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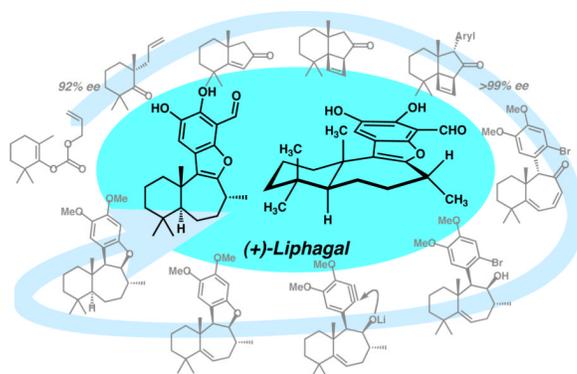
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The Catalytic Enantioselective Total Synthesis of (+)-Liphagal**

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Abstract



Ring a ding: The first catalytic enantioselective total synthesis of the meroterpenoid natural product (+)-liphagal is disclosed. The approach showcases a variety of technology including enantioselective enolate alkylation, a photochemical alkyne-alkene [2+2] reaction, microwave-assisted metal catalysis, and an intramolecular aryne capture cyclization reaction. Pivotal to the successful completion of the synthesis was a sequence involving ring expansion from a [6-5-4] tricycle to a [6-7] bicyclic core followed by stereoselective hydrogenation of a sterically occluded tri-substituted olefin to establish the trans homodecalin system found in the natural product.

Keywords

total synthesis; terpenoids; arynes; asymmetric catalysis; palladium; rearrangement

The tetracyclic meroterpenoid natural product (+)-liphagal (**1**) was isolated in 2006 by Andersen and co-workers from the Caribbean sponge *Aka coralliphaga*^[1] and is one of a number of natural product inhibitors of phosphatidyl inositol 3-kinase (PI3K) including myricetin, quercetin, resveratrol, staurosporine, viridin, and wortmannin (Figure 1).^[2] The

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

PI3K family of enzymes participates in the regulation of numerous biological functions and has been directly implicated in the pathogenesis of diabetes and cancer.^[3] The inhibitory activity of liphagal is noteworthy due to selective inhibition of PIK3 α , a lipid kinase isoform that holds a central role in several cancers.^[4] In this context, liphagal was found to have an IC₅₀ of 100 nM against PI3K α and was 10-fold more potent against isoform α than γ . Additionally, liphagal is cytotoxic toward LoVo (human colon), CaCo (human colon), and MDA-468 (human breast) tumor cell lines with IC₅₀ values of 0.58, 0.67, and 1.58 μ M, respectively.^[1]

From a structural perspective, liphagal possesses an unprecedented [6-7-5-6] tetracyclic skeleton and has attracted significant attention from the synthetic organic community. Andersen's isolation and structure determination was reported concomitantly with the first total synthesis of (\pm)-**1** using a biomimetic strategy.^[1,5] Subsequently, the same group determined the absolute stereochemistry,^[6] which was corroborated by other laboratories with formal and total syntheses.^[7,8,9] Our laboratory became interested in both the potent biological activity and the complex tetracyclic structure of liphagal, 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 1).^[7] Disconnection of the tetracycle along the benzofuran moiety led back to α -bromoaryl dienone **3**. Reduction of the sterically hindered tri-substituted olefin to establish the trans ring fusion was seen as a major challenge. The α -bromoaryl dienone (**3**) could arise from a ring expansion of strained cyclobutene **4**. Excision of the cyclobutene and α -aryl group from ketone **4** revealed chiral cyclopentenone (*R*)-**5**. The enantiomeric enone (*S*)-**5**^[10] was previously prepared from achiral enol carbonate **6**^[11a] as part of our ongoing research program aimed at the stereoselective synthesis of natural products containing quaternary carbon centers.^[11,12] 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 β -ketoesters to produce a wide array of α -quaternary substituted ketones.^[11,12,13,14] 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 2).^[11,15] This intermediate was elaborated to bicycle **5** following our previously reported two-step sequence.^[10] The synthesis continued with exposure of enone **5** to trimethylsilylacetylene under UV irradiation, which promoted a [2+2] photocycloaddition.^[16] Exposure of the crude reaction mixture to BF₃•OEt₂ formed a single silylated cyclobutene product (**8a**).^[17] 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.^[18,19] A microwave-assisted palladium-catalyzed α -arylation with 4-bromoveratrole installed the electron rich aromatic moiety, producing aryl ketone **4** as a single diastereomer.^[20,21]

At this stage in our synthesis, Lewis acid-mediated ring expansion by selective cleavage of strained cyclobutane **4** was attempted (Scheme 3). Exposure of tricyclic ketone **4** to BF₃•OEt₂ at 50 °C, provided the desired cycloheptadienone product **9** in modest yield. Serendipitously, this compound was isolated alongside a crystalline byproduct (i.e., **10**), which was suitable for X-ray diffraction analysis and structure determination.^[22] Bridged polycyclic ketone **10** is presumably the result of a Cargill rearrangement, which proceeds

through two concerted [1, 2]-carbon-carbon bond migrations.^[23] More specifically, activation of ketone **4** with BF₃ (i.e., **11**) promotes carbon bond migration to rupture the cyclobutene and produce an allylic carbocation intermediate (**12**). The second carbon bond migration forms a [2.2.1] bridged bicyclic core of Lewis acid complex **13**. Finally, loss of BF₃ reveals the isolated product (**10**). Importantly, the stereospecific rearrangement mechanism allowed assignment of the relative stereochemistry of cyclobutenes **8** from the unequivocal assignment of bridged bicycle **10**. In addition to BF₃•OEt₂, we discovered that AlCl₃ 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**, arising 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 close proximity to the tri-substituted 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 benzofuran formation and could serve to deactivate the aromatic residue of **9** toward unwanted Friedel-Crafts chemistry. We were impressed to find that chemoselective aromatic bromination occurred in the presence of the strained cyclobutene, furnishing bromoarene **15** (Scheme 4). 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 AlCl₃ 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 with microwave heating at 250 °C in *o*-dichlorobenzene.^[24] 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 hydrogenation of the tri-substituted olefin to establish the desired [6-7] trans ring fusion.^[25] Our strategy to effect this transformation was guided by our previous isolation of 1,6-addition product **14**, which provided evidence that hydrogenation to form a trans ring fusion would be sterically demanding (vide supra). To alleviate steric congestion, we proceeded with epimerization of the aryl substituent, forming the β -oriented α -aryl ketone (**17**). The mass recovery for this equilibration averaged 97% and a 78% overall yield of **17** was obtained after three cycles of equilibration ($K_{eq(av)} = 0.76$).^[25] With the arene substituent further removed from the tri-substituted olefin we planned to rigidify the polycyclic system via formation of the fourth ring. This began with a diastereoselective methylation, affording the desired α -methyl cycloheptenone (**18**) in 68% yield.^[26] Reduction of this hindered ketone with DIBAL produced alcohol **19**, a substrate poised for dihydrobenzofuran formation. Initial attempts to form dihydrobenzofuran **21** were unsuccessful^[27] and prompted an unconventional strategy to accomplish the desired transformation. Gratifyingly, formation of dihydrobenzofuran **21** was accomplished upon exposure of bromoarene **19** to LDA, proceeding through a putative aryne intermediate (**20**).^[28] This powerful aryne capture cyclization strategy generated the highly congested dihydrobenzofuran product in 83% yield. With tetracycle **21** in hand, we set out to test the key stereoselective hydrogenation of the tri-substituted olefin. To our delight, using catalytic Pd/C in ethanol under 1 atm H₂, we isolated 97% yield of saturated homodecalin **22**, observing exclusive formation of the [6-7] trans ring fusion.

Having executed the synthesis of the challenging trans fused system, the completion of (+)-liphagal required three additional transformations: 1) benzofuran construction, 2) aldehyde installation, and 3) demethylation, the final two of which were known from previous syntheses.^[1,7] Oxidation of dihydrobenzofuran **22** to benzofuran **2** proved surprisingly

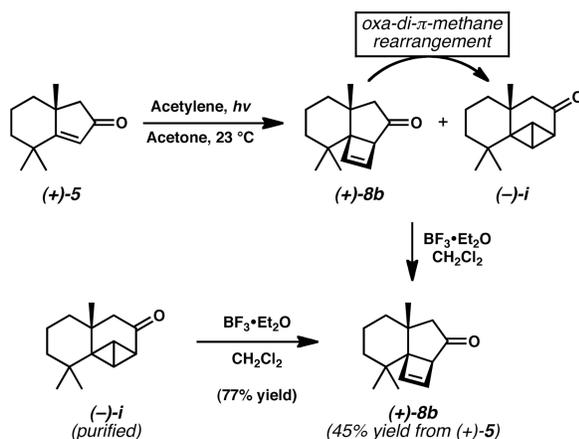
difficult, and with DDQ a tendency for over-oxidation was observed.^[29] Upon switching to nitrosonium tetrafluoroborate, which oxidizes by hydride abstraction, dehydrogenation occurred in 70% yield to give benzofuran **2**.^[30] Aryl lithiation with *n*-butyllithium•TMEDA and quenching with anhydrous DMF installed the aldehyde functional group in **23**.^[7] Finally, this was followed by demethylation using boron triiodide to generate (+)-liphagal (**1**), which was identical in all respects to data reported in the literature.¹

In summary, we have successfully completed the first catalytic enantioselective total synthesis of (+)-liphagal (**1**) in 15 steps from known compounds (19 steps from commercially available materials). By applying a combination of catalytic enantioselective alkylation (**6**→**7**), two-carbon ring expansion via cyclobutene **15**, and an intramolecular aryne cyclization (**19**→**20**→**21**) we were able to access the tetracyclic core of the natural product in enantioenriched form. Judicious choice of tetracyclic hydrogenation substrate **21** established the critical trans-[6-7] ring fusion and enabled completion of the total synthesis.

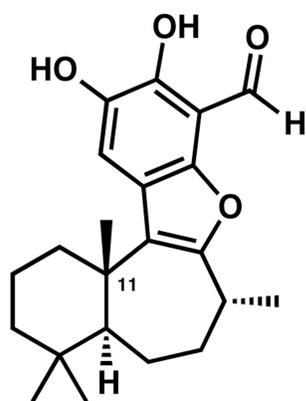
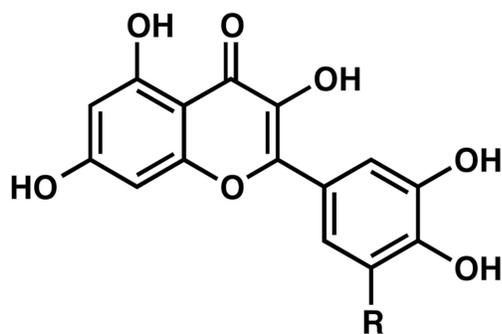
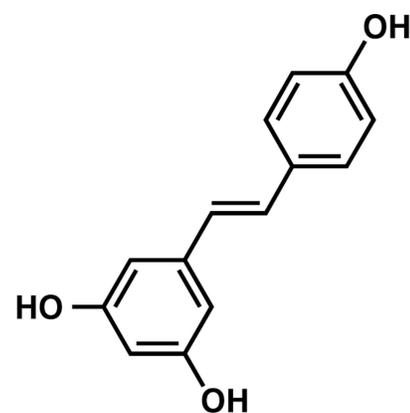
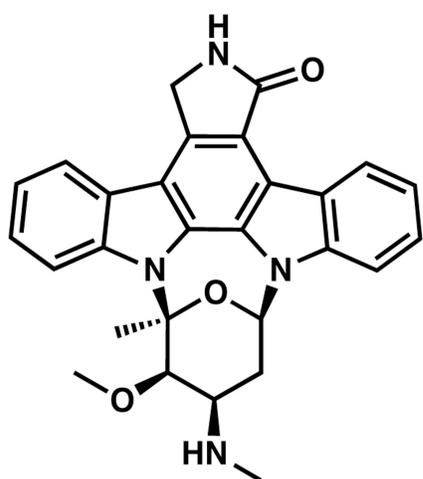
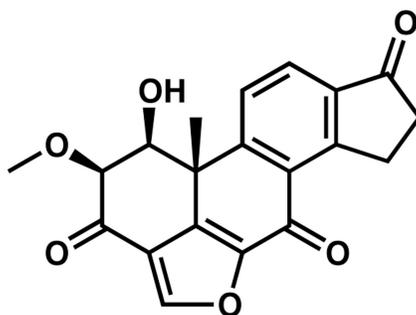
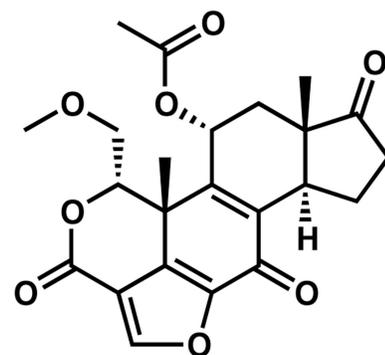
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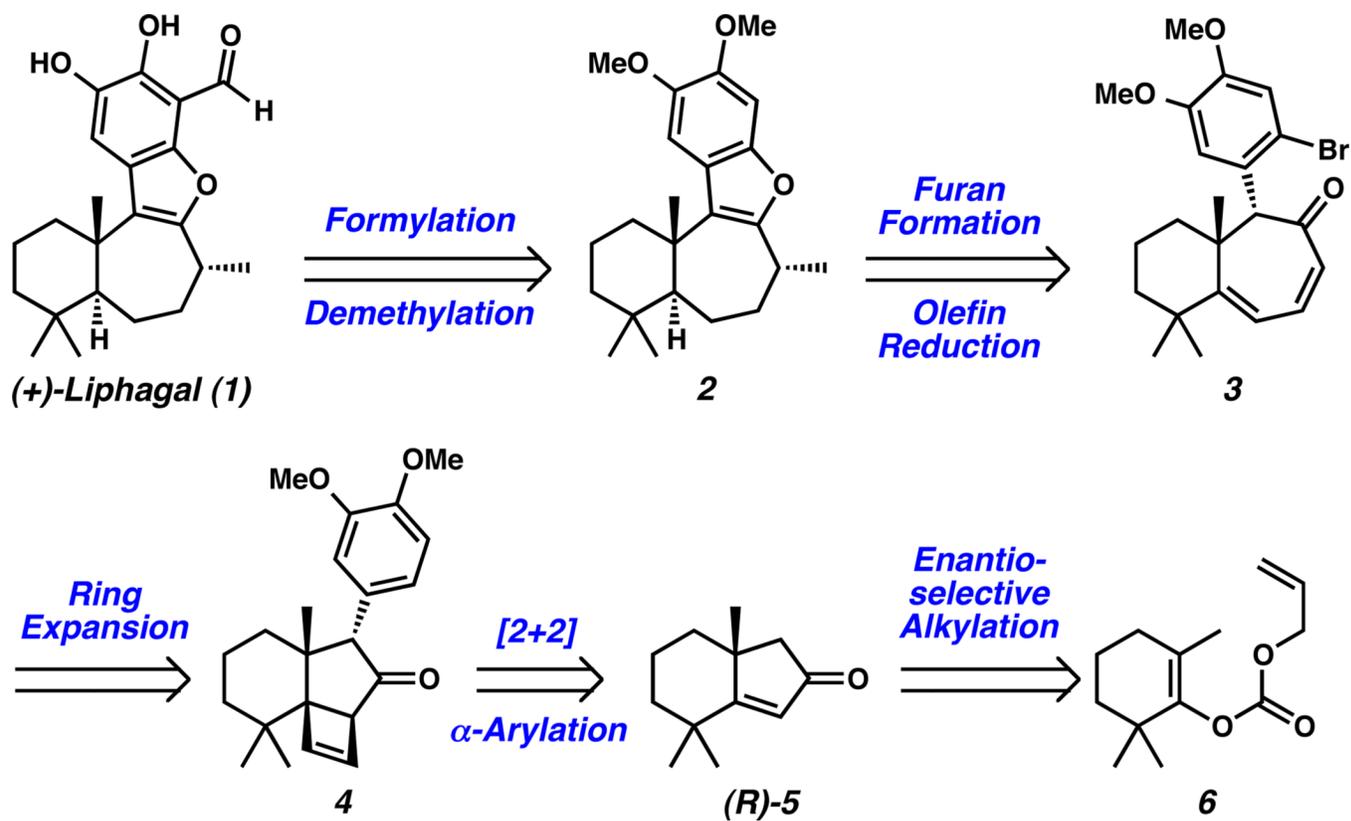
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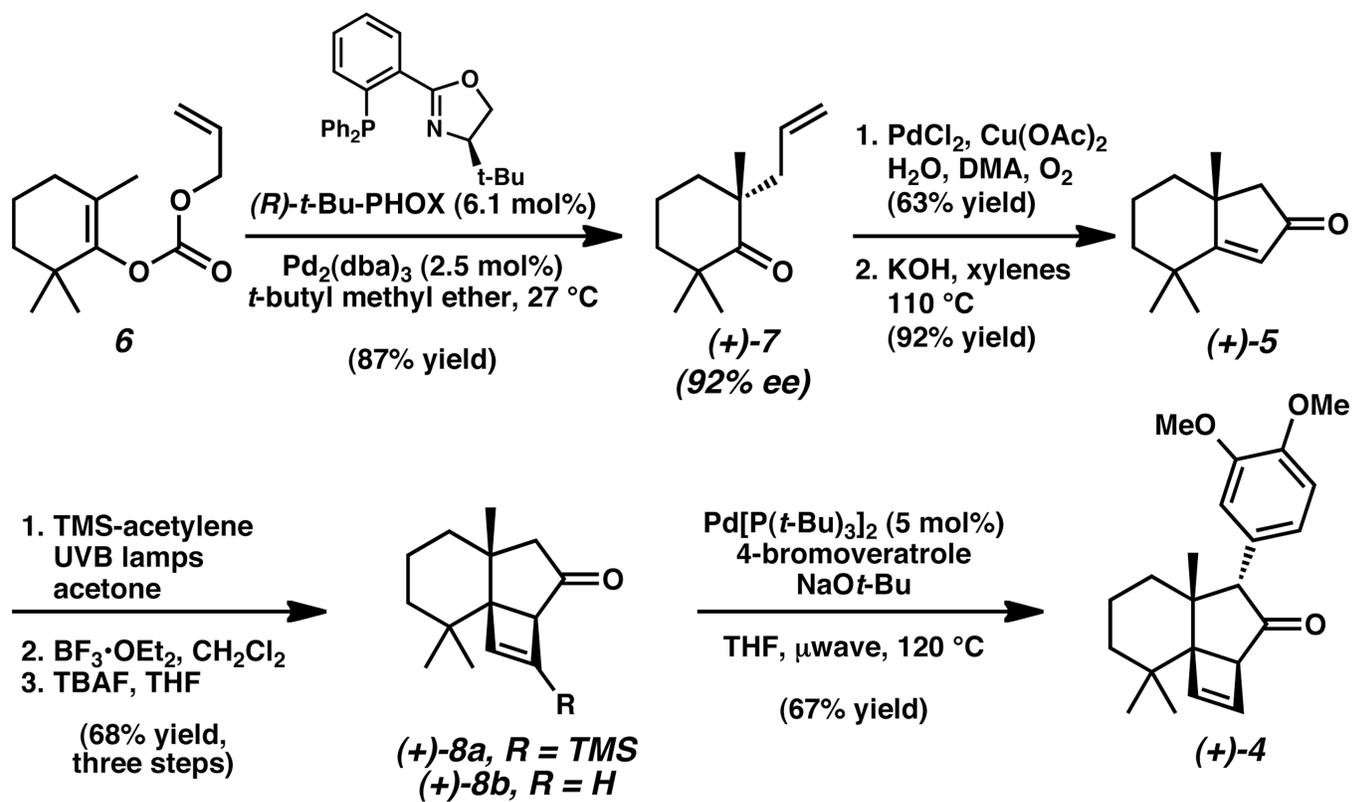


18. See Supporting Information for experimental details.
19. At this stage in the synthesis it was not possible to determine the relative stereochemistry of tricycle **8**.
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**(+)-Liphagal (1)*****R=OH: Myricetin***
R=H: Quercetin***Resveratrol******Staurosporine******Viridin******Wortmannin*****Figure 1.**
Natural Product Inhibitors of PI3K.

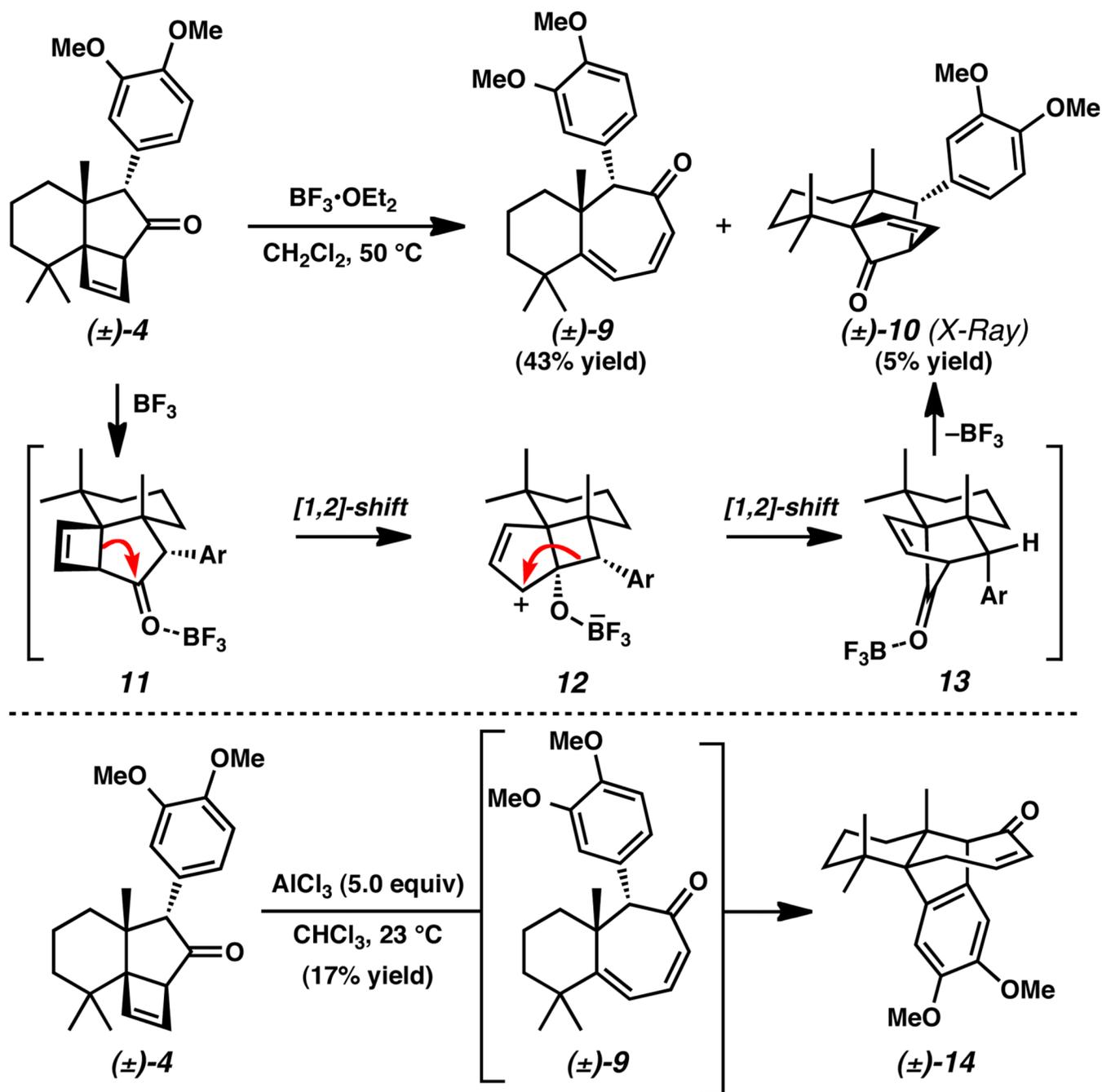


Scheme 1.
Liphagal Retrosynthesis

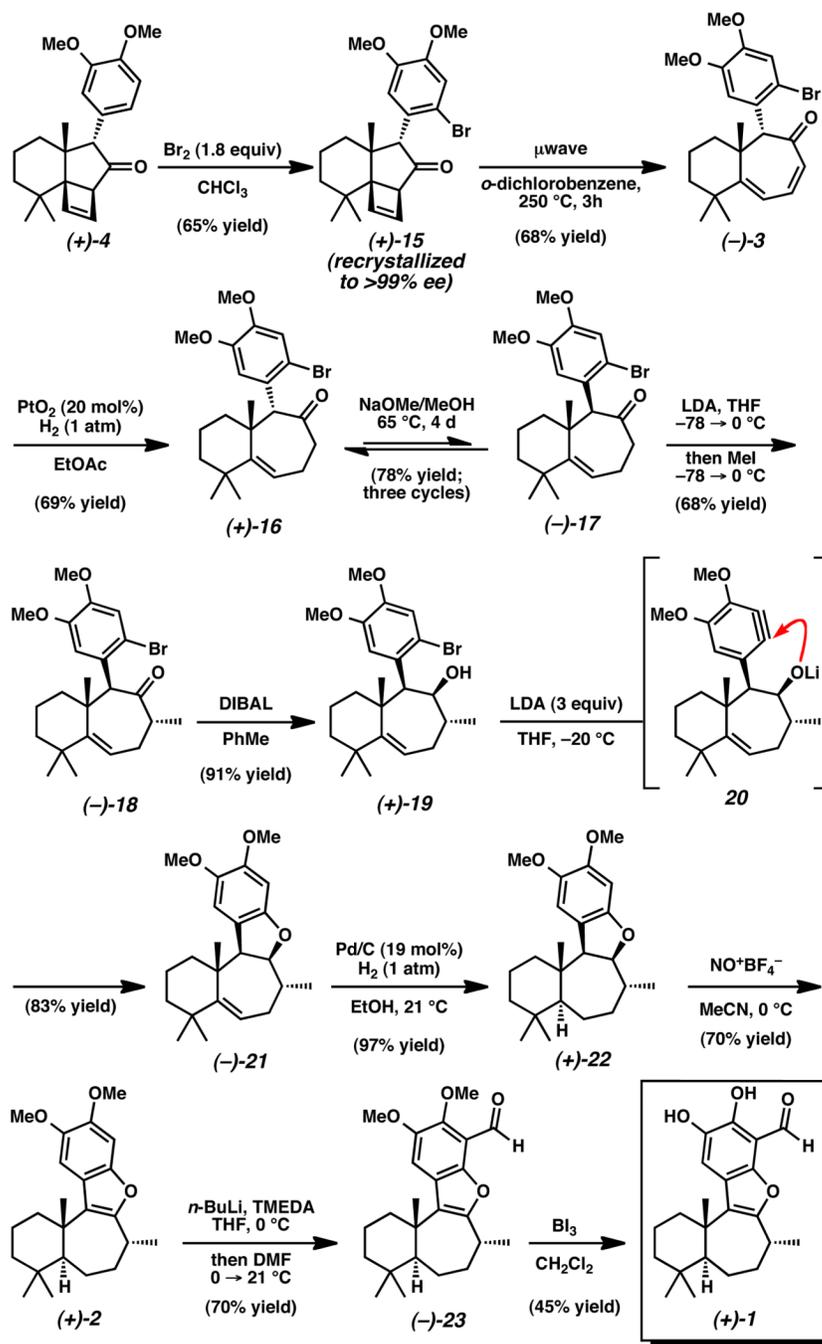


Scheme 2.

Catalytic enantioselective preparation of synthetic building block (+)-7 and chemical elaboration to (+)-4.



Scheme 3.
Unexpected rearrangement and reactivity of strained cyclobutane 4.



Scheme 4.
Completion of the total synthesis of Liphagal (+)-1.