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Short, Enantioselective Total Synthesis of Chatancin**

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In memory of Carlos F. Barbas III

Abstract: *An enantioselective total synthesis of the polycyclic diterpene (+)-chatancin, a potent PAF antagonist, is reported. Proceeding in seven steps from dihydrofarnesal, this synthetic route was designed to circumvent macrocyclization-based strategies to complex, cyclized cembranoids. The described synthesis requires only six chromatographic purifications, is high yielding, and avoids protecting-group manipulations. An X-ray crystal structure of this fragile marine natural product was obtained.*

Marine corals produce a rich array of structurally diverse natural products with intriguing biological profiles.[1] The *Sarcophyton* species in particular has provided chemists with an abundance of diterpenes, including many interesting architectures of cembrane biosynthetic origin.[2] In a search for naturally occurring antagonists of platelet-activating factor (PAF), Sato and co-worker isolated the structurally unique diterpene chatancin (**1**) from a soft coral (*Sarcophyton* sp.) off the coast of Okinawa, Japan (Figure 1 a).[3] PAF is a small-molecule phospholipid mediator of numerous biological processes including platelet aggregation, smooth muscle contraction, and hypotension.[4] Altered levels of PAF have been implicated in numerous diseases, including those of the respiratory and cardiovascular systems.[5] Chatancin inhibits both PAF-induced platelet aggregation ($IC_{50} = 2.2\ \mu M$) and PAF receptor binding ($IC_{50} = 0.32\ \mu M$) but has no effect on platelet aggregation induced by arachidonic acid, adenosine diphosphate, or collagen.[3] Structurally, chatancin possesses a complex carbon skeleton featuring two *cis*-decalin motifs folded into a unique polycyclic arrangement by virtue of a hemiketal bridge. This locking element is crucial for eliciting its biological effects.[3] Chatancin bears striking structural resemblance to the diterpene sarcophytin (**2**), isolated from a geographically far-removed *Sarcophyton* species.[6]

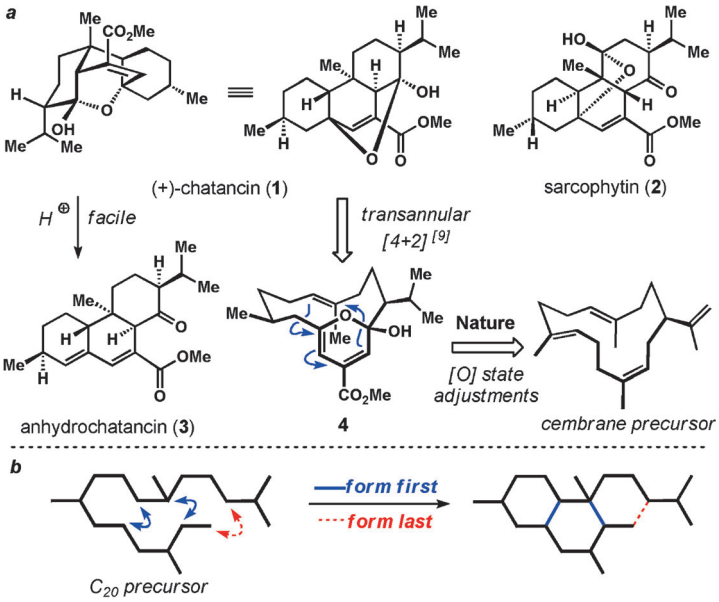

Figure 1. a) Chatancin (**1**): related diterpene **2**, chemical fragility, and postulated biosynthetic origins. b) Abiotic synthetic strategy.

The compact structure of **1**, containing seven stereocenters (six of which are contiguous), has proven to be a formidable synthetic challenge that is further exacerbated by its extreme acid sensitivity; it rapidly dehydrates to anhydrochatancin (**3**) under even mildly acidic conditions. Gossinger and co-workers reported the first synthesis of (±)-**1** in 33 chemical steps from thymoquinone (0.7% overall yield),[7] and in 2003, after significant chemical experimentation,[8] the group of Deslongchamps reported a fundamentally disparate synthetic strategy to (+)-**1** (23 steps from *cis*-2-butene-1,4-diol).[9] Guided by the biosynthetic hypothesis shown (Figure 1 a), chatancin was postulated to be of cembrane biosynthetic origins and its complex polycyclic skeleton the result of a transannular Diels–Alder cycloaddition (TADA) of pyranophane precursor **4**. This hypothesis evolved from earlier attempts at eliciting a TADA reaction of a furanocembranoid-type precursor followed by ring shift; the latter reaction could not be successfully executed in a flask owing to the facile conversion of **1** to **3**.[8e] While the conditions employed for the conversion of **4** to **1** are not compatible with a cellular setting (temperatures $>100\,^{\circ}C$), this work did provide evidence for the possible intermediacy of pericyclic processes in the biogenesis of **1**.[10] While this

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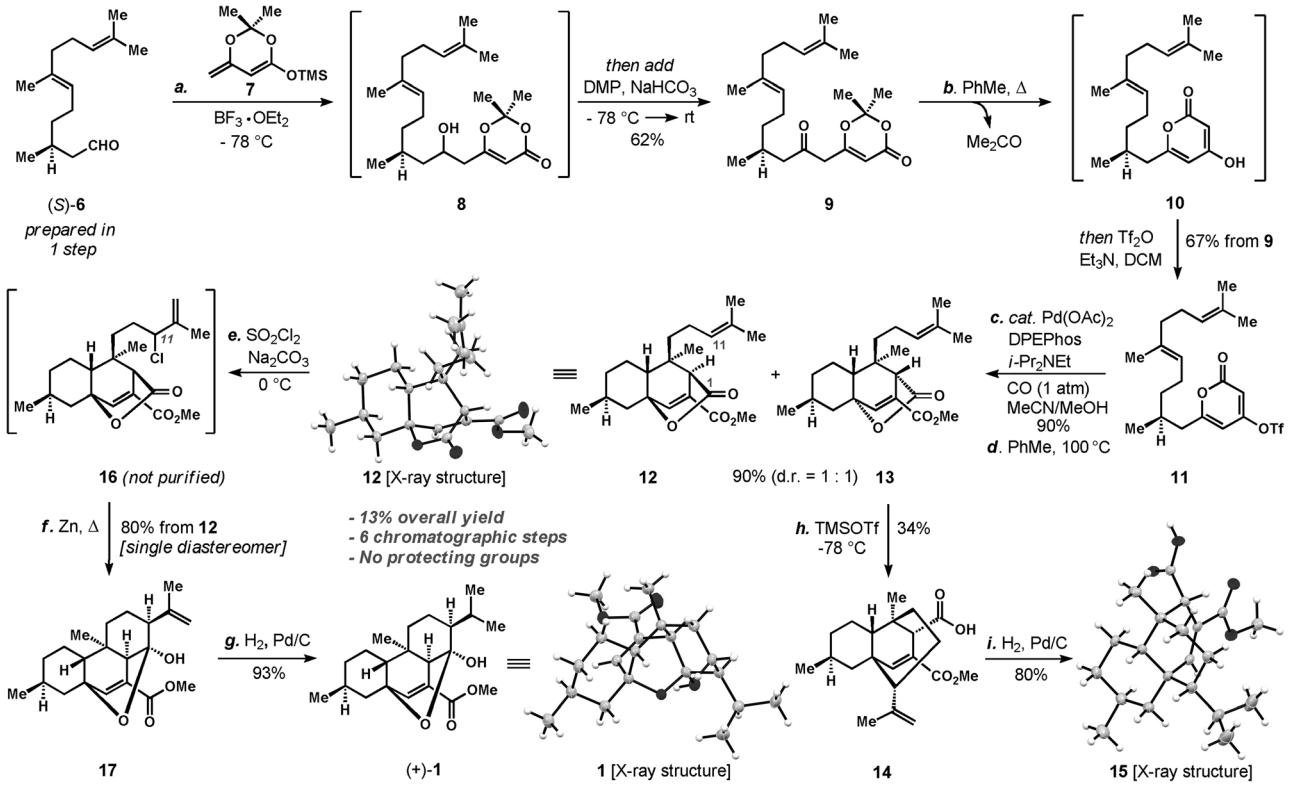
synthesis certainly provided invaluable biosynthetic insight, many steps were required to craft the stereodefined, 14-membered-ring precursor. Historically, numerous cembrane syntheses devote significant effort to linear precursor assembly and macrocycle closure.[11,12] This is at odds with the synthetic strategy employed by nature to construct such terpenes wherein large rings are made in the inaugural step and subsequently functionalized. Herein we describe a non-macrocyclization-based synthetic route to this complex, transannularly cyclized cembranoid, instead relying on the alternative bond-forming orchestration shown (Figure 1b). By using this strategy, a highly concise and protecting-group-free route to this fascinating bioactive substance has been realized.

Our synthetic studies commenced with the Lewis acid mediated addition of silyl ketene acetal **7** to (*S*)-dihydrofarnesal **6**, affording ketone **9** after in situ oxidation of the intermediate alcohol **8** (Scheme 1). Both **6** and **7** are available in one step from commercial materials and this transformation could be performed reliably on a multigram scale.[13] Slow addition of a solution of **9** to refluxing toluene very cleanly elicited thermal acetone extrusion with concomitant cyclization to hydroxypyrone **10**, conditions originally reported by Sato et al.[14,15] The intermediate hydroxypyrone was triflated (Tf_2O, Et_3N), providing vinyl triflate **11** after column chromatography (67% yield from **9**). Attachment of the requisite methyl ester initially proved challenging when standard Pd-catalyzed methoxycarbonylation conditions ($Pd(OAc)_2/PPh_3$, CO, MeOH) were employed and only trace amounts of product were obtained along with substantial quantities of hydroxypyrone **10**. Ultimately it was discovered that the catalyst system reported by Fürstner and co-workers ($Pd(OAc)_2$/DPEPhos), utilized for similar electron-deficient substrates, was exceptionally active in this context, affording near quantitative yields of product (90–95%).[16] Notably this transformation was robust and could be performed on a gram scale with no drop in yield.

With four-step access to an intermediate containing all of the requisite carbons of **1**, we were in a position to test the first key C–C bond-forming reaction, a pyrone/alkene cycloaddition;[17,18] elegant synthetic work directed toward the transtaganolide and basiliolide diterpenes served as inspiration.[19] Ultimately it was discovered that heating a toluene solution of the methoxycarbonylated pyrone for 4 days at 100 °C smoothly elicited a [4+2] cycloaddition in high yield (90%) and without the need for high dilution. This process forges four stereocenters in a single operation (Scheme 1). Equimolar amounts of diastereomers **12** and **13** were formed in



Scheme 1. Enantioselective total synthesis of (+)-chatancin (**1**). Reagents and conditions: a) **6** (1.0 equiv), **7** (1.1 equiv), $BF_3{\cdot}OEt_2$ (1.5 equiv), CH_2Cl_2, −78 °C, 1 h, then addition of DMP (3.0 equiv), $NaHCO_3$ (6.0 equiv), −78 °C→rt, 9 h, 62%; b) **9** (1.0 equiv) added slowly to PhMe, 120 °C→rt, 1.5 h, then Tf_2O (1.0 equiv), Et_3N (2.5 equiv), DCM, −78 °C→rt, 67% from **9**; c) **11** (1.0 equiv), $Pd(OAc)_2$ (10 mol%), DPEPhos (10 mol%), *i*Pr_2NEt (2.0 equiv), CO (1 atm), 4.2:1 MeCN/MeOH (v/v), rt, 8 h, 90%; d) PhMe (0.05 M), 100 °C, 4 d, 90% (**12**/**13** = 1:1); e) **12** (1.0 equiv), SO_2Cl_2 (1.1 equiv), Na_2CO_3 (4.0 equiv), DCM, 0 °C, 30 min; Zn (40.0 equiv), THF, 65 °C, 24 h, 80% from **12**; g) **17** (1.0 equiv), 5% Pd/C (10 mol%), H_2 (1 atm), MeOH, 8 h, 93%; h) **13** (1.0 equiv), TMSOTf (2.0 equiv), DCM, −78 °C, 1 h, 34%; i) **14** (1.0 equiv), 5% Pd/C (10 mol%), H_2 (1 atm), MeOH, 8 h, 80%. DMP = Dess–Martin periodinane, Tf = trifluoromethanesulfate, DPEPhos = bis-[2-(diphenylphosphino)-phenyl]ether, DCM = dichloromethane.

this process; the relative configuration of the former was confirmed by X-ray crystallography (Scheme 1). Four diastereomers are possible in this cycloaddition reaction, but only two are observed. Bicycles **12** and **13** appear to arise from favorable chairlike transition states as opposed to the alternative, boatlike structures shown in Figure 2. Owing to

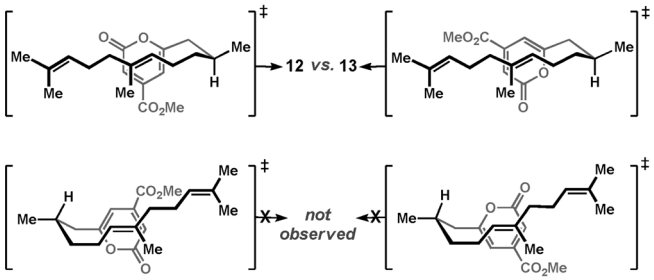
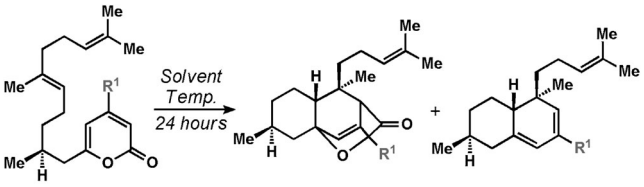


Figure 2. Analysis of Diels–Alder transition states.

a lack of allylic strain, which has benefitted related intramolecular pyrone/alkene cycloadditions,[19] the pyrone group in this system does not have a biasing element favoring a given pyrone rotamer.[20] The gram-scale synthesis of **12** only became possible after significant exploration of a number of individual cycloaddition reactions, substrates, and conditions (Table 1). Notably, hydroxypyrone **10** could not be coaxed into a productive cycloaddition under either thermal or high-pressure conditions (entry 1) and pyrone triflate **11** afforded only decarboxylated diene **20** when heated (entry 2).[17] Decarboxylation was also observed for the successful ester substrate, but could be minimized by judicious choice of solvent and temperature. In toluene at 80 °C, the initial [4+2] reaction did not proceed at an appreciable rate, and at 120 °C, substantial decarboxylation was observed. Polar solvents also greatly facilitated this process (entries 3–6).[17] The reaction at 100 °C in toluene, although requiring several days, was optimal for material throughput; multigram quantities of **12** have been easily procured by this simple sequence.

Table 1: Thermal cycloaddition studies.[a,b]



18 **19** **20**

Entry	R^1	Solvent	*T* [°C]	Ratio **18**/**19**/**20**[b]
1	OH	toluene	165	1:0:0
2	OTf	toluene	100	1:0:0.15
3	CO_2Me	heptane	100	1:0.9:0.02
4	CO_2Me	$PhCF_3$	100	1:1.4:0.07
5	CO_2Me	MeCN	100	1:2.4:0.4
6	CO_2Me	DMF	100	1:3.1:0.7

[a] Conditions: **18** (0.03 M in solvent). [b] Ratios determined by ^{1}H NMR analysis. Cycloadducts **19** were formed as an approximate 1:1 mixture of diastereomers.

With tricyclic lactone **12** secured all that remained to construct the chatancin cembrane ring system was the forging of the C1–C11 bond (Scheme 1). This transformation turned out to be surprisingly challenging owing to the lack of reactivity at C-1 and the presence of a reactive conjugated ester. Despite their very close proximity, the lactone carbonyl in **12** (C-1) was completely inert towards Lewis acid mediated addition of the electron-rich alkene (C-11). Interestingly, however, undesired diastereomer **13** underwent an unusual, and facile, Prins-type opening of the lactone ring affording tricyclic acid **14** when treated with TMSOTf (Scheme 1). X-ray crystallographic analysis of the hydrogenation product of **14** confirmed its interesting structure (see **15**, Scheme 1). While **12** could be chemo- and regioselectively hydroborated (Et_2BH, 0 °C) at the desired, internal position (C-11), the highly hindered borane intermediate resisted efficient transmetalation with $Zn(Et)_2$ or $Zn(iPr)_2$.[21]

Ultimately, a practical and high-yielding solution for the conversion of **12** to chatancin was devised. Mild allylic chlorination (SO_2Cl_2, Na_2CO_3, 0 °C)[22] of the electron-rich alkene produced secondary chloride **16** as a single, unassigned diastereomer, and without purification, this compound was heated with an excess of freshly activated Zn dust. These conditions forged the C1–C11 bond in excellent yield (80 % from **12**). Gratifyingly this transformation produced a single isomer of **17**, setting both newly formed stereocenters correctly. Hydrogenation of **17** (H_2, Pd/C) afforded (+)-chatancin in high yield (93 %).[23] After a number of attempts, an X-ray crystal structure of this sensitive natural product could be obtained.

In summary, a highly concise synthetic route to the complex PAF antagonist (+)-chatancin has been accomplished via a simple, seven-step sequence (13 % overall yield) that avoids protecting-group manipulations[24] and appears to be suitable for straightforward construction of analogues. Moreover, we anticipate that adaptations to the general strategy described herein will facilitate the synthesis of other complex, cembrane-derived natural products with interesting biological activity.

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