Published in final edited form as:
Angew Chem Int Ed Engl. 2015 January 19; 54(4): 1223–1226. doi:10.1002/anie.201410443.

Short, Enantioselective Total Synthesis of Chatancin**

Dr. Yu-Ming Zhao and **Prof. Dr. Thomas J. Maimone**
Thomas J. Maimone: maimone@berkeley.edu

Abstract

An enantioselective total synthesis of the polycyclic diterpene chatancin (**1**), 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 chemistry. An X-ray crystal structure of this fragile marine natural product was obtained.

Keywords

terpene; biomimetic synthesis; natural products; cycloaddition reaction; asymmetric synthesis

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 1a).[3] PAF is a small molecule phospholipid mediator of numerous biological processes including platelet aggregation, smooth muscle contraction, and hypotension, among others.[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 μM) and PAF receptor binding (IC_{50} = 0.32 μM) 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]

**This work was supported by generous start-up funds from UC-Berkeley, The UC-Berkeley Hellman Fellows Fund, and The University of California Cancer Research Coordinating Committee (CRCC). We thank Dr. Chris Canlas for NMR spectroscopic assistance. Dr. Antonio DiPasquale is acknowleged for X-ray crystallographic analysis and support from NIH Shared Instrument Grant (S10-RR027172). Takasago Co. is greatfully acknowledged for providing a generous sample of *l*-dihydrofarnesol.

Correspondence to: Thomas J. Maimone, maimone@berkeley.edu.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201xxxxxx

The compact structure of **1**, containing 7 stereocenters (6 of which are contiguous), has proven to be a formidable synthetic challenge that is further exacerbated by its extreme acid sensitivity, rapidly dehydrating to anhydrochatancin (**3**) under even mildly acidic conditions. Gossinger and co-workers reported the first synthetic solution to (±)-**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 1a), 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 of which 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 °C), this work did provide evidence for the possible intermediacy of pericyclic processes in the biogenesis of **1**.[10] While certainly providing 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 described 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 1-step from commercial materials and this transformation could be performed reliably on a multi-gram 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.[14,15] The intermediate hydroxypyrone could be triflated (Tf_2O, Et_3N) yielding vinyl triflate **11** after column chromatography (67% from **9**). Attachment of the requisite methyl ester initially proved challenging employing standard Pd-catalyzed methoxycarbonylation conditions ($Pd(OAc)_2/PPh_3$, CO, MeOH), affording only trace amounts of product 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 4-step access to 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 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 favourable chair-like transition states as opposed to the alternative, boat-like structures shown (Figure 2). Owing to 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 favouring a given pyrone rotamer.[20] The gram- scale synthesis of **12** only became possible after significantly exploring 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 careful choice of solvent and temperature. In toluene at 80 °C, the initial [4+2] reaction did not proceed at an appreciably 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; multiple grams of **12** have been easily procured via this simple sequence.

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 or 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 off the lactone ring affording tricyclic acid **14** when treated with TMSOTf (Scheme 1). The structure 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 transmetallation with $Zn(Et)_2$ or $Zn(i\text{-}Pr)_2$.[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, 7-step sequence (13% overall yield) that avoids protecting group chemistry[24] and appears to be suitable for straightforward analog

construction. 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. This work will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. a) Radjasa OK, Vaske YM, Navarro G, Vervoort HC, Tenney K, Linington RG, Crews P. Bioorg Med Chem Lett. 2011; 19:6658.b) Blunt JW, Copp BR, Keyzers RA, Munro MHG, Prinsep MR. Nat Prod Rep. 2014; 31:160. [PubMed: 24389707] c) Rodríguez AD. Tetrahedron. 1995; 51:4571.d) Leal MG, Puga J, Serôdio J, Gomes NCM, Calado R. PloS ONE. 2012; 7:e30580. [PubMed: 22276216]
2. a) Aratake S, Tomura T, Saitoh S, Yokokura R, Kawanishi Y, Shinjo R, Reimer JD, Tanaka J, Maekawa H. PloS ONE. 2012; 7:e30410. [PubMed: 22272344] b) Coll JC. Chem Rev. 1992; 92:613.c) Liang LF, Guo YW. Chem Biodivers. 2013; 10:2161. [PubMed: 24327439] d) Yang B, Zhou XF, Lin XP, Liu J, Peng Y, Yang XW, Liu Y. Curr Org Chem. 2012; 16:1512.e) Wahlberg, I.; Eklund, A-M. Cyclized Cembranoids of Natural Occurrence. In: Herz, W.; Kirby, GW.; Moore, RE.; Steglich, W.; Tamm, Ch, editors. Prog Chem Nat Prod. Springer Verlag; 1992. p. 1
3. Sugano M, Shindo T, Sato A, Iijima Y, Oshima T, Kuwano H, Hata T. J Org Chem. 1990; 55:5803.
4. Prescott SM, Zimmerman GA, Stafforini DM, McIntyre TM. Annu Rev Biochem. 2000; 69:419. [PubMed: 10966465]
5. For a recent review on naturally occurring inhibitors of PAF, see: Singh P, Singh IN, Mondal SC, Singh L, Garg VK. Fitoterapia. 2013; 84:180. [PubMed: 23160091]
6. Anjaneyulu ASR, Venugopal MJRV, Sarada P, Rao GV, Clardy J, Lobkovsky E. Tetrahedron Lett. 1998; 39:135.
7. Aigner J, Gössinger E, Kählig H, Menz G, Pflugseder K. Angew Chem Int Ed. 1998; 37:2226.
8. a) Toró A, Wang Y, Deslongchamps P. Tetrahedron Lett. 1999; 40:2765.b) Toró A, Wang Y, Drouin M, Deslongchamps P. Tetrahedron Lett. 1999; 40:2769.c) Toró A, L'Heureux A, Deslongchamps P. Org Lett. 2000; 2:2737. [PubMed: 10964353] d) Marsault E, Toró A, Nowak P, Deslongchamps P. Tetrahedron. 2001; 57:4243.e) Toró A, Deslongchamps P. J Org Chem. 2003; 68:6847. [PubMed: 12946121]
9. Soucy P, L'Heureux A, Toró A, Deslongchamps P. J Org Chem. 2003; 68:9983. [PubMed: 14682691]
10. The biosynthesis of numerous cembrane derivatives are believed to involve pericyclic reactions, see: Roethle PA, Trauner D. Nat Prod Rep. 2008; 25:298. [PubMed: 18389139] Li Y, Pattenden G. Nat Prod Rep. 2011; 28:1269. [PubMed: 21637894]
11. Tius MA. Chem Rev. 1988; 88:719.
12. Notable exceptions exist. For recent concise synthetic routes toward complex cembranoids, see: Roethle PA, Trauner D. Org Lett. 2006; 8:345. [PubMed: 16408911] Huang Q, Rawal VH. Org Lett. 2006; 8:543. [PubMed: 16435880] Tang B, Bray CD, Pattenden G. Tetrahedron Lett. 2006; 47:6401.Roethle PA, Hernandez PT, Trauner D. Org Lett. 2006; 8:5901. [PubMed: 17134301]
13. a) Fettes A, Carreira EM. J Org Chem. 2003; 68:9274. [PubMed: 14629147] b) Mayer S, List B. Angew Chem Int Ed. 2006; 45:4193. (S)-**6** can also be prepared in 1-step from l-dihydrofarnesol which is commercially available.
14. Sato M, Sakaki JI, Sugita Y, Yasuda S, Sakoda H, Kaneko C. Tetrahedron. 1991; 47:5689.
15. For a recent application of this chemistry in total synthesis, see: Rentsch, M Kalesse. Angew Chem Int Ed. 2012; 51:11381.
16. Kondoh A, Arlt A, Gabor B, Fürstner A. Chem Eur J. 2013; 19:7731. [PubMed: 23589394]

17. a) Afarinkia K, Vinader V, Nelson TD, Posner G. Tetrahedron. 1992; 48:9111.b) Afarinkia K, Bearpark MJ, Ndibwami A. J Org Chem. 2005; 70:1122. [PubMed: 15704944] c) Matsumoto K, Hamana H, Iida H. Helv Chim Acta. 2005; 88:2033.

18. For selected, recent examples of pyrone cycloaddition reactions in total synthesis, see: Baran PS, Burns NZ. J Am Chem Soc. 2006; 128:3908. [PubMed: 16551088] Shin IJ, Choi ES, Cho CG. Angew Chem Int Ed. 2007; 46:2303.Jung YJ, Kang HU, Cho HK, Cho CG. Org Lett. 2011; 13:5890. [PubMed: 21985106] Zhao P, Beaudry CM. Org Lett. 2013; 15:402. [PubMed: 23301524] Smith MW, Snyder SA. J Am Chem Soc. 2013; 135:12964. [PubMed: 23964983] Zhao P, Beaudry CM. Angew Chem Int Ed. 2014; 53:10500.

19. a) Nelson HM, Stoltz BM. Org Lett. 2008; 10:25. [PubMed: 18062693] b) Kozytska MV, Dudley GB. Tetrahedron Lett. 2008; 49:2899.c) Zhou X, Wu W, Liu X, Lee CS. Org Lett. 2008; 10:5525. [PubMed: 19053740] d) Larsson R, Sterner O, Johansson M. Org Lett. 2009; 11:657. [PubMed: 19140719] e) Nelson HM, Stoltz BM. Tetrahedron Lett. 2009; 50:1699.f) Nelson HM, Murakami K, Virgil SC, Stoltz BM. Angew Chem Int Ed. 2011; 50:3688.g) Nelson HM, Gordon JR, Virgil SC, Stoltz BM. Angew Chem Int Ed. 2013; 52:6699.h) Larsson R, Scheeren HW, Aben RWM, Johansson M, Sterner O. Eur J Org Chem. 2013:6955.i) Min L, Zhang Y, Liang X, Huang J, Bao W, Lee CS. Angew Chem Int Ed. 2014; 53:11294.j) Gordon JR, Nelson HM, Virgil SC, Stoltz BM. J Org Chem. 2014; 79:9740. [PubMed: 25244187]

20. Common Lewis acids examined (e.g. BF_3•OEt_2, Et_2AlCl, $AlCl_3$, BINOL) either exerted no influence on the diastereoselectivity of the cycloaddition reaction or resulted in decomposition of the pyrone substrate.

21. Hupe E, Calaza MI, Knochel P. Chem Eur J. 2003; 9:2789. [PubMed: 12866543]

22. Li W, Li Y, Li Y. Org Prep Proceed Int. 1996; 28:83.

23. Synthetic **1** exhibited $[\alpha]_D$ = +10.7 ($CHCl_3$, *c* = 0.01), natural **1** displays $[\alpha]_D$ = +10.5 ($CHCl_3$, *c* = 1.0)[3]

24. a) Young IS, Baran PS. Nature Chem. 2009; 1:193. [PubMed: 21378848] b) Gaich T, Baran PS. J Org Chem. 2010; 75:4657. [PubMed: 20540516] c) Saicic RN. Tetrahedron. 2014; 70:8183.

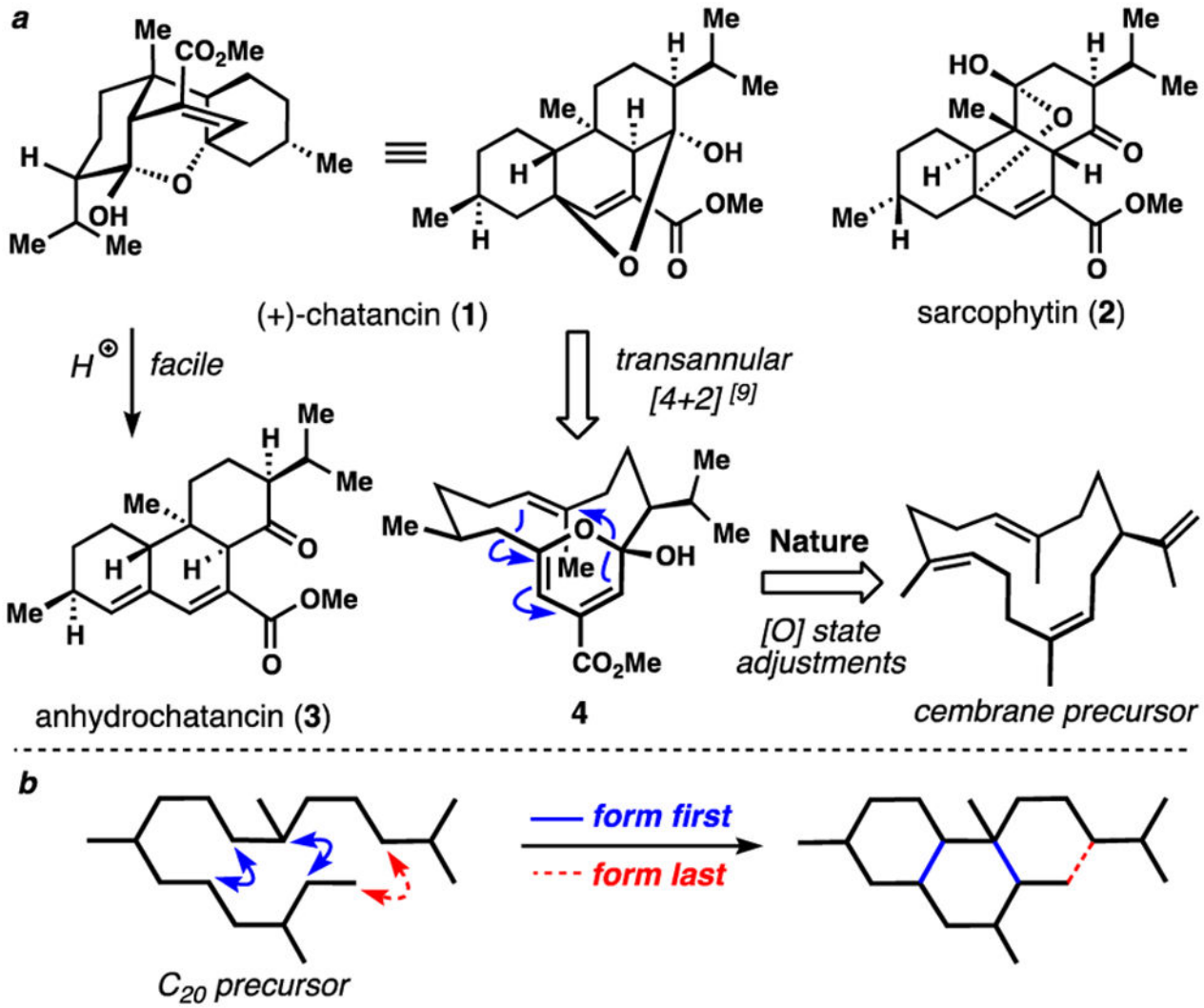


Figure 1.

a) Chatancin (**1**): related diterpene **2**, chemical fragility, and postulated biosynthetic origins.

b) Abiotic synthetic strategy.

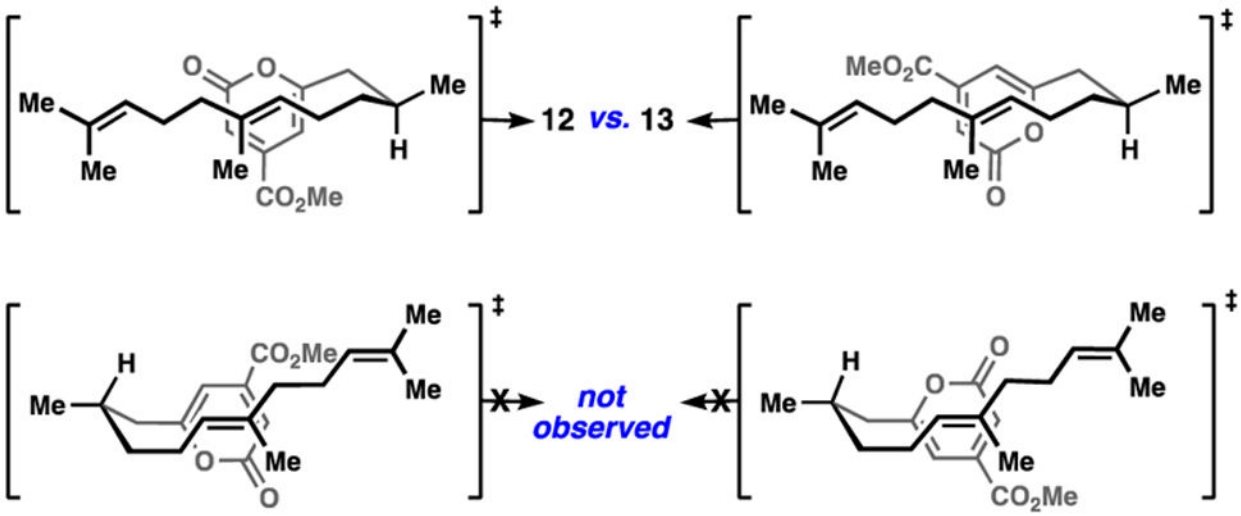
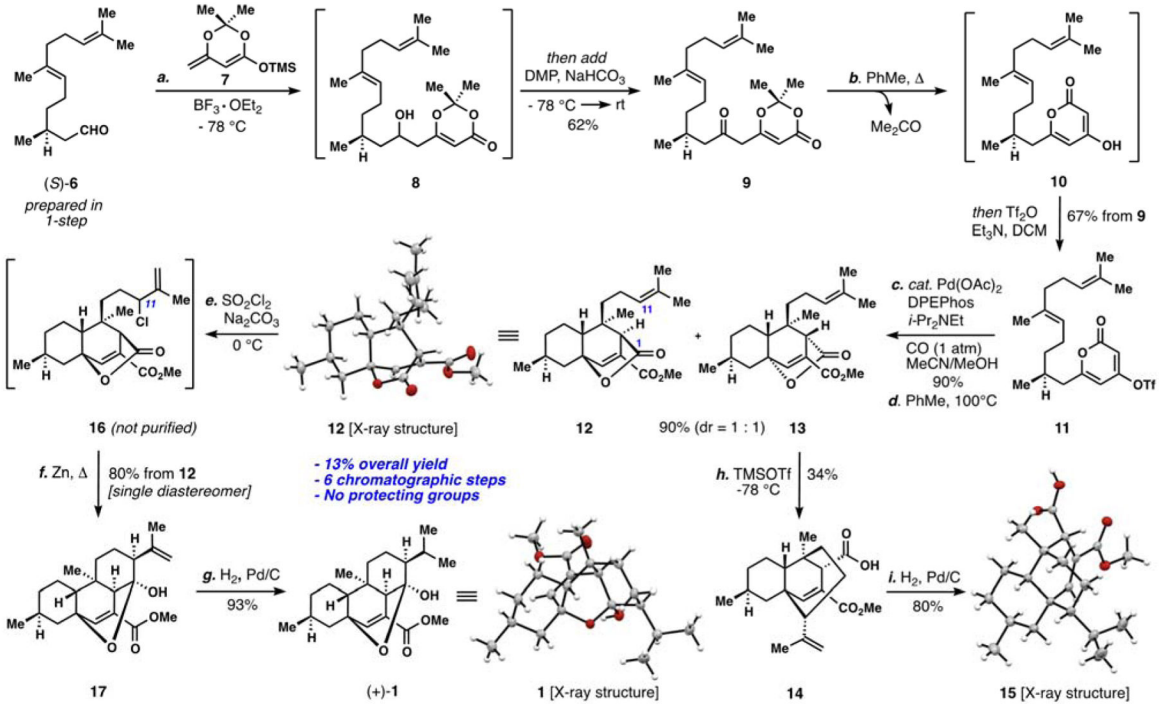


Figure 2.
Diels-Alder transition state analysis.

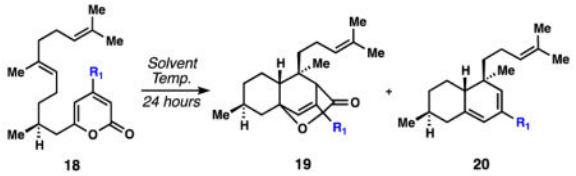


Scheme 1.

Enantioselective total synthesis of (+)-chatancin (**1**). Reagents and Conditions: a) **6** (1.0 equiv), **7** (1.1 equiv), BF_3•OEt_2 (1.5 equiv), CH_2Cl_2, −78 °C, 1 h, *then add* 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.

Table 1

Thermal cycloaddition studies.[a,b]



18 19 20

Entry	R_1	Solvent	Temp. (°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 ^1H NMR. Cycloadducts (**19**) were formed as an approximate 1:1 mixture of diastereomers.