=6.1 Hz), 1.87-1.78 (2 H, m), 1.71-1.61 (2 H, m), 1.51-1.40 (4 H, m), 1.37 (6 H, d, *J*=6.1 Hz), 1.36-1.25 (12 H, m), 0.80 (6 H, t, *J*=6.9 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 164.5, 132.8, 106.4, 75.7, 36.7, 31.9, 29.4, 25.7, 22.8, 20.0, 14.3; HRMS (ESI): calcd for C<sub>22</sub>H<sub>39</sub>BNaO<sub>4</sub> ([M+Na]<sup>+</sup>): 401.2834, found 401.2856.

### 3.3.5. 2,6-Bis(octan-2-yloxy)phenyl(phenyl)iodonium triflate (**16**):

Prepared from iodoarene **13** and vinylidonium salt **10** as described for **11**. The crude product was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:MeOH 100:0→100:1) to give **16** (60 mg, 44%) as a light brown oil. Two diastereomers of **16** were observed in NMR; (*R,S,S,R*) as major and (*R,R,S,S*) as minor, see Table 1; HRMS (ESI): calcd for C<sub>28</sub>H<sub>42</sub>IO<sub>2</sub> ([M-OTf]<sup>+</sup>): 537.2224, found 537.2230.

### 3.3.6. (*S,S*)-(2-Bromo-1,3-bis(octan-2-yloxy)-benzene (**17**):

Prepared from 2-bromobenzene-1,3-diol and (*R*)-**6** as described for **7**, obtained in 89% yield as a pale yellow oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.13 (1 H, t, *J*=8.3 Hz), 6.51 (2 H, d, *J*=8.3 Hz), 4.37 (2 H, app sex, *J*=6.1 Hz), 1.80 (2 H, dddd, *J*=13.5, 10.1, 6.5, 5.2 Hz), 1.61 (2 H, ddt, *J*=13.5, 10.1, 5.5 Hz), 1.51-1.37 (4 H, m), 1.36-1.24 (12 H, m), 1.33 (6 H, d, *J*=6.1 Hz), 0.88 (6 H, t, *J*=6.9 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 156.4, 127.7, 107.5, 104.9, 76.0, 36.6, 31.9, 29.4, 25.6, 22.7, 20.0, 14.2; [α]<sub>D</sub><sup>20</sup> -54.1 (*c* 0.29 in CH<sub>2</sub>Cl<sub>2</sub>); HRMS (ESI): calcd for C<sub>22</sub>H<sub>37</sub>BrNaO<sub>2</sub> ([M+Na]<sup>+</sup>): 435.1869, found 435.1870.

### 3.3.7. (*S,S*)-(2,6-Bis(octan-2-yloxy)phenyl)(phenyl)iodonium triflate (**18**):

Prepared from bromoarene **17** and vinylidonium salt **10** as described for **11**. The crude product was purified by column chromatography (CH<sub>2</sub>Cl<sub>2</sub>:MeOH 100:0→100:1) to give **18** (50.0 mg, 36%) as a light orange oil. NMR data: see Table 1; [α]<sub>D</sub><sup>20</sup> -39.2 (*c* 0.12 in CH<sub>2</sub>Cl<sub>2</sub>); HRMS (ESI): calcd for C<sub>28</sub>H<sub>42</sub>IO<sub>2</sub> ([M-OTf]<sup>+</sup>): 537.2224, found 537.2220.

## 3.4. Synthesis of trisubstituted target **III**

### 3.4.1. 1,3,5-Tris(octan-2-yloxy)benzene (**19**):

To a suspension of K<sub>2</sub>CO<sub>3</sub> (0.96 g, 6.97 mmol) in MeCN (3 mL) was added 1,3,5-trihydroxybenzene (0.18 g, 1.40 mmol) and (*rac*)-**6** (1.45 g, 6.97 mmol) and the reaction was refluxed for 18 hours. H<sub>2</sub>O (10 mL) was added to the reaction mixture and extracted with Et<sub>2</sub>O (3×20 mL). The combined organic phases were washed with brine (1×20 mL), dried with MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (pentane:EtOAc 100:0 → 100:1) to give **19** (0.46 g, 72%) as an orange oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.04 (3 H, s), 4.30 (3 H, app sex, *J*=6.1 Hz), 1.73 (3 H, m), 1.54 (3 H, m), 1.48-1.24 (24 H, m), 1.29 (9 H, d, *J*=6.1

Hz), 0.89 (9 H, t, *J*=6.9 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 160.23, 96.21, 73.92, 36.71, 31.96, 29.43, 25.71, 22.75, 19.98, 14.20; HRMS (ESI): calcd for C<sub>30</sub>H<sub>54</sub>NaO<sub>3</sub> ([M+Na]<sup>+</sup>): 485.3965, found 485.5998.

### 3.4.2. 2,4,6-Tris(octan-2-yloxy)phenyl(phenyl)iodonium tosylate (**20**):

Arene *rac*-**14** (150 mg, 0.32 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) and the reaction mixture was cooled to -10 °C. PhI(OH)OTs (127 mg, 0.32 mmol) was added in one portion and the reaction was stirred at room temperature for 21 hours. The reaction mixture was applied to a silica column and purified by flash chromatography (CH<sub>2</sub>Cl<sub>2</sub>:MeOH 100:0 → 10:1) to give **20** (256 mg, 96%) as a dark orange oil. Two diastereomers of **20** were observed in NMR; (*R,S,R/S,R,S*) and (*R,R,S/S,S,R*). Furthermore, different NMR signals were observed in a 2:1 ratio for the *o*- and *p*-substituents, see Table 1; HRMS (ESI): calcd for C<sub>36</sub>H<sub>58</sub>IO<sub>3</sub> ([M-OTs]<sup>+</sup>): 665.3425, found 665.3435.

### 3.4.3. (*R,R,R*)-1,3,5-Tris(octan-2-yloxy)benzene (**21**):

To a suspension of NaH (83 mg, 1.98 mmol) in anhydrous NMP (2 mL) was added (*R*)-**4** (0.24 mL, 1.51 mmol) drop-wise at 0 °C and the reaction was left to stir for 15 min. 1,3,5-Trifluorobenzene (39 μL, 0.38 mmol) was added to the mixture and the reaction was refluxed at 100 °C during 17 hours. The reaction was quenched by addition of sat. NH<sub>4</sub>Cl, after cooling to room temperature. The organic phase was separated and the water phase was extracted with Et<sub>2</sub>O (3×10 mL). The combined organic phases were washed with H<sub>2</sub>O (1×20 mL) and brine (1×20 mL), dried with MgSO<sub>4</sub> and concentrated under reduced pressure. The crude material was purified by flash chromatography (pentane:Et<sub>2</sub>O, 500:1 → 200:1) to give **21** (89 mg, 51%) as a dark orange oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 6.03 (3 H, s), 4.29 (3 H, app sex, *J*=6.1 Hz), 1.72 (3 H, m), 1.54 (3 H, m), 1.47-1.25 (24 H, m), 1.28 (9 H, d, *J*=6.1 Hz), 0.89 (9 H, t, *J*=6.9 Hz); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 160.20, 96.11, 73.90, 36.69, 31.95, 29.43, 25.71, 22.75, 19.99, 14.22; [α]<sub>D</sub><sup>20</sup> +25.6 (*c* 1.87 in CH<sub>2</sub>Cl<sub>2</sub>); HRMS (ESI): calcd for C<sub>30</sub>H<sub>54</sub>NaO<sub>3</sub> ([M+Na]<sup>+</sup>): 485.3965, found 485.5997.

### 3.4.4. (*R,R,R*)-(2,4,6-Tris(octan-2-yloxy)phenyl)(phenyl)iodonium tosylate (**22**):

Prepared from (*R,R,R*)-**14** as described for *rac*-**15**, obtained in 82% yield as a dark orange oil. Different NMR signals were observed in a 2:1 ratio for the *o*- and *p*-substituents, see Table 1. [α]<sub>D</sub><sup>20</sup> +37.6 (*c* 0.78 in CH<sub>2</sub>Cl<sub>2</sub>); HRMS (ESI): calcd for C<sub>36</sub>H<sub>58</sub>IO<sub>3</sub> ([M-OTs]<sup>+</sup>): 665.3425, found 665.3446.

### 3.4.5. (*R*)-(Octan-2-yloxy)benzene (**23**):

Prepared from fluorobenzene and (*R*)-**4** as described for arene **21**. The reaction was stopped after 18 h, before complete conversion had been obtained, to give arene **23** (89 mg, 51 %) as a pale yellow oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.27 (2 H, ddt, *J*=8.7, 7.3, 1.3 Hz), 6.92 (1 H, tt, *J*=7.3, 1.0 Hz), 6.90 (2 H, m), 4.35 (1 H, app sex, *J*=6.1 Hz), 1.74 (1 H, m), 1.57 (1 H, m), 1.50-1.36 (2 H, m), 1.35-1.25 (6 H, m), 1.30 (3 H, d, *J*=6.1 Hz), 0.87 (3 H, t, *J*=6.9 Hz); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 158.4, 129.6, 120.5, 116.0, 74.0, 36.7, 32.0, 29.5, 25.7, 22.8, 19.9, 14.2; [α]<sub>D</sub><sup>20</sup> +19.1 (*c* 0.47 in CH<sub>2</sub>Cl<sub>2</sub>); HRMS (ESI): calcd for C<sub>28</sub>H<sub>45</sub>O<sub>2</sub> ([2M+H]<sup>+</sup>): 413.3414, found 413.3310.

## Acknowledgements

This work was financially supported by the Swedish Research Council, the Royal Swedish Academy of Sciences and K & A Wallenberg Foundation.

## Supplementary data

<sup>1</sup>H and <sup>13</sup>C-NMRs of all reported compounds are available in the online version, at doi:10.1016/j.tet.2010.xxxxx.

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