

# The Catalytic Enantioselective Total Synthesis of (+)-Liphagal\*\*

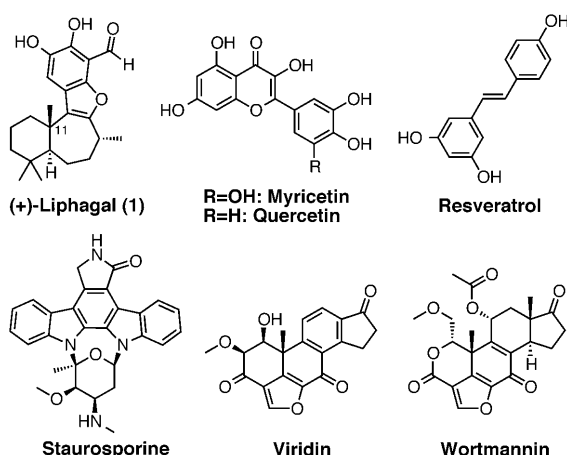
Joshua J. Day, Ryan M. McFadden, Scott C. Virgil, Helene Kolding, Jennifer L. Alleva, and Brian M. Stoltz\*

The tetracyclic meroterpenoid natural product (+)-liphagal (**1**) was isolated in 2006 by Andersen and co-workers from the Caribbean sponge *Aka coralliphaga*,<sup>[1]</sup> and is one of a number of natural product inhibitors of phosphatidylinositol 3-kinase (PI3K). Other natural product inhibitors include myricetin, quercetin, resveratrol, staurosporine, viridin, and wortmannin (Scheme 1).<sup>[2]</sup> The PI3K family of enzymes participates in the

cancer.<sup>[3]</sup> The inhibitory activity of liphagal is noteworthy because of its selective inhibition of PI3K  $\alpha$ , a lipid kinase isoform that holds a central role in several cancers.<sup>[4]</sup> In this context, liphagal was found to have an  $IC_{50}$  value of 100 nM against PI3K  $\alpha$  and was tenfold more potent against isoform  $\alpha$  than  $\gamma$ . In addition, liphagal is cytotoxic toward LoVo (human colon), CaCo (human colon), and MDA-468 (human breast) tumor cell lines, with  $IC_{50}$  values of 0.58, 0.67, and 1.58  $\mu$ M, respectively.<sup>[1]</sup>

From a structural perspective, liphagal possesses an unprecedented [6-7-5-6] tetracyclic skeleton, and has attracted significant attention from the synthetic organic community. The isolation and structure determination was reported concomitantly with the first total synthesis of ( $\pm$ )-**1** through a biomimetic strategy.<sup>[1,5]</sup> Subsequently, Andersen and co-workers determined the absolute configuration,<sup>[6]</sup> which was corroborated by other research groups through formal and total syntheses.<sup>[7-9]</sup> We became interested in both the potent biological activity and the complex tetracyclic structure of liphagal, as highlighted by the chiral quaternary carbon center at C(11). Herein we report the first catalytic enantioselective total synthesis of (+)-liphagal.

Retrosynthetically, we envisioned simplification of the aromatic ring of liphagal to dimethoxybenzofuran **2**, a known precursor to the natural product (Scheme 2).<sup>[7]</sup> Disconnection of the tetracycle along the benzofuran moiety led back to  $\alpha$ -bromoaryl dienone **3**. Reduction of the sterically hindered trisubstituted olefin to establish the *trans* ring fusion was seen as a major challenge. The  $\alpha$ -bromoaryl dienone **3** could arise from a ring expansion of strained cyclobutene **4**. Excision of the cyclobutene and  $\alpha$ -aryl group from ketone **4** revealed chiral cyclopentenone (*R*)-**5**. The enantiomeric enone (*S*)-**5**<sup>[10]</sup> was previously prepared from achiral enol carbonate **6**<sup>[11a]</sup> as part of our ongoing research program aimed at the stereose-



Scheme 1. Natural product inhibitors of PI3K.

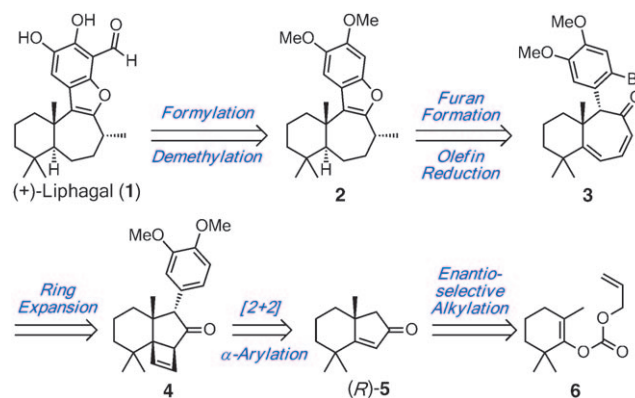
regulation of numerous biological functions and has been directly implicated in the pathogenesis of diabetes and

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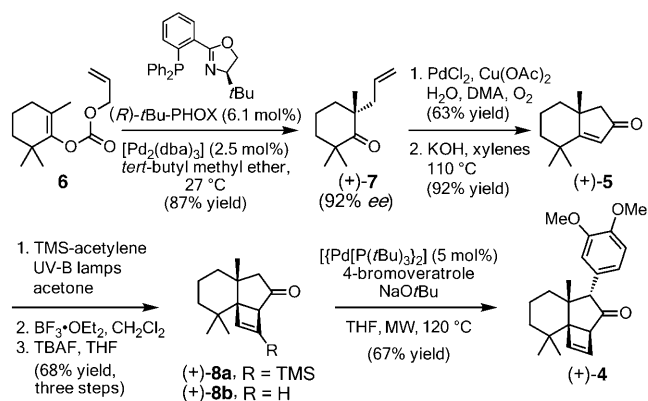
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201101842>.



Scheme 2. Retrosynthesis of liphagal.

lective synthesis of natural products containing quaternary carbon centers.<sup>[11,12]</sup> To this end, we have reported a series of palladium-catalyzed enantioselective decarboxylative alkylation reactions that employ the *t*Bu-PHOX ligand scaffold in conjunction with allyl enol carbonates, silyl enol ethers, and racemic  $\beta$ -ketoesters to produce a wide array of  $\alpha$ -quaternary substituted ketones.<sup>[11–14]</sup> With this general strategy in mind, we initiated efforts toward a total synthesis of (+)-liphagal.

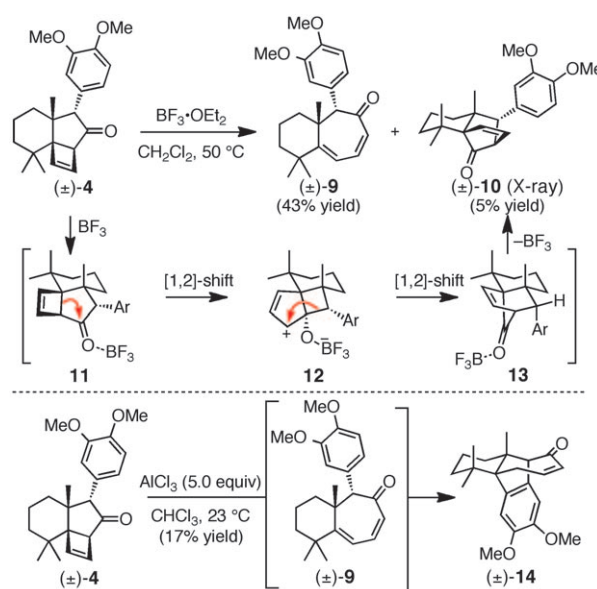
The forward synthesis commenced with a palladium-catalyzed decarboxylative alkylation of enol carbonate **6** to furnish tetrasubstituted ketone **7** in 87% yield and 92% *ee* (Scheme 3).<sup>[11,15]</sup> This intermediate was elaborated to bicycle



**Scheme 3.** Catalytic enantioselective preparation of synthetic building block (+)-**7** and chemical elaboration to (+)-**4**. dba = *trans,trans*-dibenzylideneacetone, DMA = *N,N*-dimethylacetamide, MW = microwave, TBAF = tetrabutylammonium fluoride, TMS = trimethylsilyl.

**5** following our previously reported two-step sequence.<sup>[10]</sup> The synthesis continued with exposure of enone **5** to trimethylsilylacetylene under UV irradiation, which promoted a [2+2] photocycloaddition.<sup>[16]</sup> Exposure of the crude reaction mixture to  $\text{BF}_3\cdot\text{OEt}_2$  resulted in the formation of a single silylated cyclobutene product (**8a**).<sup>[17]</sup> Subsequent removal of the trimethylsilyl group with TBAF yielded the chromatographically stable and pleasantly fragrant cyclobutene **8b**, a compound that contains three contiguous quaternary centers within the strained carbon framework.<sup>[18,19]</sup> A microwave-assisted palladium-catalyzed  $\alpha$ -arylation with 4-bromoveratrole installed the electron-rich aromatic moiety, thereby producing aryl ketone **4** as a single diastereomer.<sup>[20,21]</sup>

At this stage in our synthesis, a Lewis acid mediated ring expansion by selective cleavage of strained cyclobutene **4** was attempted (Scheme 4). Exposure of tricyclic ketone **4** to  $\text{BF}_3\cdot\text{OEt}_2$  at 50 °C provided the desired cycloheptadienone product **9** in modest yield. Serendipitously, this compound was isolated alongside a crystalline by-product (**10**), which was suitable for X-ray diffraction analysis and structure determination.<sup>[22]</sup> Bridged polycyclic ketone **10** is presumably the result of a Cargill rearrangement, which proceeds through two concerted [1,2]-carbon–carbon bond migrations.<sup>[23]</sup> More specifically, activation of ketone **4** with  $\text{BF}_3$  (to give **11**) promotes carbon–bond migration to rupture the cyclobutene and produce an allylic carbocation intermediate (**12**). The

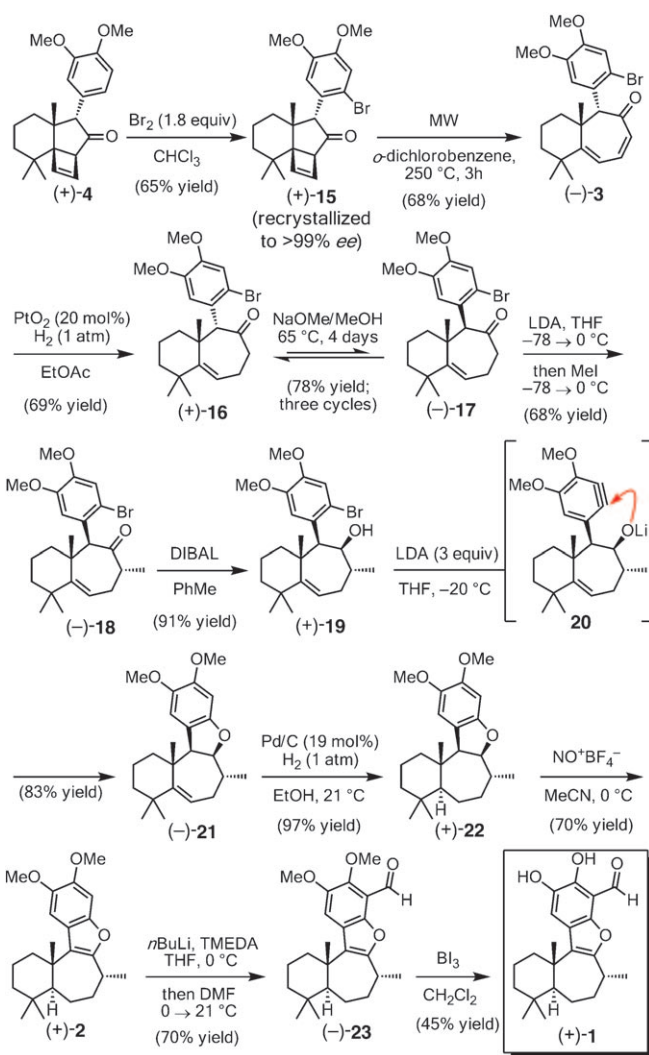


**Scheme 4.** Unexpected rearrangement and reactivity of strained cyclobutene **4**.

second carbon–bond migration forms a [2.2.1] bridged bicyclic core of Lewis acid complex **13**. Finally, loss of  $\text{BF}_3$  generates the isolated product (**10**). Importantly, the stereospecific rearrangement mechanism allowed assignment of the relative configuration of cyclobutenes **8** from the unequivocal assignment of bridged bicycle **10**. In addition to  $\text{BF}_3\cdot\text{OEt}_2$ , we discovered that  $\text{AlCl}_3$  also promotes ring expansion of aryl cyclobutene **4** without formation of Cargill product **10**. However, under these reaction conditions we were intrigued to find a new side product, enone **14**, which arises from intramolecular 1,6-addition of the electron-rich arene fragment of **9** to the cycloheptadienone system. This result suggests that the arene resides in proximity to the trisubstituted olefin and also indicated that the aromatic moiety should be deactivated before ring expansion to avoid formation of **14**.

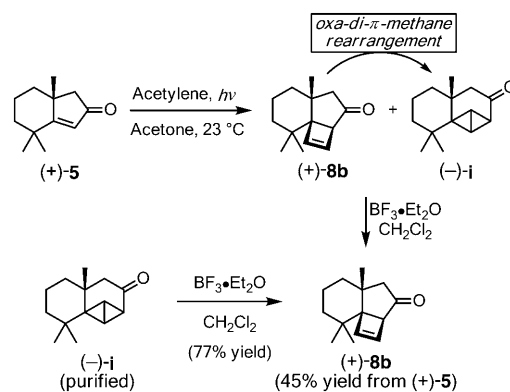
With this in mind, we sought to install a functional group handle on the aromatic ring that could be utilized for eventual formation of the benzofuran unit and could serve to deactivate the aromatic residue of **9** toward unwanted Friedel–Crafts reactions. We were impressed to find that chemoselective aromatic bromination occurred in the presence of the strained cyclobutene to furnish bromoarene **15** (Scheme 5). At this stage, crystallization of the crude product increased the enantiomeric excess to >99%. With the deactivated aromatic ketone in hand, we were pleased to find that treatment of bromide **15** with  $\text{AlCl}_3$  furnished much improved yields of the corresponding ring-expanded product **3**. An optimized ring expansion from the [6-5-4] system to the desired [6-7] core (**3**) was accomplished in the absence of a Lewis acid by using microwave heating at 250 °C in *o*-dichlorobenzene.<sup>[24]</sup> Chemoselective reduction of dienone **3** with Adams catalyst in ethyl acetate furnished ketone **16**, leaving the aromatic halide intact.

With the core carbon framework of liphagal (**1**) secured, our focus turned to the challenging stereoselective hydro-





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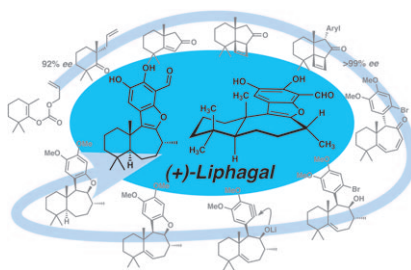
## Communications



### Natural Product Synthesis

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B. M. Stoltz\* ————— ■■■■-■■■■

The Catalytic Enantioselective Total  
Synthesis of (+)-Liphagal



**Ring a ding:** The meroterpenoid natural product (+)-liphagal has been synthesized enantioselectively in 19 steps from commercially available materials. The *trans*-homodecalin system was achieved by ring expansion followed by stereoselective hydrogenation.