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Total Syntheses of (+)- and (−)-Cacospongionolide B, Cacospongionolide E, and Related Analogues. Preliminary Study of Structural Features Required for Phospholipase A_2 Inhibition

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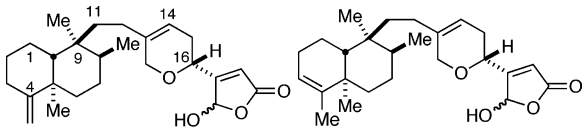
The total syntheses of the antiinflammatory marine sponge metabolites (+)-cacospongionolide B and E are described. The pivotal steps in the synthetic route include a three-step sequence that couples the two main regions of the natural product, as well as generates the side chain dihydropyran ring. The activity of the synthetic analogues against bee venom phospholipase A_2 suggests that the cacospongionolides have enantiospecific interactions with the enzyme that may be independent of the γ-hydroxybutenolide moiety.

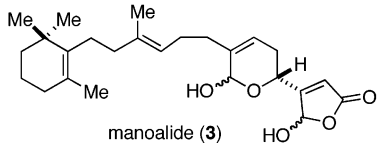
Introduction

The marine sponge metabolites, cacospongionolide B[1] (**1**) and E[2] (**2**), as well as related congeners have biological properties that include antimicrobial, cytotoxic, and antiinflammatory activities.[3] The antiinflammation activities, in particular, are thought to result from the inhibition of secretory phospholipase A_2 (sPLA$_2$).[4] This activity was anticipated in light of the structural features that the cacospongionolides share with manoalide (**3**), another known inhibitor sPLA$_2$.[5]

sPLA$_2$ catalyzes the hydrolytic release of arachidonic acid from phospholipids in the lipid bilayer. This unsaturated fatty acid leads to potent proinflammatory agents such as prostaglandins, thromboxanes, and leukotrienes. In this regard, the development of effective inhibitors of sPLA$_2$ could offer new opportunities for treating diseases such as asthma, sepsis, and rheumatoid arthritis.[6]



(+)-cacospongionolide B (**1**) (+)-cacospongionolide E (**2**)



manoalide (**3**)

The biologically active region of manoalide is known to include the γ-hydroxybutenolide moiety, a functionality that can serve as a masked α,β-unsaturated aldehyde. The γ-hydroxybutenolide is believed to form a covalent interaction with a lysine residue at the PLA$_2$-lipid interface near the active site of the enzyme.[7] Likewise, the cacospongionolides may also involve this type of interaction with sPLA$_2$; however, no experimental evidence has confirmed this hypothesis. Herein, we describe the total syntheses of cacospongionolides B and E and the initial study into the mechanism of their antiinflammatory activities.[8]

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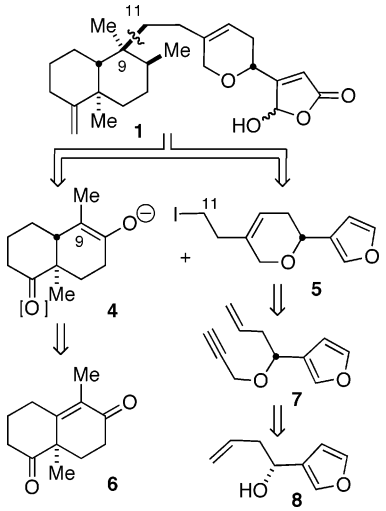


FIGURE 1. Retrosynthesis of cacospongionolide B.

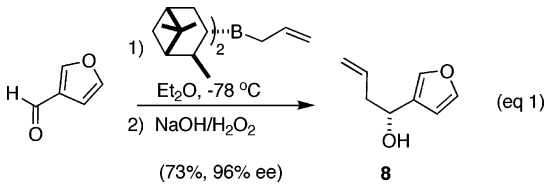
Results and Discussion

To provide access to a wide range of cacospongionolide structural variants, a convergent strategy was pursued.[9] The coupling of various reaction partners could give rise to new compounds with useful handles for attaching fluorescent,[10] radiolabel,[11] biotin,[12] or photoaffinity labels.[13]

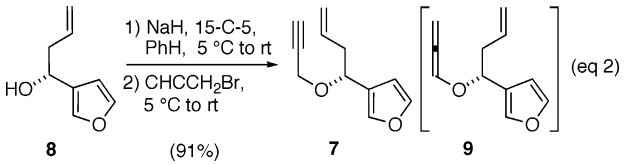
Retrosynthetic Analysis of Cacospongionolide B. As illustrated in Figure 1, cacospongionolide can be dissected into two sections; an aliphatic Decalin region possessing four contiguous stereocenters and a γ-hydroxybutenolide-containing section with a remote stereogenic center.[14]

Our plan was to join the two fragments at the C9−C11 bond[15] through a reductive alkylation of the type pioneered by Stork and co-workers in the early 1960s.[16] The requisite Decalin **6** is similar to the known Wieland−Mischer ketone.[17] We thought to create the dihydropyran ring functionality found in **5** through an enyne ring-closing metathesis. Enyne **5** is accessible from the known alcohol **8**. To accomplish a diastereo- and enantioselective preparation of the cacospongionolides, both fragments of the molecule will need to be prepared with absolute control over stereochemistry.

Initial Approach to Cacospongionolide B. An asymmetric preparation of the oxygenated side chain began with the synthesis of the homoallylic alcohol **8**. This known compound was prepared utilizing Brown's asymmetric allylboration protocol.[18] Treatment of 3-furfural with allyl diisopinocampheylborane, followed by oxidative workup provides the desired alcohol **8** in 73% yield and 96% ee (eq 1). Other catalytic asymmetric allylation procedures were considered; however, Brown's methodology proved convenient and effective.[19]



Etherification of alcohol **8** with propargyl bromide to prepare enyne **7** was investigated next.[20] Optimal yields of the desired propargyl ether **7** with minimal contamination by allenyl ether **9** was possible by using NaH in benzene with 15-crown-5 to catalyze the alkylation.



With compound **7** in hand, the intramolecular enyne reaction was investigated.[21] As observed by Mori and co-workers,[21e] a dramatic improvement in the efficiency of the metathesis was noted when the reaction was carried out under an atmosphere of ethylene using ruthenium

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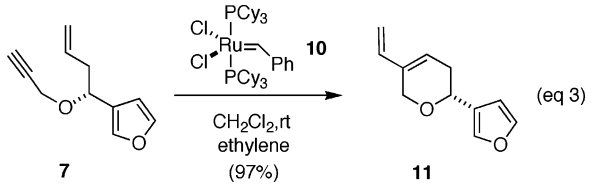
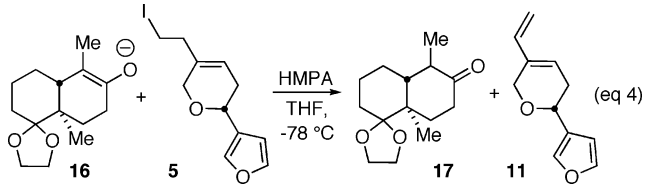
alkylidene **10**. Optimized conditions provided the desired diene **11** in nearly quantitative yield.



Further functionalization of diene **11** into the requisite homoallylic iodide **5** was examined next. A hydrozirconation/iodination sequence was envisioned as an attractive single-step solution;[22] however, this strategy proceeded in unacceptably low yields in our hands. A two-step solution to the electrophilic side chain proved more successful. Hydroboration of the diene **11** with 9-BBN generated homoallylic alcohol **12** in 87% yield.[23] Alcohol **12** was then converted to iodide **5** in 83% yield with PPh_3, imidazole, I_2, in Et_2O/CH_3CN (3:1) at 0 °C.[24]

With the precursor to cacospongionolide's oxygenated side chain in hand, the preparation of the Decalin portion was investigated. An asymmetric Robinson annulation, as optimized by Hagiwara and Uda, appeared particularly well-suited for preparing this functionality.[25] Commercially available 2-methyl-1,3-cyclohexadienone was treated with ethyl vinyl ketone, KOH in methanol at 65 °C to provide triketone **14** in 95% yield. Compound **14** in the presence of D-phenylalanine and camphorsulfonic acid in DMF with careful control over reaction temperature, 30−70 °C, 10 °C per day for 4 days, generated enone **6** in 79% yield and 93% ee. Recrystallization from Et_2O/hexanes afforded enantiomerically pure material (i.e., >99% ee). Effective differentiation of the carbonyls was achieved with ethylene glycol as solvent, *p*-TsOH, and 4 Å molecular sieves at room temperature to generate enone **15** in 83% yield.[26]

With access to the two regions of the molecule, the key reductive coupling reaction was investigated. Metal/ammonia reduction of enone **15** provided the desired enolate that was examined as the nucleophilic partner in an alkylation of our electrophilic side-chain precursor.[27] Unfortunately, conditions could not be identified where the enolate **16**, used either directly from the metal/ammonia reduction or derived from the corresponding trimethylsilyl enol ether,[28] provided more than a minor amount (i.e., 10%) of the desired alkylation product.[29] The major byproducts from these reactions were diene **11** and the protonated enolate (eq 4). Since conditions could be found for alkylating other electrophiles, such as iodopentane (75% yield), the problem apparently resided with facile elimination of iodide **5**.



To improve the results of the alkylation, other conditions, including various alkylation partners and additives, were studied. The enolate counterion and solvent additives were investigated to moderate the basicity of the enolate and perhaps favor the alkylation over the elimination. The addition of HMPA/Me_2Zn to the lithium enolate[30] provided only a few percent increase in the yield of desired product. Similarly, modification of the enolate with copper cyanide was also not successful.[31] Metal enolates generated from Et_3B,[32] *n*-Bu_2BOTf,[33] Ti(*On*-Bu)$_4$,[34] and $TiCl_4$[35] yielded similar results. Basically, the hindered nature of the enolate and the enhanced acidity of the homoallyic iodide presented an insurmountable problem at this point. Without the key reductive coupling reaction, we opted to explore an alternate approach that would generate the dihydropyran functionality after the key coupling reaction.

Alternative Retrosynthesis of Cacospongionolide B. The failure of the key fragment coupling reaction

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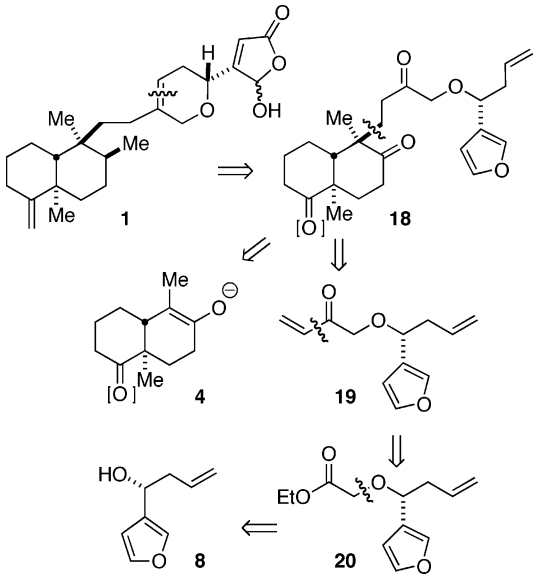
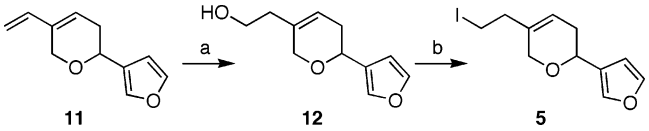


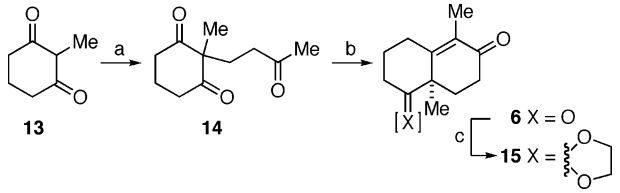
FIGURE 2. Revised retrosynthesis of cacospongionolide B.

SCHEME 1. Preparation of Homoallylic Iodide 5[a]



[a] (a) 9-BBN, THF, rt; H_2O_2, NaOH (87%). (b) PPh_3, imid., I_2, Et_2O/CH_3CN, 0 °C (83%).

SCHEME 2. Asymmetric Robinson Annulation[a]

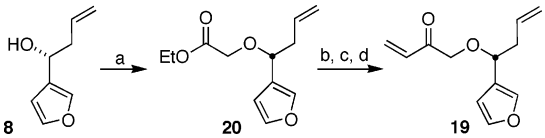


[a] (a) Ethyl vinyl ketone, MeOH, KOH, 65 °C (95%). (b) D-Phe, (+)-CSA, DMF, 30−70 °C (79%). (c) Ethylene glycol, *p*-TsOH, 4 Å MS, rt (83%).

forced us to reexamine the synthetic plan. To circumvent the problematic alkylation, we thought to introduce the side chain via a Michael addition.[36] This strategy would require an α,β-unsaturated carbonyl, such as vinyl ketone **19**, as the electrophilic precursor to the oxygenated side chain (Figure 2). In this approach, the natural product's dihydropyran ring would be formed at a later stage in the synthesis through a selective ring-closing metathesis between the two olefins on the side-chain.

Total Synthesis of Cacospongionolide B. Preparation of the vinyl ketone intermediate **19** was the initial focus of our investigation. As illustrated in Scheme 3, accessing the necessary vinyl ketone **19** should be possible from the same homoallyl alcohol **8** used in the first generation strategy. Alcohol **8** can be converted to ester

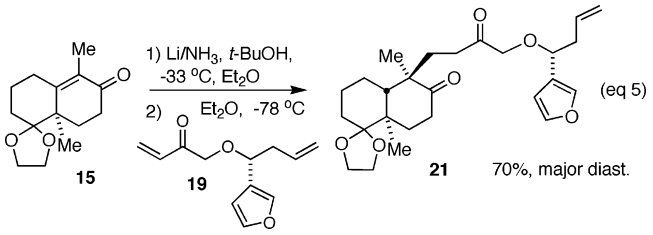
SCHEME 3. Synthesis of Vinyl Ketone 19[a]



[a] Reagents: (a) NaH, THF, 0 °C-rt; $BrCH_2CO_2C_2H_5$, 0 °C (84% at 76% conv.). (b) LiOH, MeOH/H_2O (3:1), rt. (c) MeO(Me)NH•HCl, DIC, DMAP, TEA, CH_2Cl_2, 0 °C-rt (86%, two steps). (d) H_2C=CHMgBr, THF, −78 to 0 °C, (83%).

20 through an etherification with ethyl bromoacetate in 84% yield (based on 76% conversion). The saponification of ester **20** and conversion to the Weinreb amide proceeds in 86% yield for the two steps.[37] Addition of vinyl Grignard into the Weinreb amide occurred in 83% yield and completes the preparation of vinyl ketone **19** in an enantiomerically enriched fashion.

The key Michael addition of the Decalin enolate into the vinyl ketone **19** was explored next.[38] In THF, the Michael addition afforded only 25% of the desired alkylation product and 5% of multiple alkylation products. Switching to Et_2O proved to be the key for optimizing the addition and suppressing undesired proton exchange and over alkylation products. As depicted in eq 5, lithium ammonia reduction of enone **15** in the presence of *t*-BuOH generates the *trans*-decalin lithium enolate that can be trapped by vinyl ketone **19** to provide the alkylation product **21** in 70% yield as a single diastereoostereomer.[39] The high diastereoselectivity of this reaction arises through the kinetic facial selectivity of the Michael addition. Approach of the electrophile from one face of the Decalin enolate is blocked partially by the axial methyl group. The other face, however, is free of such steric encumbrance.[40]



With the alkylation product in hand, the next two steps in the plan were to generate the dihydropyran ring and complete the core structure of the natural product (Scheme 4). Bis-olefination of diketone **21** was accomplished in the presence of the Ph_3P=CH_2 in DMSO. Purification of the crude material by basic alumina chromatography provided a 60% yield of the desired triene **22**.

(36) For related Michael reactions, see (a) Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152−6153. (b) Marshall, J. A.; Fanta, W. I. *J. Org. Chem.* **1964**, *29*, 2501−2505. (c) Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 6867−6869. (d) Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 6179−6181. (e) Stork, G.; Singh, J. *J. Am. Chem. Soc.* **1974**, *96*, 6181−6182.

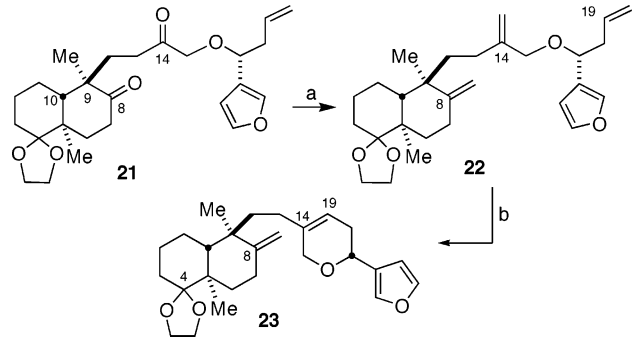
(37) (a) Piscopio, A. D.; Minowa, N.; Chakraborty, T. K.; Kiode, K.; Bertinato, P.; Nicolaou, K. C. *J. Chem. Commun.* **1993**, 617−618. (b) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *39*, 3815−3818.

(38) For examples of related transformations, see (a) Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152−6153. (b) Stork, G.; Singh, J. *J. Am. Chem. Soc.* **1974**, *96*, 6181−6182. (c) Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 6867−6869. (d) Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 6179−6181.

(39) The minor diastereomer resulting from the enantiomer of **19** was not detected by ^{1}H NMR (i.e., <5%).

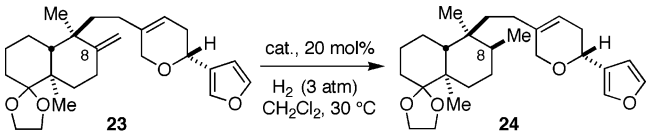
(40) For a related example, see Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726−9728.

SCHEME 4. Installation of Dihydropyran Moiety[a]



[a] (a) $Ph_3P{=}CH_2$, DMSO, 75 °C (60%). (b) $Cy_3P(iMes)(Cl)_2Ru{=}CHPh$, CH_2Cl_2, rt (91%).

SCHEME 5. Reduction of Decalin Olefin



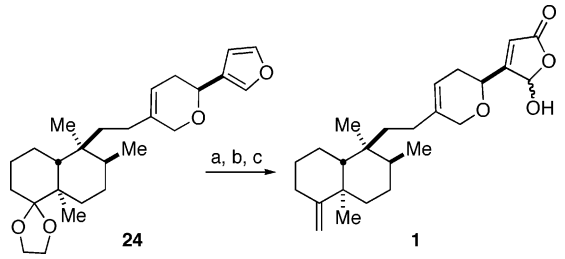
Cat.	Yield	dr
Rh(I)/(**R**)-BINAP	91%	3.3 : 1
Rh(I)/(**S**)-BINAP	95%[1]	3.0 : 1
$(Ph_3P)_3RhCl$[2]	90%	1.7 : 1

[1]Yield based on 60% conversion.
[2]Conditions: rt, 1 atm H_2, CH_2Cl_2

Triene **22** is now ready for the intramolecular RCM reaction. We were confident that the RCM reaction would occur selectively generating the stable six-membered ring with a trisubstituted olefin over the less stable alternate ring closures. As anticipated, exposure of triene **22** to 8 mol % of Grubbs' Ru metathesis catalyst[41] in CH_2Cl_2 provided the dihydropyran **23** in 91% yield and completed the carbon skeleton of cacospongionolide B.

With the natural product's skeleton in place, the next challenge was to introduce appropriate functionality throughout the molecule. A diastereoselective reduction of the exocyclic olefin on the Decalin (C8) to a methyl group was explored first. Selective reductions of similar olefins of *trans*-decalin ring systems were known with catalysts such as Pd/C, Rh/C, Ir-black, and Pt-black.[42] These catalysts, however, proved nonselective under a variety of conditions, reducing both isolated olefins as well as the furan ring in some cases. Wilkinson's catalyst [$(Ph_3P)_3RhCl$], on the other hand, reduced the desired disubstituted olefin selectively in high yield (90%), however, with only modest diastereoselectivity (1.7:1) favoring the desired product **24** (Scheme 5). Crabtree's iridium catalyst [(cod)IrPCy_3Pyr]PF_6 is known to be more reactive than Wilkinson's catalyst, and its use in the reduction of **23** showed significant loss of the trisubstituted pyranyl olefin, in addition to the desired reduction of the *exo*-olefin.

SCHEME 6. Final Steps to Cacospongionolide B[a]



[a] (a) 1 N HCl/THF (1:2), rt (90%). (b) $Ph_3P{=}CH_2$, DMSO, 75 °C (84%). (c) O_2, rose bengal, *i*-Pr_2NEt, 150 W tungsten lamp, CH_2Cl_2 −78 °C (69%).

To improve the diastereoselectivity of the hydrogenation step, other potentially more selective catalyst/ligand systems were considered.[43] Interestingly, a more selective reduction was obtained with the chiral rhodium catalyst developed by Takaya and co-workers.[44] As depicted in Scheme 5, the (*R*)-BINAP/Rh(I) catalyst (20 mol %) in CH_2Cl_2 at 30 °C under H_2 (3 atm) provided the desired isomer **24** in 91% yield (based on 76% conversion)[45] in a 3.3:1 mixture of diastereomers. The desired isomer was separated by silica gel chromatography. The double diastereoselectivity imparted by the chiral ligand was slight with the (*S*)-BINAP ligand providing the same reduction product in a 3:1 diastereomeric ratio. This result suggests that the improved diastereoselectivity of this catalyst/ligand system was influenced by the steric bulk of the BINAP ligands and not necessarily the result of a matched/mismatched transition state. X-ray crystallography confirmed that all the stereocenters of cacospongionolide B were in place in reduced intermediate **24**.

With all the stereocenters in place, completion of the synthesis required only the conversion of the protected ketone to the *exo*-olefin and installation of the γ-hydroxybutenolide. As depicted in Scheme 6, removal of the acetal (**24**) under acidic conditions and subsequent Wittig olefination of the ketone with excess methyl triphenylphosphonium ylide in DMSO at 75 °C proceeded to the desired product in 76% overall for the two steps. Photooxidation of the furan moiety under basic conditions[46] unmasked the desired γ-hydroxybutenolide functionality in 69% yield,[47] thus completing the first total synthesis

(41) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(42) (a) Bruner, S. D.; Radeke, H. S.; Tallarico, J. A.; Snapper, M. L. *J. Org. Chem.* **1995**, *60*, 1114−1115. (b) Almstead, J.-I. K.; Demuth, T. P., Jr.; Ledoussal, B. *Tetrahedron: Asymmetry* **1998**, *9*, 3179−3183. (c) Markó, I. E.; Wiaux, M.; Warriner, S. M.; Giles, P. R.; Eustace, P.; Dean, D.; Bailey, M. *Tetrahedron Lett.* **1999**, *40*, 5629−5632. (d) Ling, T.; Xiang, A. X.; Theodorakis, E. A. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3089−3091. (e) Kende, A. S.; Rustenhoven, J. J.; Zimmermann, K. *Tetrahedron Lett.* **2000**, *41*, 843−846.

(43) For recent reviews on catalytic asymmetric hydrogenation, see (a) Noyori, R. *Acta Chem. Scand.* **1996**, *50*, 380−390. (b) Nugent, W. A.; RajanBabu, T. V.; Burk, M. J. *Science* **1993**, *259*, 479−483. (c) Ratovelomanana-Vidal, V.; Genêt, J.-P. *J. Organomet. Chem.* **1998**, *567*, 163−171. (d) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336−345. (e) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345−350.

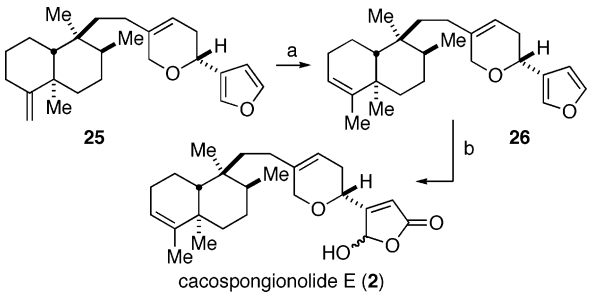
(44) Otha, T.; Ikegami, H.; Miyake, T.; Takaya, H. *J. Organomet. Chem.* **1995,** *502*, 169−176.

(45) Higher conversions gave significant amounts of pyran-olefin reduction that can be removed at a later stage by RP-HPLC.

(46) Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2773−2776.

(47) For other syntheses of γ-hydroxybutenolide rings, see (a) Boukouvalas, J.; Lachance, N. *Synlett* **1998**, 31−32. (b) Gerlach, K.; Hoffmann, H. M. R.; Wartchow, R. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3867−3872. (c) Katsumura, S.; Hori, K.; Fujiwara, S.; Isoe, S. *Tetrahedron Lett.* **1985**, *26*, 4625−4628. (d) Larcheveque, M.; Legueut, C.; Debal, A.; Lallemand, J. Y. *Tetrahedron Lett.* **1981**, *22*, 1595−1598.

SCHEME 7. Synthesis of Cacospongionolide E[a]



[a] (a) $RhCl_3{\cdot}H_2O$, EtOH/$CHCl_3$, 70 °C (70%). (b) $^1O_2$, rose bengal, *i*-Pr_2NEt, CH_2Cl_2, −78 °C (54%).

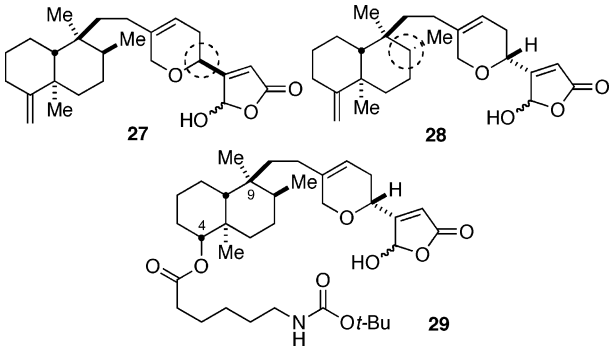
of (+)-cacospongionolide B (**1**). In an analogous fashion, the enantiomer of the natural product was also prepared using the appropriate enantiomeric catalysts and reagents.

Synthesis of Cacospongionolide E. Cacospongionolide E (**2**) differs from cacospongionolide B (**1**) only in the position of its olefin in the Decalin ring system. On the basis of biological studies, this region may be crucial for inhibiting PLA_2 activity.[48] In any case, we expected that a metal-catalyzed isomerization of the *exo*-olefin of **1** could be used to yield the more potent isomer **2**.

The synthesis of cacospongionolide E (**2**) was accomplished in two steps from the furanyl intermediate **25** (Scheme 7). The *exo*-cyclic olefin of **25** was isomerized to the more stable internal position utilizing $RhCl_3{\cdot}H_2O$ in a mixture of EtOH/$CHCl_3$ (1:1). Heating the mixture to 70 °C for 6 days provided the desired olefin isomerization product **26** in 70% yield with no detectable pyran olefin isomerization by ^1H NMR. Adduct **26** was converted to cacospongionolide E in 54% yield by the same photooxidation procedure used for completing compound **1**. The spectroscopic data for the synthetic cacospongionolide E matched data reported for the natural product.

The synthetic route to cacospongionolides B and E allowed us to begin exploring the structural requirements necessary for these compound's antiinflammatory activity. In this regard, the synthesis was particularly well-suited to prepare diastereomers of the natural products. For example, compound **27** includes a stereochemical inversion at the dihydropyran ring. The use of the enantiomeric side chain in the Michael addition could give rise to this isomer. To access the alternate configuration for the C8 methyl group on the Decalin ring in compound **28**, the distereoselectivity of the *exo*-olefin reduction could be inverted. In addition, as a step toward preparing functional cacospongionolide probe reagents, linker groups could be added to the natural product.[49] For example, the *exo*-olefin on cacospongionolide B could be converted to the *N*-Boc-protected linker **29**.

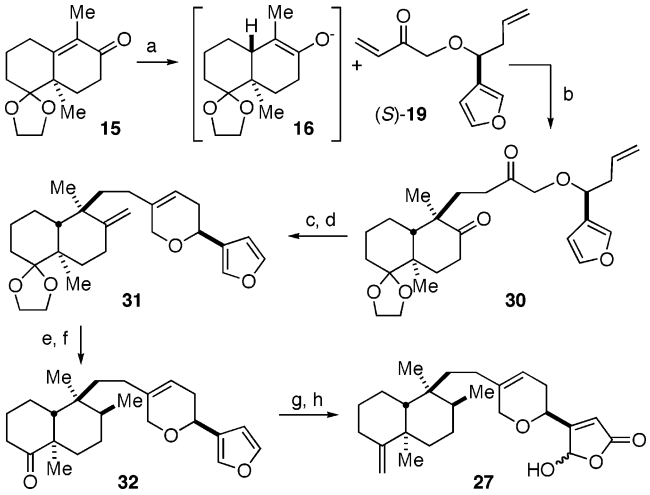
Synthesis of Cacospongionolide Diastereomers. Preparation of analogue **27** with the S-configuration at the stereocenter on the dihydropyran ring was accomplished utilizing cacospongionolide B's synthetic strategy. As depicted in Scheme 8, enone **15** was coupled with the (*S*)-antipode of vinyl ketone **19** through a reduction/Michael addition sequence to yield diketone **30** in 60% as the major diastereomer. Bis-olefination of the diketone **30** provided a triene in 52% yield. RCM completed the ring system of the side chain to give **31** in 88% yield.



As described previously, the diastereoselective reduction of the Decalin *exo*-olefin was affected with Rh(I)/(*R*)-BINAP, and H_2 (3 atm) in CH_2Cl_2 at room temperature proceeds in 65% yield (90% conversion) as a mixture of diastereomers (3.3:1) again favoring the stereochemistry of the natural product.[50] Acetal deprotection with aqueous acid followed by Wittig olefination of the resulting ketone gave a furan in 47% yield for the two steps. Photooxidation with in situ generated singlet oxygen under basic conditions unmasked the γ-hydroxybutenolide of analogue **27** in 42% yield.

As discussed earlier, the diastereoselectivity for the reduction of the *exo*-olefin of compound **23** is moderate (1.7:1) with the use of Wilkinson's catalyst [$(Ph_3P)_3RhCl$]. This lack of selectivity in the hydrogenation allowed us to use the minor diastereomer to access the structural variant **28** (Scheme 9). The reaction mixture containing the minor component in the hydrogenation[51] can be

SCHEME 8. Synthesis of Cacospongionolide Diastereomer[a]

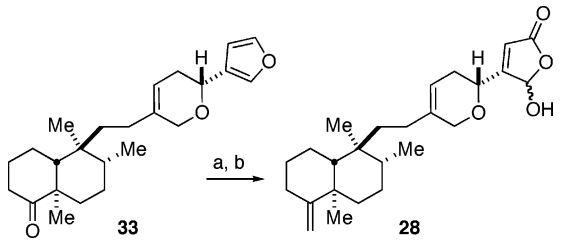


[a] Reagents: (a) Li/NH_3, *t*-BuOH, Et_2O, −33 °C; (*S*)-**19**, Et_2O, −78 °C (60%). (b) $Ph_3P{=}CH_2$, DMSO, 75 °C (52%). (c) Cy_3P(iMes)-$(Cl)_2Ru{=}CHPh$, CH_2Cl_2, rt (88%). (d) $[(cod)RhCl]_2$, (*R*)-BINAP, H_2 (3 atm), CH_2Cl_2, 30 °C (65%). (e) 1 N HCl/THF (1:2), rt. (f) $Ph_3P{=}CH_2$, DMSO, 75 °C (47%, two steps). (g) O_2, rose bengal, *i*-Pr_2NEt, 150 W tungsten lamp, CH_2Cl_2, −78 °C (42%).

(48) De Rosa, S.; Crispino, A.; De Giulio, A.; Iodice, C.; Benrezzouk, R.; Terencio, M. C.; Ferrándiz, M. L.; Alcaraz, M. J.; Payá, M. *J. Nat. Prod.* **1998**, *61*, 931−935.

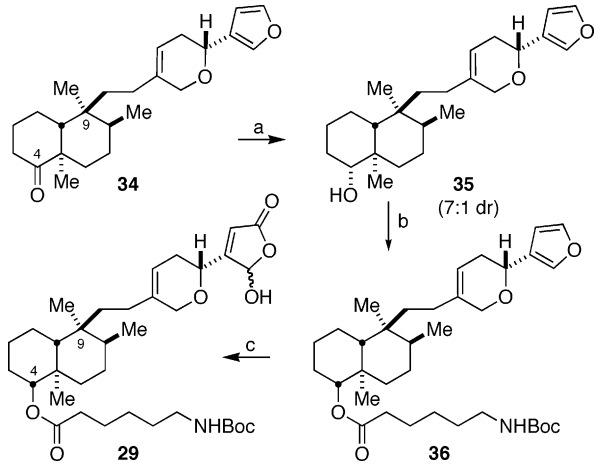
(49) (a) Casaubon, R. L.; Snapper, M. L. *Chem. Biol.* **1999**, *6*, 639−647. (b) Radeke, H. S.; Snapper, M. L. *Bioorg. Med. Chem.* **1998**, *6*, 1227−1232.

SCHEME 9. Synthesis of Cacospongionolide Diastereomer[a]



[a] (a) $Ph_3P{=}CH_2$, DMSO, 75 °C (79%). (b) O_2, rose bengal, *i*-Pr_2NEt, 150 W tungsten lamp, CH_2Cl_2, −78 °C (62%).

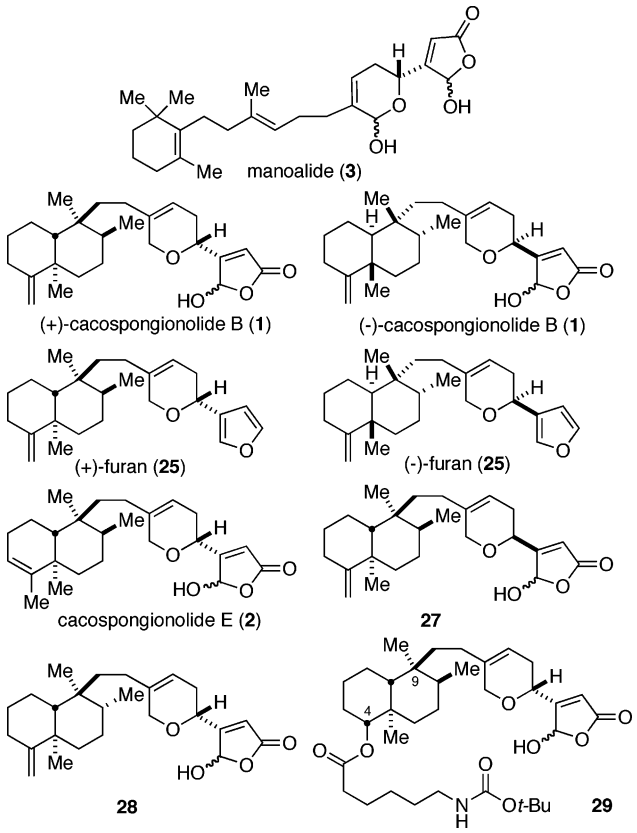
SCHEME 10. Synthesis of C4 Linker Analogue 29[a]



[a] (a) $NaBH_4$, EtOH (80%). (b) EDCI, DMAP, $BocHN(CH_2)_5CO_2H$, CH_2Cl_2 (66%). (c) O_2, rose bengal, *i*-Pr_2NEt, 150 W tungsten lamp, CH_2Cl_2 −78 °C (87%).

deprotected to ketone **33** and then isolated by RP-HPLC to provide the desired diastereomer in approximately 23% yield. The ketone **33** was then converted in two steps to the corresponding diastereomeric analogue **28**. Treatment of ketone **33** with excess Ph_3PCH_2 then oxidation provides the α-diastereomeric structural variant **28** in 62% yield.

Synthesis of C4 Linker Variant. Analogue **29** was pursued to determine the feasibility of linking reporter groups at the C4 position on the Decalin ring. The compound's preparation was achieved in three steps from the cacospongionolide B precursor **34** (Scheme 10). Diastereoselective reduction of the ketone was affected with $NaBH_4$ in EtOH to give a 7:1 mixture of diastereomeric alcohols in 80% favoring compound **35**.[52] Isolation by silica gel chromatography and coupling with *N*-Boc-6-aminohexanoic acid in the presence of EDCI and DMAP in CH_2Cl_2 provided the C_4 esterified precursor **36** in 66% yield. Unmasking of the γ-hydroxybutenolide moiety with in situ generated singlet oxygen under basic conditions gave access to the desired Decalin-substituted variant **29** in 87% yield. The higher yield for this oxidation may be due to the absence of the *exo*-olefin on the Decalin, functionality that is likely to also react with singlet oxygen.



Inhibition of Bee Venom sPLA$_2$. With access to cacospongionolide B (**1**), cacospongionolide E (**2**), and structural variants, we could begin screening these natural and nonnatural compounds against *s*PLA$_2$. We chose to first evaluate the potency of the inhibitors utilizing an in vitro enzyme activity assay.[53] The ease of use and microtiter plate nature of the in vitro *s*PLA$_2$ assay makes it particularly well-suited for rapid compound screening.[54]

Manoalide (**2**), a known inhibitor of bee venom *s*PLA$_2$, (+)-cacospongionolide B (**1**) and its enantiomer (−)-**1**, and their respective furan precursors, (+)-**25** and (−)-**25**, were compared. The inhibition of each compound was determined over a range of concentrations (400−1 μM), and from those results, the IC_{50} values were calculated. The results are summarized in Table 1. Several important aspects about the interaction between the substrates and their target enzyme were noted. The natural enantiomer of cacospongionolide, (+)-**1**, is two times more potent as an inhibitor of *s*PLA$_2$ than the unnatural enantiomer (−)-**1**, suggesting that the inhibition of bee venom *s*PLA$_2$ is enantiospecific. Also of note, the furan precursor with the natural stereochemistry (+)-**25** shows potency greater than that of the γ-hydroxybutenolide containing (−)-

(50) At higher conversions, lower yields of the desired compound are obtained due to reduction of the trisubstituted dihydropyran olefin.

(51) Contaminated with starting material and over-reduced materials.

(52) (a) Dutcher, J. S.; Macmillan, J. G.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 2663−2669. (b) Radeke, H. S.; Digits, C. A.; Bruner, S. D.; Snapper, M. L. *J. Org. Chem.* **1997**, *62*, 2823−2831.

(53) Most *s*PLA$_2$-inhibitory assays involve live animals or radiolabeled phospholipids. For examples, see (a) Garcia Pastor, P.; De Rosa, S.; De Giulio, A.; Payá, M.; Alcaraz, M. J. *Brit. J. Pharm.* **1999**, *126*, 301−311. (b) Potts, B. C. M.; Faulkner, D. J.; Jacobs, R. S. *J. Nat. Prod.* **1992**, *55*, 1701−1717.

(54) *s*PLA$_2$ Assay Kit from Cayman Chemical, Ann Arbor, MI (Catalog 765001).

TABLE 1. *s*PLA$_2$ Inhibition

inhibitor	IC_{50} (μM)
manoalide (**3**)	38 (±3)
(+)-cacospongionolide B (**1**)	49 (±9)
(−)-cacospongionolide B (**1**)	114 (±7)
(+)-furan (**25**)	72 (±4)
(−)-furan (**25**)	167 (±32)
Cacospongionolide E (**2**)	27 (±7)
(*S*)-dihydropyran (**27**)	19 (±7)
C8-methyl diastereomer (**28**)	29 (±13)
C4-linker (**29**)	44 (±21)

cacospongionolide B. This result suggests that more than the pyranofuranone portion of the molecule interacts with the enzyme and that the hydrophobic region may provide some yet-to-be-determined role in inhibition.[55]

Compound **27**, which incorporates a stereochemical inversion on the dihydropyran ring, is the most potent inhibitor with an IC_{50} value of 19 μM. The result suggests that the stereocenter on the dihydropyran ring is relevant. The diastereomeric methyl group on the Decalin ring of compound **28** does not adversely affect its binding to the enzyme. The addition of the *N*-Boc-protected linker to the C4 position of variant **29**, however, does appear to reduce its ability to inhibit bee venom *s*PLA$_2$. Cacospongionolide E (**2**) with an IC_{50} value of 27 μM has been shown to be a more potent inhibitor than cacospongionolide B (**1**) due to its internal olefin on the Decalin ring.[56] A major modification to the C4 region, such as variant **29**, however, was detrimental toward enzyme activity. The assay results suggest that for use as a molecular probe, conjugation of cacospongionolide analogues to reporter functionality at the C8 methyl may provide a more effective strategy.

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Summary

The first total syntheses of (+)- and (−)-cacospongionolide B have been accomplished in a longest linear sequence of 12 steps from commercially available starting materials with an overall yield of 8%. The pivotal transformations include a key three-step reaction sequence that couples the two fragments of the natural product and generates the dihydropyran ring. In addition, cacospongionolide E and other structural variants of the natural product were prepared through this synthetic strategy.

The synthetic cacospongionolides were utilized to investigate the structural requirements necessary for secretory phospholipase A_2 inhibition. Eight compounds including the natural product, its enantiomer, synthetic precursors to the natural product, cacospongionolide E (**2**), two diastereomeric variants of cacospongionolide B (**27** and **28**), and a linker-containing analogue **29** have been prepared and compared with manoalide. The activity of these analogues against bee venom *s*PLA$_2$ suggests that binding is enantiospecific and independent of the γ-hydroxybutenolide moiety. This information provides new directions for the preparation of more potent *s*PLA$_2$ inhibitors.

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Supporting Information Available: Experimental procedures and data on new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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