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Enantiospecific, Biosynthetically Inspired Formal Total Synthesis of (+)-Liphagal

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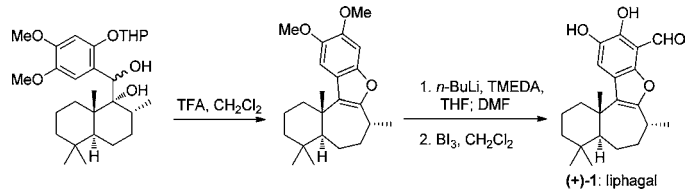
ABSTRACT



A biosynthetically inspired synthesis of (+)-liphagal has been achieved from (+)-sclareolide in 13 steps (9% overall yield). The key step is a biomimetic ring expansion of a highly stabilized benzylic carbocation, which generates the seven-membered ring and the benzofuran of the natural product in a single cascade reaction.

Liphagal (**1**) is a tetracyclic meroterpenoid natural product isolated by Andersen et al.[1] in 2006 during a program designed to discover new inhibitors of the phosphoinositide-3-kinase (PI3K) signaling pathway.[2] A library of marine invertebrate extracts were screened in a fluorescent polarization assay using human PI3K α expressed in SF9 insect cells, and the MeOH extract of the Dominican marine sponge *Aka Coralliphaga* showed promising activity. Liphagal (**1**) was subsequently isolated from this extract, and its unusual structure, featuring a 6−7 ring system fused to a benzofuran, was assigned by comprehensive NMR studies. Liphagal (**1**) showed inhibitory activity against PI3K α with an IC_{50} of 100 nM in the primary fluorescent polarization enzyme assay, and it was observed to be approximately 10-fold more potent against PI3K α than PI3K γ. In addition, liphagal was found to be cytotoxic 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) cell lines in secondary *in vitro* cell assays.

Two possible biosynthetic pathways to form the fused 6−7 ring system of liphagal (**1**) were proposed by Andersen.[1] In the first pathway, polyene cyclization of a farnesylated trihydroxybenzaldehyde **I** could give the tertiary carbocation **II**, which contains a fused 6−6 ring system (Scheme 1). This carbocation could be converted to the known natural product siphonodictyal B[3] (**4**), also isolated from *Aka Coralliphaga*, via hydride shift and deprotonation. Siphonodictyal B (**4**) could then be transformed into liphagal via epoxidation, ring expansion of the resultant epoxide **III** to give ketone **V**, epimerization at C-8 to give **VI**, and finally dehydration to form the fused benzofuran of **1**. Furthermore, we propose that the ring expansion of **III** → **V** may occur via the *o*-quinone methide **IV** in a process analogous to an α-hydroxy aldehyde rearrangement or a pinacol rearrangement. *o*-Quinone methides have been invoked in a range of biosynthetic pathways and used in several biomimetic

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(2) For a review of known PI3K inhibitors see Sundstrom, T. J.; Anderson, A. C.; Wright, D. L. *Org. Biomol. Chem.* **2009**, *7*, 840.

(3) (a) Sullivan, B.; Djura, P.; McIntyre, D.; Faulkner, D. J. *Tetrahedron* **1981**, *37*, 979. (b) Sullivan, B. W.; Faulkner, D. J. *J. Org. Chem.* **1986**, *51*, 4568.

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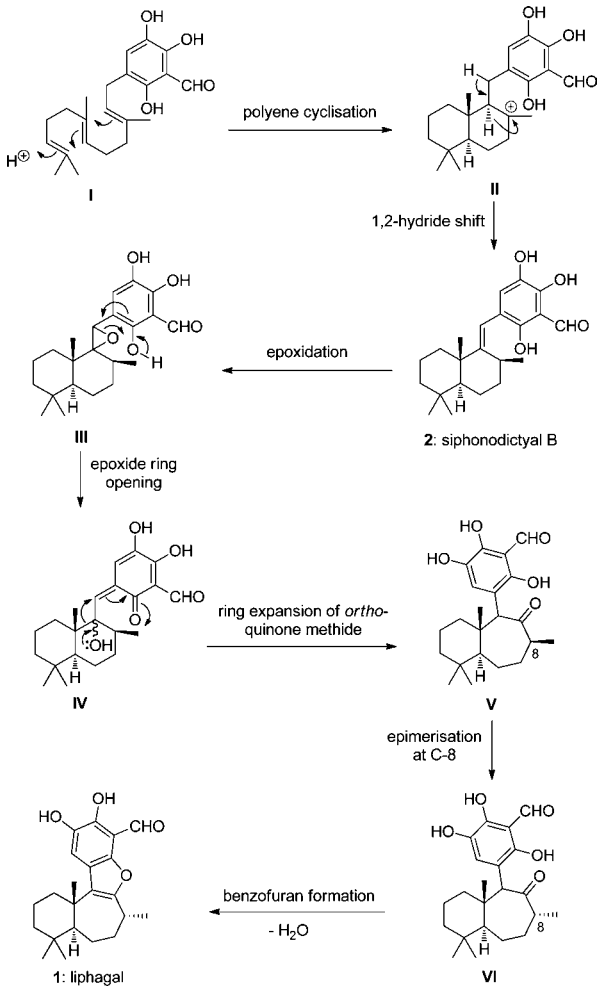
Scheme 1. Proposed Biosynthesis of Liphagal via Ring Expansion of an *o*-Quinone Methide Intermediate



syntheses,[4] although their rearrangement via alkyl shifts has not been reported. However, in the case of liphagal biosynthesis the intermediacy of an *o*-quinone methide seems likely. Several stable *o*-quinone methides tethered to bicyclic sesquiterpenoids similar to **IV** have been reported.[5]

The biosynthesis of liphagal via quinone methide intermediates is supported by the co-isolation of corallidictyals A (**3**) and B (**4**) from *Aka Coralliphaga*,[6] which are presumably formed by spirocyclization of the *p*-quinone methide **VII** (Scheme 2).

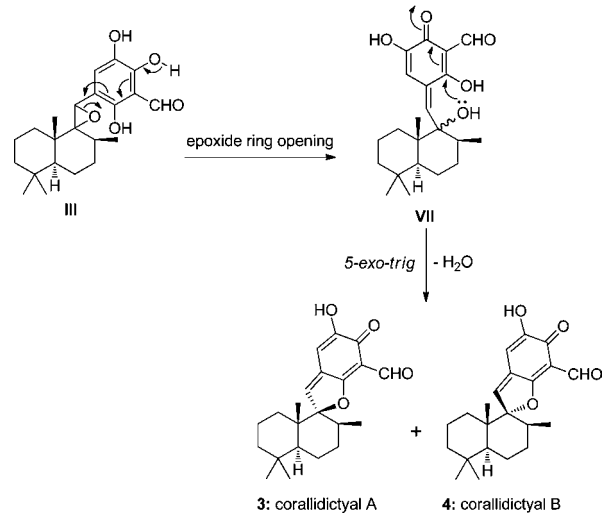
The second biosynthetic pathway to liphagal proposed by Andersen involves polyene cyclization of a benzofuran to generate the 6−7 ring system directly.[1] This more direct pathway has been investigated in the course of biomimetic

(4) For a review of *o*-quinone methides in organic synthesis, see: Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367.

(5) Barrero, A. F.; Alvarez-Manzaneda, E. J.; Chahboun, R.; Cortes, M.; Armstrong, V. *Tetrahedron* **1999**, *55*, 15181.

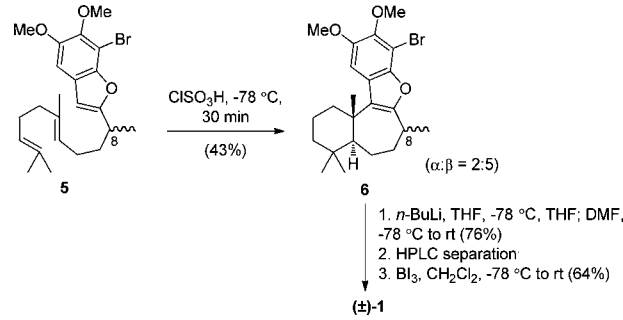
(6) (a) Chan, J. A.; Freyer, A. J.; Carte, B. K.; Hemling, M. E.; Hofmann, G. A.; Mattern, M. R.; Mentzer, M. A.; Westley, J. W. *J. Nat. Prod.* **1994**, *57*, 1543. (b) Grube, A.; Assmann, M.; Lichte, E.; Sasse, F.; Pawlik, J. R.; Kock, M. *J. Nat. Prod.* **2007**, *70*, 504.

Scheme 2. Proposed Biosynthesis of Corallidictyal A and B via Spirocyclization of a *p*-Quinone Methide Intermediate



syntheses of liphagal by Andersen[1] and Mehta,[7] who both synthesized the brominated benzofuran **5**. Acid-mediated cyclization of this compound gave **6** in 40% yield as a 2:5 mixture of C-8 epimers in favor of the undesired β-isomer (Scheme 3).

Scheme 3. Andersen's Synthesis of (±)-Liphagal

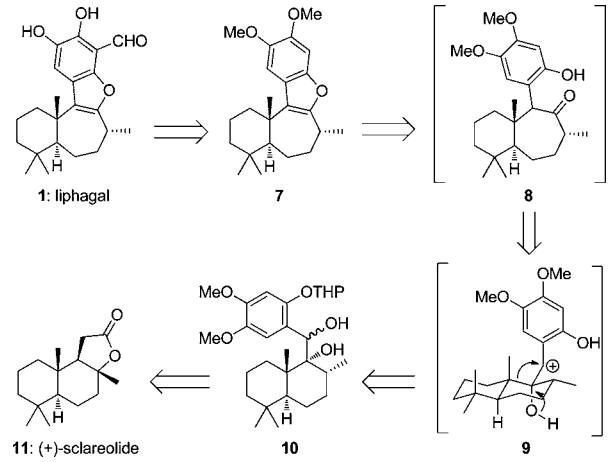


As part of our continuing interest in the biomimetic synthesis of marine derived natural products we proposed to investigate the ring-expansion biosynthetic pathway to liphagal, which we believe to be the more plausible biogenesis because of the co-isolation of siphonodictyal B (**2**) and corallidictyals A (**3**) and B (**4**) from *Aka Coralliphaga* with liphagal. Furthermore, this strategy could form the 6−7 fused ring system from a more readily accessible 6−6 ring system and could therefore lead to a more efficient synthesis of the natural product that avoids the poor yield and low stereoselectivity of the direct polyene cyclization reported by Andersen and Mehta.

Our proposed retrosynthesis of liphagal (**1**) is outlined in Scheme 4. It was our belief that **1** could be generated from

(7) Mehta, G.; Likhite, N. S.; Kumar, C. S. A. *Tetrahedron Lett.* **2009**, *50*, 5260.

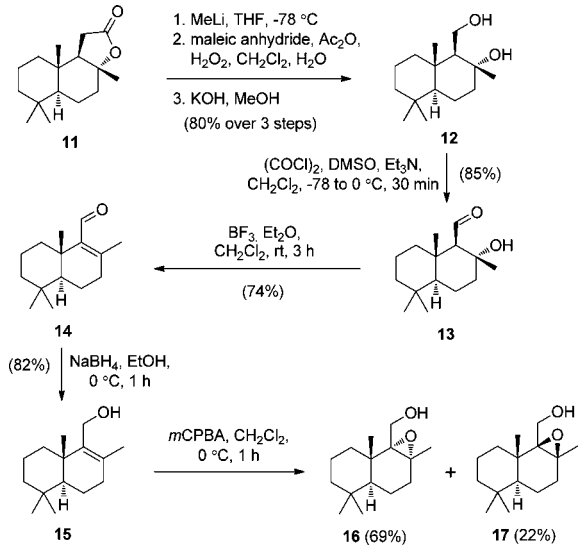
Scheme 4. Biosynthetically Inspired Retrosynthesis of Liphagal



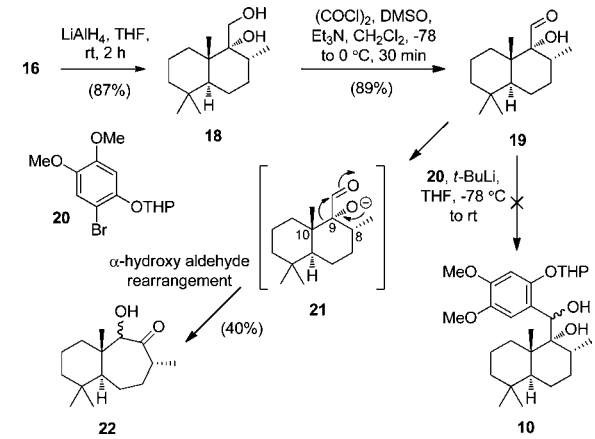
the dimethoxy compound **7** via a formylation reaction followed by demethylation. Benzofuran **7** could be formed from ring expansion of the stabilized benzylic carbocation **9** (a synthetic equivalent of the *o*-quinone methide **IV**) via a pinacol-type rearrangement to give ketone **8** followed by dehydration. The stabilized carbocation intermediate **9** could be generated under mild conditions from an *o*-hydroxybenzyl alcohol that could be formed by the acid-mediated removal of the THP group from **10**. It was envisaged that the key ring-expansion substrate **10** could be synthesized from the cheap, chiral starting material (+)-sclareolide (**11**). Use of this enantiopure building block would ultimately allow the absolute configuration of liphagal to be determined.

Our synthesis commenced with the conversion of (+)-sclareolide (**11**) into diol **12** in three steps according to a modified version of the procedure of Kuchkova et al. (Scheme 5).[8] Swern oxidation of **12** gave the β-hydroxy aldehyde **13**,[9] which was dehydrated with $BF_3.Et_2O$ in CH_2Cl_2 to give α,β-

Scheme 5. Synthesis of Epoxide **16** from (+)-Sclareolide



Scheme 6. Attempted Addition of an Aryllithium to α-Hydroxy Aldehyde **19**



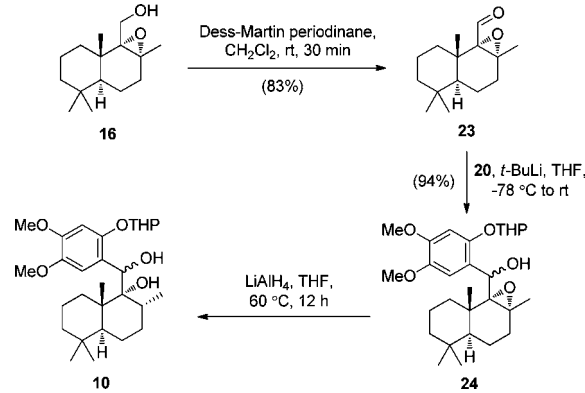
unsaturated aldehyde **14**. Reduction of this compound with $NaBH_4$ gave allylic alcohol **15**, which was epoxidized with *m*CPBA to give epoxides **16** and **17** as a 3:1 mixture (separable by SiO_2 flash column chromatography).[10]

Reductive ring opening of epoxide **16** with $LiAlH_4$ gave diol **18**, which was subjected to a Swern oxidation to give α-hydroxy aldehyde **19**. The aryllithium generated from **20**[11] and *t*-BuLi in THF at −78 °C failed to add to **19** to give **10**. Instead, the main isolated product was the α-hydroxy ketone **22**, which was formed in 40% yield (1.5:1 mixture of C-10 epimers). The ring expansion product **22** was presumably formed by deprotonation of the hydroxy group of **19** to give tertiary alkoxide **21**, followed by an α-hydroxy aldehyde rearrangement[12] to give **22**.

Although not the desired outcome, this reaction did at least indicate selective migration of the more electron-rich C(9)−C(10) bond instead of the C(8)−C(9) bond, as required in our planned biomimetic synthesis of liphagal.

One approach to improve the addition of an aryllithium species to the α-hydroxy-aldehyde **19** would be to protect the hydroxy group. Alternatively, the order of the epoxide ring opening, oxidation, and aryllithium addition could be altered, as shown in Scheme 7. Oxidation of **16** with

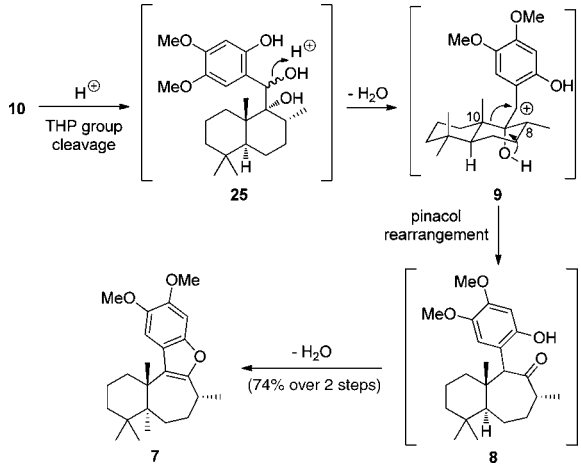
Scheme 7. Synthesis of Ring Expansion Precursor **10**



Dess−Martin periodinane gave aldehyde **23**, which reacted smoothly with the aryllithium generated from **20** and *t*-BuLi to give **24** in 94% yield. Reductive ring opening of the epoxide of **24** with $LiAlH_4$ then gave **10**, which was used without further purification.

With **10** in hand, the key biomimetic ring-expansion reaction could be investigated. Treatment of crude **10** with TFA in CH_2Cl_2 at −78 °C followed by gradual warming to room temperature gave the ring-expanded product **7** in 74% yield over two steps (Scheme 8).

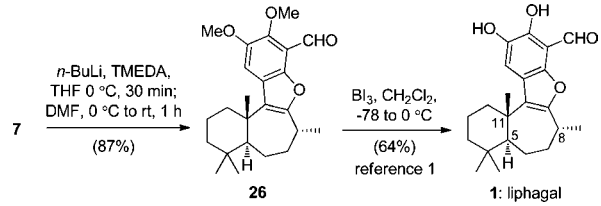
Scheme 8. Ring Expansion via Pinacol-Type Rearrangement of a Stabilized Benzylic Carbocation



This cascade reaction presumably proceeds via initial removal of the labile phenolic THP group to give **25**, which could undergo a facile dehydration to generate the highly stabilized benzylic carbocation **9**. Pinacol rearrangement of this transient intermediate via selective migration of the C(9)−C(10) bond would then give the cycloheptanone **8**, which could undergo dehydration to form the benzofuran of **7**. Note that similar acidic reaction conditions have been used to generate *o*-quinone methides from suitably substituted benzylic alcohols,[13] so it is possible that the ring expansion **10** → **8** proceeds via an *o*-quinone methide rather than a stabilized carbocation.

The synthesis of (+)-liphagal was continued by *ortho*-lithiation of **7** and quenching of the resultant aryllithium species with DMF to install the aromatic aldehyde group of **26** (Scheme 9). This compound has previously been dem-

Scheme 9. Completion of the Synthesis of Liphagal



ethylated with BI_3 by Andersen et al. to give **1**. The ^1H and ^{13}C NMR spectra of **26** were identical to those previously reported,[1] as was the $[\alpha]_D$,[1b] which confirms that the absolute configuration of (+)-liphagal is (5*S*,8*R*,11*S*).

In summary, a concise and enantiospecific formal total synthesis of a potent PI3K inhibitor, liphagal (**1**), has been achieved in 13 steps (9% overall yield) from (+)-sclareolide (**11**). The key step is a biosynthetically inspired cascade reaction involving ring expansion of a benzylic alcohol, followed by benzofuran formation. Importantly, the late-stage introduction of the aryl group in the synthesis should allow access to a range of liphagal analogues with differentially substituted benzofuran rings for evaluation as PI3K inhibitors.

Acknowledgment. We thank F. Hoffman-La Roche Ltd, Basel, Switzerland for postdoctoral funding (J.G.).

Supporting Information Available: Experimental procedures and spectral data for compounds **7**, **10**, **15**−**19**, **23**, **24**, and **26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For a review see: Paquette, L. A.; Hofferberth, J. E. The a-Hydroxy Ketone (a-Ketol) and Related Rearrangements. In *Organic Reactions*; Overman, L. E., Ed.; John Wiley & Sons: New York, 2003; Vol. 63, pp 477−567.

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