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Total Synthesis and Stereochemistry of (−)-Cacospongionolide F†

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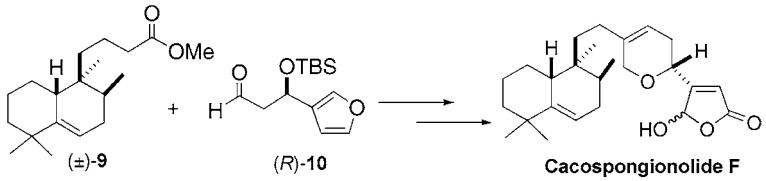
ABSTRACT



The most recently described member of the cacospongionolide class of marine natural products has been assembled using a diastereochemically divergent total synthesis strategy that independently establishes the complete stereochemistry of cacospongionolide F and provides a new entry toward expansion of this phospholipase A_2 inhibitor chemotype.

The cacospongionolides are sesterterpenes isolated from Mediterranean region sponges of the Thorectidae family. These compounds are characterized by distinct lipophilic and polar domains and by a range of potent and unique biological activities. The archetypal member, cacospongionolide (**1**),[1] is joined by congeners with structural variations primarily in the lipophilic domain. These include cacospongionolides B[2,3] (**2**), E[4] (**3**), and F[5] (**4**) (Figure 1). As specific inhibitors of phospholipase A_2 (PLA_2), members of this chemotype hold potential for addressing inflammatory diseases.[6] Preliminary structure−activity relationship studies of analogues of cacospongionolide B and the structurally related *Luffariella variablis* sponge isolate manoalide (**5**)[7] indicated that the lipophilic domain of each may confer both enhanced inhibitory activity and specificity.[6a] Notably, the dihydropyran hemiacetal of manoalide that is absent from the comparable C24 position of the cacospongionlides is not required for potent or irreversible PLA_2 inhibition. Furthermore, the γ-hydroxybutenolide moiety of **2** is not essential for potent inhibition of bee venom $sPLA_2$.[3] To facilitate the development of the cacospongionolides, the most recently described member (**4**) has been synthesized via a diastereochemically divergent strategy that establishes the complete relative and absolute configuration.

The bicyclic cores of **1**−**4** likely result from cationic cyclization of a triene, such as that in cacospongionolide D (**6**, Figure 1),[8] whereas the oxacyclic moieties may arise independently of carbocyclization. The variably substituted decalin cores may represent snapshots of rearrangements leading to isolabdane (**4**) and clerodane (**3**) terpenoids. As such, the cacospongionolides encompass an extensive range of rearrangements. Common cationic cyclizations would suggest that **1**−**4** share the same sense of absolute configurations at C5 (**1**−**3**) and C8−C10 (**1**−**4**).

† Dedicated to the memory of Prof. D. John Faulkner, an inspirational leader in marine natural products chemistry research.

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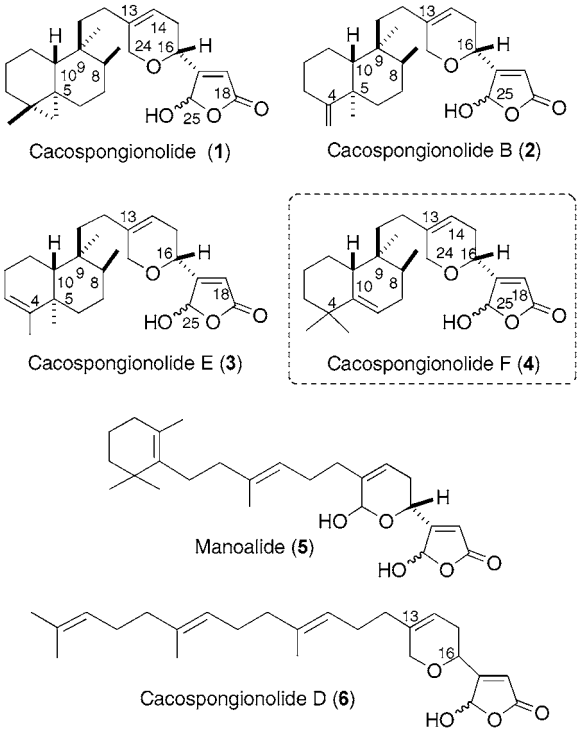


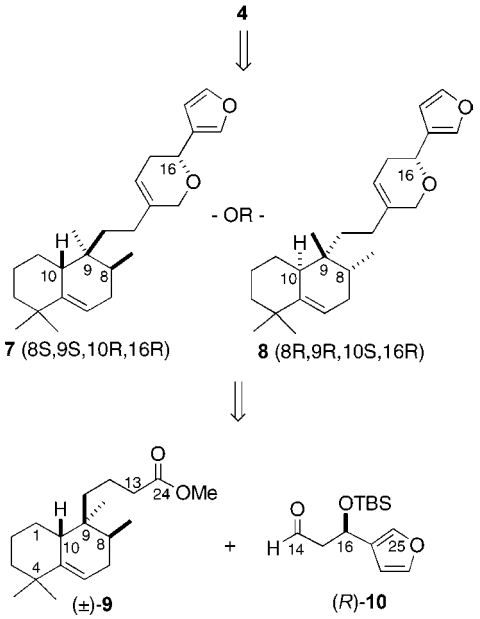
Figure 1. Structures of cacospongionolides and manoalide.

The (16*R*) configuration of **1**,[9] **3**,[4] and **4**[5] was inferred via analyses of C25 acyl derivatives. However, the relative stereochemistry between C16 and the decalin core has been rigorously established only for **1**[9] and 25-deoxy-**2**[10] via X-ray crystallography and for **2** via total synthesis.[3]

Because carbocycle versus oxacycle formation may occur via biogenetically distinct processes (cf. **6** vs **1**−**4**), the relative configuration of the oxacyclic C16 stereogenic center could, in principle, vary with respect to that of the decalin core. In developing the total synthesis of **4**, the C8−C10 core stereogenic centers have been independently correlated with the remote C16 center by synthetic design.

In designing a synthesis of **4**, the γ-hydroxy-butenolide moiety could be installed in the final stage via Faulkner's regioselective oxidation of a penultimate 3-substituted furan.[11] To address the two major relative stereochemical possibilities for naturally occurring **4**, two diastereomeric furans (8*S*,9*S*,10*R*,16*R*)-**7** and (8*R*,9*R*,10*S*,16*R*)-**8** could be targeted from two key fragments representing C1−C24 [(±)-**9**], bearing the relative stereochemical array of the dehydrodecalin core in racemic form, and C14−C25 [(*R*)-**10**], containing the (16*R*) stereogenic center (Scheme 1). This disconnection requires the de novo formation of the dihydropyran moiety but allows for the simultaneous generation of diastereomeric probes from an aldol coupling of the

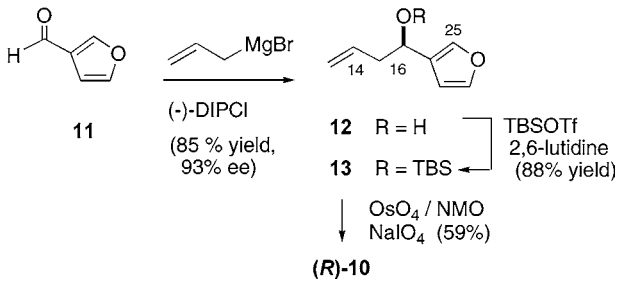
Scheme 1. Strategic Building Blocks



racemic ester (±)-**9** and aldehyde (*R*)-**10**. A planned late-stage partitioning of the racemic core of (±)-**9** into diastereomeric derivatives using (*R*)-**10** would provide (8*R*,9*R*,-10*S*,16*R*)-**4** and (8*S*,9*S*,10*R*,16*R*)-**4** via **7** and **8** for independent stereochemical correlation with naturally occurring **4**. The success of this strategy would rely upon the generation and unambiguous stereochemical assignment of diastereomeric products derived from (±)-**9** and (*R*)-**10**.

The synthesis of aldehyde (*R*)-**10** began with the reported[12] Brown allylation[13] of 3-furfural (**11**, Scheme 2). The product

Scheme 2. Synthesis of Aldehyde (*R*)-**10**



of asymmetric allylation (**12**) was converted into silyl ether **13** before the terminal alkene was oxidatively cleaved[14] to give aldehyde (*R*)-**10**.

The synthesis of the core domain utilized enone (±)-**14** (Scheme 3), a versatile synthetic intermediate employed in

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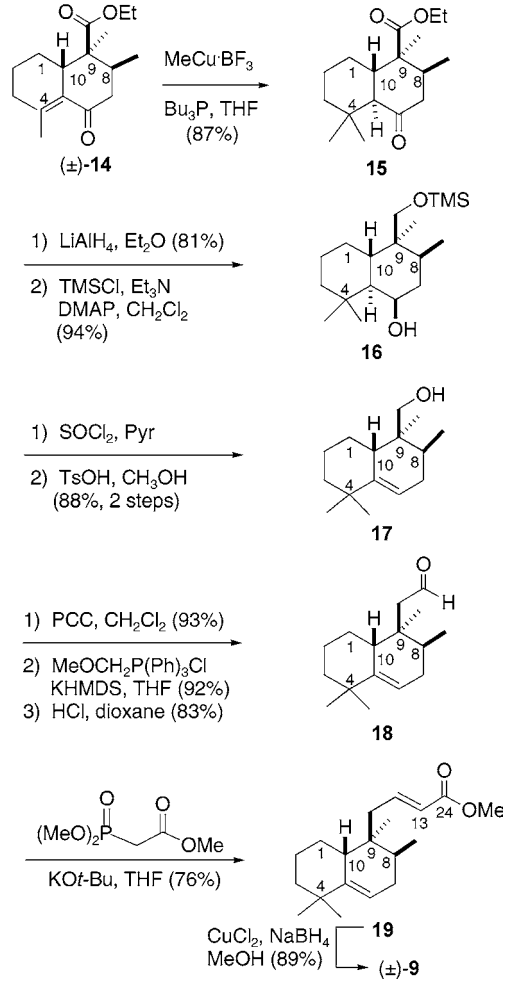
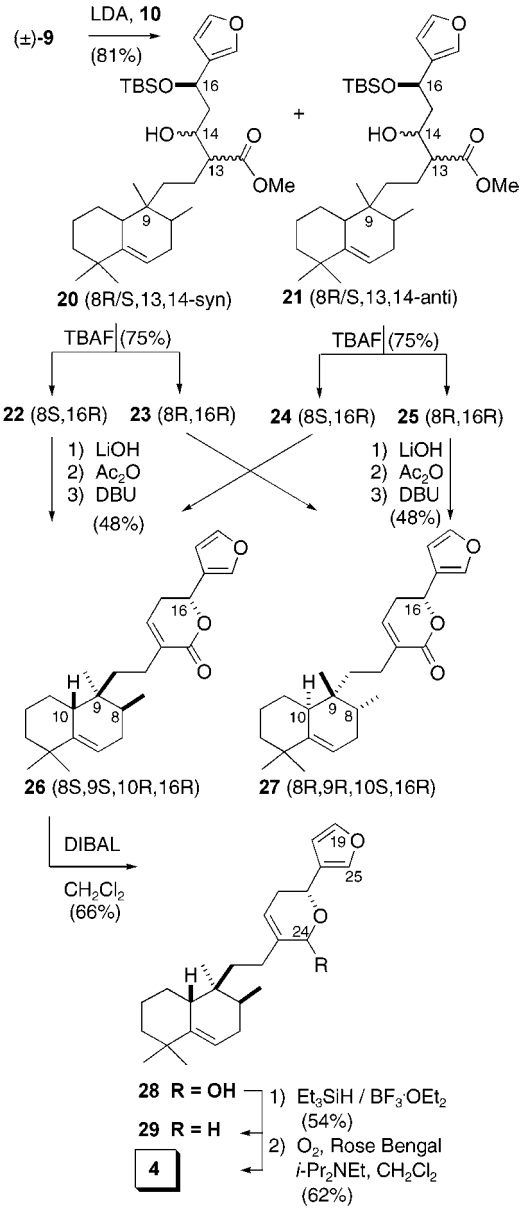
Scheme 3. Synthesis of the Dehydrodecalin Intermediate **9**



Scheme 4. Diastereochemically Divergent Total Synthesis



a total synthesis of dysidiolide.[15] Although the enone system is distorted from planarity in the ground-state conformation of **14**, conjugate addition of a methylcopper-(I)-BF_3 species[16] in the presence of tributylphosphine[17] provided the geminal β-dimethylated ketone **15** in high yield. Simultaneous reduction of both the ketone and the ester functionalities of **15** using $LiAlH_4$ gave a diol that was selectively monosilylated to provide secondary alcohol **16**. Subsequent dehydration with thionyl chloride and pyridine followed by desilylation installed the core isolabdane trisubstituted alkene and liberated the side chain alcohol of **17**. The primary alcohol of **17** was elaborated into the one-carbon-homologated aldehyde **18** via a reliable three-step sequence.[18] Thereafter, aldehyde **18** was converted into α,β-unsaturated ester **19** in a routine fashion. Regioselective reduction[19] of α,β-unsaturated ester **19** completed the preparation of (±)-**9**.

The two strategic building blocks were joined as a prelude to formation of the linking dihydropyran moiety. For this, the lithium enolate of ester (±)-**9** was added to aldehyde (*R*)-**10** to generate two sets of chromatographically separable diastereomers **20** and **21** (Scheme 4). Each set contained both (8*R*,9*R*,10*S*)- and (8*S*,9*S*,10*R*)-dehydrodecalin cores, vide infra, and presumably (13,14)-*syn* and (13,14)-*anti* aldol-type products, respectively. The latter supposition was inconsequential as the C13 and C14 stereogenic centers were subsequently eliminated. After cleavage of the C16 silyl ethers the sets of (8*S*,16*R*)-(**22** + **24**) and (8*R*,16*R*)-(**23** +

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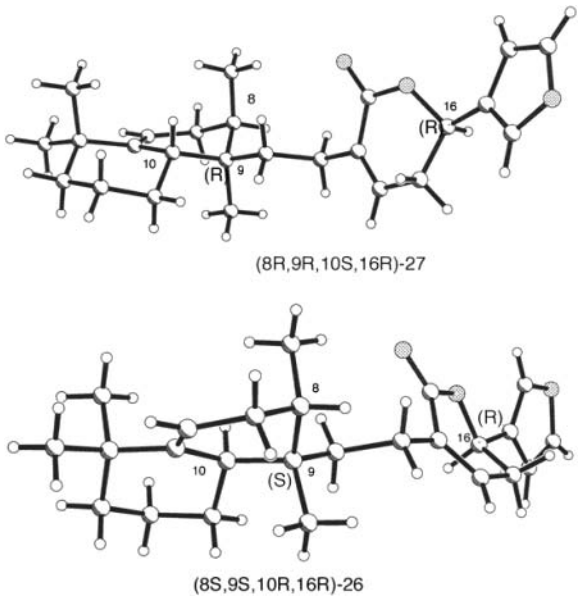

Figure 2. X-ray structures of lactones **26** and **27**.[20]

25) diastereomers were readily separated. Using the isolated diastereomers, dihydropyran ring formation was initiated by ester saponification followed by lactonization and C14 hydroxyl acetylation using acetic anhydride, after De Rosa et al.[6b] Exposure of the β-acetoxy-lactones to DBU-induced β-elimination across the C13,14 position to generate α,β-unsaturated lactones (8*S*,9*S*,10*R*,16*R*)-**26** and (8*R*,9*R*,10*S*,16*R*)-**27**. At this critical stage of the total synthesis and stereochemical definition effort, the stereochemistry of each lactone, **26** and **27**, was firmly established by X-ray crystallography.[20] The assigned absolute configurations of **26** and **27** derive from the asymmetric allylation leading to (*R*)-**10**.[12]

(20) Analyses by N. R. Brooks, University of Minnesota, Department of Chemistry, X-Ray Crystallographic Laboratory, Young, V. G., Jr. Director. CIF files (01348) are available as Supporting Information.

Furans **26** and **27** were separately advanced to (8*S*,9*S*,-10*R*,16*R*)-**4** and (8*R*,9*R*,10*S*,16*R*)-**4** as indicated in Scheme 4 for compound **26**. This involved reduction of the C24 lactone carbonyl to the corresponding lactol followed by deoxygenation[21] to form the dihydropyran. Final regioselective oxidation of the furan moiety was accomplished using singlet oxygen according to Faulkner.[11] As noted previously, the C25 hemiacetal center of **4** exists as a readily isomerizable mixture of epimers.[5]

Synthetic (8*S*,9*S*,10*R*,16*R*)-**4** ($[\alpha]_D$ −120° (*c* 0.01, $CHCl_3$)) obtained from **26** uniquely matched cacospongionolide F isolated from *Fasciospongia cavernosa*.[22] Thus, the original assignment of relative and absolute configuration of **4**[5] has been corroborated via unambiguous total synthesis. The relative and absolute configurations of cacospongionolide **4** determined here via a total synthesis that is supported by X-ray crystallography of key intermediate **26** match those of **1**,[9] 25-deoxy-**2**,[10] and **2**.[3] In addition to supporting a common stereochemical relationship between the decalin core and oxacycle domains among the cacospongionolide natural products, this work represents a convergent and stereochemically flexible entry that is amenable to further synthetic diversification of this biomedically promising chemotype.

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Supporting Information Available: Preparation and characterization data for **15**−**19**, **9**, **20**−**23**, **26**, **27**, **29**, and (8*S*,9*S*,10*R*,16*R*)-**4** and CIF files for **26** and **27**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) The ^{1}H NMR, $[\alpha]_D$, HRMS, IR, chromatographic, and UV data of synthetic (8*S*,9*S*,10*R*,16*R*)-**4** matched those of cacospongionolide F that was isolated from *Fasciospongia cavernosa* and generously provided by Prof. De Rosa, S. See Supporting Information.