ORGANIC LETTERS

2010
Vol. 12, No. 20
4450−4453

Enantioselective Total Synthesis of the Selective PI3 Kinase Inhibitor Liphagal

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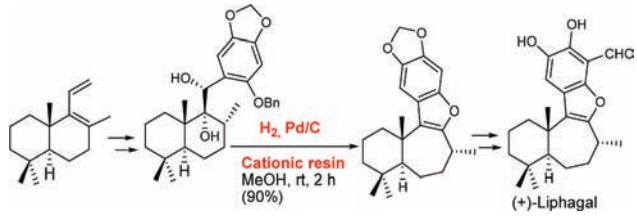
Received May 21, 2010

ABSTRACT



The enantioselective total synthesis of liphagal, a selective inhibitor of PI3K α isolated from the marine sponge *Aka coralliphaga*, has been achieved. The novel tetracyclic "liphagane" skeleton is formed in one step, after the hydrogenation of a dihydroxydrimane phenol benzyl ether in the presence of cationic resin.

In recent decades, marine organisms appear to have become an almost inexhaustible source of natural products, showing very different structural patterns and a wide variety of interesting biological activities.[1] A paradigmatic example of this type of metabolites is liphagal (**1**, Figure 1), a merot-erpenoid recently isolated from the marine sponge *Aka coralliphaga*,[2] which exhibits the novel "liphagane" carbon skeleton. Besides its uncommon structure, liphagal (**1**) presents considerable therapeutic potential, with inhibitory activity against PI3K α (phosphoinositide-3-kinase α). It is more potent than the synthetic LY 294002 and more selective than wortmanin, making it a promising candidate as an agent for the treatment of inflammatory and autoimmune disorders as well as cancer and cardiovascular diseases.[3] In fact, liphagal (**1**) has been observed to be cytotoxic, in secondary in vitro assays, to LoVo (human colon: IC_{50} 0.58 μM), CaCo (human colon: IC_{50} 0.67 μM), and MDA-468 (human breast: IC_{50} 1.58 μM) tumor cell lines. The protein kinase C inhibitors corallidictyals, such as corallidictyal B (**2**) and D (**3**), are spirosesquiterpene aldehydes closely related to compound **1** and isolated from the same natural source.[4]

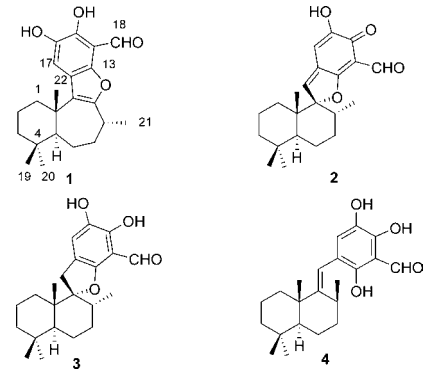


Figure 1. Metabolites from *Aka coralliphaga*.

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(1) For a recent review on marine natural products, see: Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2010**, *27*, 165.

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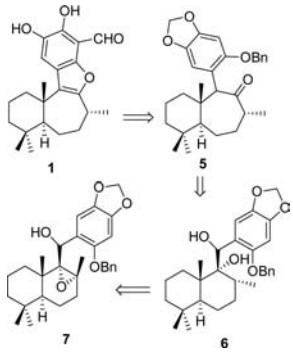
10.1021/ol101173w
Published on Web 06/02/2010

Two racemic syntheses of liphagal (**1**) have been reported. Andersen et al., after isolating compound **1** from its natural source, developed a synthesis of this bioactive metabolite, which involves as the key step the cation-initiated cyclization of a dienyl benzofuran.[2] Recently, Mehta et al. described a closely related strategy to synthesize (±)-**1**, based on the acid-promoted cyclization of a cyclohexenyl benzofuran.[5]

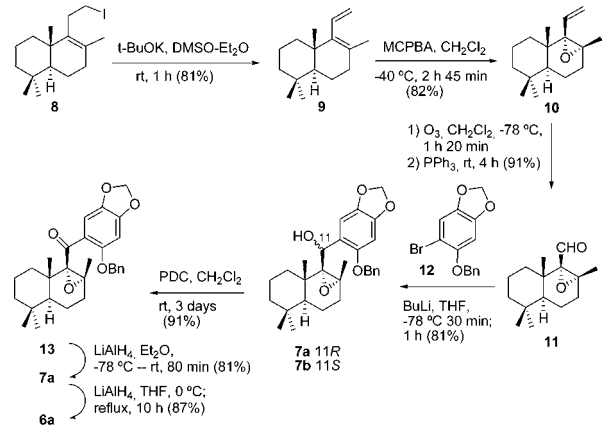
Andersen's group proposed two possible biogenic pathways to liphagal (**1**), starting from a farnesyl trihydroxybenzaldehyde. One of these pathways takes place via the bicyclofarnesyl trihydroxybenzaldehyde siphonodictyal B (**4**),[6] a metabolite also found in the sponge *Aka coralliphaga*. In the alternative pathway, the benzofuran system is first formed from an acyclic ketone and the 6,7-ring system is subsequently created, after the acid promoted cyclization of a dienyl benzofuran.[2]

Scheme 1. Retrosynthesis of Liphagal (**1**)



During our research into the synthesis of bioactive natural products, we were interested in developing an enantioselective synthesis of liphagal (**1**), making it possible to establish its absolute stereochemistry. Scheme 1 shows the retrosynthesis planned for compound **1**. The furan ring will be formed by dehydration of the hemiketal resulting from the hydroxy ketone derived from compound **5**. This will result from the pinacol rearrangement of diol **6**, resulting from the regioselective reduction of epoxy alcohol **7**. This will be obtained after the addition of an aryllithium to an epoxy aldehyde. Scheme 2 shows the synthesis of epoxy alcohols **7a**,**b** via epoxy aldehyde **11**. The synthesis of compound **11** is not a trivial task. Different synthetic procedures have been reported for the construction of the (2,5,5,8a-tetramethyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methylene skeleton of this compound, including total syntheses,[7] biomimetic cyclizations,[8] or hemisyntheses starting from polycyclic natural products.[9]

Scheme 2. Synthesis of Epoxy Alcohols **7a**,**b**



However, the stereoselective introduction of the epoxide function involves certain difficulties.

It is well-known that the epoxidation of the allyl alcohol precursor of aldehyde **11** is not stereoselective, leading to a 2.5:1 mixture of the corresponding α- and *β*-epoxy derivatives, respectively.[10] In order to improve the efficiency of synthetic sequence, the utilization of this allyl alcohol as an intermediate was ruled out, and the diene **9** was investigated as an alternative precursor; this compound underwent chemo- and stereoselective epoxidation at low temperatures, affording the epoxy alkene **10** in high yield. Diene **9** has been easily synthesized from various starting materials, such as a (*S*)-(+)-Wieland−Miescher ketone analogue[11] or the natural monoterpene (*R*)-(−)-carvone;[12] compound **9** has also been obtained after dehydrohalogenation of allyl iodide **8**, synthesized after the lipase-catalyzed kinetic resolution following the acid cyclization of homofarnesyl acetate[13] or from commercial sclareolide, the latter being the most efficient procedure for synthesizing diene **9** (three steps, 65% overall yield).[14] Ozonolysis of epoxy alkene **10**, whose relative stereochemistry was established on the basis of NOE experiments, gave aldehyde **11** in good yield.

(3) For recent reviews on the therapeutic potential of phosphoinositide-3-kinase inhibitors, see: (a) Ward, S. G.; Sotsios, Y.; Dowden, J.; Bruce, I.; Finan, P. *Chem. Biol.* **2003**, *10*, 207. (b) Ward, S. G.; Finan, P. *Curr. Opin. Pharmacol.* **2003**, *3*, 426.

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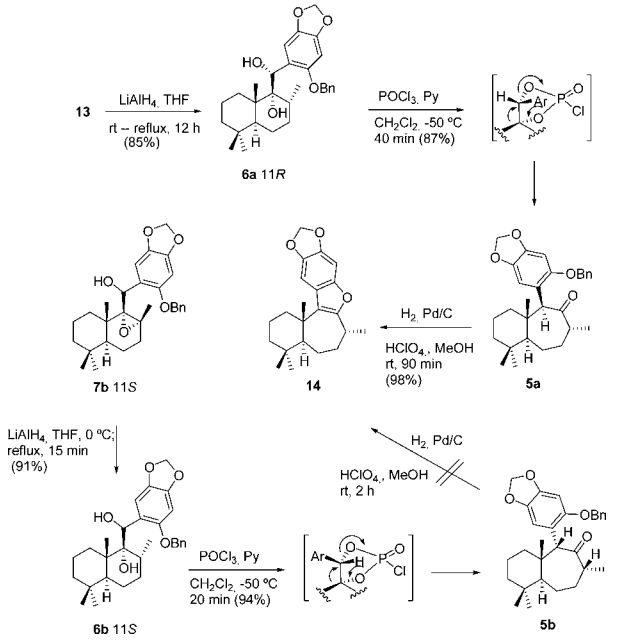
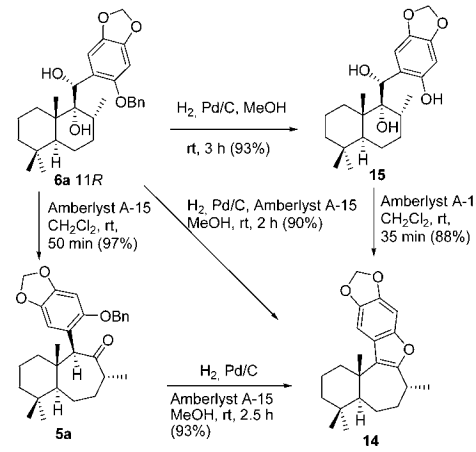
Treatment of this with the aryllithium derived from bromide **12**, which is straightforwardly prepared from the very accessible sesamol,[15] gave epoxy alcohols **7a**,**b** as a 1:1 mixture, which was resolved after combined column chromatography and crystallization. Oxidation of the mixture of epoxy alcohols **7a**,**b** with PDC gave ketone **13**, which after treatment with $LiAlH_4$ in Et_2O cooled at −78 °C and further stirring at room temperature for 80 min gave compounds **7a**,**b** in a 5:1 ratio; further recrystallization afforded pure stereoisomer **7a**. The configuration on the C-11 of compounds **7a** and **7b** was established on the basis of chemical evidence and by chemical correlation with compounds **5a** and **5b**. Epoxy alcohol **7b** underwent fast epoxide ring-opening with complete regio- and stereoselectivity to give the corresponding 11*S* diol **6b** by refluxing with $LiAlH_4$ in THF; under the same reaction conditions, epoxy alcohol **7a** was slowly converted into the corresponding 11*R* diol **6a**. This could be attributed to the steric hindrance of angular methyl and the aromatic ring arising in the alkoxyaluminium intermediate generated during the reduction of compound **7a**.

Scheme 3. Construction of the "Liphagane" Skeleton



The next step was to address the construction of the liphagane skeleton (scheme 3). The elaboration of the fused 6,7-ring system was achieved after the pinacol rearrangement of diols **6a**,**b**. Treatment of the 11*R* diol **6a** with $POCl_3$ and pyridine in dichloromethane at −50 °C for 40 min gave in 87% yield the corresponding cycloheptanone **5a**; the 11*S* diol **6b** under these reaction conditions led to the epimeric ketone **5b**. The C-10 configurations for compounds **5a** and **5b** were established on the basis of NOE experiments. Hydrogenation of compound **5a** in the presence of perchloric acid afforded in excellent yield benzofuran **14**, which possesses the tetracyclic liphagane skeleton. Under the same reaction conditions, the isomer **5b** gave compound **14** in trace amounts, together with an unresolvable mixture of compounds. All attempts at converting compound **5b** into its epimer **5a**, under different acid (e.g., concd HCl or concd H_2SO_4 in refluxing dioxane) or basic conditions (e.g., DBU in refluxing toluene or KOH in diglyme under reflux), were unsuccessful.

Scheme 4. Direct Synthesis of Liphagane Precursor **14**



Once the liphagane precursor **14** was achieved, our efforts were directed toward shortening the synthetic sequence, and so one-step benzyl ether deprotection and B ring expansion were investigated. With this purpose in mind, the rearrangement of diol **6a** promoted by perchloric acid was studied. Unfortunately, the treatment of compound **6a** with this acid afforded a 1:1 mixture of epimers **5a**,**b**. After perchloric acid was ruled out, the utilization of mild acid conditions was investigated. Diol **6a** was transformed into ketone **5a** in good yield with complete stereospecificity by treatment with Amberlyst A-15 in methanol. Interestingly, the dihydroxyphenol **15** underwent simultaneous rearrangement and formation of the furan ring, directly affording the liphagane intermediate **14**, after cationic resin treatment (Scheme 4). Next, hydrogenation in the presence of cationic resin was investigated. The treatment of a mixture of ketone **5a**, palladium on carbon, and Amberlyst in methanol, under a hydrogen atmosphere, gave in good yield the liphagane precursor **14**. Finally, the simultaneous rearrangement, benzyl ether deprotection, and furan ring formation were tackled. When a methanolic solution of diol **6a** was treated with palladium on carbon and cationic resin, under a hydrogen atmosphere, the liphagane compound **14** was obtained (Scheme 4); the hydroxyl phenol **16** was also obtained as a minor constituent when the hydrogen pressure was increased and the proportion of cationic resin reduced.

A possible mechanism for the direct formation of the liphagane precursor **14** from diol **6a**, via dihydroxy phenol

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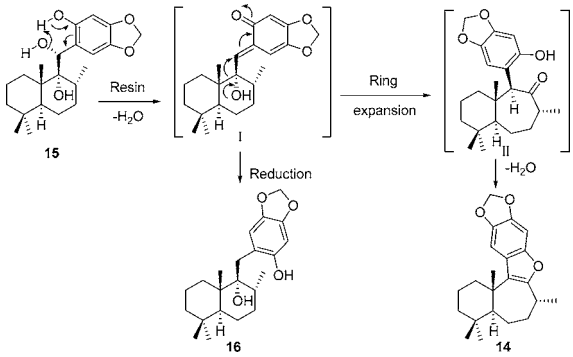
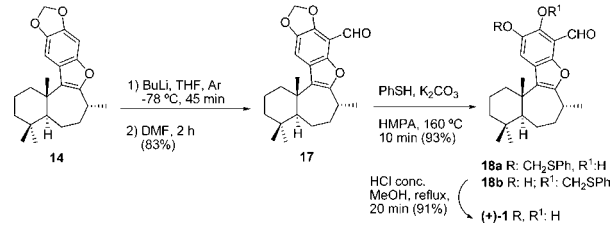
Scheme 5. Mechanism for the Formation of **14** and **16**



Scheme 6. Synthesis of Liphagal (**1**) from Benzofuran **14**



15, promoted by cationic resin, is depicted in Scheme 5. The cycloheptanone derivative **II** could be generated after the rearrangement of the hydroxy trienone **I**; further hemiketalization and dehydration would lead to the liphagane intermediate **14**. The hydroxyl phenol **16** would be formed by reduction of the intermediate **I**, prior to the rearrangement process. The lack of stereospecificity observed during the perchloric acid promoted ring expansion can be attributed to the formation of an intermediate benzyl cation.

Finally, compound **14** was transformed into liphagal (**1**) (Scheme 6). Treatment of this with BuLi in THF at −78 °C followed by the addition of DMF and further reaction for 2 h gave aldehyde **17**. Deprotection of the methylenedioxy group was achieved utilizing a modification of the Imakura procedure.[16] A 6:1 mixture of phenylsulfides **18a** and **18b** resulted when compound **17** was heated with PhSH and K_2CO_3 in HMPA at 160 °C for 10 min. Refluxing a methanolic solution of sulfides **18a**,**b** in the presence of catalytic concd HCl led to liphagal (**1**). This compound had the same spectroscopic properties as reported in the literature. The $[\alpha]_D$ +17.9 [lit.[2] +12.0] confirms the absolute stereochemistry.

In summary, the first enantioselective synthesis of the selective inhibitor of PI3 kinase α liphagal (**1**) is reported; this allows us to establish absolute stereochemistry for this marine metabolite. Key steps of the synthetic sequence are the chemo- and stereoselective epoxidation of a homodrimane diene and the one-step transformation of a dihydroxydrimane phenol benzyl ether into the tetracyclic "liphagane" precursor, which involves a stereospecific pinacol rearrangement, the benzyl ether deprotection, the formation of a hemiketal, and its subsequent dehydration.[17]

Acknowledgment. We thank the Spanish Ministry of Science and Innovation (Project No. CTQ2009-09932).

Note Added after ASAP Publication. Reference 17 was added to the version reposted on June 17, 2010.

Supporting Information Available: Experimental details and ^{1}H NMR and ^{13}C NMR spectra for compounds **1**, **5a**,**b**, **6a**,**b**, **7a**,**b**, **9**−**11**, and **13**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101173W

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(17) While this manuscript was in preparation, a similar approach to liphagal was published, see: George, J. H.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2010**, *12*, 2394.