EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201200631

Synthesis of SHIP1-Activating Analogs of the Sponge Meroterpenoid Pelorol

Labros G. Meimetis,[a][‡] Matt Nodwell,[a][‡] Lu Yang,[a] Xiaoxia Wang,[a] Joyce Wu,[b] Curtis Harwig,[b] Grant R. Stenton,[b] Lloyd F. Mackenzie,[b] Thomas MacRury,[b] Brian O. Patrick,[a] Andrew Ming-Lum,[c] Christopher J. Ong,[c] Gerald Krystal,[d] Alice L. -F. Mui,[c] and Raymond J. Andersen*[a]

Dedicated to the memory of Ernesto Fattorusso

Keywords: Natural products / Medicinal chemistry / Biomimetic synthesis / Enzymes / Terpenoids / Enantioselectivity

Two biomimetic approaches have been used to synthesize analogs of the SHIP1-activating sponge meroterpenoid pelorol (**1**). One approach started from the chiral pool plant natural product sclareolide, which has the same absolute configuration as pelorol. The second approach utilized an enantioselective polyene cyclization to efficiently access both absolute configurations of the pelorol meroterpenoid skeleton and to prepare A-ring functionalized compounds. Selected analogs have been evaluated for water solubility and biological activity. It was found that the undesirable catechol and ester functionalities in **1** could be removed to give MN100 (**3**), without a decrease in SHIP1-activating ability. A further refinement led to the resorcinol analog **18**, which is the most effective SHIP1-activating pelorol analog made to date. The HCl salt of *ent*-**28**, a C-3 amino analog of **18**, is about 500,000-fold more soluble in water than MN100 (**3**). (±)-**28·HCl** activates SHIP1 in vitro, inhibits Akt phosphorylation in stimulated MOLT-4 (SHIP+) cells, and is active in a dose-dependent manner in a mouse model of inflammation when administered by oral gavage ($ED_{50} \approx 0.1$ mg/kg). Pelorol analogs *ent*-**28** or (±)-**28** are promising chemical tools for further preclinical in vivo evaluation of the potential of SHIP1 activators as therapeutics for treating hematopoietic diseases involving aberrant activation of PI3K cell signaling.

Introduction

The activation of phosphoinositide 3-kinase (PI3K) is stimulated by highly specific binding interactions between a variety of extracellular ligands and their membrane bound receptors and leads to initiation of signal transduction cascades that enhance cellular activation, proliferation, and/or survival depending on the cell type and external stimulus.[1,2] PI3K phosphorylates phosphatidylinositol-4,5-bisphosphate (PI-4,5-P_2) to generate the important second messenger phosphatidylinositol-3,4,5-trisphosphate (PI-3,4,5-P_3, or more commonly PIP_3) in the plasma membrane. PIP_3 then mediates downstream signaling by interacting with pleckstrin homology (PH) domain-containing proteins such as protein kinase B (PKB, also known as Akt), which becomes phosphorylated during active signaling. The levels of PIP_3 in unstimulated cells is very low, but it is rapidly synthesized from PI-4,5-P_2 in response to extracellular stimuli. To ensure that activation of the PI3K pathway is appropriately restrained under normal circumstances, the tumor suppressor phosphatase and tensin homolog (PTEN) hydrolyzes PIP_3 back to PI-4,5-P_2 and the Src homology 2-containing inositol 5-phosphatases (SHIP1, sSHIP, and SHIP2) hydrolyze it to phosphatidylinositol-3,4-bisphosphate (PI-3,4-P_2), events that in both cases reduce the levels of the second messenger PIP_3 and dampen the signal.

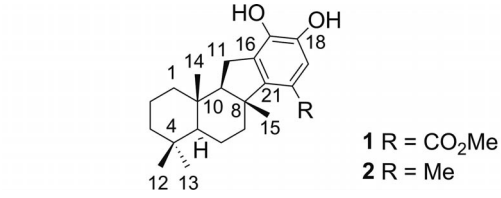
PI3K signaling is aberrantly activated in many human cancers and inflammatory diseases.[2] It has been estimated that mutation of PI3K pathway components such as PTEN accounts for up to 50% of all human cancers. As a consequence, drugs targeting the PI3K signaling pathway are being actively developed.[3] These drugs are designed to prevent the formation of the second messenger PIP_3 by inhibiting PI3K itself or by blocking signal transmission by inhibiting protein kinases downstream in the pathway.

We recently proposed that an attractive alternative approach to modulating aberrant PI3K signaling would be

[a] Departments of Chemistry and Earth, Ocean & Atmospheric Sciences, University of British Columbia,
2036 Main Mall, Vancouver, B.C. V6T 1Z1, Canada
Fax: +1-604-822 6091
E-mail: Raymond.andersen@ubc.ca
[b] Aquinox Pharmaceuticals Inc.,
Suite 430-5600 Parkwood Way, Richmond, B.C. V6V 2M2, Canada
[c] Department of Surgery, University of British Columbia, Vancouver, B.C. V5Z 1L3, Canada
[d] Terry Fox Laboratory, B.C. Cancer Control Agency, Vancouver, B.C. V5Z 1L3, Canada
[‡] These authors contributed equally to the research.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201200631.

to activate the phosphatase SHIP1.[4] The hematopoietic-restricted expression of SHIP1 should limit the effects of a highly selective SHIP1 agonist to target cells. Furthermore, activation of a phosphatase is expected to occur through an allosteric binding interaction of the agonist rather than by competitive binding at the active site. The major challenge in developing selective kinase inhibitors, which are predominately competitive with ATP binding, is the high degree of homology at kinase active sites.[4] A high degree of homology between allosteric activation sites on phosphatases is not expected and, therefore, the goal of much higher target selectivity should be easier to achieve.

In order to find a first-generation SHIP1 activator for a proof-of-principle (POP) test of our target hypothesis, we used a chromogenic kinetic assay that monitors SHIP1 phosphatase activity to screen a library of crude extracts prepared from marine invertebrates. This screen identified the meroterpenoid pelorol (**1**), isolated from the sponge *Dactylospongia elegans* collected in Papua New Guinea, as a selective and relatively potent SHIP1 activator.[5] We completed a total synthesis of pelorol in order to confirm the absolute configuration of the natural product and to provide more compound for biological evaluation. The initial synthesis also generated a small number of analogs for preliminary SAR. One of the analogs, designated 16A (**2**), in which the C-20 methyl ester substituent in pelorol had been replaced by a methyl group, was more readily synthesized than pelorol (**1**) and also showed more potent SHIP1 activation than the natural product.[5]



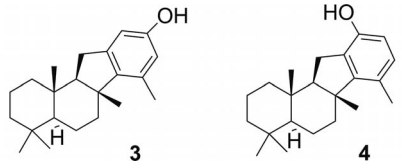
The target specificity and biological efficacy of 16A (**2**) was evaluated by comparing its effects on PI3K-regulated processes in primary SHIP1+/+ vs. SHIP1–/– murine macrophages and mast cells.[3] Data generated in these experiments were consistent with 16A (**2**) inhibiting PI3K-dependent macrophage and mast-cell responses in a SHIP1-dependent manner. 16A (**2**) was also tested for its efficacy at inhibiting inflammatory reactions in vivo by assessing its ability to provide protection in mouse models.[3] As predicted for an activator of SHIP1, 16A (**2**) reduced the levels of serum TNF-α in a mouse model of endotoxic shock and topically applied 16A (**2**) inhibited allergen-induced inflammation in a standard mouse ear edema/cutaneous anaphylaxis model. The biological profile of 16A (**2**) in the cell-based assays and mouse models provided a convincing POP demonstration that SHIP1 activators should be viable drug candidates for treating inflammatory diseases and it indicated that pelorol (**1**) and 16A (**2**) were promising lead structures for developing such a drug candidate.

Although the biological activities of **1** and **2** were promising, these compounds have two liabilities as potential drug candidates or biological tools. First, the catechol functionality in **1** and **2** could undergo either chemical or enzymatic oxidation to orthoquinones that could form covalent linkages with proteins by non-selective Michael addition reactions leading to off target biological effects. Second, both **1** and **2** are highly insoluble in water, which severely limits their administration to animals and, therefore, their usefulness as tools to explore the full range of in vivo biological properties of a SHIP1 activator.

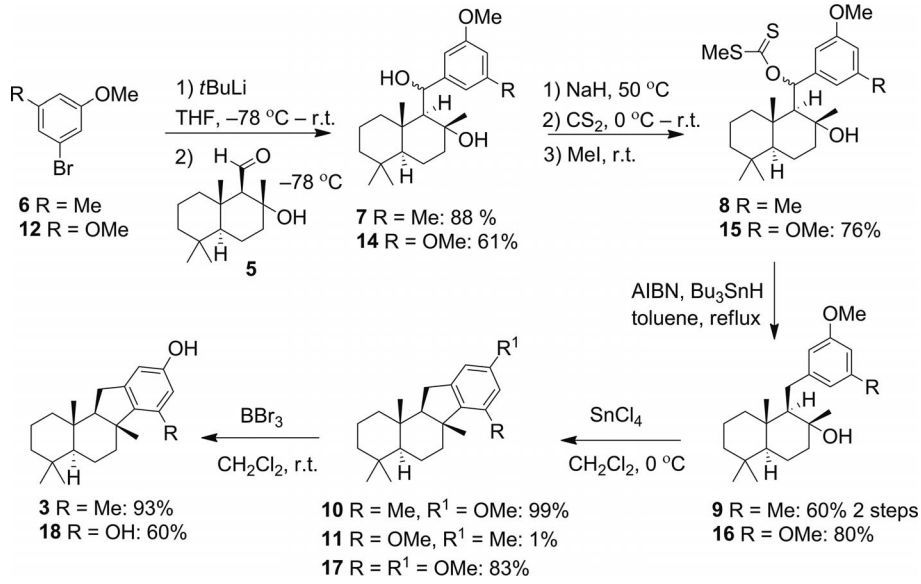
In order to address these issues, we have developed two biomimetic synthetic routes to pelorol analogs in order to find compounds with increased SHIP1 activation abilities and enhanced water solubility. The first route, which starts with the plant natural product sclareolide to establish the absolute configuration of analogs, was used in our reported synthesis of the natural product pelorol (**1**) and the simplified analog 16A (**2**).[5] The second route utilizes a newly developed enantioselective polyene cyclization approach to make both absolute configurations of the pelorol meroterpenoid skeleton and to add polar water-solubilizing functionalities to the A ring. Details of the application of these approaches to the synthesis of pelorol analogs are presented below.

Results and Discussion

First we focused our attention on making 16A (**2**) analogs that did not possess the catechol functionality. Two possible target molecules were the C-17 and C-18 monophenolic analogs **3** and **4**. Based on literature precedent and our own experience in the pelorol synthesis,[5] it was anticipated that a phenyl ring activated by a strongly electron donating OMe substituent *ortho* or *para* to the C-21 carbon where the new alkyl bond would form would be required for successful biomimetic cation-initiated cyclization (see Scheme 1, **9** to **10**) to give the five membered ring C of 16A analogs. Therefore, the monophenolic 16A analog **3**, designated MN100, was chosen as the initial target.



The synthesis of MN100 (**3**) started from the 8-hydroxy-11-drimanal intermediate **5** prepared from sclareolide as described in our pelorol synthesis (Scheme 1).[5] Reaction of **5** with the phenyllithium reagent prepared from commercially available 3-bromo-5-methylanisole (**6**), gave a mixture of the epimeric benzylic alcohols **7**. Attempts to remove the C-11 benzylic alcohol from **7** by hydrogenolysis using Pd and Pt catalysts produced only small amounts of desired product **9**, even under conditions of very high hydrogen pressure and long reaction times. Therefore, the benzylic alcohol was removed using the standard Barton-McCombie deoxygenation sequence.[6] Treatment of diastereomeric mixture **7** with sodium hydride and carbon disulfide in THF and then



Scheme 1. Synthetic route to MN100 (**3**) and resorcinol **18** starting from sclareolide.

with methyl iodide gave the diastereomeric mixture of methyl xanthates **8** in high yield. Reaction of xanthates **8** with tributyltin hydride and AIBN in refluxing toluene cleanly gave deoxygenated intermediate **9**. Cyclization of **9** using tin tetrachloride in dichloromethane gave tetracyclic product **10** as the major product, along with a small amount of regiosiomer **11**, in nearly quantitative yield.[7] Demethylation of **10** using BBr_3 cleanly generated MN100 (**3**), the desired monophenolic analog of 16A (**2**). MN100 (**3**) turned out to be a more effective SHIP1 activator than 16A (**2**),[3] but suffered from very low solubility in water (Table 1).

Table 1. Water or buffer solubilities of selected pelorol analogs.

	Solubility in water [μg/mL]	Solubility in Tris buffer [μg/mL]
MN100 (**3**)	–	0.003
18	–	0.92
ent-**28**·**HCl**	1,400	–

Lipinski's Rules are a commonly used guide to assess the drug-like properties of molecules.[8] One of the important criteria that a drug-like substance must meet under these rules is having a CLogP of less than 5. CLogP is a measure of the lipophilicity of the molecule and it is a good predictor of oral bioavailability and water solubility.[9] Pelorol (**1**), the lead compound in this SHIP1-activating series has a CLogP of 5.74, outside of the acceptable Lipinski range. Similarly, 16A (**2**) (CLogP 5.57) and MN100 (**3**) (CLogP 6.16) are too lipophilic to be drug-like. As a first step in decreasing the CLogP and increasing the water solubility of pelorol analogs, we made the resorcinol derivative **18**, which has a CLogP of 4.99 and provides the synthetic advantage that no regioisomers should be formed in the cation initiated cyclization step (**16** to **17**, Scheme 1) in its synthesis.

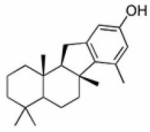
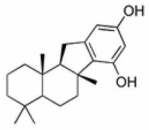
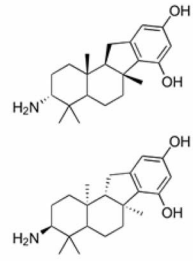
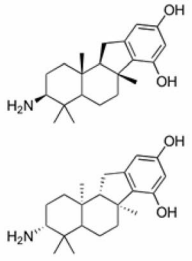
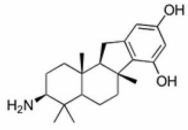
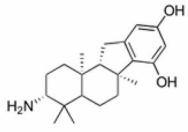
The synthesis of **18** started with the dimethoxybromobenzene **12** and followed the route to MN100 (**3**) as outlined in Scheme 1. Resorcinol **18** was about 300-fold more water soluble than MN100 (**3**) (Table 1) and it was a more effective in vitro activator of SHIP1 than MN100 (**3**) (Table 2). Therefore, compound **18** became the core template for the design of further CLogP-reduced analogs.

In an attempt to produce analogs of **18** with even lower CLogP values, we next explored A-ring functionalized compounds. Extensive unpublished SAR from our lab had shown that the aromatic ring was a critical part of the pelorol SHIP1-activating pharmacophore. Hence, we decided to add water solubilizing functionality to the A-ring of **18** in order to have minimal impact on the aromatic binding site. The 3-amino derivative **28** was of particular interest because the neutral form has a CLogP of 3.58, well within the drug-like range. In addition, the amino group should be protonated at physiological pH and the resulting ammonium ion salt would be expected to have increased water solubility.

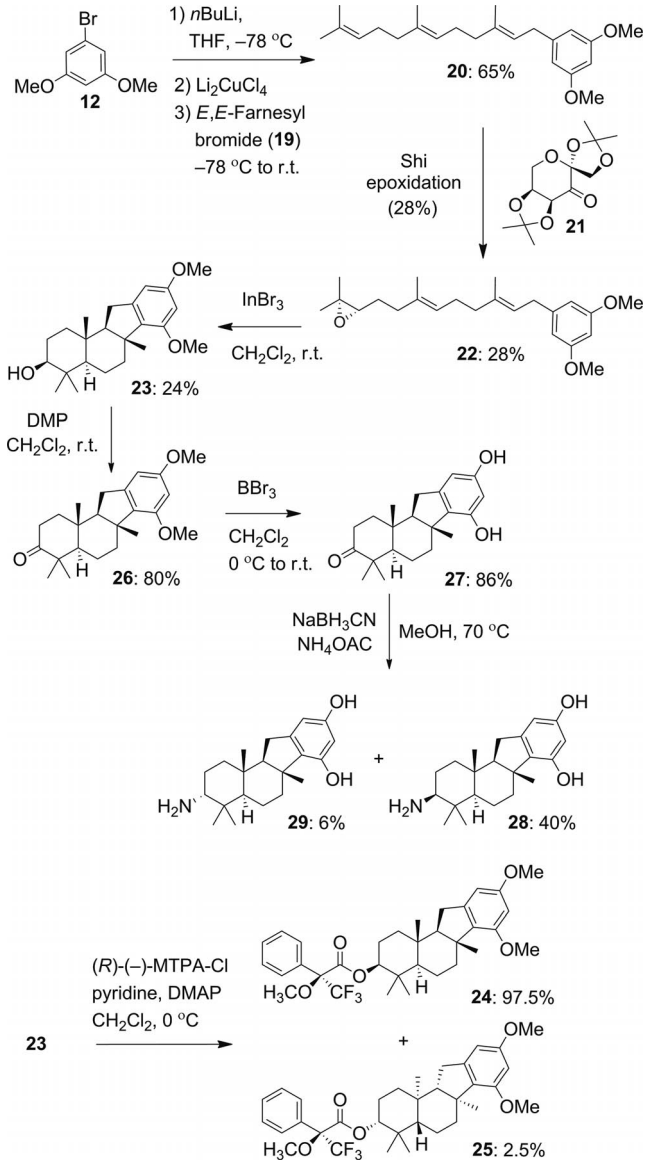
The synthetic route to **28** outlined in Scheme 2 featured a cation-initiated polyene cyclization to generate the tetracyclic ring system. Lithiation of 3,5-dimethoxybromobenzene (**12**) followed by alkylation with farnesyl bromide (**19**) gave the prenylated 3,5-dimethoxybenzene intermediate **20** in moderate yield.[10] Initially, racemic epoxide (±)-**22** was formed from **20** using *meta*-chloroperbenzoic acid (not shown) and the remaining steps in the synthesis (Scheme 2) were explored using racemic intermediates to give racemic (±)-(**28**) product.

Subsequently, an enantioselective Shi epoxidation of **20** with the *ent*-Shi catalyst **21** was used to generate the *S* terminal epoxide **22** and the following steps in the synthesis were optimized starting with this single enantiomer intermediate.[11] Treatment of epoxide **22** with $InBr_3$ initiated the

Table 2. Activation of His-hSHIP1 enzyme. Percent (%) activation is expressed as a percentage increase relative to background. Scoring is expressed as follows: + (< 25%); ++ (≥ 25% but < 50%); +++ (≥ 50%).

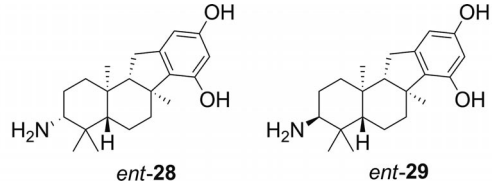
Compound		Scoring
MN100 (3)		++
18		+++
(±)-**29**·HCl		++
(±)-**28**·HCl		++
28·HCl		+
ent-**28**·HCl		++

polyene cyclization to give the desired tetracyclic intermediate **23**.[12,13] The *ee* (94%) for the combined epoxidation and cyclization steps was determined by analyzing the ratio of Mosher esters **24** and **25** formed from reaction of **23** with (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride [(*R*)-MTPA-Cl] (Scheme 2). One recrystallization of alcohol **23** gave material that was > 99.5% of the single enantiomer shown. The absolute configuration of **23** was confirmed by single-crystal X-ray diffraction analysis (Supporting Information).

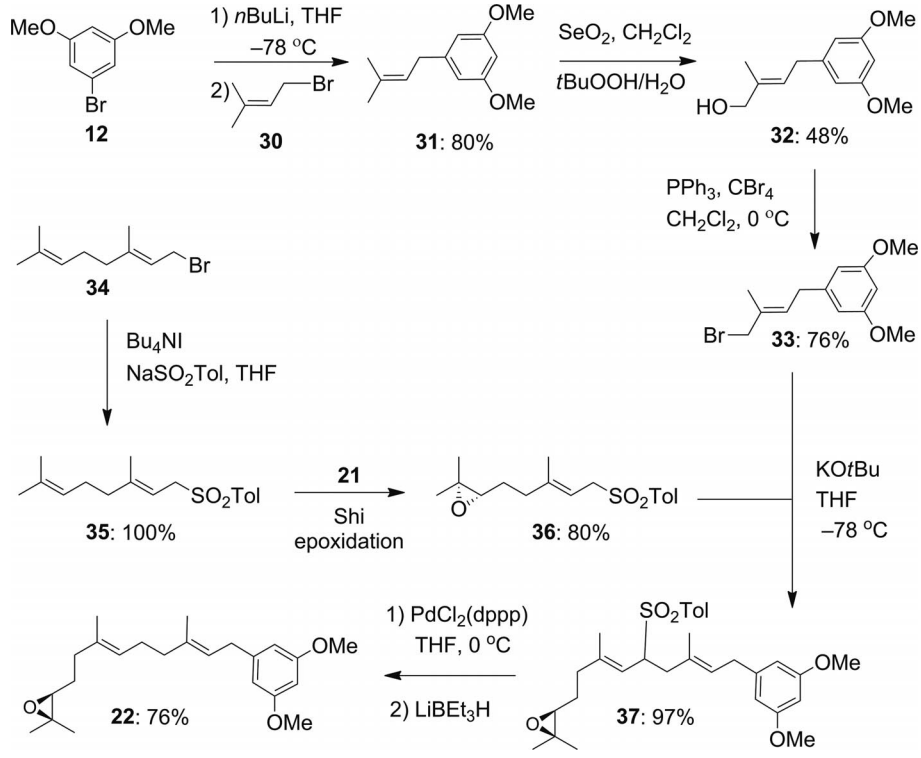


Scheme 2. Polyene cyclization route to pelorol analogs.

Dess–Martin oxidation of the C-3 secondary alcohol in **23** gave ketone **26** (Scheme 2). Removal of the methyl ether protecting groups in **26** with BBr_3 generated resorcinol intermediate **27**. Reductive amination of **27** gave desired 3β-amino analog **28** as the major product along with a small amount of 3α-amino product **29**.[14] Repeating the synthesis with the Shi catalyst that is the enantiomer of **21**[11] gave 3β-amino analog *ent*-**28** and 3α-amino analog *ent*-**29**.[15]



The epoxidation of **20** (Scheme 2) gave a low yield (28%) of desired terminal epoxide **22**, that could only be obtained as a single compound after a challenging chromatography



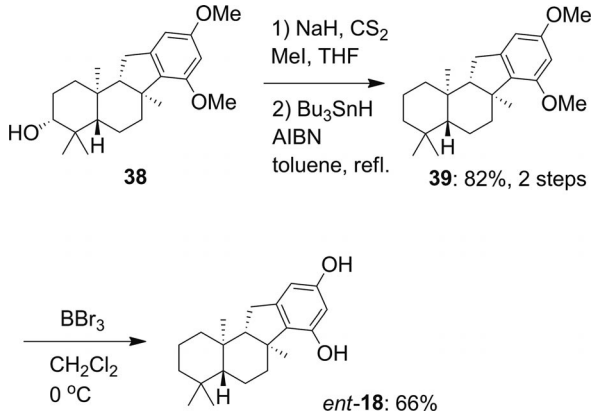
Scheme 3. Improved route to epoxide intermediate **22**.

step. In order to improve this part of the synthesis of amino analog **28**, an alternate synthesis of epoxide **22** was developed as shown in Scheme 3. Lithiation of bromobenzene **12** followed by alkylation with dimethylallyl bromide (**30**) gave the prenylated resorcinol derivative **31**. Selenium dioxide oxidation of the prenyl substituent in **31** gave *E* allylic alcohol **32**,[16] that was converted into corresponding *E* allylic bromide **33** using Appel reaction conditions.[17]

Reaction of geranyl bromide (**34**) with tetrabutylammonium iodide and sodium *p*-tolunesulfinate gave allylic sulfone **35** in quantitative yield (Scheme 3).[18] Shi epoxidation of **35** gave terminal epoxide **36** enantio- and regioselectively in high chemical yield. Deprotonation of allylic sulfone **36** with potassium *tert*-butoxide followed by alkylation with allylic bromide **33** afforded epoxide **37** in nearly quantitative yield.[19] Palladium catalyzed reductive elimination of tosyl sulfone moiety in **37** gave desired epoxide **22** in good yield.[20] This convergent synthesis of critical epoxide intermediate **22** proceeded in 59% overall though 4 linear steps from the readily available starting material geranyl bromide (**34**) without any difficult chromatography steps (Scheme 3), a significant improvement over the direct epoxidation of **20** (Scheme 2).

One major objective of the synthetic program described above was to prepare pelorol analogs with CLogP values in the Lipinksi-range for drug-like molecules in order to generate enhanced water solubilities. Table 1 gives the solubilities of MN100 (**3**), resorcinol analog **18**, and the HCl salt of *ent*-**28** either in pure water or Tris buffer. As anticipated, there was a significant ca. 500,000 fold increase in water/buffer solubility in going from MN100 (**3**) to *ent*-**28**·**HCl**.

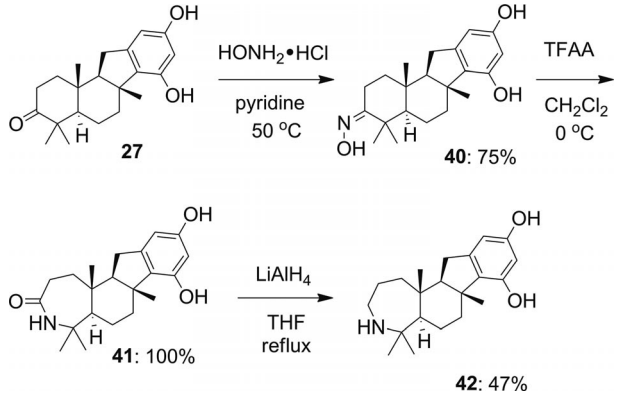
The synthesis of **18** from sclareolide gave the resorcinol analog with the same absolute configuration as pelorol. Starting with compound **38**, the intermediate in the polyene cyclization route to amino derivative *ent*-**28**, we carried out a Barton–McCombie deoxygenation to give **39** followed by removal of the methyl ether protecting groups to give *ent*-**18**, so that we could assess the role of absolute configuration on SHIP1 activation (Scheme 4).



Scheme 4. Synthesis of *ent*-**18**.

Reaction of the ketone **27** (Scheme 2) with hydroxylamine afforded oxime **40** (Scheme 5). Beckmann rearrangement of **40** gave ring expanded lactam **41** as the major product, and LAH reduction of **41** gave A-ring azepine analog **42**. The synthesis of **27**, **40**, **41**, and **42** illustrates a small

sampling of the wide variety of A-ring functionalized analogs that can be easily accessed as either enantiomer by the polyene cyclization route.



Scheme 5. Synthesis of A ring functionalized analogs of pelorol.

Biological Activity of Pelorol Analogs

Only selected synthetic analogs have been tested for biological activity thus far. The analog MN100 (**3**), in which the undesirable catechol functionality found in pelorol (**1**) and 16A (**2**) has been removed by replacing the C-17 phenol functionality with a hydrogen atom, was found to be a slightly more effective SHIP1 activator than 16A.[3] We have used MN100 (**3**) to provide further in vitro and in vivo POP demonstrations of the drug potential of SHIP1 activators in this family and to demonstrate that pelorol analogs bind to the C-2 allosteric activation domain of SHIP1.[3,21]

Even though MN100 (**3**) showed good activity in the in vitro and in vivo mouse model experiments, its large CLogP and very low water solubility made it an unlikely drug candidate and a poor chemical tool for exploring the therapeutic potential of SHIP1 activators in other mouse models. The next step in the progression of pelorol analogs towards drug-like molecules was the synthesis of the resorcinol-containing analog **18**, which had a lower CLogP and was more efficient to synthesize than MN100 (**3**) because it produced no regioisomers in the cation initiated cyclization step. As shown in Table 1, **18** was a more effective in vitro activator of SHIP1 than MN100 (**3**) and it became the reference standard for the evaluation of further CLogP-reduced analogs. Interestingly, **18** and *ent*-**18** showed nearly identical SHIP1-activating properties, suggesting that the absolute configuration of the meroterpenoid skeleton was not crucial for this analog.

Racemic A-ring α and β 3-amino analogs (±)-**29·HCl** and (±)-**28·HCl** were both in vitro SHIP1 activators, but neither was as effective as the reference compound **18** (Table 1). Analog **28·HCl** was somewhat less active than racemic (±)-**28·HCl**, whereas *ent*-**28·HCl** had identical SHIP1-activating ability in comparison with the racemic mixture, indicating that in the 3-amino series the absolute configuration was important. Racemate (±)-**28·HCl** inhibited the phosphorylation of Akt in SHIP(+) Molt-4 cells stimulated with IGF1 but not in SHIP1(–) Jurkat cells, consistent with SHIP1 activation in whole cells (Supporting Information, Figure S61). The same racemic (±)-**28·HCl** mixture was also evaluated in a standard mouse passive cutaneous anaphylaxis ear model of inflammation.[22] When administered by oral gavage, (±)-**28·HCl** showed effective anti-inflammatory activity with a clear dose response and an ED_{50} of about 0.1 mg/kg (Figure 1).

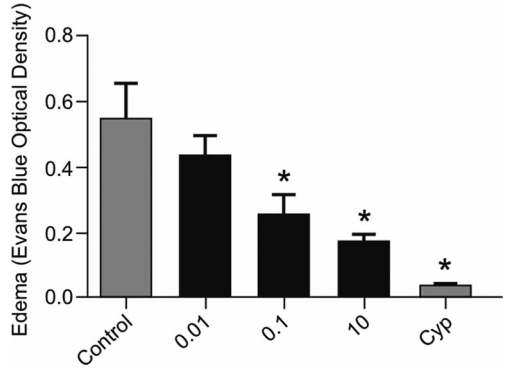


Figure 1. Efficacy of (±)-**28·HCl** or cyproheptadine (Cyp, 1 mg/kg) in a mouse passive cutaneous anaphylaxis (PCA) model. PCA response results in the extravasation of Evans Blue in the ears of mice. Evans Blue was extracted by dimethyl formamide and data are presented as the optical density. Data represent mean ± SEM (n = 10), *p < 0.05 shows the effect of (±)-**28·HCl** or of cyproheptadine, compared to the response of the vehicle-treated control animals.

Conclusions

Two biomimetic synthetic routes have been developed for the preparation of analogs of the SHIP1-activating sponge meroterpenoid pelorol (**1**). Both routes are efficient and give products with high *ee*. They have facilitated the preparation of structurally diverse analogs on > 100 mg scales useful for further exploration of the SAR and in vivo biological activities of this new pharmacophore. The results described above successfully address the major challenge of providing an effective renewable supply of a sponge natural product or more drug-like pharmacophore analogs for preclinical biological evaluation.

Amino derivative *ent*-**28·HCl**, one of the new synthetic pelorol (**1**) analogs prepared in this work, had significantly enhanced water solubility compared with the natural product and other SHIP1-activating analogs such as MN100 (**3**). Pure *ent*-**28·HCl** and racemate (±)-**28·HCl** both activated SHIP1 in vitro (Table 2) and racemate (±)-**28·HCl** was found to inhibit the phosphorylation of Akt in a manner consistent with SHIP1 activation in whole cells (Supporting Information, Figure S61). The same racemic mixture (±)-**28·HCl** showed potent in vivo anti-inflammatory activity (ED_{50} of ca. 0.1 mg/kg) in a mouse model with a clear dose-response when administered by oral gavage (Figure 1). The facile synthetic accessibility of either *ent*-**28·HCl** or racemate (±)-**28·HCl**, combined with their enhanced water solubility and SHIP1-activating properties, makes them at-

tractive chemical tools for the further preclinical in vivo evaluation of the hypothesis that activating SHIP1 is a viable approach to treating blood diseases caused by aberrant activation of PI3K cell signaling.

Experimental Section

General Experimental Procedures: Optical rotations were measured with a Jasco -1010 polarimeter with sodium light (589 nm) in EtOAc. The ^{1}H and ^{13}C NMR spectra were recorded with either a Bruker AV-400 spectrometer or a Bruker AV-600 spectrometer with a 5 mm CPTCI cryoprobe. ^{1}H chemical shifts are referenced to the residual $CDCl_3$, CD_2Cl_2, $(CD_3)_2CO$, and CD_3OD signals (d 7.24, 5.32, 2.05, 3.31 ppm, respectively) and ^{13}C chemical shifts are referenced to the $CDCl_3$, CD_2Cl_2, $(CD_3)_2CO$, and CD_3OD signals (d 77.0, 54.0, 29.9, 49.1 ppm, respectively). Low and high resolution ESI-QIT-MS were recorded with a Bruker–Hewlett Packard 1100 Esquire–LC system mass spectrometer. Merck Type 5554 silica gel plates and Whatman MKC18F plates were used for analytical thin layer chromatography. Flash chromatography was carried out on Silicycle SiliaFlash 60A. Reversed-phase HPLC analyses of purity were performed on a C-18 column on a Waters 600E System Controller liquid chromatography attached to a Waters 996 Photodiode Array Detector. All solvents used for HPLC were Fisher HPLC grade. All final compounds tested for biological activity had a purity of > 95% as assessed by HPLC.

Preparation of 7: To 1-bromo-3-methoxy-5-methylbenzene (**6**) (3.64 g, 18.29 mmol) dissolved in THF (35 mL), and cooled to –78 °C, was added 1.7 M *t*BuLi (21.5 mL, 36.6 mmol). The solution was stirred for 10 min at –78 °C, and then warmed to room temp. for 20 min. The solution was again brought to –78 °C, and a solution of aldehyde **5** (1.45 g, 6.09 mmol) in THF (6 mL) was added. The solution was stirred at –78 °C for 2 h, and then the reaction was quenched by addition of 1 M HCl (5 mL). EtOAc (100 mL) was added, and the organic phase was washed with 1 M HCl (25 mL), followed by saturated $NaHCO_3$ (50 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated. The crude reaction mixture was purified by flash chromatography (hexanes/EtOAc) to yield diol **7** (1.94 g, 5.39 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.85 (s, 1 H), 6.78 (s, 1 H), 6.61 (s, 1 H), 4.79 (d, J = 8.1 Hz, 1 H), 3.79 (s, 3 H), 2.33 (s, 3 H), 2.12 (d, J = 8.1 Hz, 1 H), 1.84 (dt, J = 12.2, 3.3 Hz, 1 H), 1.63 (m, 1 H), 1.56 (m, 1 H), 1.54 (s, 3 H), 1.40 (m, 1 H), 1.33 (m, 1 H), 1.23 (m, 1 H), 1.16 (m, 1 H), 1.13 (m, 1 H), 1.02 (s, 3 H), 0.97 (td, J = 13.5, 3.6 Hz, 1 H), 0.90 (m, 1 H), 0.82 (s, 3 H), 0.77 (s, 3 H), 0.34 (td, J = 13.3, 3.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 159.7, 149.0, 139.8, 120.7, 113.6, 110.5, 76.0, 62.85, 62.84, 55.8, 55.1, 44.0, 41.3, 40.8, 38.6, 33.5, 33.2, 26.1, 21.53, 21.50, 19.8, 18.3, 15.9 ppm. HRESIMS $[M + Na]^+$ calcd. for $C_{23}H_{36}O_3Na$ 383.2562, found 383.2563.

Preparation of 8: Diol **7** (1.94 g, 5.39 mmol) was dissolved in THF (20 mL). To this solution was added NaH (237 mg, 60% in oil, 5.93 mmol). The reaction was then heated to 50 °C until the solution was clear orange in color. The reaction was cooled to 0 °C, and CS_2 (1 mL, 16.6 mmol) was added. The solution was stirred for 20 min at 0 °C, and then warmed to room temp. for an additional 20 min, after which methyl iodide (1 mL, 16.6 mmol) was added. The reaction was stirred at room temp. for 1 h, and then concentrated to dryness in vacuo. The crude mixture was dissolved in EtOAc (150 mL), and washed with 3× H_2O (100 mL). The organic solution was dried with $MgSO_4$, filtered, and concentrated in vacuo. A portion of this mixture was purified by flash chromatography (hexanes/EtOAc) for characterization; however, this product mixture could be used in the next step without further purification. **8**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.8 (s, 1 H), 6.7 (s, 1 H), 6.5 (s, 1 H), 5.18 (d, J = 5.2 Hz, 1 H), 3.75 (s, 3 H), 2.38 (s, 3 H), 2.28 (s, 3 H), 2.18 (d, J = 5.2 Hz, 1 H), 1.81 (m, 1 H), 1.78 (m, 1 H), 1.75 (m, 1 H), 1.65 (m, 1 H), 1.55 (m, 1 H), 1.50 (s, 3 H), 1.45 (m, 1 H), 1.34 (m, 1 H), 1.31 (m, 1 H), 1.28 (m, 1 H), 1.02 (s, 3 H), 0.99 (dt, J = 13.6, 3.8 Hz, 1 H), 0.87 (dd, J = 12.2, 2.4 Hz, 1 H), 0.80 (s, 3 H), 0.77 (s, 3 H), 0.56 (td, J = 12.9, 3.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 189.7, 159.4, 149.9, 139.5, 120.9, 112.3, 110.9, 74.2, 65.1, 55.9, 55.0, 46.8, 46.0, 41.3, 41.0, 40.2, 33.30, 33.26, 26.3, 21.6, 21.3, 20.2, 18.3, 15.9, 13.0 ppm. HRESIMS $[M + Na]^+$ calcd. for $C_{25}H_{38}O_3S_2Na$ 473.2160, found 473.2159.

Preparation of 9: The crude mixture of xanthate **8** was dissolved in toluene (50 mL). Bu_3SnH (2.9 mL, 10.8 mmol) was added, and the solution was heated. Once at reflux, a catalytic amount of AIBN (50 mg, 8.21 mmol) was added through the top of the condenser. The solution was refluxed for 1 h, and then an additional amount of AIBN was added (50 mg, 8.21 mmol). The solution was refluxed for another 45 min, after which TLC analysis indicated the reaction to be complete. The reaction was cooled, and then concentrated to dryness. Flash chromatography (hexanes/EtOAc) of the crude product yielded alcohol **9** (1.12 g, 3.23 mmol, 60%, 2 steps) as a white foam. **24**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.68 (s, 1 H), 6.63 (s, 1 H), 6.49 (s, 1 H), 3.75 (s, 3 H), 2.70 (dd, J = 14.7, 5.9 Hz, 1 H), 2.60 (dd, J = 14.7, 4.5 Hz, 1 H), 2.27 (s, 3 H), 1.84 (dt, J = 12.4, 3.1 Hz, 1 H), 1.70 (m, 1 H), 1.64 (m, 1 H), 1.54 (m, 1 H), 1.43 (m, 1 H), 1.39 (m, 1 H), 1.35 (m, 1 H), 1.31 (m, 1 H), 1.25 (s, 3 H), 1.09 (td, J = 13.3, 3.9 Hz, 1 H), 0.96 (m, 1 H), 0.93 (m, 1 H), 0.90 (m, 1 H), 0.87 (s, 3 H), 0.85 (s, 3 H), 0.78 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 159.5, 145.9, 139.2, 122.1, 111.9, 111.3, 74.1, 63.0, 56.0, 55.0, 44.0, 41.7, 40.3, 39.1, 33.3, 33.2, 31.2, 24.5, 21.5, 21.4, 20.2, 18.4, 15.4 ppm. HRESIMS $[M + Na]^+$ calcd. for $C_{23}H_{36}O_2Na$ 367.2613, found 367.2615.

Preparation of 10: Alcohol **9** (1.12 g, 3.23 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C. To this solution was added neat $SnCl_4$ (1 mL, 8.5 mmol). The orange solution was then stirred for 1 h at 0 °C, followed by quenching with MeOH (1 mL). The reaction was diluted with EtOAc (200 mL), and washed with saturated $NaHCO_3$ (50 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated. The crude was purified by flash chromatography to yield tetracycle **10** (1.05 g, 3.20 mmol, 99%). **10**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.62 (s, 1 H), 6.41 (s, 1 H), 3.74 (s, 3 H), 2.60 (m, 1 H), 2.49 (dd, J = 14.5, 6.2 Hz, 1 H), 2.34 (m, 1 H), 2.27 (s, 3 H), 1.71 (m, 4 H), 1.54 (m, 2 H), 1.40 (m, 2 H), 1.24 (m, 1 H), 1.17 (td, J = 13.5, 4.2 Hz, 1 H), 1.06 (s, 3 H), 1.02 (s, 3 H), 0.98 (m, 1 H), 0.86 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 157.3, 143.8, 132.5, 117.9, 113.4, 107.9, 64.2, 56.7, 54.8, 42.1, 39.7, 38.5, 37.9, 36.5, 32.9, 32.6, 28.6, 20.7, 19.9, 19.1, 18.6, 17.9, 15.7 ppm. HRESIMS $[M + H]^+$ calcd. for $C_{23}H_{35}O$ 327.2688, found 327.2685.

Preparation of 3: To **10** (1.05 g, 3.20 mmol) dissolved in 15 mL of CH_2Cl_2, was added a solution of BBr_3 (3.2 mL, 1.0 M in CH_2Cl_2, 3.2 mmol). The solution was stirred at room temp. for 2 h, then concentrated to dryness. The brown residue was dissolved in EtOAc (200 mL), and washed with H_2O (200 mL) until the pH of the aqueous layer was neutral. The crude product was purified by flash chromatography (hexanes/EtOAc) to yield **3** (931 mg, 2.98 mmol, 93%) as a white solid. **3**: $[\alpha]_D^{24}$ = +7.22 (c = 3.35). ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 6.54 (s, 1 H), 6.34 (s, 1 H), 2.58 (m, 1 H), 2.47 (dd, J = 14.4, 6.04 Hz, 1 H), 2.33 (dt, J = 11.7, 3.0 Hz,

1 H), 2.25 (s, 3 H), 1.75 (m, 1 H), 1.74 (m, 1 H), 1.73 (m, 1 H), 1.70 (m, 1 H), 1.59 (m, 1 H), 1.52 (m, 1 H), 1.43 (m, 1 H), 1.41 (m, 1 H), 1.17 (td, J = 13.7, 4.4 Hz, 1 H), 1.06 (s, 3 H), 1.02 (s, 3 H), 1.00 (m, 1 H), 0.98 (m, 1 H), 0.86 (s, 6 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ = 153.4, 144.7, 144.3, 133.2, 115.0, 109.8, 64.5, 57.1, 47.0, 42.5, 40.1, 38.9, 36.9, 33.4, 33.1, 28.9, 21.1, 20.4, 19.6, 18.9, 18.3, 16.1 ppm. HRESIMS $[M + H]^+$ calcd. for $C_{22}H_{33}O$ 313.2531, found 313.2526; Elemental analysis calcd. (found) for $C_{22}H_{32}O$: Theoretical to be C, 84.56 (84.28); H, 10.32 (10.68). The structure and absolute configuration of **3** were confirmed by single-crystal X-ray diffraction analysis. (See Supporting Information).

Preparation of 14: Following a procedure similar to that used to prepare **7**, the following amounts were used; 1-bromo-3,5-dimethoxybenzene (**12**) (4.84 g, 22.3 mmol) in THF (40 mL); *t*BuLi (26.2 mL, 1.7 M in pentane, 44.6 mmol); aldehyde **7** (1.77 g, 7.44 mmol) in THF (20 mL). Yields **14** (1.7 g, 4.5 mmol, 61%) as a white foam. **14**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.57 (d, J = 2.4 Hz, 2 H), 6.32 (t, J = 2.2 Hz, 1 H), 4.75 (d, J = 8.3 Hz, 1 H), 3.76 (s, 6 H), 2.07 (d, J = 8.1 Hz, 1 H), 1.81 (dt, J = 12.2, 3.0 Hz, 1 H), 1.54–1.68 (m, 2 H), 1.51 (s, 3 H), 1.25–1.44 (m, 2 H), 1.24 (m, 1 H), 1.14 (m, 2 H), 1.00 (s, 3 H), 0.95 (m, 1 H), 0.87 (dd, J = 12.1, 1.8 Hz, 1 H), 0.82 (s, 3 H), 0.76 (s, 3 H), 0.37 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 160.7, 150.1, 105.8, 99.1, 75.8, 74.4, 62.8, 55.8, 55.3, 44.1, 41.3, 40.6, 38.6, 33.5, 33.2, 26.0, 21.6, 19.8, 18.3, 15.9 ppm. HRESIMS $[M + Na]^+$ calcd. for $C_{23}H_{36}O_4Na$ 399.2511, found 399.2510.

Preparation of 15: Following a procedure similar to that used to prepare **8**, the following amounts were used; diol **14** (1.60 g, 4.25 mmol) in THF (20 mL); NaH (187 mg, 60% in oil, 4.67 mmol); CS_2 (280 mL, 4.67 mmol); methyl iodide (293 mL, 4.67 mmol); Yields **15** (1.22 g, 3.25 mmol, 76%). **15**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.60 (d, J = 2.2 Hz, 2 H), 6.25 (t, J = 2.2 Hz, 1 H), 5.18 (d, J = 5.0 Hz, 1 H), 3.75 (s, 6 H), 2.38 (s, 3 H), 2.19 (d, J = 5.2 Hz, 1 H), 1.79 (m, 3 H), 1.66 (m, 1 H), 1.56 (dt, J = 13.7, 3.5 Hz, 1 H), 1.51 (s, 3 H), 1.46 (m, 1 H), 1.32 (m, 2 H), 1.01 (s, 3 H), 0.99 (m, 1 H), 0.87 (m, 1 H), 0.81 (s, 3 H), 0.77 (s, 3 H), 0.60 (td, J = 12.9, 3.5 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 189.9, 160.6, 151.0, 106.2, 97.9, 74.2, 65.0, 55.9, 55.2, 46.9, 46.2, 41.4, 41.0, 40.2, 33.4, 33.3, 26.4, 21.3, 20.3, 18.4, 15.9, 14.1, 13.0 ppm. HRESIMS $[M + Na]^+$ calcd. for $C_{25}H_{38}O_4NaS_2$ 489.2109, found 489.2112.

Preparation of 16: Following the procedure used to prepare **9**, the following amounts were used; xanthate **15** (1.1 g, 2.36 mmol), Bu_3SnH (1.25 mL, 4.72 mmol) in toluene (6 mL); AIBN (10 mg, 1.64 mmol) added every hour until reaction was complete. Yields **16** (681 mg, 1.88 mmol, 80%): **16**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.46 (d, J = 2.2 Hz, 2 H), 6.25 (t, J = 2.2 Hz, 1 H), 3.77 (s, 6 H), 2.73 (dd, J = 14.6, 5.5 Hz, 1 H), 2.59 (dd, J = 14.6, 4.6 Hz, 1 H), 1.86 (dt, J = 12.4, 3.1 Hz, 1 H), 1.61–1.72 (m, 3 H), 1.57 (dt, J = 13.5, 3.1 Hz, 1 H), 1.45 (m, 1 H), 1.40 (m, 3 H), 1.29 (m, 1 H), 1.26 (s, 3 H), 1.10 (td, J = 13.5, 4.1 Hz, 1 H), 0.95 (dd, J = 12.1, 2.0 Hz, 1 H), 0.89 (s, 3 H), 0.86 (s, 3 H), 0.80 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 160.6, 147.2, 107.1, 97.1, 74.0, 63.0, 56.1, 55.2, 55.2, 44.1, 41.7, 40.3, 39.2, 33.4, 33.2, 31.6, 24.5, 21.5, 20.3, 18.5, 15.4 ppm. HRESIMS $[M + Na]^+$ calcd. for $C_{23}H_{36}O_3Na$ 383.2562, found 383.2567.

Preparation of 17: Following the procedure used to prepare **10**, the following amounts were used; **16** (680 mg, 1.88 mmol) in CH_2Cl_2 (20 mL); $SnCl_4$ (2 mL, 17.0 mmol). Yields **17** (540 mg, 1.56 mmol, 83% yield). **17**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.41 (s, 1 H), 6.21 (s, 1 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 2.62 (m, 1 H), 2.52 (dd, J = 14.4, 6.3 Hz, 1 H), 2.43 (m, 1 H), 1.77 (dd, J = 12.6, 6.3 Hz, 1 H), 1.59–1.74 (m, 3 H), 1.54 (m, 2 H), 1.40 (m, 2 H), 1.19 (td, J = 13.5, 4.5 Hz, 1 H), 1.09 (s, 3 H), 1.04 (s, 3 H), 0.98–1.01 (m, 2 H), 0.88 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 159.3, 155.8, 145.2, 133.7, 101.9, 96.7, 64.7, 57.5, 55.4, 55.1, 46.3, 42.6, 40.2, 38.5, 37.0, 33.4, 33.1, 29.5, 21.1, 20.4, 19.5, 18.4, 16.2 ppm. HRESIMS $[M + H]^+$ calcd. for $C_{23}H_{35}O_2$ 343.2637, found 343.2633.

Preparation of 18: Following the procedure used to prepare **3**, the following amounts were used; compound **17** (536 mg, 1.56 mmol) in CH_2Cl_2 (50 mL); BBr_3 (7 mL, 1.0 M in CH_2Cl_2, 7.0 mmol). The crude residue was crystallized from CH_2Cl_2 to yield **18** (295 mg, 0.94 mmol, 60%). **18**: ^{1}H NMR (600 MHz, CD_3OD, 25 °C): δ = 6.15 (s, 1 H), 6.01 (s, 1 H), 2.51 (m, 1 H), 2.44 (m, 1 H), 2.38 (dd, J = 14.2, 6.0 Hz, 1 H), 1.72 (m, 1 H), 1.67–1.69 (m, 2 H), 1.55–1.64 (m, 2 H), 1.51 (m, 1 H), 1.41 (m, 2 H), 1.20 (td, J = 13.4, 4.5 Hz, 1 H), 1.06 (s, 3 H), 1.03 (s, 3 H), 1.00 (m, 2 H), 0.88 (s, 3 H), 0.87 (s, 3 H) ppm. ^{13}C NMR (150 MHz, CD_3OD, 25 °C): δ = 157.1, 154.1, 146.4, 146.4, 104.7, 101.8, 66.2, 58.9, 47.2, 43.9, 41.5, 39.9, 38.1, 34.1, 34.0, 30.2, 21.6, 21.0, 20.7, 19.5, 16.8 ppm. HRESIMS $[M + H]^+$ calcd. for $C_{21}H_{31}O_2$ 315.2324, found 315.2323.

Preparation of 20: 3,5-dimethoxybromobenzene (**12**) (1.0 g, 4.60 mmol) was dissolved in THF (23 mL) and cooled to –78 °C, to which *n*BuLi (1.6 M, 3.45 mL, 5.52 mmol) was added dropwise, and allowed to stir for 15 min. To this solution was added Li_2CuCl_4 (0.1 M, 1.38 mL, 0.1 mmol) was allowed to stir for 10 min at –78 °C before *E*,*E*-farnesyl bromide (**19**) (1.64 g, 5.75 mmol) dissolved in THF (20 mL) was added dropwise. The reaction mixture was warmed with stirring from –78 °C to room temp. overnight and it was then quenched with saturated NH_4Cl (50 mL). The aqueous phase was extracted 3× with CH_2Cl_2 (150 mL) and the organic extracts were dried with $MgSO_4$, and concentrated in vacuo. The crude mixture was purified with flash chromatography (hexanes/EtOAc, 30:1), to give **20** as a clear oil (1.02 g, 2.99 mmol, 65%). **20**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.36 (d, J = 2.3 Hz, 2 H), 6.30 (t, J = 2.7 Hz, 1 H), 5.34 (t, J = 7.3 Hz, 1 H), 5.15–5.08 (m, 2 H), 3.78 (s, 6 H), 3.31 (d, 2 H), 2.16–1.96 (m, 8 H), 1.71 (s, 3 H), 1.69 (s, 3 H), 1.60 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 160.8, 160.8, 144.2, 136.5, 135.1, 131.2, 124.4, 124.1, 122.6, 106.4, 106.4, 97.6, 55.2, 55.2, 39.7, 39.7, 34.4, 26.7, 26.6, 25.7, 17.6, 16.2, 16.0 ppm. HRESIMS $[M + Na]^+$ calcd. for $C_{23}H_{35}O_2Na$ 343.2637, found 343.2628.

Preparation of (10*S*)-22: Epoxide **22** was prepared according to literature procedures using the *ent*-Shi catalyst **21**.[11,15] Polyene **20** (1 g, 2.90 mmol) was oxidized to **22** (113.0 mg, 0.315 mmol, 11%), which was purified by flash chromatography (hexanes/EtOAc, 12:1). Based on recovered starting material **20** (622.5 mg, 1.82 mmol), the yield of **22** was 28%. **22**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.34 (d, J = 2.2 Hz, 2 H), 6.29 (t, J = 2.2 Hz, 1 H), 5.33 (t, J = 6.1 Hz, 1 H), 5.18 (t, J = 5.7 Hz, 1 H), 3.76 (s, 6 H), 3.29 (d, J = 7.2 Hz, 2 H), 2.68 (t, J = 6.2 Hz, 1 H), 2.11–2.14 (m, 4 H), 2.04–2.08 (m, 4 H), 1.71 (s, 3 H), 1.62 (s, 3 H), 1.29 (s, 3 H), 1.25 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 160.6, 143.9, 136.1, 134.0, 124.6, 122.7, 106.3, 97.4, 63.9, 58.0, 55.0, 39.5, 36.1, 34.3, 27.3, 26.4, 24.7, 18.6, 16.0, 15.9 ppm. HRESIMS $[M + Na]^+$ calcd. for $C_{23}H_{34}O_3Na$ 381.2406, found 381.2415.

Preparation of Racemic 22: To polyene **20** (9.62 g, 27.9 mmol) dissolved in CH_2Cl_2 (100 mL) was added *m*CPBA (5.06 g, 29.3 mmol) dissolved in CH_2Cl_2 (100 mL). The reaction was allowed to stir at room temp. for 3.5 h, after which it was quenched with saturated $NaHCO_3$ (100 mL), and extracted 3× with CH_2Cl_2 (300 mL). The organic extracts were combined, dried with $MgSO_4$, and concen-

trated. The crude mixture was purified with flash chromatography to give racemic **22** (2.24 g, 6.24 mmol, 22%). ^{1}H, ^{13}C, and mass spectrometry data matched that of (10*S*)-**22** listed above.

Preparation of 23: To epoxide **22** (3.53 g, 9.86 mmol) dissolved in CH_2Cl_2 (105 mL) was added $InBr_3$ (6.99 g, 19.7 mmol), and the reaction mixture was allowed to stir at room temp. for 1 h, before being quenched with saturated $NaHCO_3$ (150 mL). The aqueous layer was extracted 3× with CH_2Cl_2 (300 mL) and the organic extracts were combined and dried with $MgSO_4$, then concentrated. The crude reaction mixture was purified with flash chromatography (hexanes/EtOAc, 3:1), to give a mixture of **23** and various uncyclized products. The product mixture was crystallized using boiling solvent (hexanes/EtOAc, 15:1), to give **23** (860 mg, 2.39 mmol, 24%). The structure and absolute configuration of **23** were confirmed by single-crystal X-ray diffraction anlysis. (See Supporting Information). Subsequent reaction with (*R*)-MTPA-Cl gave the Mosher derivatives **24**. **23**: $[\alpha]_D^{24}$ = +19 (*c* = 0.16). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.40 (d, *J* = 1.8 Hz, 1 H), 6.26 (d, *J* = 1.9 Hz, 1 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.22 (m, 1 H), 2.62 (m, 1 H), 2.50 (dd, *J* = 14.4, 6.2 Hz, 1 H), 2.45 (dd, *J* = 9.5, 3.2 Hz, 1 H), 1.74–1.55 (m, 7 H), 1.18–1.11 (m, 1 H), 1.08 (s, 3 H), 1.03 (s, 3 H), 0.99 (s, 3 H), 0.91 (m, 1 H), 0.84 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 159.3, 155.8, 144.8, 133.4, 101.9, 96.8, 79.1, 64.4, 56.1, 55.4, 55.0, 46.0, 38.8, 38.5, 38.2, 36.6, 29.5, 27.9, 27.1, 20.3, 19.2, 16.2, 15.1 ppm. HRESIMS [M + Na]$^+$ calcd. for $C_{23}H_{34}O_3Na$ 381.2406, found 381.2415.

Preparation of 26: To alcohol **23** (600 mg, 1.67 mmol) dissolved in CH_2Cl_2 (85 mL) was added Dess–Martin periodinane (1.41 g, 3.34 mmol) and the mixture was allowed to stir at room temp. for 1.5 h. The reaction was quenched by addition of saturated $NaHCO_3$ (75 mL), and the aqueous phase was extracted 3× with CH_2Cl_2 (200 mL). The organic extracts were combined, dried with $MgSO_4$, and concentrated. The crude product was purified using flash chromatography (hexanes/EtOAc, 7:1), to give **26** (476 mg, 1.34 mmol, 80%) as a white crystalline solid. **26**: $[\alpha]_D^{24}$ = +26.78 (*c* = 0.083). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.41 (s, 1 H), 6.27 (s, 1 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 2.71–2.65 (m, 1 H), 2.64–2.56 (m, 2 H), 2.54–2.41 (m, 2 H), 1.87–1.81 (m, 1 H), 1.78–1.73 (m, 2 H), 1.71–1.48 (m, 4 H), 1.13 (s, 3 H), 1.11 (s, 6 H), 1.09 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 217.2, 159.5, 155.8, 144.4, 132.9, 101.9, 96.8, 63.4, 55.4, 55.3, 54.9, 47.5, 45.8, 38.8, 37.4, 36.2, 33.9, 29.5, 26.5, 20.7, 20.5, 19.8, 15.5 ppm. HRESIMS [M + Na]$^+$ calcd. for $C_{23}H_{32}O_3Na$ 379.2249, found 379.2243.

Preparation of 27: To ketone **26** (240 mg, 0.67 mmol), dissolved in CH_2Cl_2 (20 mL) stirring at 0 °C was added BBr_3 (1.0 M, 2.7 mL, 2.69 mmol). After stirring for 1 h at 0 °C, **26** was still present, so the reaction was allowed to reach room temp. over the next 2 h. The reaction was quenched with MeOH (1 mL), and H_2O (50 mL) was added to the mixture. The aqueous phase was extracted 3× with CH_2Cl_2 (150 mL). The combined organic extracts were dried with $MgSO_4$ and concentrated. The crude mixture was purified with flash chromatography (hexanes/EtOAc, 3:2) to give **27** (190 mg, 0.578 mmol, 86%) as a white crystalline solid. **27**: $[\alpha]_D^{24}$ = +24.07 (*c* = 0.81). ^{1}H NMR [400 MHz, $(CD_3)_2CO$, 25 °C]: δ = 7.76 (s, 1 H), 7.73 (s, 1 H), 6.24 (t, *J* = 1.0 Hz, 1 H), 6.13 (d, *J* = 1.6 Hz), 2.66–2.61 (m, 1 H), 2.59–2.52 (m, 2 H), 2.49–2.46 (m, 1 H), 2.44–2.37 (m, 1 H), 1.86–1.82 (m, 1 H), 1.81–1.77 (m, 1 H), 1.76–1.71 (m, 1 H), 1.67–1.55 (m, 4 H), 1.15 (s, 3 H), 1.13 (s, 3 H), 1.07 (s, 3 H), 1.09 (s, 3 H) ppm. ^{13}C NMR [100 MHz, $(CD_3)_2CO$, 25 °C]: δ = 216.9, 158.5, 154.8, 146.7, 131.9, 105.8, 102.8, 65.4, 57.2, 48.9, 47.3, 40.5, 39.6, 38.0, 35.4, 30.9, 27.9, 22.2, 22.1, 21.3, 16.9 ppm. HRESIMS [M + Na]$^+$ calcd. for $C_{21}H_{28}O_3Na$ 351.1936, found 351.1929.

Preparation of 28 and 29: To a suspension of ketone **27** (250 mg, 0.761 mmol) in MeOH (50 mL) was added $NaBH_3CN$ (71.7 mg, 1.14 mmol) and NH_4OAc (586.5 mg, 7.61 mmol). The reaction was refluxed at 70 °C overnight. Upon the disappearance of staring material, the reaction mixture was cooled, then concentrated to dryness. The crude material was partitioned between H_2O (150 mL) and CH_2Cl_2 (150 mL) and acidified to pH 5 with 6 M HCl. The H_2O phase was then extracted 5× with CH_2Cl_2 (200 mL). The resultant H_2O phase was frozen and lyophilized overnight, which gave a white amorphous solid. To this solid was added H_2O (10 mL) and the suspension was sonicated to give a heterogeneous mixture which was loaded on to a 10 g reversed phase Sep-pak. [which had been pre-washed with MeOH (100 mL) followed by H_2O (100 mL)]. Once loaded, the column was flushed with water (100 mL), 60:40 H_2O:MeOH (100 mL, 3×), and MeOH (100 mL). The fractions of interest were the first 60:40 H_2O:MeOH fraction containing 78.2 mg of **28** pure, and the second and third fraction contained 50.7 mg of a 2:1 mixture of **28** and **29** which was subsequently repurified using the same method. When fully purified the result was **28** (112 mg, 0.306 mmol, 40%), and **29** (16.9 mg, 0.0461 mmol, 6%), with a diastereomeric ratio between the two epimers of 20:3.

Compound 28: $[\alpha]_D^{24}$ = –8.27 (*c* = 3.68). ^{1}H NMR (600 MHz, CD_3OD, 25 °C): δ = 6.16 (s, 1 H, 17-H), 6.02, (d, *J* = 1.5 Hz, 1 H, 19-H), 2.93 (dd, *J* = 12.5, 4.3 Hz, 1 H, 3-H), 2.57 (t, *J* = 13.6 Hz, 1 H, 15-H), 2.51 (dt, *J* = 12.5, 2.9 Hz, 1 H, 7-H), 2.42 (dd, *J* = 14.3, 6.0 Hz, 1 H, 15-H), 1.85 (qd, *J* = 13.1, 3.4 Hz, 1 H, 2-H), 1.79–1.73 (m, 2 H, 1-H/2-H), 1.71–1.67 (m, 3 H, 6-H/7-H), 1.63 (td, *J* = 12.3, 3.5 Hz, 1 H, 9-H), 1.27 (td, *J* = 13.3, 3.4 Hz, 1 H, 1-H), 1.11 (dd, *J* = 11.3, 2.3 Hz, 1 H, 5-H), 1.085 (s, 3 H, 13-H), 1.081 (s, 3 H, 14-H), 1.076 (s, 3 H, 11-H), 0.94 (s, 3 H, 12-H) ppm. ^{13}C NMR (150 MHz, CD_3OD, 25 °C): δ = 157.5 (C-18), 154.2 (C-20), 145.9 (C-16), 131.7 (C-21), 104.7 (C-17), 101.9 (C-19), 65.6 (C-9), 61.7 (C-3), 57.6 (C-5), 46.8 (C-8), 39.6 (C-7), 39.2 (C-6), 37.8 (C-1), 37.7 (C-4), 30.1 (C-15), 28.2 (C-10), 24.3 (C-2), 20.8 (C-13), 20.2 (C-11), 16.4 (C-14), 15.9 (C-12) ppm. HRESIMS [M + H]$^+$ calcd. for $C_{21}H_{32}NO_2$ 330.2433, found 330.2441.

Compound 29: $[\alpha]_D^{24}$ = +6.98 (*c* = 1.80). ^{1}H NMR (600 MHz, CD_3OD, 25 °C): δ = 6.16 (s, 1 H), 6.02 (d, *J* = 1.2 Hz, 1 H), 3.09 (m, 1 H), 2.58 (t, *J* = 13.7 Hz, 1 H), 2.51 (m, 1 H), 2.44 (dd, *J* = 14.2, 6.0 Hz, 1 H), 2.29 (tt, *J* = 14.9, 3.3 Hz, 1 H), 1.83 (dd, *J* = 12.9, 6.1 Hz, 1 H), 1.71–1.69 (m, 1 H), 1.68–1.66 (m, 1 H), 1.64–1.59 (m, 1 H), 1.49 (dt, *J* = 11.4, 2.1 Hz, 1 H) 1.39 (d, *J* = 8.5 Hz, 1 H), 1.34–1.27 (m, 2 H), 1.11 (s, 3 H), 1.09 (s, 3 H), 1.07 (s, 3 H), 1.01 (s, 3 H) ppm. ^{13}C NMR (150 MHz, CD_3OD, 25 °C): δ = 157.5, 154.2, 146.0, 131.8, 104.7, 101.9, 65.1, 59.5, 51.4, 47.1, 39.6, 37.9, 36.6, 34.1, 30.1, 28.4, 22.9, 22.7, 20.9, 20.2, 16.5 ppm. HRESIMS [M + H]$^+$ calcd. for $C_{21}H_{32}NO_2$ 330.2433, found 330.2440.

Preparation of 31: To dimethoxybromobenzene **12** (21.7 g, 0.1 mol) dissolved in THF (200 mL) and cooled to –78 °C, *n*BuLi (69 mL, 1.6 M in hexanes, 0.11 mol) was added dropwise by syringe over a period of 30 min, and the solution was stirred for 20 min. Bromide **30** (17.1 g, 0.11 mol) in THF (50 mL) was added dropwise over a period of 30 min, and the reaction mixture was stirred at –78 °C for 45 min. The reaction was then quenched with H_2O (25 mL), and the reaction mixture was extracted into EtOAc (200 mL) and washed with 2× H_2O (150 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated to dryness. The crude product was purified by column chromatography to yield **31** (16.5 g, 0.08 mol, 80% yield) as a pale yellow oil. **31**: ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C): δ = 6.40 (s, 2 H), 6.34 (s, 1 H), 5.38 (t, *J* = 7.2 Hz, 1 H), 3.81 (s, 6 H), 3.34 (d, *J* = 7.2 Hz, 2 H), 1.81 (s, 3 H), 1.78 (s,

3 H) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2, 25 °C): δ = 161.3, 144.7, 133.0, 123.3, 106.7, 97.9, 55.5, 34.9, 25.9, 17.9 ppm. HRESIMS [M + H]$^+$ calcd. for $C_{13}H_{19}O_2$ 207.1385, found 207.1380.

Preparation of 32: SeO_2 (1.34 g, 12.1 mmol) was slurried in CH_2Cl_2 (100 mL). *t*BuOOH solution (6.95 mL, 70% in H_2O, 48.6 mmol) was then added and the resulting mixture was stirred until all solids had dissolved. A solution of **31** (5 g, 24.3 mmol) in CH_2Cl_2 (25 mL) was added and the reaction mixture was stirred rapidly at room temp. for 20 h. The CH_2Cl_2 was removed under reduced pressure, and the resulting residue was dissolved in Et_2O (100 mL). The organic phase was washed with 3× 10% KOH (200 mL), dried with Na_2SO_4, filtered and concentrated to yield a pale yellow oil. This residue was dissolved in 40 mL of MeOH, cooled to 0 °C and $NaBH_4$ (920 mg, 24.3 mmol) was added in portions. Once added, the reaction mixture was stirred for 1 h. The reaction was quenched by the addition of 1 M HCl, and the crude product was extracted into EtOAc. The organic phase was washed with saturated $NaHCO_3$ (100 mL), dried with Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography (hexanes/EtOAc, 2:1) to yield **32** (2.59 g, 11.7 mmol, 48%) as a pale yellow oil. **32**: ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C): δ = 6.34 (s, 2 H), 6.29 (s, 1 H), 5.57 (t, *J* = 7.1 Hz, 1 H), 3.99 (s, 2 H), 3.75 (s, 6 H), 3.32 (d, *J* = 7.1 Hz, 2 H), 1.88 (s, 1 H), 1.74 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2, 25 °C): δ = 161.2, 143.9, 136.4, 124.1, 106.7, 97.9, 68.6, 55.5, 34.4, 13.8 ppm. HRESIMS [M + Na]$^+$ calcd. for $C_{13}H_{18}O_3Na$ 245.1154, found 245.1147.

Preparation of 33: Alcohol **32** (2.59 g, 11.7 mmol) and PPh_3 (3.65 g, 13.9 mmol) were dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. CBr_4 (4.25 g, 12.8 mmol) was added and the reaction mixture was stirred for 1 h at 0 °C. The solution was concentrated to dryness and the crude product was purified by flash chromatography (hexanes/EtOAc, 2:1) to yield bromide **33** (2.53 g, 8.87 mmol, 76%) as a colorless oil. **33**: ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C): δ = 6.33 (s, 2 H), 6.31 (s, 1 H), 5.79 (t, *J* = 7.3 Hz, 1 H), 4.04 (s, 2 H), 3.76 (s, 6 H), 3.33 (d, *J* = 7.3 Hz, 2 H), 1.87 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2, 25 °C): δ = 161.3, 142.9, 133.6, 129.7, 106.6, 98.2, 55.5, 41.8, 34.9, 14.9 ppm. HREIMS [M]$^+$ calcd. for $C_{13}H_{17}O_2{}^{79}Br$ 284.04119, found 284.04102.

Preparation of 35: Geranyl bromide (**34**) (10 g, 46 mmol), Bu_4NI (1.7 g, 4.6 mmol) and sodium *p*-toluenesulfonate (12.3 g, 69 mmol) were combined in THF (500 mL) and stirred at room temp. for 24 h. The reaction was quenched by the addition of saturated $Na_2S_2O_5$ (100 mL) and the crude product was extracted into EtOAc (400 mL). The organic phase was washed with 2× H_2O (200 mL) and 1× saturated $NaHCO_3$ (100 mL), dried with Na_2SO_4 and concentrated to yield **35** (13.4 g, 46 mmol, quantitative yield) as a yellow oil that crystallized upon standing. **35**: ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C): δ = 7.71 (d, *J* = 8.1 Hz, 2 H), 7.35 (d, *J* = 7.9 Hz, 2 H), 5.15 (t, *J* = 7.3 Hz, 1 H), 5.05 (m, 1 H), 3.77 (d, *J* = 7.9 Hz, 2 H), 2.44 (s, 3 H), 2.01 (s, 4 H), 1.68 (s, 3 H), 1.59 (s, 3 H), 1.32 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2, 25 °C): δ = 146.4, 144.9, 136.4, 132.2, 129.9, 128.8, 123.9, 110.9, 56.5, 40.1, 26.6, 25.7, 21.7, 17.7, 16.3 ppm. HRESIMS [M + Na]$^+$ calcd. for $C_{17}H_{24}O_2NaS$ 315.1395, found 315.1388.

Preparation of 36: Sulfone **35** (3 g, 10.3 mmol) was dissolved in a mixture of CH_3CN:dimethoxymethane (51 mL:103 mL). $Na_2B_7O_7$ (0.5 M, 103 mL) in 4×10^{-4} M Na_2(EDTA) was added, followed by the *ent*-Shi catalyst **21** (810 mg, 3.1 mmol) and NH_4HSO_4 (153.9 mg, 0.45 mmol). The mixture was cooled to –10 °C, and solutions of oxone (8.73 g, 14.2 mmol) in Na_2(EDTA) (4×10^{-4} M, 67 mL) and K_2CO_3 (8.22 g, 59.5 mmol) in H_2O (67 mL) were added using a syringe pump over 2 h. The reaction mixture was warmed to room temp. and concentrated to half its original volume under vacuum. H_2O (250 mL) and EtOAc (400 mL) were added and the organic phase was washed with 2× H_2O (200 mL). The organic phase was dried with Na_2SO_4, and concentrated to dryness. The crude product was purified by column chromatography to yield **36** (2.5 g, 8.11 mmol, 80%) as a colorless semisolid. **36**: ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C): δ = 7.69 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 7.9 Hz, 2 H), 5.19 (t, *J* = 6.8 Hz, 1 H), 3.77 (d, *J* = 7.9 Hz, 2 H), 2.61 (t, *J* = 6.2 Hz, 1 H), 2.42 (s, 3 H), 2.11 (m, 2 H), 1.53 (m, 2 H), 1.34 (s, 3 H), 1.25 (s, 3 H), 1.21 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2, 25 °C): δ = 145.7, 145.0, 136.2, 129.9, 128.7, 111.4, 63.7, 58.3, 56.3, 36.7, 27.5, 24.9, 21.7, 18.8, 16.3 ppm. HRESIMS [M + Na]$^+$ calcd. for $C_{17}H_{24}O_3NaS$ 331.1344, found 331.1338.

Preparation of 37: Sulfone **36** (355 mg, 1.15 mmol) and bromide **35** (393 mg, 1.38 mmol) were dissolved in THF (12 mL) and cooled to –78 °C. KO*t*Bu (143 mg, 1.27 mmol) was then added and the reaction mixture was stirred at –78 °C for 2 h. The reaction was quenched with H_2O (100 mL) and extracted into EtOAc (150 mL). The organic phase was dried with Na_2SO_4, filtered and concentrated. The crude reaction mixture was purified by column chromatography to yield **37** (574 mg, 1.12 mmol, 97%) as a colorless oil. **37**: ^{1}H NMR (400 MHz, CD_2Cl_2, 25 °C): δ = 7.68 (d, *J* = 7.9 Hz, 2 H), 7.68 (d, *J* = 7.9 Hz, 2 H), 7.31 (d, *J* = 7.8 Hz, 2 H), 6.25 (s, 3 H), 4.91 (m, 1 H), 3.92 (m, 1 H), 3.72 (s, 6 H), 3.22 (d, *J* = 7.2 Hz, 2 H), 2.86 (d, *J* = 13.1 Hz, 1 H), 2.58 (m, 1 H), 2.42 (s, 3 H), 2.30 (m, 1 H), 2.03 (m, 1 H), 1.64 (s, 3 H), 1.43 (m, 2 H), 1.26 (s, 3 H), 1.25 (s, 3 H), 1.22 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2, 25 °C): δ = 161.2, 144.9, 144.8, 144.7, 143.8, 135.5, 135.4, 131.7, 129.7, 129.5, 126.9, 117.9, 106.7, 97.7, 63.6, 63.6, 58.2, 55.5, 38.1, 37.9, 36.6, 36.5, 34.7, 27.5, 24.9, 21.7, 18.8, 16.6, 16.3, 16.2 ppm. HRESIMS [M + Na]$^+$ calcd. for $C_{30}H_{40}O_5NaS$ 535.2494, found 535.2507.

Preparation of 22: Sulfone **37** (400 mg, 0.78 mmol) and $PdCl_2$(dppp) (92 mg, 0.156 mmol) were slurried in THF (16 mL) and cooled to 0 °C. $LiBEt_3H$ (1.0, 1.56 mL, 1.56 mmol) was then added dropwise over a period of 10 min. The reaction mixture was stirred at 0 °C for 1 h, then H_2O was added (100 mL). The reaction mixture was extracted into EtOAc (200 mL) and washed with H_2O (150 mL). The organic phase was dried with Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography to yield **22** (212 mg, 0.59 mmol, 76%) as a colorless oil. **22**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.34 (d, *J* = 2.2 Hz, 2 H), 6.29 (t, *J* = 2.2 Hz, 1 H), 5.33 (t, *J* = 6.1 Hz, 1 H), 5.18 (t, *J* = 5.7 Hz, 1 H), 3.76 (s, 6 H), 3.29 (d, *J* = 7.2 Hz, 2 H), 2.68 (t, *J* = 6.2 Hz, 1 H), 2.11–2.14 (m, 4 H), 2.04–2.08 (m, 4 H), 1.71 (s, 3 H), 1.62 (s, 3 H), 1.29 (s, 3 H), 1.25 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 160.6, 143.9, 136.1, 134.0, 124.6, 122.7, 106.3, 97.4, 63.9, 58.0, 55.0, 39.5, 36.1, 34.3, 27.3, 26.4, 24.7, 18.6, 16.0, 15.9 ppm. HRESIMS [M + Na]$^+$ calcd. for $C_{23}H_{34}O_3Na$ 381.2406, found 381.2415.

Preparation of 24 and 25: Alcohol **23** (219.4 mg, 0.610 mmol) obtained by flash chromatography purification (hexanes/EtOAc, 3:1) of the reaction mixture produced by cyclization of epoxide **22** (Scheme 3) was dissolved in CH_2Cl_2 (4 mL) and to this mixture was added pyridine (0.074 mL, 0.92 mmol) and DMAP (7.4 mg, 0.061 mmol) and the solution was cooled to 0 °C. (*R*)-(–)-MTPA-Cl (169.5 mg, 0.671 mmol) was added and the mixture was warmed to room temp. overnight. The reaction was quenched with saturated NH_4Cl (50 mL) and the H_2O layer was extracted 3× with CH_2Cl_2 (200 mL). The organic extracts were combined, dried with $MgSO_4$, and concentrated. The product mixture was the purified

using flash chromatography (hexanes/EtOAc, 12:1), to give a mixture of **24** and **25**. The structure and absolute configuration of **25** were confirmed by single-crystal X-ray diffraction analysis. (See Supporting Information). Integration of signals for diastereomers in the ^{1}H NMR spectrum of the crude mixture gave a diastereomeric ratio of 97:3 (**24:25**) meaning that the epoxidation proceeded in ca. 95% *ee*. **24**: $[\alpha]_D^{24}$ = –32 (*c* = 0.65). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.54 (m, 2 H), 7.41 (m, 3 H), 6.40 (d, *J* = 1.7 Hz, 1 H), 6.26 (d, *J* = 1.8 Hz, 1 H), 4.72 (dd, *J* = 11.5, 4.9 Hz, 1 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.54 (s, 3 H), 2.62 (m, 1 H), 2.51 (dd, *J* = 14.4, 6.1 Hz, 1 H), 2.46 (dd, *J* = 8.4, 2.9 Hz, 1 H), 1.85–1.76 (m, 1 H), 1.74–1.67 (m, 3 H), 1.65–1.57 (m, 3 H), 1.23 (td, *J* = 13.4, 4.1 Hz, 1 H), 1.07 (s, 3 H), 1.04 (s, 3 H), 1.04 (m, 1 H), 0.92 (s, 3 H), 0.87 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.3, 159.5, 155.8, 144.7, 133.2, 132.3, 129.5, 128.3, 128.3, 127.6, 127.6, 124.9, 122.0 101.9, 96.9, 84.5, 64.2, 56.2, 55.4, 55.3, 55.1, 46.1, 38.1, 38.0, 37.9, 36.5, 29.5, 28.1, 23.0, 20.3, 19.0, 16.2, 16.1 ppm. HRESIMS [M + Na]$^+$ calcd. for $C_{33}H_{41}O_5F_3Na$ 597.2804, found 597.2814.

25: $[\alpha]_D^{24}$ = –23 (*c* = 1.20). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.57 (m, 2 H), 7.41 (t, 3 H), 6.41 (s, 1 H), 6.26 (d, *J* = 1.5 Hz, 1 H), 4.75 (dd, *J* = 10.4, 5.9 Hz, 1 H), 3.77 (s. 3 H), 3.75 (s, 3 H), 3.58 (s, 3 H), 2.64 (t, *J* = 13.8 Hz, 1 H), 2.52 (dd, *J* = 14.3, 6.1 Hz, 1 H), 2.46 (m, 1 H), 1.91–1.79 (m, 2 H), 1.75–1.70 (m, 2 H), 1.66–1.62 (m, 4 H), 1.25 (td, *J* = 12.5, 4.9 Hz, 1 H), 1.08 (s, 3 H), 1.07 (s, 3 H), 0.86 (s, 3 H), 0.83 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 166.1, 159.5, 155.8, 144.7, 133.2, 132.7, 129.5, 128.3, 127.3, 124.9, 122.1, 101.9, 96.9, 84.3, 64.2, 56.2, 55.42, 55.39, 55.1, 46.1, 38.1, 38.0, 37.9, 36.5, 29.5, 27.7, 23.4, 20.3, 19.0, 16.2, 15.9 ppm. HRESIMS [M + Na]$^+$ calcd. for $C_{33}H_{41}O_5F_3Na$ 597.2804, found 597.2814.

Preparation of *ent*-28 and *ent*-29: Preparation was identical to **28** and **29**, with the exception that the original Shi catalyst[11] was used in the epoxidation step in place of the *ent*-Shi catalyst **21**. ^{1}H, and ^{13}C NMR spectroscopic data for *ent*-**28** and *ent*-**29** matched that of **28** and **29**, respectively. The structure and absolute configuration of *ent*-**28** were confirmed by single-crystal X-ray diffraction anlysis. (See Supporting Information). *ent*-**28**: $[\alpha]_D^{24}$ = +8.3 (*c* = 3.21). ESIMS [M + H]$^+$ calcd. for $C_{21}H_{32}NO_2$ 330.2433, found 330.2440. *ent*-**29**: $[\alpha]_D^{24}$ = –5.7 (*c* = 1.47). HRESIMS [M + H]$^+$ calcd. for $C_{21}H_{32}NO_2$ 330.2433, found 330.2433.

Preparation of 39: To sodium hydride (8.0 mg, 60% in mineral oil, 0.20 mmol) washed two times with hexanes (1 mL) was added THF (0.5 mL). To this heterogeneous mixture was added **38** (24.3 mg, 067 mmol) dissolved in THF (2 mL) and allowed to stir for 10 min. To this mixture was added CS_2 (0.024 mL, 0.402 mmol), and allowed to stir for thirty minutes, after which methyl iodide (0.037 mL, 0.60 mmol) was added neat and the mixture allowed to stir overnight at room temp. The mixture was quenched with MeOH (0.1 mL), concentrated under a stream of nitrogen and filtered through a plug of Si gel with hexanes/EtOAc (20 mL, 3:1), and concentrated. The crude mixture was used in the following step without further purification. The mixture was dissolved in toluene (3 mL) to which was added tributyltin hydride (87.5 mg, 0.30 mmol) and AIBN (0.06 mL, 0.012 mmol), and the reaction mixture heated to 120 °C for thirty min. The reaction was then allowed to cool down to room temp., and concentrated under a stream of nitrogen. The crude mixture was purified with flash chromatography (hexanes/EtOAc, 15:1), to give **39** (18.8 mg, 0.054 mmol, 82% over two steps). The ^{1}H and ^{13}C NMR spectra were identical to compound **17**. $[\alpha]_D^{24}$ = –4.25 (*c* = 0.07). HRESIMS [M + H]$^+$ calcd. for $C_{23}H_{35}O_2$ 343.2637, found 343.2640.

Preparation of *ent*-18: To **39** (20 mg, 0.058 mmol) dissolved in CH_2Cl_2 (20 mL) and was added boron tribromide (0.17 mL, 0.175 mmol, 1.0 M solution in CH_2Cl_2). After stirring for 90 min the reaction was quenched with the addition of MeOH (0.1 mL), and concentrated under a stream of nitrogen. The crude mixture was the purified with flash chromatography to give *ent*-**18** (12.1 mg, 0.038 mmol, 66%). The ^{1}H and ^{13}C NMR spectra were identical to **18**. $[\alpha]_D^{24}$ = –18.1 (*c* = 0.05). HRESIMS [M + H]$^+$ calcd. for $C_{21}H_{29}O_2$ 313.2176, found 313.2168.

Preparation of 40: To **27** (20 mg, 0.060 mmol) dissolved in pyridine (1 mL) was added hydroxylamine hydrochloride (33.8 mg, 0.49 mmol), and heated at 50 °C. After 3.5 h the reaction mixture was cooled to room temp., saturated NH_4Cl (10 mL) solution was added, and the aqueous phase was extracted three times with CH_2Cl_2 (75 mL). The organic extracts were combined and dried with $MgSO_4$, and concentrated. The crude was purified with flash chromatography (hexanes/EtOAc, 1:1) to give **40** as a white solid (15.5 mg, 0.045 mmol, 75%). $[\alpha]_D^{24}$ = –14.94 (*c* = 0.02). ^{1}H NMR [400 MHz, $(CD_3)_2CO$, 25 °C]: δ = 6.22 (s, 1 H), 6.12 (s, 1 H), 3.06 (ddd, *J* = 15.9, 3.2, 2.7 Hz, 1 H), 2.59 (t, *J* = 14.1 Hz, 1 H), 2.53 (dt, *J* = 12.1, 3.1 Hz, 1 H), 2.44 (dd, *J* = 14.4, 6.1 Hz, 1 H), 2.29 (ddd, *J* = 18.5, 6.4, 5.8 Hz, 1 H), 1.75–1.72 (m, 1 H), 1.71–1.69 (m, 2 H), 1.68–1.66 (m, 1 H), 1.65–1.61 (m, 1 H), 1.29–1.23 (m,2 H), 1.15 (s, 3 H), 1.14 (s, 3 H), 1.11 (s, 3 H), 1.08 (s, 3 H) ppm. ^{13}C NMR [100 MHz, $(CD_3)_2CO$, 25 °C]: δ = 171.9, 165.8, 158.5, 154.8, 146.8, 132.1, 105.8, 102.8, 65.9, 61.5, 58.3, 47.4, 41.7, 40.0, 38.4, 29.2, 24.3, 21.7, 18.1, 16.8, 15.5 ppm. HRESIMS [M + H]$^+$ calcd. for $C_{21}H_{30}O_3N$ 344.2226, found 344.2230.

Preparation of 41: To **40** (10.3 mg, 0.029 mmol) dissolved in CH_2Cl_2 (1 mL) at 0 °C was added trfifluoroacetic anhydride (0.11 mL, 0.79 mmol) and allowed to stir for 1 h. The reaction was quenched with H_2O (0.1 mL) and the reaction mixture was concentrated under a stream of nitrogen. The crude was purified with flash chromatography (CH_2Cl_2:MeOH 12:1) to give **41** (10.0 mg, 0.029 mmol, 100%) as a white solid. $[\alpha]_D^{24}$ = +122.1 (*c* = 0.07). ^{1}H NMR (400 MHz, CD_3OD, 25 °C): δ = 6.17 (d, *J* = 1.7 Hz, 1 H), 6.02 (d, *J* = 1.9 Hz, 1 H), 3.45 (s, 1 H), 2.65–2.56 (m, 2 H), 2.51–2.43 (m, 3 H), 1.83–1.70 (m, 4 H), 1.69–1.61 (m, 2 H), 1.59–1.52 (m, 1 H), 1.33 (s, 3 H), 1.32 (s, 3 H), 1.22 (s, 3 H), 1.11 (s, 3 H) ppm. ^{13}C NMR (100 MHz, CD_3OD, 25 °C): δ = 179.3, 157.5, 154.3, 145.8, 131.6, 104.6, 101.9, 65.5, 57.8, 56.9, 46.6, 41.2, 39.3, 39.0, 33.7, 32.6, 30.6, 26.4, 24.3, 20.3, 17.5 ppm. HRESIMS [M + Na]$^+$ calcd. for $C_{21}H_{29}NO_3Na$ 366.2045, found 366.2035.

Preparation of 42: To **41** (8.0 mg, 0.023 mmol) dissolved in THF (4 mL) was added $LiAlH_4$ (0.072 mL. 2.0 M in THF, 0.14 mmol) and allowed to reflux overnight. Upon completion, the reaction was quenched with MeOH (0.1 mL), and HCl (6 M, 0.1 mL) was added. The mixture was concentrated and lyophilized, and purified using a 2 g reversed phase Sep-Pak (which was washed with 10 mL of MeOH followed by 10 mL of H_2O). Once loaded, the column was flushed with H_2O (20 mL), 60:40 H_2O:MeOH (50 mL), and MeOH (50 mL). The H_2O:MeOH fraction after concentration and lyophilization contained **42** (4 mg, 0.011 mmol, 47%) as a white solid. $[\alpha]_D^{24}$ = +20.50 (*c* = 0.02). ^{1}H NMR (600 MHz, CD_3OD, 25 °C): δ = 6.16 (s, 1 H), 6.03 (d, *J* = 1.5 Hz, 1 H), 3.23–3.15 (m, 2 H), 2.62 (t, *J* = 13.9 Hz, 1 H), 2.57 (dd, *J* = 8.2 Hz, 1 H), 2.52 (dt, *J* = 12.9, 2.9 Hz, 1 H), 2.00–1.96 (m, 1 H), 1.94–1.87 (m, 3 H), 1.75–1.72 (m, 2 H), 1.70–1.66 (m, 1 H), 1.64–1.58 (m, 1 H), 1.48 (s, 3 H), 1.42 (s, 3 H), 1.39 (m, 1 H), 1.22 (s, 3 H), 1.13 (s, 3 H) ppm. ^{13}C NMR (150 MHz, CD_3OD, 25 °C): δ = 157.7, 154.3, 145.2, 131.2, 104.4, 101.9, 64.6, 63.6, 54.7, 46.2, 43.9, 42.6, 42.2, 38.3, 31.2, 27.9, 24.9, 24.3, 24.0, 19.5, 14.9 ppm. HREIMS [M]$^+$ calcd. for $C_{21}H_{31}NO_2$ 329.23548, found 329.23569.

His-hSHIP1 Enzyme Assay: His-hSHIP1 enzyme assay was performed in 96-well microtiter plates with 2.5 to 10 ng enzyme/well and 50 ng/well, respectively, in a total volume of 25 μL of SHIP1 assay buffer [20 mM Tris HCl (pH 7.5), 10 mM $MgCl_2$ and 0.02% Tween-20]. Recombinant His-hSHIP1 enzyme was incubated with test articles or vehicle (2% ethanol) and 50 μM inositol-1,3,4,5-tetrakisphosphate (IP4) for 15 min at 37 °C in a shaking incubator. After 15 min at 37 °C, the amount of inorganic phosphate released was assessed by the addition of BIOMOL GREEN™ reagent and incubation for 20 min at room temp. before measuring the absorbance at 650 nm.

Akt Activation Assay.

Cell Culture: MOLT-4 and Jurkat T-ALL cells were cultured in RPMI 1640 containing 10% FBS and 1% penicillin/streptomycin at 37 °C in a water jacketed CO_2 (5%) incubator. Cells were seeded at $0.2–0.3 \times 10^6$ cells/mL and grown for 2 to 3 d before passaging. Cells that exceeded 25 passages were not used for studies and were discarded. *Akt phosphorylation assay.* Cells were cultured in serum free RPMI at 1×10^6 cells/mL. After overnight culture, $2–3 \times 10^6$ cells were treated in a 15 mL conical tube with test article for 30 min followed by IGF-1 stimulation at 0.1 μg/mL for 60 min. The final concentration of the drug vehicle (DMSO) was 0.1%. After treatment, cells were washed once with ice cold DPBS and lysed with lysis buffer (20 mM Tris-HCl, pH 7.5, 140 mM NaCl, 1% NP-40, Complete Mini Protease Inhibitor Cocktail, 10 mM NaF, 1 mM Na_3VO_4, and 1 mM β-glycerol phosphate) on ice for 30 min with vortexing every 10 min. Samples were then centrifuged at 14,000 rpm for 20 min, and supernatants were collected as total cell lysates. Akt phosphorylation at S473 in each sample was determined by western blotting.

Western Blotting: Protein concentration in each sample was determined colorimetrically using bicinchoninic acid (BCA) assay. Approximately 15–20 μg of total protein from each sample was mixed with 6× sample loading buffer (250 mM Tris-HCl, pH 6.8, 30% glycerol, 10% SDS, 0.012% bromophenol blue and 0.6 M DTT) and boiled for 5 min before loading onto a polyacrylamide gel for SDS-PAGE. Proteins from each sample were separated on a 4–12% Tris-Glycine gel for 1.5 h with a constant voltage of 125 Volts. After electrophoresis, proteins were transferred to a nitrocellulose membrane using the iBlot Dry Transfer system (Life Technologies, Carlsbad, CA, USA). The membrane was then blocked in 5% BSA in PBS containing 0.1% Tween-20 (PBS-T) for 1 h at room temp. before probing with primary antibodies overnight at 4 °C. The following antibodies were used: mouse anti-SHIP1 (1:500; v/v), rabbit anti-pAkt (S473) (1:1000; v/v), rabbit anti-Akt (1:2000), and rabbit anti-β-actin (1:2000; v/v). The membrane was then incubated with goat anti-rabbit IgG HRP-linked or goat anti-mouse IgG HRP-linked secondary antibodies (1:3000; v/v) for 1 h at room temp. Target proteins on the membrane were detected with ECL solution and exposed on a film.

Mouse Passive Cutaneous Anaphylaxis Model: The in vivo animal study protocols were approved by the local ethics committee. Forty BALB/c male mice (8 weeks old) were obtained from Charles River Laboratories (Hollister, CA, USA). Animals were acclimated for a minimum of five days prior to the start of the study. They were housed five animals per cage in polypropylene cages, and were allowed free access to food and water. A 12 h light/dark cycle was maintained. Each animal was injected intradermally in the right ear with 25 ng of anti-DNP-IgE in 20 μL PBS. The left ears were not injected and served as a negative control. 24 h post-injection, (±)-**28** was administered once by oral gavage in saline (0.01, 0.1, or 10 mg/kg; 10.0 mL/kg dose volume) in a model of IgE-mediated passive cutaneous anaphylaxis. Sixty minutes after dosing, each animal was given a tail vein injection of 2% Evans' blue (0.22 μm filtered, in 200 μL saline) followed by a second tail intravenous injection of 100 μg DNP-HSA (in 200 μL PBS) (Sigma). Sixty minutes following the DNP-HSA injection, mice were euthanized using CO_2 inhalation. Ear biopsies were performed with four millimeter punches from both ears placed into 100 μL formamide in 96 well PCR plates to elute the Evans' Blue dye. To minimize evaporation, plates were then sealed during incubation in a 70 °C water bath overnight. Eighty μL of eluents were transferred to flat-bottom 96-well plates and read using a SpectraMax M5 spectrophotometer (Molecular Devices, Sunnyvale, CA, USA) at 620 nm. Background readings from all samples were taken at 740 nm and subtracted from the 620 nm readings. A blank reading was made on a sample of formamide and subtracted from all readings. Data are reported as optical density.

Water Solubility of Pelorol Analogs: Samples were weighed accurately in duplicate (ca. 3 mg each) in 4 mL glass vials. The appropriate amount of deionized water was added to obtain a final concentration of 6 mg/mL. A stir bar was placed in the vial and the two mixtures were stirred for 24 h, after which the samples were filtered using a glass filter membrane. The resulting filtrate was centrifuged in a glass conical tube for 10 min at 10,000 rpm to sediment any precipitate that may have passed through the glass membrane. The supernatant was sampled for HPLC analysis. The concentration of the test compound was determined by HPLC using a six-point standard curve of the compound prepared in methanol. Data are summarized in Table 1.

Supporting Information (see footnote on the first page of this article): NMR spectra for all new synthetic compounds. Evidence for inhibition of AKT phosphorylation by (±)-**28**. ORTEP diagrams for **3**, **23**, **25**, and **28**.

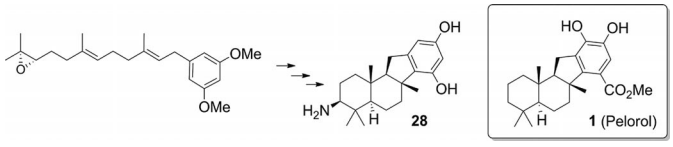
Acknowledgments

Financial support was provided by the Natural Sciences and Engineering Research Council of Canada (NSERC) (to R. J. A.), the Canadian Cancer Society Research Institute (CCSRI) (to R. J. A., #017289), the Canadian Institutes of Heath Research (CIHR) (to A. L. F. M., MOP-84359) and Aquinox Pharmaceuticals Inc.

[1] T. Sasaki, S. Takasuga, J. Sasaki, S. Kofuji, S. Eguchi, M. Yamazaki, A. Suzuki, *Prog. Lipid Res.* **2009**, *48*, 307–343.
[2] a) T. D. Bunney, M. Katan, *Nature Rev. Cancer* **2010**, *10*, 342–352; b) A. M. Martelli, C. Evangelisti, F. Chiarini, C. Grimaldi, L. Manzoli, J. A. McCubrey, *Expert Opin. Invest. Drugs* **2009**, *18*, 1333–1349; c) S. J. Harris, R. V. Parry, J. Westwick, S. G. Ward, *J. Biol. Chem.* **2008**, *283*, 2465–2469.
[3] P. A. Janne, N. Gray, J. Settleman, *Nat. Rev. Drug Discovery* **2009**, *8*, 709–723.
[4] C. J. Ong, A. Ming-Lum, M. Nodwell, A. Ghanipour, Y. Yang, D. E. Williams, J. Kim, L. Demirjian, P. Qasimi, J. Ruschmann, L.-P. Cao, K. Ma, S. W. Chung, V. Duronio, R. J. Andersen, G. Krystal, A. L.-F. Mui, *Blood* **2007**, *110*, 1942–1949.
[5] L. Yang, D. E. Williams, A. Mui, C. Ong, G. Krystal, R. van Soest, R. J. Andersen, *Org. Lett.* **2005**, *7*, 1073–1076.
[6] D. H. R. Barton, S. W. McCombie, *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574–1585.
[7] a) M. A. Tius, *Acc. Chem. Res.* **2003**, *36*, 284–290; b) C. Santelli-Rouvier, M. Santelli, *Synthesis* **1983**, *6*, 429–442.
[8] C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Delivery Rev.* **2001**, *46*, 3–26.
[9] A. Leo, C. Hansch, D. Elkins, *Chem. Rev.* **1971**, *71*, 525–616.

[10] S. Nunomoto, Y. Kawakami, Y. Yamashita, *J. Org. Chem.* **1983**, *11*, 1912–1914.
[11] Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang, Y. Shi, *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235.
[12] J.-F. Zhao, Y. J. Zhao, T.-P. Loh, *Chem. Commun.* **2008**, *11*, 1353–1355.
[13] M. Bogenstätter, A. Limberg, L. E. Overman, A. L. Tomasi, *J. Am. Chem. Soc.* **1999**, *121*, 12206–12207.
[14] R. F. Borch, M. D. Bernstein, H. D. Durst, *J. Am. Chem. Soc.* **1971**, *93*, 2897–2904.
[15] M.-X. Zhao, Y. Shi, *J. Org. Chem.* **2006**, *71*, 5377–5379.
[16] I. J. S. Fairlamb, J. M. Dickinson, M. Pegg, *Tetrahedron Lett.* **2001**, *42*, 2205–2208.
[17] T. W. Baughman, J. C. Sworen, K. B. Wagener, *Tetrahedron* **2004**, *60*, 10943–10948.
[18] R. Tong, J. C. Valentine, F. E. McDonald, R. Cao, X. Fang, K. I. Hardcastle, *J. Am. Chem. Soc.* **2007**, *129*, 1050–1051.
[19] J. Kuk, B. S. Kim, H. Jung, S. Choi, J.-Y. Park, S. Koo, *J. Org. Chem.* **2008**, *73*, 1991–1994.
[20] M. Mohri, H. Kinoshita, K. Inomata, H. Kotake, *Chem. Lett.* **1985**, *4*, 451–454.
[21] M. Kennah, T. Y. Yau, M. Nodwell, G. Krystal, R. J. Andersen, C. J. Ong, A. L.-F. Mui, *Exp. Hematol.* **2009**, *37*, 1274–1283.
[22] Z. Ovary, *J. Immunol.* **1958**, *81*, 355–357.

Received: May 8, 2012
Published Online: ■



Two biomimetic routes have been used to synthesize analogs of the SHIP1-activating sponge meroterpenoid pelorol (**1**) in high *ee*. Resorcinol analog **18** is the most effective SHIP1-activating pelorol analog made to date and racemic **28·HCl**, an amino analog, activates SHIP1 in vitro, and has effective antiinflammatory activity in a mouse model ($ED_{50} \approx 0.1$ mg/kg).

Natural Product Synthesis

Keywords: Natural products / Medicinal chemistry / Biomimetic synthesis / Enzymes / Terpenoids / Enantioselectivity

