



## BOTPPI, a new Wittig salt for the synthesis of 12-(*S*)-hydroxy-eicosatetraenoic acid [12-(*S*)-HETE]

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### ABSTRACT

An efficient route to (*Z*)-(8-benzyloxy-8-oxooct-3-en-1-yl)triphenylphosphonium iodide, or BOTPPI, is disclosed, complete with full experimental details, NMR spectra, and HRMS data. BOTPPI serves as a surrogate for (*Z*)-(8-methoxy-8-oxooct-3-en-1-yl)triphenylphosphonium iodide, or MOTPPI, a Wittig salt previously used in two 12-HETE syntheses. BOTPPI has the advantage over MOTPPI of being derived from a sequence for which every intermediate is UV-active and amenable to large-scale chromatographic purification. A formal asymmetric total synthesis of 12-(*S*)-HETE is also reported, involving a stereoselective phase-transfer catalyzed (PTC) alkylation in its key step.

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### Introduction

Arachidonic acid (AA, **1**, Scheme 1) is a polyunsaturated fatty acid bound within glycerolic constituents of the phospholipid membrane.<sup>1</sup> Hydrolysis of **1**, mediated by phospholipase A<sub>2</sub>, releases AA into the cytosol and enables it to serve as a synthetic precursor for the eicosanoids, a key class of signaling molecules, which are subdivided into three groups: the prostaglandins, thromboxanes, and leukotrienes.<sup>2</sup>

One leukotriene of particular interest is 12-(*S*)-hydroxy-eicosatetraenoic acid, 12-(*S*)-HETE (**2**, Fig. 1), which was first discovered in 1974 by Hamberg and Samuelsson.<sup>3</sup> Although its complete functions have yet to be exhaustively determined, 12-(*S*)-HETE is a highly bioactive molecule, being implicated in various physiological processes including inflammation,<sup>4</sup> stimulation of neutrophils<sup>5</sup> and smooth muscle cells,<sup>6</sup> hypertension,<sup>7</sup> COX attenuation,<sup>8</sup> cellular response to epidermal growth factor and insulin,<sup>9</sup> human pancreatic cancer cell proliferation,<sup>10</sup> endothelial cell retraction,<sup>11</sup> angiogenesis,<sup>12</sup> tumor cell metastasis,<sup>13</sup> atherogenesis,<sup>14</sup> coronary thrombosis,<sup>15</sup> type I diabetes induction,<sup>16</sup> psoriasis,<sup>4a,15</sup> and inhibition of apoptosis.<sup>18</sup>

Given its biological importance and the difficulty in obtaining adequate amounts of this material, great interest has arisen in synthesizing **2**, resulting in the development of five asymmetric routes disclosed by the groups of Corey et al.,<sup>19</sup> Just,<sup>20</sup> Sato and co-work-

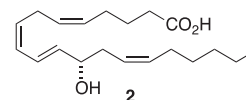


Figure 1. 12-(*S*)-HETE.

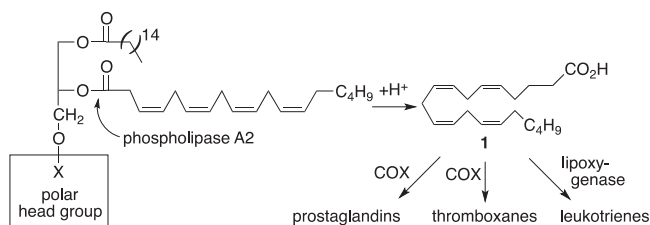
ers,<sup>21</sup> Spur and co-workers,<sup>22</sup> and Suh et al.<sup>23</sup> More recently, the Corey group has also reported a synthesis of 12-(*R*)-HETE,<sup>4a</sup> which likewise possesses intriguing biological properties.

While formulating our own route to 12-(*S*)-HETE, we recently became interested in Wittig salt **3**,<sup>4a,22</sup> (*Z*)-(8-methoxy-8-oxooct-3-en-1-yl)triphenylphosphonium iodide, or MOTPPI. Our retrosynthetic disassembly of 12-(*S*)-HETE began as Scheme 2 depicts with the Wittig coupling of synthons **3** and **4** to yield **2**. Aldehyde **4** would be formed through the coupling of **5** and **6**, and **6** through methanolysis/reduction of key imidazolyl ketone **7**.<sup>24</sup> Compound **7**, in turn, was thought to be accessible through a stereoselective phase-transfer catalyzed (PTC) alkylation of substrate **8** with bromide **9**, which would exploit recent methodology developed by our group.<sup>24</sup>

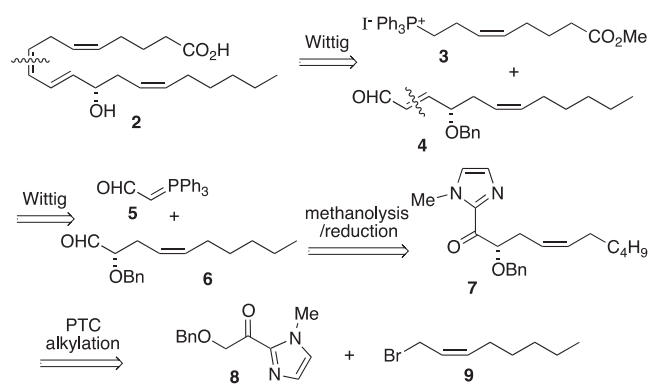
Given its essentiality to our planned synthesis, our attention turned to the assembly of Wittig salt **3**. We initially assumed that this would be straightforward, since **3** had been employed in both Spur's synthesis of 12-(*S*)-HETE<sup>22</sup> and in Corey's synthesis 12-(*R*)-HETE.<sup>4a</sup> However, further literature investigation revealed a surprising lack of experimental detail for this compound. An examination of the three reported routes to **3**<sup>20,25,26</sup> revealed the most descriptive one

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Scheme 1. Eicosanoids derived from arachidonic acid.



Scheme 2. Retrosynthesis of 12-(S)-HETE (2).

(disclosed by Rokach and co-workers<sup>26</sup>) to also be the most efficient and highest yielding. This accordingly became our center of focus.

The Rokach route<sup>26</sup> proceeds according to Scheme 3 with the coupling of Wittig salt **10** with aldehyde **11**<sup>27</sup> (obtained from  $\delta$ -valerolactone), followed by desilylation, to afford alcohol **12a**. This was then converted into an intermediate bromide (not shown), which when treated with NaI gives alkyl iodide **12b**. When reacted with  $\text{Ph}_3\text{P}$ , reagent **3** is then produced in 92% yield, as shown.

Despite being the most descriptive published route to **3**, this report contains significant omissions, having no experimental procedures or spectroscopic details; only yields, solvents, temperatures, and equivalencies are shown. And though the assembly of **10** proceeded seamlessly in our hands, every endeavor to produce **11**<sup>27</sup> from  $\delta$ -valerolactone according to published procedures failed, giving only complex mixtures, substrate decomposition, or unreacted starting materials. Another noteworthy obstacle is the fact that aldehyde **11** and its synthetic precursors are not readily visualized by TLC, making it difficult to monitor the reaction's progress and to identify the products once formed.

An alternative strategy was accordingly devised. Thus, basic hydrolysis of  $\delta$ -valerolactone **13** (Scheme 4) gave the open-chain hydroxycarboxylic acid (not shown), which was then treated with BnBr to afford benzyl ester **14** in 97% yield (Scheme 4).<sup>28</sup> This intermediate has the advantage of UV activity, allowing it to be easily visualized by TLC and reproducibly purified by column

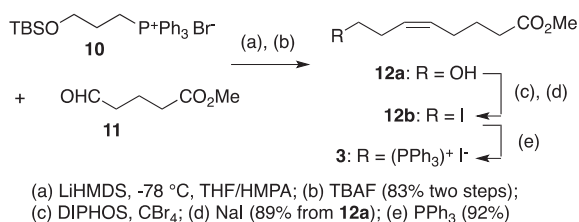
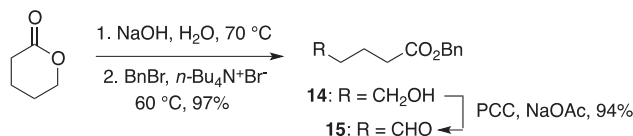
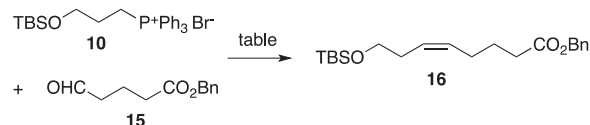
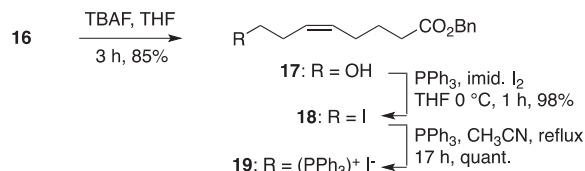
Scheme 3. Rokach route to **3**.<sup>26</sup>Scheme 4. Synthesis of aldehyde **15**.

Table 1

Condition screen for assembling **16**

Entry	Conditions	Yield (%)
1	LiHMDS, THF, HMPA, -78 °C	—
2	NaHMDS, THF, HMPA, -78 °C	—
3	<i>n</i> -BuLi, THF, -30 °C	7.7
4	NaH, THF, rt	11
5	<i>n</i> -BuLi, THF, -90 °C	22
6	<i>n</i> -BuLi, THF, rt	50
7	<i>n</i> -BuLi, THF <sup>a</sup> , -30 °C	97

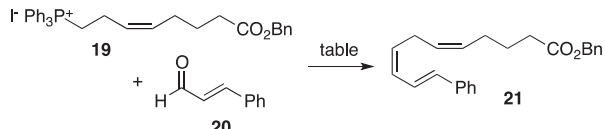
<sup>a</sup> Low vacuum was used during concentration.Scheme 5. Synthesis of BOTPPI (**19**).

chromatography on a larger scale. Alcohol **14** was then oxidized to aldehyde **15** in 94% yield, as shown.

As Table 1 illustrates, subsequent coupling proved lithium and sodium hexamethyldisilazides to be ineffective at producing **16** (entries 1 and 2), giving only dark mixtures of unidentifiable byproducts. Use of *n*-butyllithium and sodium hydride gave modest yields initially (entries 3 and 4), but *n*-butyllithium's performance improved as temperature variations were explored (entries 5–7), ultimately providing **16** in 97% yield. It was found that intermediates **14**–**16** had to be concentrated cautiously under a low vacuum to prevent product/solvent co-evaporation.

Deprotection of **16** unveiled alcohol **17** in 85% yield (Scheme 5). Direct conversion into iodide **18** was then facilitated through the use of triphenylphosphine, imidazole, and iodine (98% yield), and overnight treatment with triphenylphosphine in refluxing acetonitrile gave **19** quantitatively. Reagent **19**, (*Z*)-(8-benzyloxy-8-oxooct-3-en-1-yl)triphenylphosphonium iodide, or BOTPPI, is the benzyl ester surrogate for reagent **3**. As anticipated, each intermediate en route to **19** was stable and UV-active, which allowed for facile chromatographic purification. Once optimized, this route ultimately provided **19** from  $\delta$ -valerolactone (**13**) in 74% yield over seven steps.

In an effort to establish coupling conditions, compound **19** was reacted with cinnamaldehyde (**20**) according to Table 2. When a first trial gave no product (entry 1), **19** was purified by column chromatography in 5% MeOH/ $\text{CH}_2\text{Cl}_2$ . This salt, isolated as a dark yellow syrup, was found to be extremely hygroscopic and only functioned

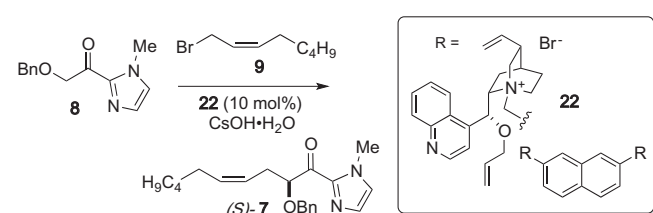
**Table 2**  
Condition screen for assembling **21**


Entry	Conditions	Yield (%)
1	<i>n</i> -BuLi <sup>a</sup> , m. sieves, THF, −30 °C	—
2	KHMDS, m. sieves, THF, HMPA, −30 °C	7
3	<i>t</i> -BuLi, m. sieves, THF, HMPA, −30 °C	35
4	<i>n</i> -BuLi, m. sieves, THF, HMPA, −30 °C	44
5	<i>n</i> -BuLi, m. sieves, THF, HMPA, −40 °C	33
6	<i>n</i> -BuLi, m. sieves, THF, HMPA, −78 °C	15
7	MeLi <sup>b</sup> , m. sieves, THF, HMPA, −78 °C	84

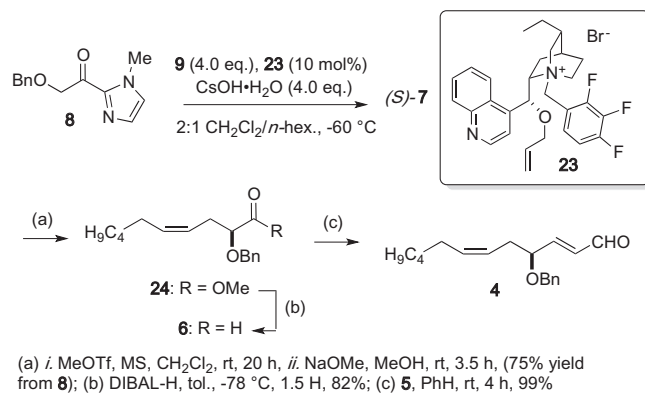
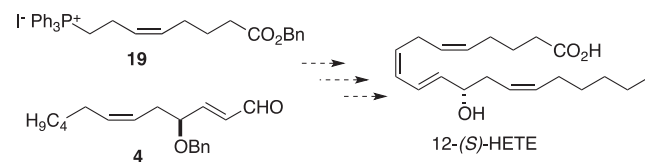
<sup>a</sup> **19** used without purification or P<sub>2</sub>O<sub>5</sub> drying.<sup>b</sup> **19** used after purification and P<sub>2</sub>O<sub>5</sub> drying.

well when subjected to overnight concentration in vacuo with in-line phosphorous pentoxide (P<sub>2</sub>O<sub>5</sub>).<sup>29</sup> Phosphonium Wittig salts of this type, typified by BOTPPI, in addition to purification issues, are further prone to undesired reactivity through the pendant ester moiety. In time, base investigations revealed the superiority of *n*-butyllithium (entries 2–4), though decreased temperature limited reactivity (entries 5 and 6). Vigorous azeotropic drying by THF/toluene, followed by in vacuo concentration overnight with P<sub>2</sub>O<sub>5</sub>, finally provided **19** in a dry form. Renewed optimization of Wittig reactivity found that methyllithium consistently produced **21** in 85% yield.

With Wittig reagent BOTPPI **19** in hand, new conditions were sought for the assembly of enal **4**. Beginning with the stereoselective PTC alkylation of acylimidazole **8**,<sup>24</sup> electrophile (*Z*)-**9** (formed from 2-octyn-1-ol),<sup>29</sup> was employed using the cinchonidinium dimer catalyst **22**<sup>29</sup> (Table 3, yields 70–80%). Decreasing to 2.0 equiv of **9** caused undesirably sluggish reactivity (entry 1), while 4.0 equiv of **9** gave (*S*)-product **7** in 65% ee (entry 2). Solvent variations showed modest improvement when a 2:1 mixture of CH<sub>2</sub>Cl<sub>2</sub>/*n*-hexane was employed (entry 3). Decreased base equivalency also caused slow reactivity (entry 4), while lowered temperature (−60 °C) provided **7** with improved selectivity, 80% ee (entry 5).

**Table 3**  
PTC conditions for producing **7**


Entry	Solvent/temperature	Modifications	Time (h)	ee (%)
1	CH <sub>2</sub> Cl <sub>2</sub> , −40 °C	2.0 equiv <b>9</b>	>48	—
2	CH <sub>2</sub> Cl <sub>2</sub> , −40 °C	4.0 equiv <b>9</b>	28	65
3	2:1 CH <sub>2</sub> Cl <sub>2</sub> / <i>n</i> -hex, −40 °C	4.0 equiv <b>9</b>	25	70
4	2:1 CH <sub>2</sub> Cl <sub>2</sub> / <i>n</i> -hex, −40 °C	2.0 equiv CsOH·H <sub>2</sub> O	>48	—
5	2:1 CH <sub>2</sub> Cl <sub>2</sub> / <i>n</i> -hex, −60 °C	4.0 equiv CsOH·H <sub>2</sub> O	23	80

**Scheme 6.** Synthesis of  $\alpha,\beta$ -unsaturated aldehyde **4**.**Scheme 7.** Formal synthesis of 12-(*S*)-HETE (**2**).

A broader catalyst screen was conducted using numerous phase-transfer catalysts with acylimidazole **8** and (*Z*)-allyl bromide **9**.<sup>30</sup> This process eventually revealed the superiority of novel dihydro-trifluorobenzyl cinchonidinium catalyst **23**, which reproducibly furnished product **7** in 88% ee on multigram scale (Scheme 6). Compound **7** was taken on and treated in crude form with methyl triflate and sodium methoxide/methanol to give ester **24** in 75% yield over two steps from **8**. Only slight epimerization was observed, with **24** being isolated in 84% ee (chiral HPLC). Conversion into aldehyde **6** proceeded smoothly in 82% yield by employing DIBAL-H at −78 °C, and treatment with the formyl Wittig reagent **5** then gave the key  $\alpha,\beta$ -unsaturated aldehyde **4** in 99% yield.

At this stage, the two key pieces are in hand, aldehyde **4** and BOTPPI **19**. In accord with previous routes of Corey and Spur,<sup>4a,22</sup> three steps allow for the formal synthesis of the target 12-(*S*)-HETE (Scheme 7). After Wittig coupling, it follows that the benzyl ether and the benzyl ester removal can in a single step directly provide the product. Various options for debenzylation under mild conditions are available at this point to facilitate this transformation and allow for systematic substrate variation for analog development.

An efficient route to Wittig salt **19**, complete with full experimental details, together with reliable Wittig coupling conditions have been completed. Compound **19** has the advantage over Wittig salt **3** of being derived from a sequence for which every intermediate is UV-active and amenable to large-scale purification. Furthermore, experimental detail of this report should enable rapid, facile, and reproducible access to **19** that was previously unavailable for the known variant **3**. We also report a formal synthesis of 12-(*S*)-HETE, in which novel phase-transfer catalyst **23** is used in a key alkylation sequence. Future developments are now facilitated toward reliable syntheses of (*S*) and (*R*)-12-HETE and related eicosanoid compounds.

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### Supplementary data

Supplementary data (NMR, HPLC, and optical rotation data) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2012.06.052>. These data include MOL files and InChIKeys of the most important compounds described in this article.

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