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A concise synthesis of the bioactive meroterpenoid natural product (±)-liphagal, a potent PI3K inhibitor

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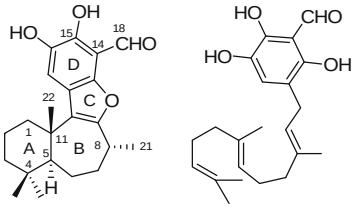
ABSTRACT

A short, diversity-oriented synthesis that follows a biomimetic route to the marine natural product liphagal, from a commercially available building block, is delineated.

Natural products from diverse marine resources have emerged as a copious repository of molecular diversity and hold considerable promise as a rich source of lead structures in drug discovery.[1,2] As a result, marine flora and fauna continue to be explored vigorously by many natural product chemists in search of new structural entities and unique biological activity.[2] During a collaborative program to screen marine invertebrate extracts using a fluorescent polarization assay against human PI3K α, Andersen et al., in 2006, reported the isolation of a novel meroterpenoid named liphagal **1** from the methanol extract of the sponge *Aka coralliphaga*, collected from reefs in Prince Rupert Bay, Portsmouth, Dominica.[3] The structure and stereochemistry of liphagal **1** were elucidated on the basis of extensive and complementary spectral analyses, particularly NMR (HMQC, HMBC, and 1D NOESY) studies.[3] Liphagal **1** represents the first member of a new 'liphagane' type of meroterpenoid carbon skeleton. A mixed biogenetic pathway for liphagal **1**, emanating from arylated farnesol **2** has been proposed[3] and it accounts for the AB rings of this natural product displaying a characteristic sesquiterpene-like architecture.

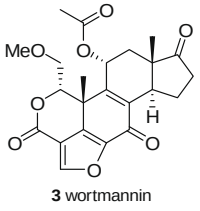


1 liphagal

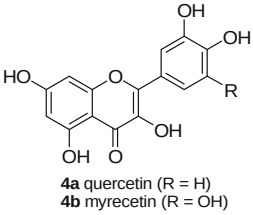
2

Liphagal **1** exhibited impressive biological activity including inhibitory activity against PI3K α (phosphoinositide-3-kinase α) with an IC_{50} of 100 nM in a primary fluorescent polarization assay.[3]

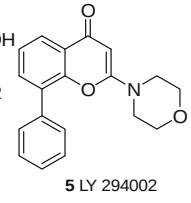
Interestingly, **1** was found to be about 10-fold more potent against PI3K α than its isoform PI3K γ.[3] Additionally, in secondary in vitro assays, liphagal was observed to be cytotoxic to LoVo (human colon: IC_{50} 0.58 μM), CaCo (human colon: IC_{50} 0.67 μM), and MDA-468 (human breast: IC_{50} 1.58 μM) tumor cell lines.[3] These impressive bioactivity profiles, particularly the inhibition of PI3K α have drawn widespread attention because phosphatidylinositol-3-kinases (PI3Ks) are pivotal enzymes that control a wide array of intracellular signaling cascades and thus regulate cell proliferation and survival, adhesion, chemotaxis, differentiation, glucose transport, membrane trafficking, and neurite outgrowth amongst others.[4] The PI3K α isoform selectivity exhibited by liphagal **1**, compared to other first generation PI3K inhibitors such as wortmannin **3**, the natural flavonoids quercetin **4a** and myrecetin **4b**, and the synthetic analogue LY 294002 **5**, which have been deployed extensively in recent years to probe the PI3K signaling pathways, makes it a lead structure with added value to explore therapeutic potential against cancer and inflammatory and autoimmune disorders.[4a,5] Mutations, translocations, and amplifications of PI3K genes have been observed in several manifestations of human cancer and therefore this lipid kinase is a promising target for small-molecule inhibition and offers promising therapeutic opportunities for the treatment of cancer.[5]



3 wortmannin



4a quercetin (R = H)
4b myrecetin (R = OH)



5 LY 294002

Thus, on account of both the structural novelty of its tetracyclic skeleton, harboring a trans-fused 6,7-bicarbocyclic core with three stereogenic centers, and its promising biological activity profile,

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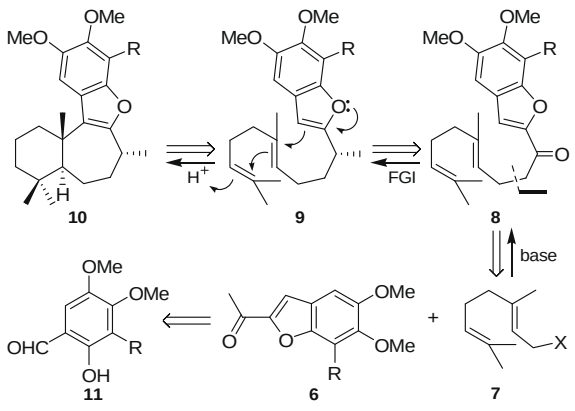
liphagal **1** holds appeal as a synthetic target for total synthesis to deliver the natural product in quantities sufficient for detailed therapeutic evaluation and to build diversity around its novel scaffold. In this Letter, we disclose our approach to liphagal **1**, which is an outcome of our ongoing interest in the synthesis of related meroterpenoids such as frondosins.[6]

The group of Andersen,[3] while elucidating the structure of liphagal **1**, also reported a total synthesis of the natural product mimicking a plausible biogenetic route. Our retrosynthetic strategy toward liphagal was based on the proposed biogenetic pathway[3] and hinged on a key C–C bond disconnection that mandated connecting a preformed benzofuran precursor **6** with a readily available monoterpenoid **7** to establish the crucial C–C bond and access the framework **8**. Further elaboration of **8** into **9** was envisaged to set up the furan polyene cationic cyclization cascade (**9**→**10**) en route to the target (Scheme 1). The key furan precursor **6** was to be accessed from a readily available aromatic precursor **11**.

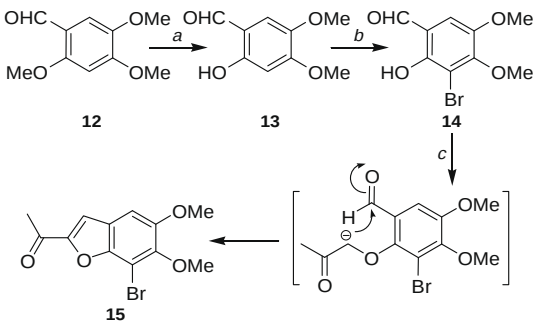
Regioselective monodemethylation of commercially available aldehyde **12** led to **13**, which on selective bromination furnished **14**. One-pot furan annulation[7] of **14** was quite smooth and furnished the requisite bromo-benzofuran **15**[8] in fair yield, Scheme 2. Intermolecular displacement by the enolate anion generated from **15**, on geranyl bromide **16**, was the key step in accessing the carbon framework of the target. After a few exploratory experiments using different bases and solvents, it was observed that the contemplated intermolecular displacement could be effected in the presence of potassium *tert*-butoxide in toluene to furnish the desired product **17** in modest yield,[8] Scheme 3.

Initially, a direct polyene cyclization of **17** was attempted but was understandably unsuccessful, as the conjugating carbonyl group in **17** significantly diminished the propensity of the furan double bond toward participation in the polyene cyclization cascade. It was therefore considered appropriate to first elaborate the carbonyl group in **17** into a surrogate functionality of the C21 methyl group in the target, prior to implementing the projected cationic cascade cyclization. Consequently, furanylketone **17** was subjected to Wittig olefination to furnish the exomethylene compound **18**,[8] Scheme 3.

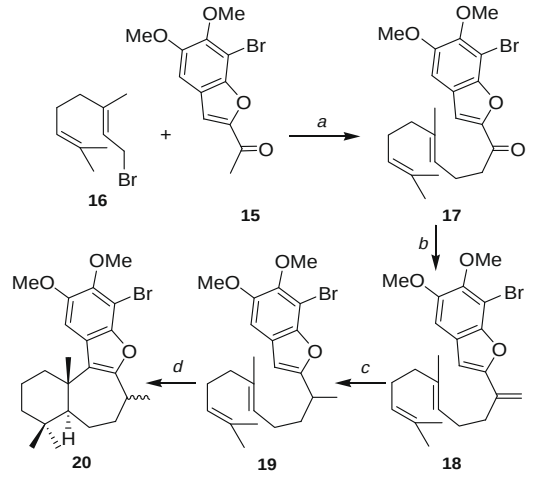
Regioselective catalytic hydrogenation of the triene **18** proceeded uneventfully to furnish the desired product **19**.[8] The stage was now set to implement the pivotal biomimetic cyclization as per a general protocol,[9] which has been adopted successfully by Andersen's group.[3] Exposure of **19** to chlorosulfonic acid in 2-nitropropane led to the formation of tetracyclic **20** (1:2.5 mixture of α- and β-C8-methyl epimers, respectively).[8] As expected, and in keeping with the well-established polyene cyclization, the 6,7-ring fusion had the desired trans stereochemistry.



Scheme 1. Retrosynthetic analysis.

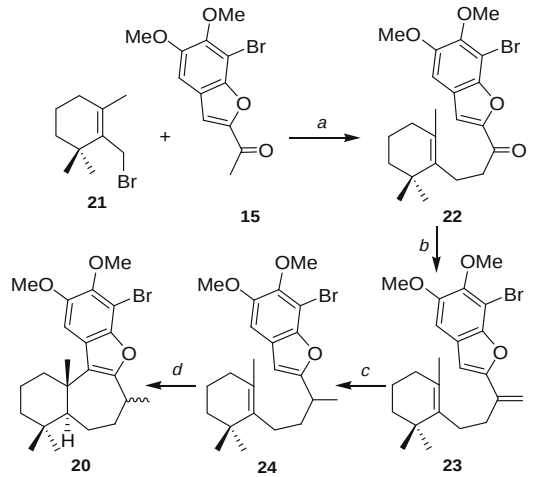


Scheme 2. Reagents and conditions: (a) BBr_3, CH_2Cl_2, 0 °C–rt, 16 h, 87%; (b) Br_2, $AlCl_3$, CH_2Cl_2, 0 °C–rt, 5 h, 77%; (c) K_2CO_3, 2-chloroacetone, butane-2-one, reflux, 3 h, 76%.

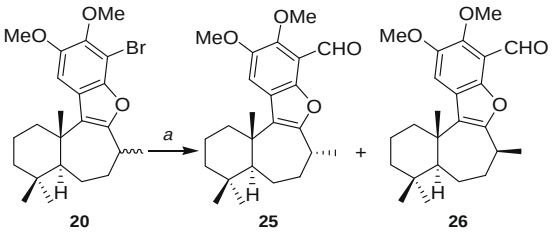


Scheme 3. Reagents and conditions: (a) ^{t}BuOK, toluene, 0 °C, 2 h, 40% based on recovered starting material; (b) $Ph_3P^+CH_3Br^-$, ^{n}BuLi, 0 °C, 30 min, 78%; (c) H_2, 5% Pd–$CaCO_3$ poisoned with Pb, MeOH, rt, 30 min, 88%; (d) $ClSO_3H$, 2-nitropropane, −78 °C, 30 min, 40%.

In a complementary sequence to **20**, cyclogeranyl bromide **21**[10] was employed in an intermolecular displacement by the enolate anion derived from the benzofuran **15** to furnish **22**,[8] Scheme 4. This key C–C bond-forming reaction was somewhat better than



Scheme 4. Reagents and conditions: (a) ^{t}BuOK, toluene, 0 °C, 2 h, 50% based on recovered starting material; (b) $Ph_3P^+CH_3Br^-$, ^{n}BuLi, 0 °C, 30 min, 80%; (c) H_2, 10% Pd–C, ethyl acetate, rt, 10 min, 90%; (d) $ClSO_3H$, 2-nitropropane, −78 °C, 30 min, 40%.



Scheme 5. Reagents and conditions: (a) (i) ^{n}BuLi, THF, −78 °C, 5 min; (ii) DMF, −78 °C–rt, 1 h, 75%.

that with geranyl bromide described above, but only marginally. Compound **22** embodying cyclogeranyl and benzofuran moieties was subjected to Wittig olefination to furnish the exomethylene product **23**,[8] which was reduced catalytically in a regioselective manner to furnish **24**.[8] Chlorosulfonic acid-mediated furan–olefin cyclization followed the desired course and afforded **20** as an epimeric mixture, which was found to be identical to that obtained above from geranyl bromide and benzofuran **15**.

With the key precursor **20** in hand, albeit as a mixture of epimers, the bromine substituent was transformed into an aldehyde group by metal exchange and DMF-mediated formylation to furnish a conveniently separable (HPLC) mixture of tetracyclic aldehydes **25** and **26**,[8] Scheme 5. The resulting liphagal dimethyl ether **25** and the 8-*epi*-liphagal dimethyl ether **26** were found to be spectroscopically identical with the reported compounds.[3,11]

Since the α-epimer **25** has already been deprotected to give the natural product liphagal **1** through boron triiodide-mediated demethylation,[3] our acquisition of the tetracyclic dimethyl ether **25** constitutes a formal synthesis of the natural product.

In conclusion, a short (nine linear steps from a commercial starting material), scalable, and diversity-oriented approach to the bioactive marine natural product liphagal has been described.

Acknowledgments

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8. All new compounds were fully characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR, and HRMS data. Spectral data of selected compounds are as follows: *Compound* **15**: IR (neat): ν_{max} 2924, 1680, 1551, 1461, 1212, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (s, 1H), 7.05 (s, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.89, 153.62, 151.53, 148.46, 148.11, 122.50, 112.43, 102.83, 100.42, 60.91, 56.29, 26.15; HRMS (ES): *m/z* calcd for $C_{12}H_{11}BrO_4$ (M+Na)$^{+}$: 320.9738, found: 320.9733; *compound* **17**: IR (neat): ν_{max} 2925, 1682, 1553, 1460, 1214, 1043 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (s, 1H), 7.07 (s, 1H), 5.20 (t, *J* = 7.0 Hz, 1H), 5.07 (t, *J* = 6.3 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.01 (t, *J* = 7.5 Hz, 2H), 2.47 (dd, *J* = 14.5, 7.3 Hz, 2H), 2.09–1.99 (m, 4H), 1.66 (s, 6H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.82, 153.97, 151.76, 148.61, 148.31, 136.73, 131.37, 124.24, 122.78, 122.43, 112.33, 103.09, 100.72, 61.19, 56.59, 39.66, 39.18, 26.66, 25.63, 22.73, 17.65, 16.05; HRMS (ES): *m/z* calcd for $C_{22}H_{27}BrO_4$ (M+Na)$^{+}$: 457.0990, found: 457.0992; *compound* **18**: IR (neat): ν_{max} 2922, 1613, 1578, 1460, 1211, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.95 (s, 1H), 6.62 (s, 1H), 5.86 (s, 1H), 5.22–5.18 (m, 2H), 5.10 (t, *J* = 6.3 Hz, 1H), 3.90 (s, 6H), 2.48–2.43 (m, 2H), 2.34–2.27 (m, 2H), 2.08–1.98 (m, 4H), 1.69 (s, 3H), 1.61 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.77, 150.76, 147.11, 145.41, 136.89, 136.01, 131.32, 124.56, 124.34, 123.37, 113.17, 102.86, 102.46, 99.87, 61.13, 56.77, 39.69, 33.18, 27.26, 26.75, 25.64, 17.65, 16.10; HRMS (ES): *m/z* calcd for $C_{23}H_{29}BrO_3$ (M+Na^{+}: 455.1198, found: 455.1186; *compound* **19**: IR (neat): ν_{max} 2927, 1460, 1211, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.93 (s, 1H), 6.34 (s, 1H), 5.15–5.07 (m, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 3.02–2.91 (m, 1H), 2.08–1.75 (m, 8H), 1.68 (s, 3H), 1.60 (s, 3H), 1.58 (s, 3H), 1.33 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.24, 150.50, 146.85, 144.28, 135.63, 131.30, 124.42, 124.38, 123.85, 102.25, 101.30, 99.80, 61.13, 56.83, 39.71, 35.48, 33.14, 26.70, 25.66, 25.51, 19.06, 17.67, 16.04; HRMS (ES): *m/z* calcd for $C_{23}H_{31}BrO_3$ (M+Na)$^{+}$: 457.1354, found: 457.1351; *compound* **22**: IR (neat): ν_{max} 2937, 1687, 1458, 1337, 1214, 1043 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.07 (s, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 3.05–2.99 (m, 2H), 2.45 (t, *J* = 8.55 Hz, 2H), 1.95 (t, *J* = 6.0 Hz, 2H), 1.69 (s, 3H), 1.62–1.57 (m, 2H), 1.48–1.42 (m, 2H), 1.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.26, 153.87, 151.71, 148.51, 148.26, 135.79, 128.52, 122.80, 112.37, 102.97, 100.72, 61.19, 56.52, 39.92, 39.82, 35.12, 32.83, 28.54, 23.21, 19.92, 19.48; HRMS (ES): *m/z* calcd for $C_{22}H_{27}BrO_4$ (M+H)$^{+}$: 435.1172, found: 435.1183; *compound* **23**: IR (neat): ν_{max} 2927, 1461, 1339, 1212, 1046 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.96 (s, 1H), 6.67 (s, 1H), 5.83 (s, 1H), 5.23 (s, 1H), 3.90 (s, 6H), 2.50–2.44 (m, 2H), 2.30–2.24 (m, 2H), 1.95 (t, *J* = 6.0 Hz, 2H), 1.69 (s, 3H), 1.62–1.54 (m, 2H), 1.47–1.41 (m, 2H), 1.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.78, 150.71, 147.04, 138.08, 136.65, 127.86, 124.52, 112.70, 102.84, 102.22, 61.16, 56.67, 39.86, 35.05, 35.02, 33.59, 32.82, 28.69, 28.65, 20.03, 19.52; HRMS (ES): *m/z* calcd for $C_{23}H_{29}BrO_3$ (M+H)$^{+}$: 433.1379, found: 433.1365; *compound* **24**: IR (neat): ν_{max} 2936, 1458, 1212, 1045, 1000 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.92 (s, 1H), 6.37 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 2.98–2.92 (s, 1H), 1.97–1.83 (m, 4H), 1.56–1.50 (m, 6H), 1.42–1.25 (m, 6H), 0.95 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.04, 150.46, 146.76, 144.20, 136.96, 127.17, 124.38, 102.09, 101.49, 99.78, 61.14, 56.77, 39.89, 35.69, 34.94, 34.36, 32.78, 28.62, 28.59, 26.19, 19.77, 19.54, 18.98; HRMS (ES): *m/z* calcd for $C_{23}H_{31}BrO_3$ (M+H)$^{+}$: 435.1536, found: 435.1529; *compound* **25**: IR (neat): ν_{max} 2932, 1693, 1606, 1463, 1239, 1054 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.56 (s, 1H), 7.47 (s, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.37–3.28 (m, 1H), 2.57–2.53 (m, 1H), 2.21–2.13 (m, 1H), 1.88–1.82 (m, 1H), 1.73–1.64 (m, 1H), 1.61–1.49 (m, 5H), 1.46 (d, *J* = 7.2 Hz, 3H), 1.37 (s, 3H), 1.30–1.22 (m, 2H), 0.99 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.43, 158.86, 149.49, 147.90, 146.34, 125.27, 124.58, 114.80, 113.09, 62.81, 57.29, 53.46, 41.87, 40.31, 39.46, 34.80, 34.77, 33.51, 33.26, 24.04, 22.11, 21.97, 20.20, 18.89; HRMS (ES): *m/z* calcd for $C_{24}H_{32}O_4$ (M+Na)$^{+}$: 407.2198, found: 407.2189; *compound* **26**: IR (neat): ν_{max} 2934, 1694, 1463, 1241, 1053 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.57 (s, 1H), 7.42 (s, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.36–3.27 (m, 1H), 2.53–2.48 (m, 1H), 1.95–1.46 (m, 9H), 1.42 (d, *J* = 6.9 Hz, 3H), 1.41 (s, 3H), 1.29–1.20 (m, 1H), 0.99 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.28, 157.65, 149.30, 148.03, 146.22, 125.28, 124.06, 115.08, 112.56, 62.79, 57.28, 50.35, 42.01, 40.35, 39.20, 35.79, 34.56, 33.72, 31.19, 22.83, 22.35, 20.45, 18.97, 18.72; HRMS (ES): *m/z* calcd for $C_{24}H_{32}O_4$ (M+Na)$^{+}$: 407.2198, found: 407.2189.
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