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Total Syntheses of (+)- and (−)-Cacospongionolide B: New Insight into Structural Requirements for Phospholipase A_2 Inhibition

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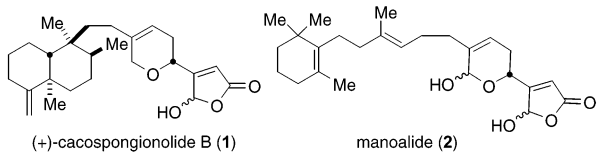
The natural product (+)-cacospongionolide B (**1**), isolated from the marine sponge *Fasciospongia cavernosa* by De Rosa and coworkers in 1995 was shown to possess antimicrobial and cytotoxic activities.[1] Moreover, the natural product's potent antiinflammatory activity[2] was attributed to its inhibition of secretory phospholipase A_2 ($sPLA_2$). Given the role of inflammation in diseases such as asthma, psoriasis, and rheumatoid arthritis,[3] identifying and developing potent inhibitors of $sPLA_2$ continues to be of importance.



The biological activities of cacospongionolide B have been attributed to its γ-hydroxybutenolide moiety, which is thought to act as a masked aldehyde. Manoalide,[4] (**2**) with a similar side chain, has been shown to bind covalently to $sPLA_2$ through the formation of a Schiff base between the γ-hydroxybutenolide-derived aldehyde and a lysine at the enzyme−lipid interface.[5] Accordingly, (+)-**1** has been tested and shown to have inhibitory activity similar to manoalide against several phospholipases.[2]

As an initial step toward exploring further the biological activities of (+)-**1**, we required access to the natural product, as well as structural variants. Given its interesting biological activity, it is not surprising that several reports have appeared describing synthetic approaches toward cacospongionolide B; however, none have yet resulted in a total synthesis.[6] *Herein we report the first total syntheses of (+)- and (−)-cacospongionolide B,[7] as well as our preliminary studies on its antiinflammatory activity and provide preliminary insight into the structural requirements for $sPLA_2$ inhibition.*

From a retrosynthetic perspective, cacospongionolide B comprises two regions connected through an ethylene linker (Figure 1). The *trans*-decalin portion is coupled through a quaternary carbon (C9) to the heterocyclic side chain. Given the distance between relevant stereocenters, absolute stereocontrol is required in the preparation of each fragment. In our initial analysis, fragments **3** and **4** were to be coupled through an established reductive alkylation protocol (Plan A).[8] While homoallylic iodide **4** is prepared readily through an enyne metathesis of compound **5**, followed by a hydroboration/oxidation of the resulting diene, all attempts to alkylate **4** were problematic in that elimination of HI was competitive with alkylation using enolate **3**. To circumvent this problem, we explored a Michael addition of enolate **3** into enone **7** (Plan B). In this approach the natural product's dihydropyran ring is generated at a later stage in the synthesis through a selective ring-closing metathesis.

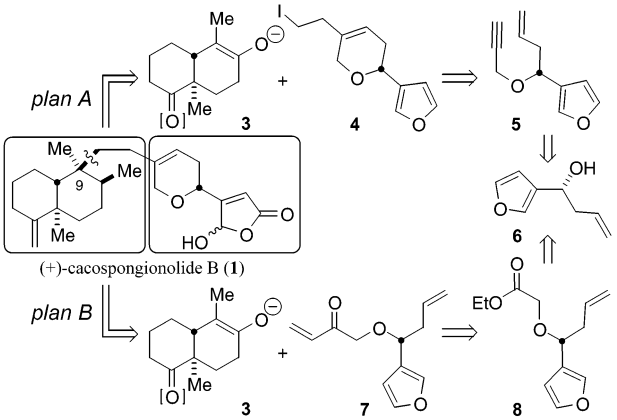
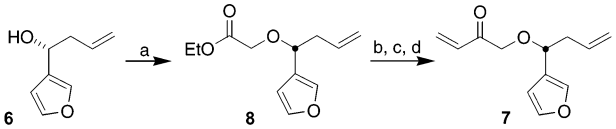


Figure 1. Retrosynthesis of cacospongionolide B.

The synthesis commences with the preparation of ketone **7**, which is generated in four steps from the known homoallylic alcohol **6** (Scheme 1). Brown's asymmetric allylboration provided alcohol **6** in 73% yield and 94% ee.[9] Alcohol **6** was then converted to ester **8** through an etherification with ethyl bromoacetate in 84% yield (based on 76% conversion). The saponification of ester **8** and conversion to the Weinreb amide proceeded in 86% yield for the two steps.[10] Addition of vinyl Grignard into the Weinreb amide occurred in 83% yield and completes the preparation of vinyl ketone **7** in an enantiomerically enriched fashion.

Scheme 1. Synthesis of Vinyl Ketone **7**[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%).

As illustrated in Scheme 2, Li/NH_3 reduction of the enone **9**[11] followed by trapping of the resulting enolate **3** with vinyl ketone **7** in Et_2O provided compound **10** as the major diastereomer with the desired relative decalin stereochemistry in 70% yield.[12] Bis-olefination of diketone **10** with $Ph_3P{=}CH_2$ formed triene **11** in 60% yield. With the desired triene **11** in hand, a selective ring-closing metathesis to install the dihydropyran ring of the side chain in lieu of the other possible five- and ten-membered ring closures was examined. Not surprisingly, Grubbs' metathesis catalyst[13]generated dihydropyran **12** selectively in 91% yield.

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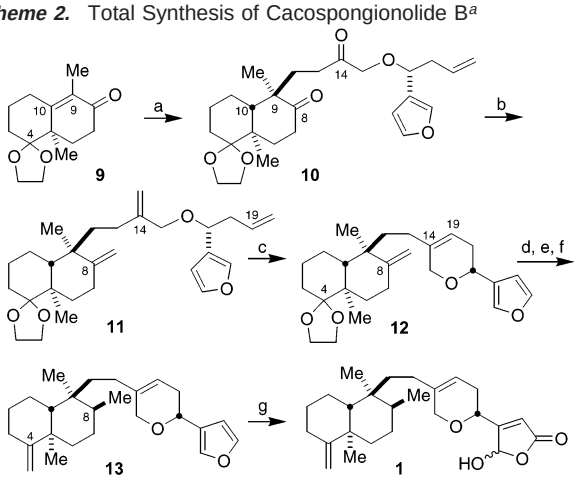
Scheme 2. Total Synthesis of Cacospongionolide B[a]



[a] Reagents: (a) Li/NH_3, *t*-BuOH, Et_2O, −33 °C; **7**, Et_2O, −78 °C (70%); (b) $Ph_3P{=}CH_2$, DMSO, 75 °C (60%); (c) $Cy_3P(iMes)(Cl)_2Ru{=}CHPh$, CH_2Cl_2, rt (91%); (d) $[(COD)RhCl]_2$, (*R*)-BINAP, H_2 (3 atm), CH_2Cl_2, 30 °C (91%, 3.3:1 dr); (e) 1 N HCl/THF (1:2), rt (90%); (f) $Ph_3P{=}CH_2$, DMSO, 75 °C (84%); (g) O_2, Rose bengal, *i*-Pr_2NEt, 150 W tungsten filament lamp, CH_2Cl_2, −78 °C (69%).

With most of the side chain in place, the next challenge was selective reduction of the decalin C8 *exo*-olefin. Heterogeneous hydrogenation catalysts (i.e., Pd/C, Rh/C, Ir-black, Pt-black) proved nonselective under a variety of conditions, reducing both isolated olefins, as well as the furan ring. Homogeneous hydrogenation catalysts can be more discriminating, and in that regard, Wilkinson's catalyst reduced selectively the desired disubstituted olefin in high yield, however with only modest diastereoselectivity (1.7:1) favoring the desired compound.[14] Improved results were obtained with a chiral rhodium catalyst.[15] (*R*)-BINAP/Rh(I) catalyst (20 mol %) in CH_2Cl_2 at 30 °C under 3 atm of H_2 provided the desired isomer in 91% yield (based on 76% conversion) as a 3.3:1 mixture of diastereomers.[16] The double diastereoselectivity imparted by the chiral ligand was slight; the (*S*)-BINAP ligand offered a 3:1 diastereomeric ratio, again favoring the desired stereochemistry.

With all stereocenters of the target molecule in place, completion of the synthesis required conversion of the protected C4 ketone into an *exo*-olefin. Removal of the acetal under acid conditions in the compound resulting from hydrogenation of **12**, followed by a Wittig olefination generated furan **13** in 76% overall yield for the two steps. Finally, photooxidation of the furan moiety under basic conditions[17] unmasked the desired γ-hydroxybutenolide functionality in 69% yield and completed the first total synthesis of (+)-cacospongionolide B. In an analogous fashion, the enantiomer of the natural product was also prepared using the appropriate enantiomeric catalysts and reagents.

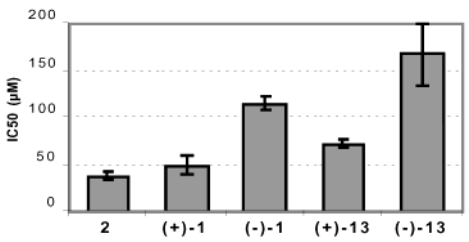


Figure 2. Inhibition of bee venom *s*PLA_2.

Inhibition of *s*PLA_2 with synthetic variants of cacospongionolide B revealed several important aspects (Figure 2). The inhibition is enantioselective; the natural product (+)-**1** is a more potent inhibitor of bee venom *s*PLA_2 than the unnatural enantiomer (−)-**1**. Moreover, the inhibition is notable for the synthetic precursor possessing the furan ring in place of the γ-hydroxybutenolide moiety (+)-**13**. *These results suggest that the γ-hydroxybutenolide is not the sole structural feature of the natural product involved in sPLA$_2$ inhibition.*

In summary, the first total syntheses of (+)- and (−)-cacospongionolide B have been accomplished in 12 linear steps from commercially available starting materials. The pivotal transformations include a three-step sequence that couples the two fragments of the natural product and generates the dihydropyran ring. The activity of the analogues against bee venom *s*PLA_2 suggests that cacospongionolide B has an enantiospecific interaction with the phospholipase that is independent of the γ-hydroxybutenolide moiety. To identify improved antiinflammatory agents, efforts are underway to prepare more potent inhibitors of *s*PLA_2 using the cacospongionolide scaffolding.

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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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