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Synthesis of Phosphatidylinositol 3-Kinase (PI3K) Inhibitory Analogues of the Sponge Meroterpenoid Liphagal

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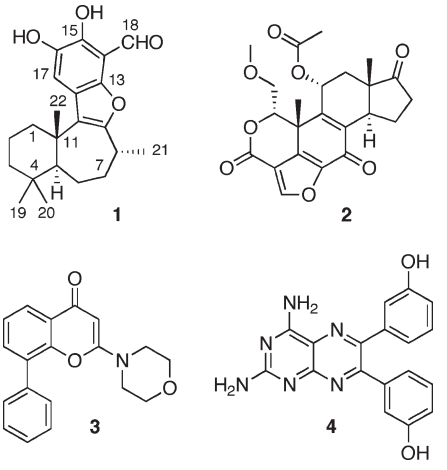
Analogues of the sponge meroterpenoid liphagal (**1**) have been synthesized and evaluated for inhibition of PI3Kα and PI3Kγ as part of a program aimed at developing new isoform-selective PI3K inhibitors. One of the analogues, compound **24**, with IC_{50} values of 66 nM against PI3Kα and 1840 nM against PI3Kγ, representing a 27-fold preference for PI3Kα, exhibited enhanced chemical stability and modestly enhanced potency and selectivity compared with the natural product liphagal (**1**).

The phosphatidylinositol 3-kinase (PI3K[a]) signaling pathway plays a central role in regulating cell proliferation and survival, adhesion, membrane trafficking, movement, differentiation, glucose transport, neurite outgrowth, and superoxide production.[1−4] There are several closely related PI3K isoforms exhibiting different biological activities,[1,4−6] and a growing appreciation of the therapeutic potential of PI3K inhibitors has encouraged significant efforts within the pharmaceutical industry to identify new inhibitory compounds with enhanced potency, selectivity, and pharmacological properties.[1,7] PI3Kδ and PI3Kγ isoforms represent promising therapeutic targets to modulate signaling pathways involved in inflammatory and autoimmune diseases[3,6,8−10] such as rheumatoid arthritis, systemic lupus erythematosus (SLE), multiple sclerosis, asthma, chronic obstructive pulmonary disease, and psoriasis. Recent interest in PI3K signaling has also been fueled by evidence that the PI3K pathway is among the most commonly activated signaling pathways in cancer.[7,11] For instance, the PI3Kα isoform was found to be activated by mutation in colon, gastric, and breast carcinomas[6] and is likely to be the most commonly mutated kinase in the human genome.[7] Such an impressive variety of potential therapeutic applications has led some authors to compare a pure hypothetical isoform-selective PI3K inhibitor with classical cyclooxygenase-inhibitor drugs like aspirin.[5]

The first-generation PI3K inhibitors, wortmannin (**2**) and LY294002 (**3**), have been extensively used to analyze PI3K-driven pathways.[7,8,11] However, these molecules do not exhibit significant selectivity for individual PI3K isoforms, and moreover, they have been shown to also block class II and class III PI3Ks, as well as other closely related enzymes such as mammalian target of rapamycin (MTOR) and unrelated enzymes such as casein kinase 2 (CK2), myosin light chain kinase (MLCK), and polo-like kinase (PLK).[1,4,8,11] Second-generation isoform-selective PI3K inhibitors include arylmorpholine compounds (based on **3**),[12−14] quinazolinone purines,[4,7,14] aminothiazoles,[15,16] amino-bis-thiazoles,[17] thiazolidinedione derivatives,[18,19] imidazo[1,2-*c*]quinazolines,[20] bis(morpholino)triazines,[21] and derivatives of the alkaloid pteridine such as TG100-115 (**4**).[22] All these molecules are reversible inhibitors that bind the adenosine 5′-triphosphate (ATP) binding pocket of PI3K.[7]



A crude methanol extract of the sponge *Aka coralliphaga* collected in Dominica showed promising activity in a screening program designed to find new isoform-selective PI3K inhibitors. Bioassay-guided fractionation of the extract identified liphagal (**1**), which has an unprecedented meroterpenoid carbon skeleton, as the active component.[2] Liphagal (**1**)

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[a] Abbreviations: PI3K, phosphatidylinositol 3-kinase; SLE, systemic lupus erythematosus; MTOR, mammalian target of rapamycin; CK2, casein kinase 2; MLCK, myosin light chain kinase; PLK, polo-like kinase; ATP, adenosine 5′-triphosphate; DCC, *N*,*N*′-dicyclohexylcarbodiimide; DMF, *N*,*N*-dimethylformamide; SAR, structure−activity relationship; NMR, nuclear magnetic resonance; HPLC, high-performance liquid chromatography; Sf9, *Spodoptera frugiperda* cell line; Lys, lysine; EI, electron impact; CD, circular dichroism; TLC, thin layer chromatography; ESI, electrospray ionization; TMSL, trimethylsilyl chloride; DMAP, 4-dimethylaminopyridine, TBAF, tetrabutylammonium fluoride; TFA, trifluoroacetic acid.

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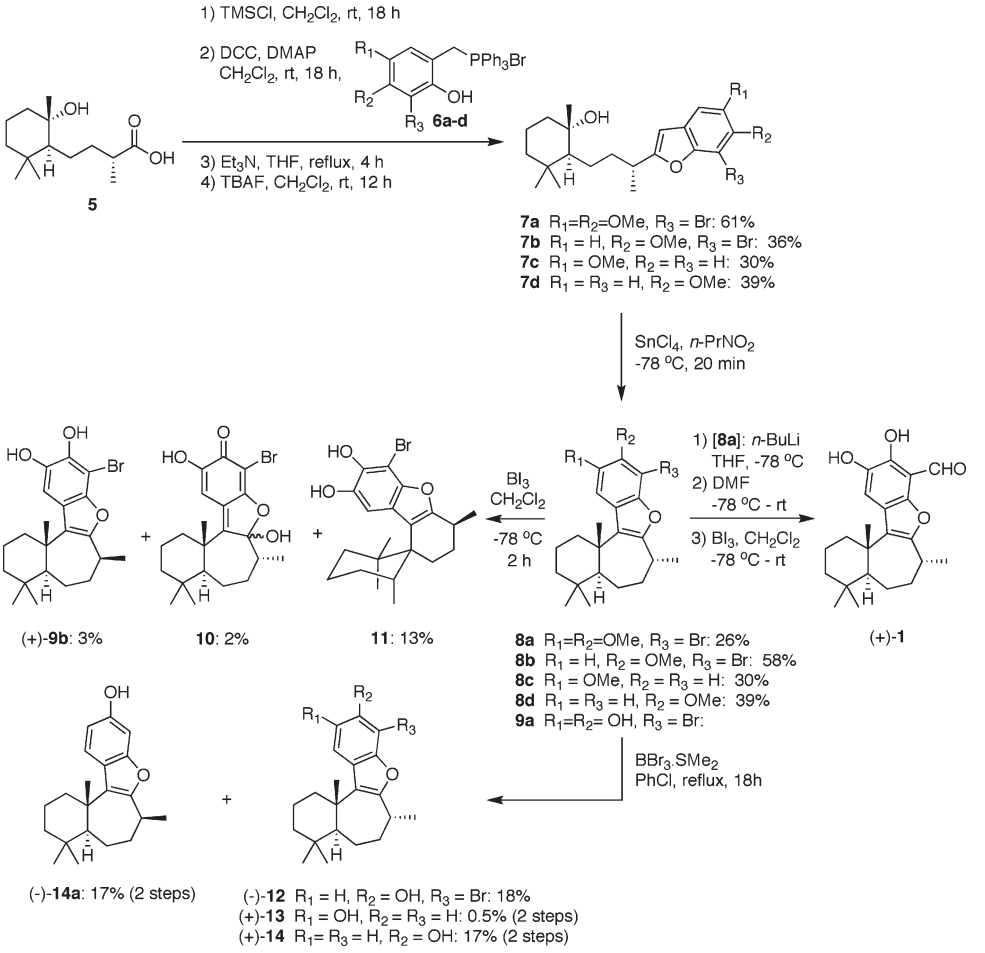
Scheme 1



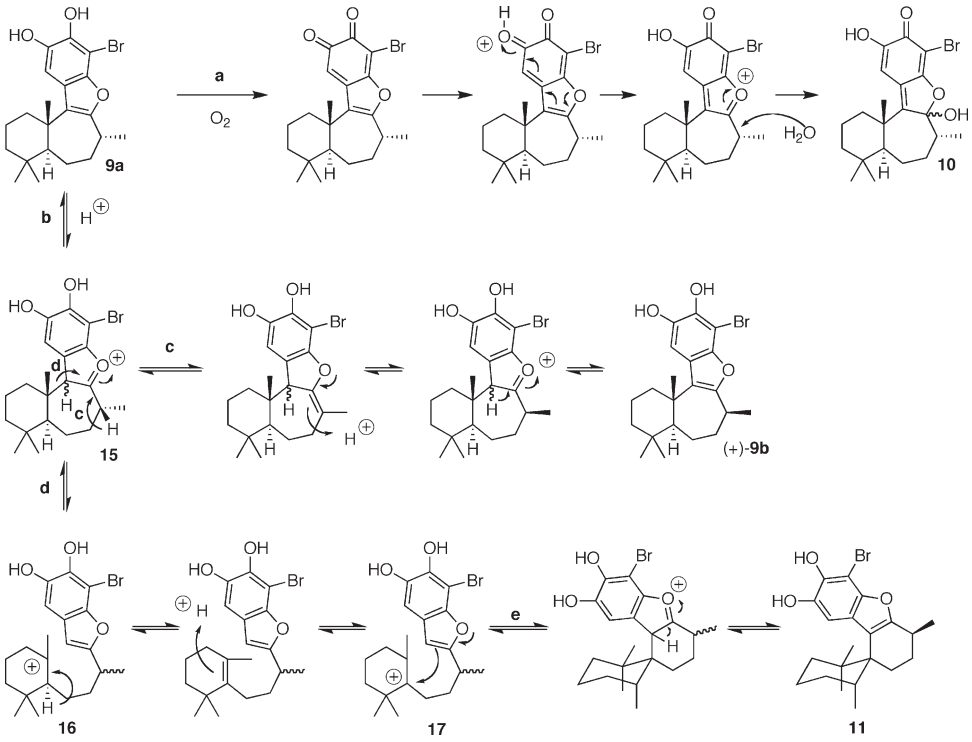
inhibited PI3Kα with an IC_{50} of 100 nM and showed an approximately 10-fold selectivity for PI3Kα compared with PI3Kγ in a fluorescent polarization enzyme bioassay.[2] The isoform selectivity and potency of liphagal (**1**) make it an attractive natural product starting point for the development of synthetic PI3K inhibitors that would represent potential drug candidates or cell biology tools. Herein, we report our efforts aimed at synthesizing stable and isoform-selective PI3K inhibitors inspired by the structure of liphagal (**1**). These efforts have culminated in the discovery of the analogue **24**, a readily accessible synthetic analogue exhibiting greater chemical stability and modestly enhanced potency and isoform selectivity compared with the natural product lead compound **1**.

Chemistry

During the original structure elucidation of the sponge-derived (+)-liphagal (**1**),[2] we were not able to assign its absolute configuration via spectroscopic or X-ray diffraction methods. Furthermore, the original synthesis produced the racemate of the natural product.[2] Therefore, the current structure−activity relationship (SAR) exploration of the PI3K inhibitory pharmacophore of liphagal began with an enantioselective synthesis of the natural product patterned on our original biomimetic approach in order to establish its absolute configuration (Scheme 1). The synthesis started with (−)-(1′*S*,2′*S*,2*R*)-4-(2′-hydroxy-2′,6′,6′-trimethylcyclohexyl)-2-methylbutanoic acid (**5**), which was accessible via literature procedures.[23−26] Acid **5** was coupled with the phenol **6a** using *N*,*N*′-dicyclohexylcarbodiimide (DCC) activation to give an ester that was converted to the benzofuran **7a** via an intramolecular Wittig reaction.[2] Carbocation initiated cyclization using $SnCl_4$ catalysis converted **7a** to the tetracyclic intermediate **8a**. Treatment of **8a** with *n*-butyllithium followed by quenching with *N*,*N*-dimethylformamide (DMF) gave a dimethyl ether protected aldehyde intermediate, and deprotection of this compound with BI_3 as previously described[2] gave (+)-liphagal (**1**) (natural **1**, $[\alpha]_D$ +12; synthetic **1**, $[\alpha]_D$ +17), thereby establishing the absolute configuration of the natural product as 5*S*,8*R*,11*S*.

Liphagal (**1**) has a number of chemical stability liabilities that would limit its development into a drug. Foremost among these are the catechol and aldehyde functionalities present in the natural product. Catechols can be oxidized via air or metabolic enzymes to give highly electrophilic orthoquinones that would be expected to react in a nonspecific manner with off-target proteins. The aldehyde functionality is likewise a reactive electrophile that could form imines and thiohemiacetals nonselectively with off-target proteins, and it is also very susceptible to oxidation to the corresponding carboxylic acid. It had been observed during the original synthesis of liphagal that the 6,7 A/B ring system rearranged to give a spiro 6,6 ring system (i.e., **11** in Scheme 1) under the acidic conditions used to remove the methyl ether protecting groups in the last step of the synthesis. This observation suggested that the core skeleton of liphagal was likely to be unstable under the acidic conditions encountered in the gut after oral administration of a drug based on this pharmacophore. Our SAR exploration of

Scheme 2



the liphagal pharmacophore was designed to find ways to circumvent the chemical instabilities described above.

First we sought to probe the requirement for the aldehyde in **1** by attempting to make the catechol **9a**, which simply had the aldehyde replaced by a bromine atom. Treatment of the dimethoxy ether **8a** with BI_3 failed to give the desired catechol **9a**, but it did produce the C-8 epimer **9b**, the oxidized mixture of C9 epimers **10**, and the rearranged product **11** (Scheme 1), which has a racemic carbon skeleton. Isolation and purification of **9b**, **10**, and **11** was very challenging and only possible after subjecting the reaction mixtures to multiple column chromatography steps followed by high-performance liquid chromatography (HPLC). Compound **9b** proved to be highly labile when exposed to acid or O_2, and it was converted to **10** in less than 5 h when dissolved in $CDCl_3$ at room temperature. However, when **9b** was dissolved in C_6D_6, it was stable enough to permit full 2D nuclear magnetic resonance (NMR) characterization. The instability of **9b** prevented us from acquiring biological data on this compound.

Scheme 2 shows a mechanistic proposal for the formation of **9b**, **10**, and **11**. The oxidized analogue **10** could be produced by pathway a in Scheme 2 starting with air oxidation of the putative intermediate **9a** to give an orthoquinone, which can add a molecule of water at C-9, perhaps with the assistance of the furan oxygen atom. The formation of the C-8 epimer **9b** and the rearrangement product **11** could start with protonation of **9a** at C-10 to give the oxonium ion **15** as indicated in pathway b. Pathway c shows that the C-8 epimer **9b** could result from loss of H-8 in **15** to quench the oxonium ion, followed by reprotonation at C-8 from the opposite face and subsequent loss of a proton from C-10. Fragmentation of the oxonium ion **15** by clevage of the C-10/C-11 bond as shown in pathway d could generate the C-11 tertiary carbocation **16**, which can undergo loss of a proton to form an alkene that can be reprotonated to give the alternate C-5 tertiary carbocation **17**. Trapping the C-5 carbocation in **17** with C-10 of the benzofuran, followed by loss of a proton, gives the rearranged product **11** as a racemic mixture. The rearrangement of **9a** to **11** in the presence of HI and air illustrates the inherent instability of the liphagane core skeleton when a catechol is present on the benzene ring. Compounds **10** and **11** were the first members of the analogue screening library.

Next we probed the requirement for a catechol functionality by preparing a series of analogues that had no aldehyde and only a single phenol at either C-15 [**12**, **14**, and **14a**] or C-16 [**13**]. These compounds were obtained by removing the methyl ether protecting groups in **8b** to **8d** with $BBr_3 \cdot SMe_2$ in refluxing chlorobenzene (Scheme 1).[27,28] Under these conditions, the precursor **8d** epimerized at C-8 to give a mixture of stereoisomers **14** and **14a**. The $BBr_3 \cdot SMe_2$ deprotection conditions minimized detectable rearranged products and improved reaction yields (Experimental Methods) compared with the use of BI_3. It has been suggested that an equilibrium is established between dimethylsulfide and the aryl methyl ether starting material, both acting as Lewis bases, leading to an exceedingly mild BBr_3 release.[27] Compounds **12**−**14** showed increased stability toward exposure to air and acidic conditions compared with their catechol counterparts.

The relatively weak PI3K inhibition observed for analogues **10**−**14** (Table 1) suggested that the 14-formyl-15,16-dihydroxy substitution pattern in the aromatic ring of liphagal (**1**) is required to achieve nanomolar potency. Furthermore, as demonstrated by the formation of the degradation products **9b**, **10**, and **11** during the attempted deprotection of **8a**, the absence of the C14-formyl group appears to destabilize the liphagane heterocyclic ring system, making it more susceptible to air oxidation and skeletal rearrangements involving ring B contraction. Guided by these observations, it was decided to synthesize analogues that had the same benzofuran substitution pattern as liphagal (**1**) but with a six-membered ring B. At the same time, the methyl substituent at C-8 was eliminated to avoid the problem of lowered yields associated with generating

Table 1. Inhibition of PI3Kα and PI3Kγ by Liphagal (**1**), Wortmannin (**2**), LY294002 (**3**), and Synthetic Liphagal Analogues[a]

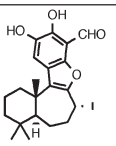
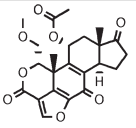
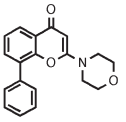
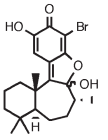
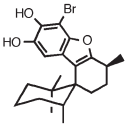
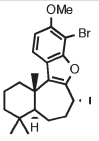
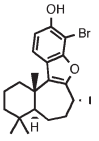
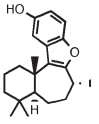
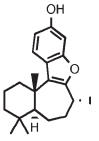
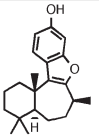
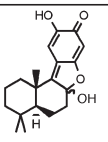
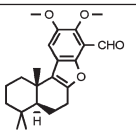
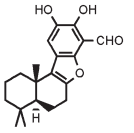
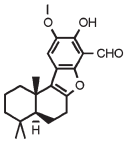
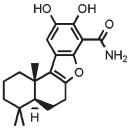
Compound number		α IC_{50} (μM)	γ IC_{50} (μM)
(+)-1		0.10	1.0
(+)-2		0.012	N.D.
3		0.55	N.D.
10		3.3	>10
(±)-11		0.70	5.3
8b		>10	>10
(-)-12		10.2	5.7
(+)-13		7.2	1.9
(+)-14		>10	>10
(-)-14a		2.2	2.2
(±)-25		1.65	9.57
(±)-23		5.12	2.64

Table 1. Continued

Compound number		α IC_{50} (μM)	γ IC_{50} (μM)
(±)-24		0.066	1.8
(±)-26		1.00	5.15
(±)-29		0.7	1.4

[a] N.D.: not determined. Each compound was assayed multiple times (two to four) on separate days, and each time it was assayed at eight concentrations (0.5 log apart) in triplicate. Reported IC_{50} values are the averages of these measurements.

mixtures of epimers at that position. Therefore, the new target analogue became **24** (Scheme 3).

The racemic synthesis of **24** started with conversion of commercially available geranyl acetone (**18**) to the carboxylic acid **19** via a haloform reaction (Scheme 3). DCC catalyzed coupling of the acid **19** and the phenol **6a** gave an intermediate ester that was converted by an intramolecular Wittig reaction to the benzofuran **20**. Chlorosulfonic acid catalyzed polyene cyclization of the benzofuran **20** gave the desired tetracyclic product **21**.[2] Treatment of the bromobenzofuran **21** with *n*-butyllithium followed by quenching with DMF gave a mixture of the desbromo compound **22** and the formylated product **23**. Deprotection of **23** with BI_3 at −78 °C gave the target liphagal analogue **24** having a six-membered B ring. Deprotection of the desformyl intermediate **22** using $BBr_3 \cdot SMe_2$ gave the oxidized product **25** as the only isolatable product, further illustrating the requirement for a formyl susbtituent to stabilize a catechol-containing benzofuran moiety toward oxidative transformations. Attempts to convert **23** to **24** using the less acidic $BBr_3 \cdot SMe_2$ conditions resulted only in formation of the monodeprotected product **26**.

As anticipated, compound **24** showed no signs of undergoing skeletal rearrangements or oxidative transformations when subjected to the acidic conditions of the BI_3 deprotection step. However, it still contained the reactive aldehyde functionality found in the natural product. In an attempt to remove this last source of instability in the pharmacophore, the aldehyde functionality in **24** was replaced with a primary amide, which could not undergo air oxidation or imine formation. Treatment of the bromobenzofuran intermediate **21** with CuCN in refluxing DMF gave the corresponding nitrile **27** (Scheme 4). Hydrolysis of the nitrile **27** with aqueous NaOH and H_2O_2 gave the primary amide **28**, and deprotection of **28** with BI_3 at −78 °C generated the desired primary amide analogue **29**.

Results

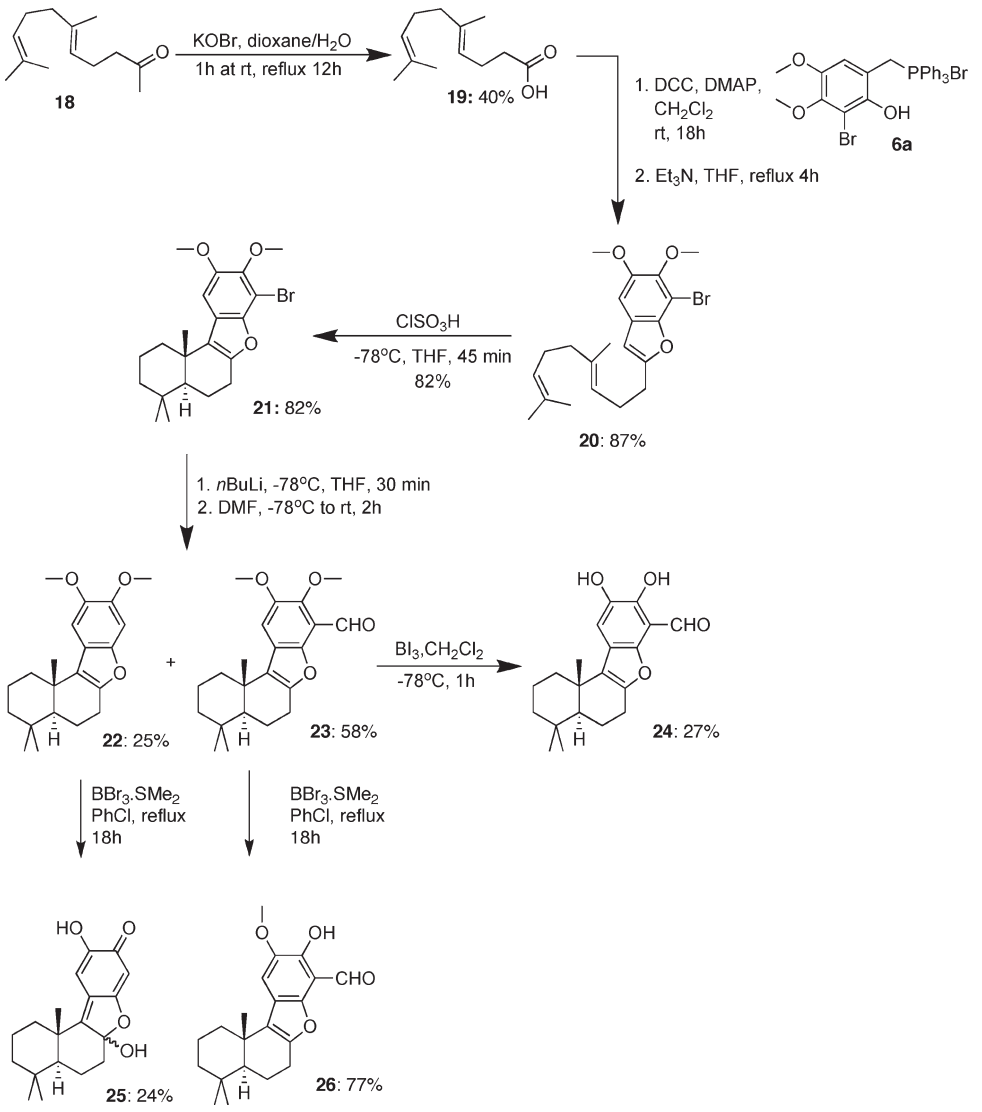
The inhibitory activity of the synthetic liphagal analogues was assessed using a fluorescent polarization assay that employs human PI3K isoforms purified after expression in *Spodoptera frugiperda* (Sf9) insect cells or purchased from Upstate Biotech (Millipore).[2] Table 1 shows the IC_{50} values measured for both the α and γ isoforms.

The benchmarks for evaluating the synthetic analogues were the IC_{50} values of 0.10 μM versus the PI3Kα isoform and 1.0 μM versus the PI3Kγ isoform, equivalent to a 10-fold greater potency versus the α isoform, observed for the natural product lead compound liphagal (**1**) (Table 1). Compounds **8b**, **12**, **13**, **14**, **14a**, and **25** having the liphagane skeleton, but missing the aldehyde substituent at C-14, showed only micromolar PI3K inhibition and none of the selectivity for the α isoform observed for liphagal (**1**). Compound **8b**, which has no phenol on the benzofuran, and **14**, which has only a single phenol at C-15, were the least active compounds tested. Some potency could be recovered by converting the OMe in **8b** to a phenol in **12** or **14a** or adding a single phenol at C-16 in **13** and **25**, but the α isoform selectivity was either completely absent as in **14a** or reversed as in **12**, **13**, and **25**. The rearranged analogue **11**, which has a C-15/C-16 catechol, showed submicromolar inhibition and ∼7 fold α isoform selectivity.

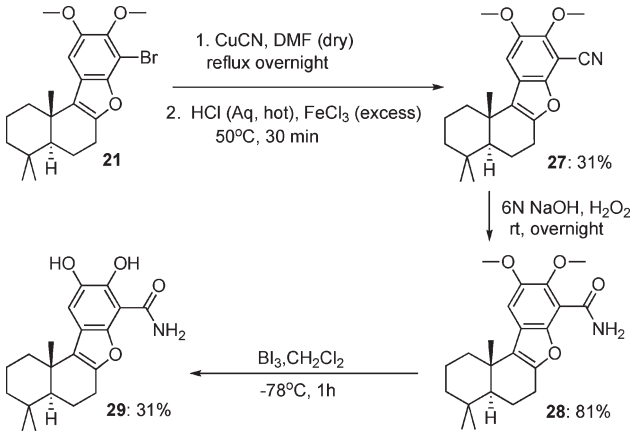
The ring B contracted analogue **24**, which has catechol and aldehyde functionalties on the benzofuran ring identical to those found in liphagal (**1**), was the most potent and α isoform selective compound tested. In multiple side by side assays it was consistently more potent (∼1.5-fold) and more isoform selective (∼2.7-fold) than the natural product lead structure, although the increase in activity was modest. Compound **26**, which has the C-16 phenol in **24** protected as a methyl ether, shows a significant decrease in potency and α isoform selectivity. When both of the phenols in **24** are protected as methyl ethers to give compound **23**, there is a further reduction in potency and a reversal of the isoform selectivity in favor of the γ isoform. Compound **29**, which simply has the aldehyde in **24** replaced by a primary amide, is roughly an order of magnitude less potent and α isoform selective than **24**.

The results described above reveal that submicromolar PI3K inhibition was only achievable in the analogues (**11**, **24**, and **29**) where the benzofuran substructure was substituted with the catechol functionality found in liphagal. Selectivity for the α isoform was only observed in analogues containing a catechol (**11**, **24**, and **29**), a hydroxy quinomethide (**10** and **25**), or a combination of a phenol ortho to an aldehyde carbonyl

Scheme 3



Scheme 4



(**26**) on the benzofuran. Interestingly, analogues **12** and **13**, which have only a single phenol substituent on the benzofuran, show a reversed selectivity for the γ isoform. A combination of the catechol and aldehyde functionalities was required in **24** to exceed both the potency and α isoform selectivity of the natural product. The ability of the aldehyde to form imines or thioacetals with functional groups on the target proteins may play a role in the enhanced activities of liphagal (**1**) and the analogue **24**, since the corresponding primary amide **29** was both less potent and less isoform selective.

The activities of the rearranged analogue **11** and the contracted ring B analogues **24** and **29** suggest that the specific carbon skeleton of the terpenoid fragment of liphagal is not critical for its activity. Liphagal (**1**) and the ring B analogues **24** and **29** are stabilized by a carbonyl group, which appears to suppress air oxidation leading to the quinomethide analogues **10** and **25** and rearrangement of the liphagane skeleton under acidic conditions to give analogues such as **11**. Compounds **24** and **25**, with six-membered B rings, are much more stable than liphagal and showed no signs of skeletal rearrangements when exposed to acidic conditions.

Air oxidation of liphagal (**1**) or the analogue **24** leading to formation of orthoquinones creates a very electrophilic site at the α carbon in their furan substructures (pathway a in Scheme 2), which provides an alternative covalent binding site with nucleophilic residues of PI3Ks. Wortmannin (**2**) and liphagal (**1**) share similar benzofuran substructures, and an equivalent position in the furan of **2** has been shown to bind

covalently with lysine (Lys) residues of p110α within the ATP-binding site.[1,7]

Conclusions

The absolute configuration of (+)-liphagal (**1**) has been established as 5*S*,8*R*,11*S* by enantioselective synthesis of the natural product.[29] Evaluation of a small library of 12 synthetic liphagal analogues has shown that the catechol and aldehyde functionalities on the benzofuran substructure, but not the specific liphagane terpenoid fragment, are required for the potency and PI3Kα isoform selectivity of the natural product. SAR provided by the synthetic liphagane analogues was used to guide the design of the ring B contracted analogue **24**, which is somewhat more potent (IC_{50} = 66 nM) and isoform selective (27-fold), has greater chemical stability, and is easier to prepare than the lead compound liphagal (**1**). Compound **24** is one of the most selective PI3Kα vs PI3Kγ inhibitors known to date and is exceeded in selectively only by 7-methyl-2-(4-morpholinyl)-9-[(phenylmethyl)amino]-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one (TGX126), an analogue of **3**.[1b] The potency and isoform selectivity of analogue **24** illustrates that the natural product liphagal (**1**) is a useful starting point for the development of new isoform selective PI3K inhibitors that might represent promising drug candidates and/or cell biology tools.

Experimental Methods

All reactions were performed under dry nitrogen or argon using glassware previously oven-dried (150 °C), unless otherwise specified. Glassware was allowed to reach room temperature under a flow of inert gas. Likewise, glass syringes and stainless steel needles, used to handle anhydrous reagents and solvents, were oven-dried, cooled in a desiccator, and flushed with inert gas prior to use. Tetrahydrofuran (THF) and CH_2Cl_2 were distilled from sodium/benzophenone and CaH_2 respectively. All chemical reagents were purchased in analytical or higher grade from Aldrich or Fluka. Cold baths were prepared using ice/water, ice/NaCl/water, MeCN/dry ice, and acetone/dry ice for 0, −10, −40, and −78 °C, respectively. Liquid nitrogen was employed for condensing ammonia. Flash chromatography was carried out with 70−230 and 230−400 mesh silica gel (Silicycle). For reverse phase column chromatography, Sep Pak C18 columns (Waters) were used. Size exclusion chromatography was performed using lipophilic Sephadex LH-20 (Sigma, bead size 25−100 μm). Precoated silica gel plates (Merck, Kieselgel 60 F_{254}, 0.25 mm and Whatman, MKC18F 60 A) were employed in normal and reversed-phase thin layer chromatography (TLC). TLC visualization was accomplish using ultraviolet light (254 nm), followed by heating the plate after staining with vanillin in H_2SO_4/EtOH (6% vanillin w/v, 4% H_2SO_4 v/v, and 10% H_2O v/v in EtOH), *p*-anisaldehyde in H_2SO_4/EtOH (5% *p*-anisaldehyde v/v and 5% H_2SO_4 v/v in EtOH), or 20% $KMnO_4$ w/v in H_2O. High performance liquid chromatography (HPLC) was carried out using a Waters 1500 series pump system, equipped with Waters 2487 dual wavelength absorbance detector and either a CSC-Inertsil 150A/ODS2 column or an Alltech Econosil silica 5 μm column. NMR spectra were recorded using chloroform-*d* ($CDCl_3$), methylene chloride-d_2 (CD_2Cl_2), dimethylsulfoxide-d_6 (DMSO-d_6), benzene-d_6 (C_6D_6). Chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane (δ 0) and were calibrated internally to the signal of the solvent in which the sample was dissolved (for $CDCl_3$ δ 7.24 ^{1}H NMR, δ 77.0 ^{13}C NMR; for CD_2Cl_2 δ 5.32 ^{1}H NMR, δ 54.0 ^{13}C NMR; for DMSO-d_6 δ 2.50 ^{1}H NMR, δ 39.51 ^{13}C NMR; for CD_4OD δ 3.31 ^{1}H NMR, δ 49.15 ^{13}C NMR; for C_6D_6 δ 7.16 ^{1}H NMR, δ 128.39 ^{13}C NMR. ^{1}H NMR data were acquired using Bruker spectrometer WH400 (400 MHz), Avance 300 (300 MHz), Avance 400 (400 MHz), or Avance 600 (600 MHz) equipped with a CRYOPROBE. ^{13}C NMR spectra were recorded on Avance 300 (75 MHz), Avance 400 (81 MHz), or Avance 600 (150 MHz). ^{31}P NMR data were collected using the Avance 400 (100 MHz) spectrometer. Low and high resolution electron impact (EI) mass spectra were recorded on Kratos MS50 or MS80 mass spectrometer at 70 eV. Low and high resolution electrospray ionization (ESI) mass spectra were obtained with Bruker Esquire-LC and Micromass LCT mass spectrometers. Circular dichroism (CD) data were recorded with a JASCO J-810 CD spectrometer at 20.0 °C, using a 2.0 mm microcell. Optical rotations were measured with a JASCO P-1010 polarimeter at 20 °C and 589 nm (sodium D line). UV spectra were acquired with a Waters 2487 dual wavelength absorbance detector, using a 1 cm cell. All final compounds had a purity of >95% as assessed by analytical HPLC.

Compounds 5, 6a−d. See Supporting Information.

Compound 7a. A solution of hydroxy acid **5** (0.68 g, 2.8 mmol), Et_3N (3.01 mL, 21.6 mmol), and trimethylsilyl chloride (TMSCl) (1.4 mL, 10.4 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 18 h. Water was added, and CH_2Cl_2 extractions were performed. The organic extracts were combined, dried (Na_2SO_4), and concentrated in vacuo. This protected material (0.78 g, 2.50 mmol) was dissolved in CH_2Cl_2 (50 mL) and stirred with phosphonium bromide **6a** (2.46 g, 4.8 mmol), DCC (1.32 g, 6.4 mmol), and 4-dimethylaminopyridine (DMAP) (73 mg, 0.6 mmol) at room temperature for 18 h. After solvent removal under reduced pressure, the obtained residue was dissolved in THF (50 mL), and Et_3N (8.0 mL) was added. The resulting mixture was refluxed for 4 h. Once at room temperature, silica was added and the THF was evaporated under reduced pressure. The resulting dried silica was poured into a silica gel column and eluted with 10% EtOAc/hexanes to yield a silyl-protected benzofuran intermediate (0.56 g, 43%), which was then dissolved in CH_2Cl_2 and stirred in the presence of tetrabutylammonium fluoride (TBAF) (2 mL) at 25 °C until TLC showed the absence of starting material. The reaction mixture was diluted with H_2O, and aqueous $NaHCO_3$ washings were performed. After drying treatment (Na_2SO_4) and filtration, solvent removal in vacuo and silica gel column chromatography (50% EtOAc/hexanes) afforded the desired compound **7a** (0.30 g, 61%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.87 (1H, s), 6.34 (1H, s), 3.83 (6H, s), 2.90 (1H, m), 1.98 (1H, m), 1.66 (1H, m), 1.62 (1H, dd, *J* = 5.6, 5.9 Hz), 1.48 (1H, m), 1,45 (1H, m), 1.33 (1H, dt, *J* = 3.4, 13.4 Hz), 1.31 (1H, m), 1.28 (3H, d, *J* = 7.0 Hz), 1.26 (1H, m), 1.25 (1H, m), 1.13 (1H, td, *J* = 4.0, 12.8 Hz), 1.08 (1H, m), 1.07 (3H, s), 0.87 (3H, s), 0.72 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.3 (C), 150.2 (C), 146.5 (C), 143.9 (C), 124.3 (C), 101.9 (CH), 101.2 (CH), 99.5 (C), 74.0 (C), 61.0 (CH_3), 57.1 (CH_3), 56.5 (CH), 43.3 (CH_2), 41.3 (CH_2), 38.3 (CH_2), 35.3 (C), 34.1 (CH_3), 32.7 (CH), 23.7 (CH_2), 23.2 (CH_3), 21.2 (CH_3), 20.3 (CH_2), 19.2 (CH_3). HRESIMS calcd for $C_{23}H_{33}O_4Na^{79}Br$ ($[M + Na]^+$): 475.1460; found 475.1468.

Compound 7b. As in the previous procedure, a solution of hydroxy acid **5** (0.21 g, 0.9 mmol), Et_3N (0.8 mL, 5.9 mmol), and TMSCl (0.4 mL, 3.0 mmol) in CH_2Cl_2 (30 mL) was stirred at room temperature for 18 h. After the usual workup, the obtained protected material was dissolved in CH_2Cl_2 (30 mL) and stirred with phosphonium bromide **6b** (1.24 g, 1.5 mmol), DCC (0.41 g, 2.0 mmol), and DMAP (20 mg, 0.16 mmol) at room temperature for 18 h. After solvent removal under reduced pressure, the obtained residue was dissolved in THF (30 mL), and Et_3N (4.0 mL) was added. The resulting mixture was refluxed for 4 h, whereupon silica gel column chromatography (20% EtOAc/hexanes) and TBAF silyl deprotection as before yielded alcohol **7b** (0.13 g, 36%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29 (1H, d, *J* = 8.4 Hz), 6.80 (1H, d, *J* = 8.5 Hz), 6.37 (1H, d, *J* = 0.76 Hz), 3.90 (3H, s), 2.94 (1H, m), 2.01 (1H, m), 1.70 (1H, m), 1.65 (1H, dd, *J* = 5.3, 5.6 Hz), 1.51 (1H, m), 1.48 (1H, dd, *J* = 4.4, 7.0 Hz), 1.39 (1H, dt, *J* = 3.2, 12.8 Hz), 1.34 (1H, m), 1.31 (3H, d, *J* = 7.0 Hz), 1.29 (1H, m), 1.28 (1H, m), 1.17 (1H, td, *J* = 4.0, 12.6 Hz), 1.15 (1H, m), 1.10 (3H, s), 0.90 (3H, s), 0.74

(3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.5 (C), 153.2 (C), 152.8 (C), 123.6 (C), 118.6 (CH), 108.0 (CH), 100.8 (CH), 93.5 (C), 74.2 (C), 57.2 (CH_3), 43.4 (CH_2), 41.4 (CH_2), 38.3 (C), 35.4 (CH_2), 35.4 (CH), 34.1 (CH), 32.7 (CH_3), 23.7 (CH_2), 23.4 (CH_3), 21.3 (CH_3), 20.4 (CH_2), 19.2 (CH_3). HRESIMS calcd for $C_{22}H_{31}O_3Na^{79}Br$ ([M + Na]$^+$): 445.1354; found 445.1366.

Compound 7c. The title compound (0.133 g, 30%) was prepared as before, from hydroxy acid **5** (0.30 g, 1.31 mmol) and phosphonium salt **6c** (0.942 g, 1.97 mmol). Colorless oil. $[\alpha]_D^{21}$ −28° (*c* 0.24, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.30 (1H, d, J = 8.9 Hz), 6.97 (1H, d, J = 2.7 Hz), 6.80 (1H, dd, J = 2.6, 8.8 Hz), 6.35 (1H, s), 3.84 (3H, s), 2.92 (1H, m), 2.03 (1H, m), 1.74 (1H, m), 1.67 (1H, m), 1.54−1.36 (5H, m), 1.35 (1H, m), 1.33 (3H, d, J = 7.0 Hz), 1.20 (1H, td, J = 3.7, 13.1 Hz), 1.14 (1H, m), 1.12 (3H, s), 0.93 (3H, s), 0.78 (3H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 165.2 (C), 155.9 (C), 149.7 (C), 129.7 (C), 111.5 (CH), 111.3 (CH), 103.4 (CH), 101.0 (CH), 74.5 (C), 57.6 (CH_3), 56.2 (CH), 43.6 (CH_2), 41.6 (C), 38.7 (CH_2), 35.7 (CH_2), 34.6 (CH), 33.0 (CH_3), 24.1 (CH_2), 23.6 (CH_3), 21.6 (CH_3), 20.7 (CH_2), 19.4 (CH_3). HRESIMS calcd for $C_{22}H_{32}O_3Na$ ([M + Na]$^+$): 367.2249; found 367.2251.

Compound 7d. The title compound (0.177 g, 39%) was prepared using the previously reported methodology from hydroxy acid **5** (0.30 g, 1.31 mmol) and phosphonium salt **6d** (0.942 g, 1.97 mmol). Colorless oil. $[\alpha]_D^{21}$ −26° (*c* 0.18, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.34 (1H, d, J = 8.3 Hz), 6.98 (1H, d, J = 1.9 Hz), 6.82 (1H, dd, J = 2.2, 8.4 Hz), 6.33 (1H, s), 3.85 (3H, s) 2.90 (1H, m), 2.02 (1H, m), 1.74 (1H, m), 1.68 (1H, m), 1.54−1.34 (5H, m), 1.32 (1H, m), 1.32 (3H, d, J = 6.9 Hz), 1.20 (1H, td, J = 3.8, 13.2 Hz), 1.14 (1H, m), 1.12 (3H, s), 0.93 (3H, s), 0.78 (3H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 163.3 (C), 157.3 (C), 155.6 (C), 122.4 (C), 120.5 (CH), 111.2 (CH), 100.5 (CH), 96.0 (CH), 74.5 (C), 57.6 (CH_3), 56.0 (CH), 43.6 (CH_2), 41.7 (CH_2), 38.8 (CH_2), 35.7 (C), 34.5 (CH), 33.0 (CH_3), 24.1 (CH_2), 23.6 (CH_3), 21.6 (CH_3), 20.7 (CH_2), 19.4 (CH_3). HRESIMS calcd for $C_{22}H_{32}O_3Na$ ([M + Na]$^+$): 367.2249; found 367.2258.

Compound 8a. To a solution of alcohol **7a** (0.29 g, 0.65 mmol) in 2-nitropropane (60 mL) at −78 °C was added $SnCl_4$ (0.6 mL, 5.0 mmol). After being stirred for 20 min, the mixture was slowly warmed to room temperature and water was then added. EtOAc extractions were performed, and the organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Silica gel column chromatography (5% EtOAc/hexanes) of the residue afforded **8a** (0.074 g, 26%) as a colorless solid and a slightly more polar fraction composed of a mixture of benzofurans (around 0.080 mg). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.11 (1H, s), 3.88 (3H, s), 3.86 (3H, s), 3.25 (1H, m), 2.55 (1H, m), 2.15 (1H, m), 1.83 (1H, m), 1.70 (1H, dt, J = 3.1, 13.6 Hz), 1.68 (1H, m), 1.58 (3H, m), 1.51 (1H, m), 1.49 (1H, m), 1.43 (3H, d, J = 7.2 Hz), 1.35 (3H, s), 1.23 (1H, td, J = 3.3, 13.8 Hz), 0.97 (3H, s), 0.93 (3H, s); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 158.0 (C), 149.0 (C), 146.0 (C), 144.0 (C), 126.0 (C), 124.1 (C), 105.3 (CH), 99.5 (C), 61.1 (CH_3), 57.3 (CH_3), 53.4 (CH), 41.9 (CH_2), 40.1 (CH_2), 38.9 (C), 36.0 (C), 34.8 (CH_2), 33.5 (CH_3), 33.3 (CH), 24.0 (CH_2), 22.02 (CH_3), 21.97 (CH_3), 20.0 (CH_3), 18.9 (CH_2). HRESIMS calcd for $C_{23}H_{32}O_3{}^{79}Br$ ([M + H]$^+$): 435.1535; found 435.1529.

Compound 8b. To a solution of alcohol **7b** (0.13 g, 0.31 mmol) in 2-nitropropane (20 mL) at −78 °C was added $SnCl_4$ (0.22 mL, 1.9 mmol). After being stirred for 20 min, the mixture was slowly warmed to room temperature and water was then added. EtOAc extractions were performed, and the organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Silica gel column chromatography (5% EtOAc/hexanes) of the residue afforded **8b** (0.073 g, 58%) as a colorless solid. ^{1}H NMR (C_6D_6, 600 MHz) δ 7.39 (1H, d, J = 8.6 Hz), 6.48 (1H, d, J = 8.8 Hz), 3.39 (3H, s), 3.06 (1H, m), 2.57 (1H, m), 1.86 (1H, m), 1.63 (1H, m), 1.61 (1H, m), 1.52 (1H, m), 1.44 (1H, m), 1.42 (1H, m), 1.38 (1H, m), 1.37 (3H, d, J = 7.2 Hz), 1.36 (1H, m), 1.31 (3H, s), 1.29 (1H, m), 1.13 (1H, td, J = 3.6, 13.5 Hz), 0.89 (3H, s), 0.88 (3H, s); ^{13}C NMR (C_6D_6, 150 MHz) δ 157.6 (C), 154.1 (C), 153.4 (C), 126.5 (C), 124.5 (C), 121.8 (CH), 107.7 (CH), 94.8 (C), 57.0 (CH_3), 54.2 (CH), 42.7 (CH_2), 41.1 (CH_2), 40.5 (C), 35.5 (CH_2), 35.4 (C), 34.3 (CH), 33.6 (CH_3), 24.8 (CH_2), 22.6 (CH_3), 22.2 (CH_3), 20.9 (CH_3), 19.7 (CH_2). HRESIMS calcd for $C_{22}H_{29}O_2Na^{79}Br$ ([M + Na]$^+$): 427.1249; found 427.1254.

Compound 8c. $SnCl_4$ (240 μL, 2.04 mmol) was added dropwise to a solution of **7c** (0.13 g, 0.38 mmol) in 2-nitropropane (30 mL) at −78 °C. The usual workup afforded a yellowish oil, which was used without any further purification in the following deprotection reaction.

Compound 8d. $SnCl_4$ (240 μL, 2.04 mmol) was added dropwise to a solution of **7d** (0.18 g, 0.51 mmol) in 2-nitropropane (30 mL) at −78 °C. The usual workup afforded a yellowish oil, which was used without any further purification in the next step.

Compounds 9b, 10, and 11. To a solution of **8a** (36 mg, 0.083 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added BI_3 (0.33 mL, 0.33 mmol, 1 M in CH_2Cl_2). The resulting mixture was warmed to room temperature (2 h) and quenched with aqueous $Na_2S_2O_3$. The organic layer was separated and washed with HCl 0.1 M, followed by Na_2SO_4 addition, filtration, and solvent evaporation. Silica gel column chromatography (30% EtOAc/hexanes) provided one main fraction (one spot by TLC), which was additionally purified by reversed-phase HPLC (C18 Inertsil, 80% CH_3CN/20% H_2O + 0.05% trifluoroacetic acid (TFA)), to yield yellow fractions of **9b** (1.1 mg, 3%), spiro compound **11** (1.2 mg, 13%), and quinone **10** (0.8 mg, 2%).

9b: CD (CH_3CN, *c* 0.22) λ 343.0 nm ($\Delta\varepsilon$ +0.078), 297.0 (−0.042). ^{1}H NMR (C_6D_6, 600 MHz) δ 7.14 (1H, s), 4.85 (1H, s, broad), 4.73 (1H, s, broad), 2.97 (1H, m), 2.42 (1H, m), 1.60 (1H, m), 1.56 (1H, m), 1.52 (1H, qt, J = 3.2, 13.9 Hz), 1.49 (1H, m), 1.47 (1H, m), 1.37 (1H, m), 1.362 (1H, m), 1.360 (1H, m), 1.32 (3H, d, J = 6.9 Hz), 1.31 (1H, m), 1.24 (3H, s), 1.15 (1H, td, J = 3.4, 13.3 Hz), 0.88 (3H, s), 0.86 (3H, s); ^{13}C NMR (C_6D_6, 600 MHz) δ 156.1 (C), 146.0 (C), 141.0 (C), 138.5 (C), 125.9 (C), 122.5 (C), 107.3 (CH), 92.5 (C), 50.5 (CH), 42.7 (CH_2), 40.5 (CH_2), 39.9 (C), 36.2 (CH_2), 34.9 (C), 34.2 (CH_3), 31.6 (CH), 23.4 (CH_2), 22.8 (CH_3), 20.7 (CH_3), 19.5 (CH_2), 19.2 (CH_3).

10: CD (CH_3CN, *c* 0.08) λ 351.0 nm ($\Delta\varepsilon$ +0.26), 323.0 (−0.026). ^{1}H NMR (C_6D_6, 600 MHz) δ 7.36 (1H, s), 6.31 (1H, s), 2.24 (1H, s, broad), 2.22 (1H, m), 1.84 (1H, d, J = 8.4 Hz), 1.71 (1H, m), 1.59 (1H, m), 1.33 (1H, qt, J = 2.9, 13.4 Hz), 1.22 (1H, m), 1.21 (1H, m), 1.179 (1H, m), 1.176 (1H, m), 1.07 (1H, m), 1.01 (3H, s), 0.99 (1H, td, J = 2.5, 12.8 Hz), 0.98 (1H, m), 0.78 (3H, s), 0.64 (3H, s), 0.47 (3H, d, J = 6.9 Hz); ^{13}C NMR (C_6D_6, 150 MHz) δ 176.6 (C), 168.3 (C), 167.5 (C), 149.2 (C), 127.0 (C), 120.0 (C), 98.5 (CH), 91.0 (C), 49.7 (CH), 43.1 (CH_2), 42.3 (C), 41.5 (CH_2), 40.4 (CH), 34.9 (C), 33.7 (CH_3), 32.8 (CH_2), 22.3 (CH_3), 22.3 (CH_3), 21.4 (CH_2), 19.8 (CH_2), 14.0 (CH_3). HRESIMS calcd for $C_{21}H_{28}O_4{}^{79}Br$ ([M+H]$^+$): 423.1171; found 423.1160.

11: CD (CH_3CN, *c* 0.24) no absorbance; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.18 (1H, s), 5.35 (1H, s, broad), 5.10 (1H, s, broad), 2.86 (1H, m), 2.57 (1H, dt, J = 3.7, 14.3 Hz), 2.51 (1H, td, J = 4.2, 13.7 Hz), 1.94 (1H, m), 1.91 (1H, m), 1.80 (1H, m), 1.61 (1H, qt, J = 4.4, 17.8 Hz), 1.50 (1H, m), 1.48 (1H, m), 1.36 (1H, m), 1.35 (3H, d, J = 6.8 Hz), 1.27 (1H, m), 1.15 (1H, m), 1.03 (3H, s), 0.88 (3H, s), 0.85 (3H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 159.1 (C), 145.8 (C), 139.6 (C), 137.1 (C), 122.7 (C), 118.1 (C), 108.3 (CH), 91.5 (C), 43.8 (C), 40.9 (C), 36.8 (CH), 36.5 (CH_2), 32.1 (CH_2), 31.2 (CH_2), 30.2 (CH_2), 29.3 (CH), 27.0 (CH_3), 21.4 (CH_2), 20.7 (CH_3), 18.9 (CH_3), 17.0 (CH_3). HRESIMS calcd for $C_{21}H_{27}O_3Na^{79}Br$ ([M + Na]$^+$): 429.1041; found 429.1050.

Compound 12. A solution of **8b** (6.9 mg, 0.017 mmol) and $BBr_3 \cdot SMe_2$ (26 mg, 0.081 mmol) was refluxed in clorobenzene until TLC analysis showed the absence of starting material (around 18 h). Once at room temperature, H_2O was added and the reaction mixture was stirred for 30 min. The aqueous layer was extracted with EtOAc, dried (Na_2SO_4), and concentrated in vacuo. Silica gel column chromatography (20% EtOAc/hexanes)

yielded one main fraction containing the desired product, which was additionally purified by reversed-phase HPLC (80% CH_3CN/20% H_2O + 0.05% TFA) to afford **12** (1.2 mg, 18%) as a pale yellow oil. UV (MeOH) λ_{max} (log ε) 262 nm (3.33). $[\alpha]^{20}_D$ −6.1 (*c* 0.2, MeOH). ^{1}H NMR (C_6D_6, 600 MHz) δ 7.23 (1H, d, J = 8.6 Hz), 6.82 (1H, d, J = 8.6 Hz), 5.07 (1H, s), 3.04 (1H, m), 2.42 (1H, m), 1.85 (1H, m), 1.62 (1H, m), 1.56 (1H, qt, J = 3.3, 13.7 Hz), 1.46 (1H, dd, J = 2.3, 8.5 Hz), 1.40 (1H, m), 1.38 (1H, m), 1.37 (1H, m), 1.36 (3H, d, J = 7.1 Hz), 1.35 (1H, m), 1.27 (1H, m), 1.22 (3H, s), 1.11 (1H, td, J = 3.2, 13.3 Hz), 0.87 (3H, s), 0.85 (3H, s); ^{13}C NMR (C_6D_6, 150 MHz) δ 157.0 (C), 152.1 (C), 150.3 (C), 126.8 (C), 123.6 (C), 122.6 (CH), 111.0 (CH), 92.7 (C), 54.0 (CH), 42.5 (CH_2), 40.8 (CH_2), 40.2 (C), 35.4 (CH_2), 35.2 (C), 34.1 (CH), 33.7 (CH_3), 24.6 (CH_2), 22.4 (CH_3), 22.0 (CH_3), 20.7 (CH_3), 19.4 (CH_2). HRESIMS calcd for $C_{21}H_{26}O_2{}^{79}Br$ ([M − H]$^-$): 389.1116; found 389.1119.

Compound 13. The resulting cyclization mixture **8c** was dissolved in clorobenzene (10 mL) and refluxed in the presence of $BBr_3 \cdot SMe_2$ (90 mg, 0.29 mmol) until TLC analysis showed the absence of starting material (around 12 h). Workup as stated in the previous experimental procedure, followed by silica gel column chromatography (10% EtOAc/hexanes) and reversed-phase HPLC (85% CH_3CN/15% H_2O + 0.05% TFA), yielded the desired (+)-16-hydroxyliphagane (**13**) as a pale yellow oil (0.6 mg, 0.5% from acyclic **7c**). $[\alpha]^{20}_D$ +4.7 (*c* 0.2, MeOH). UV (MeOH) λ_{max} (log ε) 297 nm (3.82). ^{1}H NMR (C_6D_6, 600 MHz) δ 7.17 (1H, d, J = 8.6 Hz), 7.01 (1H, d, J = 2.5 Hz), 6.45 (1H, dd, J = 2.5, 8.8 Hz), 3.73 (1H, s), 3.09 (1H, m), 2.57 (1H, m), 1.90 (1H, m), 1.66 (1H, m), 1.63 (1H, qt, J = 2.8, 13.3 Hz), 1.52 (1H, m), 1.50 (1H, m), 1.43 (1H, m), 1.42 (1H, m), 1.40 (3H, d, J = 7.2 Hz), 1.36 (1H, m), 1.32 (1H, m), 1.29 (3H, s), 1.14 (1H, td, J = 3.6, 13.3 Hz), 0.90 (3H, s), 0.88 (3H, s); ^{13}C NMR (C_6D_6, 150 MHz) δ 158.2 (C), 151.4 (C), 149.6 (C), 130.1 (C), 126.0 (C), 111.8 (CH), 111.5 (CH), 108.8 (CH), 54.0 (CH), 42.6 (CH_2), 40.6 (CH_2), 40.2 (C), 35.5 (CH_2), 35.2 (C), 34.4 (CH), 33.8 (CH_3), 24.8 (CH_2), 22.5 (CH_3), 22.0 (CH_3), 20.5 (CH_3), 19.5 (CH_2). HREIMS calcd for $C_{21}H_{28}O_2$ (M^+): 312.208 93; found 312.208 61.

Compounds 14 and 14a. The impure cyclization/debromination product **8d** (5.5 mg, 0.017 mmol) and $BBr_3 \cdot SMe_2$ (60 mg, 0.19 mmol) were refluxed in chlorobenzene until TLC analysis showed the absence of starting material (around 18 h). Once at room temperature, H_2O was added and the reaction mixture was stirred for 30 min. The aqueous layer was extracted with EtOAc, dried (Na_2SO_4), and concentrated in vacuo. Silica gel column chromatography (10% EtOAc/hexanes) yielded one main fraction containing the desired product, which was additionally purified by reversed-phase HPLC (70% CH_3CN/30% H_2O + 0.05% TFA) to afford **14** (0.9 mg, 17%) and **14a** (0.9 mg, 17%) as pale yellow oils.

14: UV (MeOH) λ_{max} (log ε) 245 nm (2.84). $[\alpha]^{20}_D$ +8.8 (*c* 0.2, MeOH). ^{1}H NMR (C_6D_6, 600 MHz) δ 7.42 (1H, d, J = 8.6 Hz), 6.71 (1H, d, J = 2.2 Hz), 6.55 (1H, dd, J = 2.3, 8.5 Hz), 3.84 (1H, s), 3.11 (1H, m), 2.56 (1H, m), 1.93 (1H, m), 1.65 (1H, m), 1.59 (1H, qt, J = 2.8, 13.4 Hz), 1.52 (1H, m), 1.50 (1H, m), 1.44 (1H, m), 1.42 (3H, d, J = 7.1 Hz), 1.40 (1H, m), 1.36 (1H, m) 1.33 (1H, m), 1.30 (3H, s), 1.14 (1H, td, J = 3.4, 13.2 Hz), 0.90 (3H, s), 0.87 (3H, s); ^{13}C NMR (C_6D_6, 150 MHz) δ 155.9 (C), 155.6 (C), 153.6 (C), 125.9 (C), 123.4 (CH), 122.8 (C), 111.0 (CH), 98.3 (CH), 54.3 (CH), 42.6 (CH_2), 40.9 (CH_2), 40.2 (C), 35.7 (CH_2), 35.2 (C), 34.3 (CH), 33.8 (CH_3), 24.8 (CH_2), 22.5 (CH_3), 22.2 (CH_3), 20.8 (CH_3), 19.5 (CH_2). HREIMS calcd for $C_{21}H_{28}O_2$ (M^+): 312.208 93; found 312.207 98. (**14a**): UV (MeOH) λ_{max} (log ε) 244 nm (3.42). $[\alpha]^{20}_D$ −10.7 (*c* 0.4, MeOH). ^{1}H NMR (C_6D_6, 600 MHz) δ 7.36 (1H, d, J = 8.6 Hz), 6.74 (1H, d, J = 2.3 Hz), 6.54 (1H, dd, J = 2.3, 8.6 Hz), 3.84 (1H, s), 3.07 (1H, m), 2.56 (1H, m), 1.70−1.52 (7H, m), 1.42 (1H, dd, J = 3.4, 6.5 Hz), 1.40 (1H, m), 1.35 (3H, d, J = 7.1 Hz), 1.34 (3H, s), 1.15 (1H, td, J = 3.7, 13.4 Hz), 0.91 (3H, s), 0.90 (3H, s); ^{13}C NMR (C_6D_6, 150 MHz) δ 155.5 (C), 155.0 (C), 153.5 (C), 125.2 (C), 123.1 (CH), 122.9 (C), 111.1 (CH), 98.5 (CH), 50.9 (CH), 42.8 (CH_2), 40.8 (CH_2), 39.9 (C), 36.5 (CH_2), 35.0 (C), 34.2 (CH), 31.7 (CH_3), 23.5 (CH_2), 22.9 (CH_3), 21.0 (CH_3), 19.63 (CH_3), 19.60 (CH_2). HREIMS calcd for $C_{21}H_{28}O_2$ (M^+): 312.208 93; found 312.209 54.

Compound 19. Bromine (1.37 mL, 26.7 mmol) was added dropwise to stirred aqueous KOH (20%, 40 mL) at 0 °C. Upon completion, geranylacetone (**18**) (2.0 mL, 8.9 mmol) in 1,4-dioxane (40 mL) was added and the biphasic mixture was stirred at room temperature for 1 h and then refluxed overnight. The resulting mixture was cooled, diluted with water, and acidified (pH 1) with concentrated HCl and the aqueous layer extracted with EtOAc. The obtained organic extracts were combined, dried (Na_2SO_4), and concentrated. Silica gel column chromatography (40% EtOAc/hexanes) afforded **19** (0.70 g, 40%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.30 (1H, s, broad), 5.07 (2H, m), 2.34 (4H, m), 2.01 (4H, m), 1.65 (3H, s), 1.60 (3H, s), 1.57 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 180.0 (C), 136.9 (C), 131.4 (C), 124.1 (CH), 121.9 (CH), 39.6 (CH_2), 34.3 (CH_2), 26.5 (CH_2), 25.6 (CH_2), 23.2 (CH_3), 17.6 (CH_3), 15.9 (CH_3). HRESIMS calcd for $C_{12}H_{19}O_2$ ([M - H]$^-$): 195.1385; found 195.1384.

Compound 20. A solution of intermediate **19** (0.70 g, 3.6 mmol), phosphonium bromide **6a** (1.42 g, 2.8 mmol), DCC (1.24 g, 6.0 mmol), and DMAP (50 mg, 0.4 mmol) was stirred at room temperature for 18 h. After solvent removal under reduced pressure, the obtained residue was dissolved in THF (50 mL), and Et_3N (3.0 mL) was added. The resulting mixture was refluxed for 4 h. Once at room temperature, silica was added and the THF was evaporated under reduced pressure. The resulting dried silica was poured into a silica gel column and eluted with 30% EtOAc/hexanes to yield **20** (0.99 g, 87%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.89 (1H, s), 6.33 (1H, s), 5.16 (1H, m), 5.05 (1H, m), 3.86 (6H, s), 2.78 (2H, t, J = 7.2 Hz), 2.41 (2H, q, J = 7.4 Hz), 2.03 (2H, m), 1.97 (2H, m), 1.64 (3H, s), 1.59 (3H, s), 1.57 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.4 (C), 150.3 (C), 146.7 (C), 144.0 (C), 136.5 (C), 131.4 (C), 124.4 (C), 124.1 (CH), 122.6 (CH), 102.6 (CH), 101.8 (CH), 99.6 (C), 61.0 (CH_3), 56.6 (CH_3), 39.6 (CH_2), 28.5 (CH_2), 26.5 (CH_2), 26.0 (CH_2), 25.6 (CH_3), 17.6 (CH_3), 16.0 (CH_3). HRESIMS calcd for $C_{21}H_{27}O_3Na^{79}Br$ ([M + Na]$^+$): 429.1041; found 429.1049.

Compound 21. To a solution of 20 (0.23 g, 0.56 mmol) in 2-nitropropane (15 mL) at −78 °C, $ClSO_3H$ (0.15 mL, 2.3 mmol) was added. The resulting mixture was allowed to stir for 45 min at the same temperature. After this time, the reaction mixture was added to aqueous $NaHCO_3$, and the aqueous layer was extracted with EtOAc, dried (Na_2SO_4), and concentrated to obtain a black residue. Silica gel column chromatography (30% EtOAc/hexanes) of the residue afforded **21** (0.19 g, 82%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.95 (1H, s), 3.86 (3H, s), 3.83 (3H, s), 2.76 (1H, dd, J = 5.4, 17.0 Hz), 2.65 (1H, m), 2.34 (1H, J = 12.6 Hz), 1.92 (1H, dd, J = 6.8, 13.3 Hz), 1.72 (1H, m), 1.62 (1H, m), 1.52 (1H, m), 1.45 (1H, m), 1.39 (2H, m), 1.22 (3H, s), 1.17 (1H, td, J = 4.2, 13.5 Hz), 0.90 (3H, s), 0.86 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.3 (C), 149.6 (C), 146.8 (C), 143.5 (C), 124.8 (C), 122.5 (C), 102.2 (CH), 99.8 (C), 60.9 (CH_3), 56.7 (CH_3), 52.4 (CH), 41.5 (CH_2), 37.4 (CH_2), 36.0 (C), 33.3 (CH_3), 32.9 (C), 24.9 (CH_2), 21.6 (CH_3), 21.1 (CH_3), 18.7 (CH_2), 18.6 (CH_2). HRESIMS calcd for $C_{21}H_{27}O_3Na^{79}Br$ ([M + Na]$^+$): 429.1041; found 429.1047.

Compounds 22 and 23. To a solution of **21** (0.35 g, 0.86 mmol) in THF (30 mL) was added at −78 °C *n*-BuLi (0.6 mL, 0.94 mmol, 1.6 M in hexanes). After the mixture was stirred for 30 min, DMF (0.70 mL, 9.0 mmol) was added. The mixture was stirred for 1.5 h at low temperature and allowed to reach room temperature in the following 1 h, to be then quenched with aqueous NH_4Cl. EtOAc extractions were performed and the organic extracts dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Silica gel column chromatography (30% EtOAc/hexanes) afforded **22** (69.8 mg, 25%) as a colorless oil and **23** (0.18 g, 58%) as a white solid.

22: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.97 (1H, s), 6.94 (1H, s), 3.88 (3H, s), 3.86 (3H, s), 2.73 (1H, m), 2.65 (1H, dd, J = 6.5, 16.8 Hz), 2.39 (1H, J = 12.2 Hz), 1.95 (1H, dd, J = 6.5, 13.3 Hz), 1.72 (1H, m), 1.78 (1H, m), 1.68 (1H, m), 1.60 (2H, m), 1.47 (1H, m), 1.28 (3H, s), 1.25 (1H, td, J = 3.9, 13.5 Hz), 0.94 (3H, s), 0.92 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.2 (C), 149.3 (C), 146.5 (C), 145.4 (C), 124.3 (C), 118.8 (C), 102.6 (CH), 95.6 (CH), 56.6 (CH_3), 56.2 (CH_3), 52.7 (CH), 41.8 (CH_2), 37.7 (CH_2), 35.9 (C), 33.5 (CH_3), 33.1 (C), 24.9 (CH_2), 21.8 (CH_3), 21.3 (CH_3), 18.9 (CH_2), 18.8 (CH_2). HRESIMS calcd for $C_{21}H_{28}O_3Na$ ($[M + Na]^+$): 351.1936; found 351.1945.

23: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.49 (1H), 7.27 (1H, s), 3.92 (3H, s), 3.88 (3H, s), 2.82 (1H, dd, J = 5.82, 17.1 Hz), 2.70 (1H, m), 2.34 (1H, J = 12.4 Hz), 1.94 (1H, dd, J = 7.2, 13.0 Hz), 1.74 (1H, m), 1.64 (1H, m), 1.54 (1H, m), 1.46 (2H, m), 1.35 (1H, d, J = 12.2 Hz), 1.23 (3H, s), 1.20 (1H, m), 0.91 (3H, s), 0.88 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.5 (C), 154.4 (C), 149.3 (C), 148.4 (C), 146.5 (C), 123.5 (2C), 115.3 (C), 109.9 (CH), 62.7 (CH_3), 56.8 (CH_3), 52.5 (CH), 41.6 (CH_2), 37.6 (CH_2), 35.8 (C), 33.4 (CH_3), 33.0 (C), 25.0 (CH_2), 21.8 (CH_3), 21.2 (CH_3), 18.7 (CH_2), 18.6 (CH_2). HRESIMS calcd for $C_{22}H_{28}O_4Na$ ($[M + Na]^+$): 379.1885; found 379.1881.

Compound 24. A solution of **23** (0.078 g, 0.22 mmol) in CH_2Cl_2 (10 mL) at −78 °C was treated with BI_3 (0.32 g, 0.80 mmol) dissolved in CH_2Cl_2 (2 mL). The resulting mixture was stirred at −78 °C for 1 h, allowed to reach room temperature for 4 h, and quenched with aqueous $Na_2S_2O_3$. After EtOAc extraction, the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. Reversed-phase column chromatography (80% CH_3CN/20% H_2O) provided one main fraction (one yellow spot by reversed-phase TLC), which was additionally purified by reversed-phase HPLC (C18 Inertsil, 85% CH_3CN/15% H_2O + 0.05% TFA) to afford **24** (0.020 g, 27%) as a yellow oil. ^{1}H NMR (C_6D_6, 600 MHz) δ 11.56 (1H, s), 10.21 (1H, s), 7.36 (1H, s), 5.22 (1H, s, broad), 2.47 (1H, dd, J = 5.3, 16.9 Hz), 2.37 (1H, m), 2.02 (1H, d, J = 12.2 Hz), 1.62 (1H, dd, J = 6.7, 13.0 Hz), 1.55 (1H, m), 1.40 (1H, dd, J = 6.1, 12.2 Hz), 1.37 (1H, m), 1.36 (1H, m), 1.24 (1H, td, J = 3.1, 12.7 Hz), 1.14 (1H, dd, J = 1.4, 12.4 Hz), 1.09 (1H, dd, J = 4.1, 13.9 Hz), 1.08 (3H, s), 0.83 (3H, s), 0.81 (3H, s); ^{13}C NMR (C_6D_6, 150 MHz) δ 192.4 (CH), 152.1 (C), 149.3 (C), 146.1 (C), 141.3 (C), 124.9 (C), 119.3 (C), 113.9 (CH), 107.6 (C), 52.8 (CH), 42.3 (CH_2), 37.8 (CH_2), 36.3 (C), 33.9 (CH_3), 33.5 (C), 25.4 (CH_2), 22.3 (CH_3), 21.7 (CH_3), 19.4 (CH_2), 19.3 (CH_2). HRESIMS calcd for $C_{20}H_{24}O_4Na$ ($[M + Na]^+$): 351.1572; found 351.1559.

Compound 25. Intermediate **22** (0.069 g, 0.21 mmol) was dissolved in chlorobenzene (30 mL) and refluxed overnight in the presence of $BBr_3 \cdot SMe_2$ (0.26 g, 0.84 mmol). Workup as stated in the previous experimental procedure, followed by silica gel column chromatography (30% EtOAc/hexanes) and reversed-phase HPLC (70% CH_3CN/30% H_2O + 0.05% TFA), yielded the desired **25** as a colorless oil (0.016 g, 24%). ^{1}H NMR (CD_2Cl_2, 600 MHz) δ 6.71 (1H, s, broad), 5.81 (1H, s, broad), 2.49 (1H, d, J = 6.9 Hz), 2.15 (1H, d, J = 2.2 Hz), 1.92 (1H, dt, J = 2.9, 12.5 Hz), 1.81 (1H, m), 1.79 (1H, m), 1.77 (1H, m), 1.63 (1H, m), 1.59 (1H, m), 1.47 (1H, d, J = 13.5 Hz), 1.41 (3H, s), 1.22 (1H, dt, J = 3.9, 13.5 Hz), 1.15 (1H, d, J = 11.2 Hz), 0.96 (3H, s), 0.92 (3H, s); ^{13}C NMR (CD_2Cl_2, 150 MHz) δ 181.6 (C), 173.2 (C), 164.5 (C), 150.0 (C), 121.5 (C), 113.5 (C), 99.7 (CH), 97.9 (CH), 55.9 (CH), 44.2 (C), 41.9 (CH_2), 39.3 ($2CH_2$), 34.8 (C), 34.1 (CH_3), 22.1 (CH_3), 19.6 (CH_2), 18.7 (CH_2), 18.5 (CH_3). HRESIMS calcd for $C_{19}H_{24}O_4Na$ ($[M+Na]^+$): 339.1572; found 339.1567.

Compound 26. Starting material **23** (0.013 g, 0.04 mmol) was dissolved in clorobenzene (30 mL) and refluxed overnight in the presence of $BBr_3 \cdot SMe_2$ (0.045 g, 0.14 mmol). Workup as stated previously, followed by silica gel column chromatography (30% EtOAc/hexanes) and reversed-phase HPLC (80% CH_3CN/20% H_2O + 0.05% TFA), yielded **26** (0.0092 g, 77%) as a yellow oil. ^{1}H NMR (C_6D_6, 600 MHz) δ 11.80 (1H, s), 10.27 (1H, s), 7.22 (1H, s), 5.19 (1H, t, J = 5.2 Hz), 3.51 (3H, s), 2.37 (2H, m), 2.00 (1H, m), 1.92 (1H, m), 1.77 (1H, td, J = 4.7, 13.8 Hz), 1.68 (1H, dd, J = 5.0, 11.9 Hz), 1.65 (3H, s), 1.59 (1H, m), 1.58 (2H, m), 1.47 (3H, s), 1.26 (1H, m), 1.22 (3H, s); ^{13}C NMR (C_6D_6, 150 MHz) δ 192.4 (CH), 153.0 (C), 151.4 (C), 149.8 (C), 145.6 (C), 131.7 (C), 125.4 (CH), 120.2 (C), 119.0 (C), 113.6 (CH), 108.4 (C), 57.7 (CH_3), 42.0 (CH_2), 35.9 (CH_2), 35.5 (CH), 27.5 (CH_3), 26.2 (CH_3), 24.2 (CH_2), 24.0 (CH_2), 20.1 (CH_2), 18.0 (CH_3). HRESIMS calcd for $C_{21}H_{26}O_4Na$ ($[M + Na]^+$): 365.1729; found 365.1740.

Compound 27. Intermediate **21** (0.35 g, 0.86 mmol) was dissolved in 10 mL of DMF. CuCN (0.15 g 1.69 mmol) was added, and the mixture was refluxed overnight. The mixture was then added to 10 mL of hot HCl (6:1), and an excess of $FeCl_3$ was added. The mixture was stirred at 50 °C for 30 min and extracted with toluene. The organic portion was dried with $MgSO_4$ and evaporated under reduced pressure. Silica gel chromatography (10% EtOAc/hexanes) afforded **27** (0.095 g, 31%). ^{1}H NMR ($CDCl_3$ 600 MHz) δ 7.22 (1H, s), 3.93 (3H, s), 3.90 (3H, s), 2.83 (1H, m), 2.77 (1H, m), 2.42 (1H, d, J = 12.2 Hz), 2.01 (1H, m), 1.80 (1H, m), 1.66 (1H, m), 1.57 (2H, m), 1.47 (1H, m), 1.31 (3H, s), 1.30 (1H, m), 0.99 (3H, s), 0.95 (3H, s); ^{13}C NMR ($CDCl_3$) 154.8 (C), 149.0 (C), 148.7 (C), 148.6 (C), 124.9 (C), 123.1 (C), 112.6 (CH), 108.8 (C), 91.6 (C), 62.4 (CH_3), 57.2 (CH_3), 52.8 (CH), 41.9 (CH_2), 37.9 (CH_2), 36.3 (C), 33.7 (CH_3), 33.4 (C), 25.2 (CH2), 22.2(CH_3), 21.6 (CH_3), 19.2 (CH_2), 18.9 (CH_2). HRESIMS calcd for $C_{22}H_{28}NO_3$ ($[M + H]^+$): 354.2069; found 354.2066.

Compound 28. Nitrile **27** (0.05 g, 0.14 mmol) was dissolved in 10 mL of 6 N NaOH in EtOH. To this, 10 mL of 30% H_2O_2 in EtOH was added, and the mixture was stirred at room temperature overnight. The reaction was quenched with 5% HCl to pH 3, extracted with ether, and washed with brine. The aqueous fraction was washed with ether. Organic extracts were combined, dried with $MgSO_4$, and evaporated under reduced pressure to afford the amide **28** (0.042 g, 81%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.15 (1H, s), 3.92 (3H, s), 3.90 (3H, s), 2.83 (1H m), 2.77 (1H, m), 2.40 (1H, d, J = 12.2 Hz), 1.98 (1H, m), 1.80 (1H, m), 1.63 (1H, m), 1.55 (1H, m), 1.50 (1H, m), 1.40 (2H, m), 1.29 (3H, s), 1.22 (1H, m), 0.97 (3H, s), 0.93 (3H, s). ^{13}C NMR 166.2 (C), 154.3 (C), 148.9 (C), 147.1 (C), 144.1 (C), 124.1 (C), 124.0 (C), 113.3 (C), 105.9 (CH), 62.4 (CH_3), 56.9 (CH_3), 52.9 (CH), 41.9 (CH_2), 37.8 (CH_2), 36.2 (C), 33.7 (CH_3), 33.4 (C), 25.4 (CH_2), 22.0 (CH_3), 21.6 (CH_3), 19.1 (CH_2), 19.0 (CH_2). HRESIMS calcd for $C_{22}H_{30}NO_4$ ($[M + H]^+$): 372.2175; found 372.2178.

Compound 29. Amide **28** (0.05 g, 0.13 mmol) was dissolved in 10 mL of DCM and cooled to −78 °C. To this, 225 mg of BI_3 in 2 mL of CH_2Cl_2 was added. The mixture was stirred for 1 h at −78 °C and then warmed to room temperature and stirred for an additional 2 h. The reaction was then quenched with $Na_2S_2O_3$, and the appropriate layer was extracted with EtOAc, dried with $MgSO_4$, and concentrated to dryness. The product was separated with a C_{18} Sep Pac column (4:1 MeCN/H_2O). The final product was purified with reversed phase HPLC (C_{18}, MeCN/H_2O) to give pure **29** (0.014 g, 31%). ^{1}H NMR (C_6D_6, 600 MHz) δ 13.75 (1H, s) 7.34 (1H, s), 6.94 (1H, S), 5.69 (1H, s), 2.32 (1H, m), 2.29 (1H, m), 2.07 (1H, d, J = 12.2 Hz), 1.63 (1H, d, J = 6.7, 13.0 Hz), 1.55 (1H, m), 1.42 (1H, m), 1.38 (2H, m), 1.27 (1H, td, J = 31., 12.7 Hz), 1.14 (1H, m), 1.12 (1H, m), 1.09 (3H, s), 0.85 (3H, s), 0.81 (3H, s); ^{13}C NMR 171.5 (C), 150.7 (C), 148.5 (C), 146.2 (C), 142.7 (C), 125.3 (C), 118.0 (C), 110.2 (CH), 100.2 (C), 52.8 (CH), 42.3 (CH_2), 37.7 (CH_2), 36.4 (C), 34.0 (CH_3), 33.5 (C), 25.3 (CH), 22.2 (CH_3), 21.7 (CH_3), 19.4 (CH_2), 19.3 (CH_2). HRESIMS calcd for $C_{2o}H_{26}NO_4$ ($[M + H]^+$): 344.1862; found 344.1851.

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Supporting Information Available: Experimental details for the synthesis of compounds **5** and **6a**−**d**; ^{1}H and ^{13}C NMR data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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