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BOTPPI, a New Wittig Salt Used in the Synthesis of 12-(S)-Hydroxy-Eicosatetraenoic Acid [12-(S)-HETE]

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

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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. Hydrolysis of 1, mediated by phospholipase A2, 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.

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. 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, stimulation of neutrophils and smooth muscle cells, hypertension, COX attenuation, cellular response to epidermal growth factor and insulin, human pancreatic cancer cell proliferation, endothelial cell retraction, angiogenesis, tumor cell metastasis, atherogenesis, coronary thrombosis, type I diabetes induction, psoriasis, and inhibition of apoptosis.

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., Just, Sato and co-workers, Spur and co-workers, and Suh et al. More recently, the Corey group has also reported a synthesis of 12-(R)-HETE, which likewise possesses intriguing biological properties.

While formulating our own route to 12-(S)-HETE, we recently became interested in Wittig salt 3, (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. 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.

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 and in Corey’s synthesis of 12-(R)-HETE. However, further literature investigation revealed a surprising lack of experimental detail for this compound. An examination of the three reported routes to 3 revealed the most descriptive one...
(disclosed by Rokach and co-workers\textsuperscript{26}) to also be the most efficient and highest yielding. This accordingly became our center of focus. The Rokach route\textsuperscript{26} proceeds according to Scheme 3 with the coupling of Wittig salt 10 with aldehyde 11\textsuperscript{27} (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 Ph3P, 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\textsuperscript{27} 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).\textsuperscript{28} This intermediate has the advantage of UV activity, allowing it to be easily visualized by TLC and reproducibly purified by column 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/CH\(_2\)Cl\(_2\). This salt, isolated as a dark yellow syrup, was found to be extremely hydroscopic and only functioned
Table 2
Condition screen for assembling 21

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi, m. sieves, THF, –30 °C</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>t-BuLi, m. sieves, THF, HMPA, –30 °C</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>n-BuLi, m. sieves, THF, HMPA, –30 °C</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>n-BuLi, m. sieves, THF, HMPA, –30 °C</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>n-BuLi, m. sieves, THF, HMPA, –40 °C</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>n-BuLi, m. sieves, THF, HMPA, –78 °C</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>MeLi, m. sieves, THF, HMPA, –78 °C</td>
<td>84</td>
</tr>
</tbody>
</table>

*a* 19 used without purification or P2O5 drying.  
*b* 19 used after purification and P2O5 drying.

well when subjected to overnight concentration in vacuo with in-  
line phosphorous pentoxide (P2O5).29 Phosphonium Wittig salts of  
this type, typified by BOTPPI, in addition to purification issues, are  
farther prone to undesired reactivity through the pendant ester  
moiety. In time, base investigations revealed the superiority of  
n-butyl lithium (entries 2–4), though decreased temperature limited  
reactivity (entries 5 and 6). Vigorous azeotropic drying by THF/tolu-  
ene, followed by in vacuo concentration overnight with P2O5, fi-

Table 3
PTC conditions for producing 7

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent/temperature</th>
<th>Modifications</th>
<th>Time (h)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH2Cl2, –40 °C</td>
<td>2.0 equiv 9</td>
<td>&gt;48</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>CH2Cl2, –40 °C</td>
<td>4.0 equiv 9</td>
<td>28</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>2:1 CH2Cl2/n-hex, –40 °C</td>
<td>4.0 equiv 9</td>
<td>25</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>2:1 CH2Cl2/n-hex, –40 °C</td>
<td>2.0 equiv CsOH H2O</td>
<td>&gt;48</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>2:1 CH2Cl2/n-hex, –60 °C</td>
<td>4.0 equiv CsOH H2O</td>
<td>23</td>
<td>80</td>
</tr>
</tbody>
</table>

A broader catalyst screen was conducted using numerous  
phase-transfer catalysts with acylimidazole 8 and (Z)-allyl bromide  
9.30 This process eventually revealed the superiority of novel dihy-  
dro-trifluorobenzyl cinchonidinium catalyst 23, which reproduc-  
tively furnished product 7 in 88% ee on multigram scale (Scheme 6).


Scheme 7. Formal synthesis of 12-(S)-HETE (2).

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search Corporation, Research Opportunity Award, and the Brigham Young University Cancer Center.

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.

References and notes

29. See Supplementary data section.