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Furanophane Transannular Diels−Alder Approach to (+)-Chatancin: An Asymmetric Total Synthesis of (+)-Anhydrochatancin

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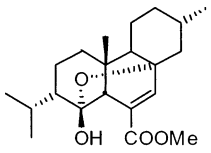
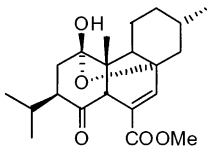
(+)-Anhydrochatancin was synthesized while attempting an enantioselective total synthesis of (+)-chatancin. The presented route constitutes the furanophane approach, one of the two ways of proposed biosynthesis which may involve transannular Diels−Alder (TADA) reaction to link this diterpene biogenetically to the furanocembranoids. Highlights of the synthetic work include the assembly of chiral, acyclic, trisubstituted furan **28** via a coupling of aldehyde **10** and dilithiofuroic acid **11**, a macrocyclization to furanophane **29E** via ring-closing metathesis, a TADA reaction to reach tetracyclic intermediate **4**, and a hydride shift mediated oxygen transposition as a final rearrangement to the target. Unfortunately, the strongly acidic condition required for the last step allows only the isolation of anhydrochatancin **30** due to the acid sensitivity of chatancin **1**.

(+)-Chatancin (**1**)[1a] was isolated in 1990 from soft coral *Sarcophyton* sp. as a result of a screening program to identify new platelet activating factor (PAF) antagonists from marine origins (Chart 1). PAF has been associated with a variety of biological effects including platelet aggregation, smooth muscle contraction, hypotension, and vascular permeability. It is also implicated as a causative factor in septic shock, inflammatory, respiratory, and cardiovascular diseases. In 1998, a remarkably similar natural product, i.e., (+)-sarcophytin (**2**),[2] was isolated from yet another soft coral. These diterpenes share a *cis-anti-cis* (CAC)-dodecahydrophenanthrene framework with an almost identical functional pattern possessing seven stereogenic centers. Furthermore, both of the diterpenes contain a hemiketal bridge, although the size and the nature of their bridgeheads differ, the latter as a consequence of the extra oxidation in ring-A

CHART 1. Structures of (+)-Chatancin and (+)-Sarcophytin



(+)-chatancin (**1**)



(+)-sarcophytin[2b] (**2**)

of **2**. This resemblance further extends to their equatorial isopropyl groups. Such structural propinquities allude to a novel tetracyclic diterpene family. Aside from the important biological activity elicited by such tetracyclic diterpenes, their structural complexity spurred us to undertake the challenge of their total synthesis using the transannular Diels−Alder (TADA) reaction, which has been vigorously investigated in our laboratories[3a] and applied recently in two impressive total synthesis.[3b,c] A total synthesis of (±)-chatancin has been reported recently through a different strategy.[1b]

Sarcophyton soft corals are reported to produce a variety of diterpenoids including furanocembranoids and other oxygenated cembranoids.[4] Upon close scrutiny of

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(1) For isolation studies, see: (a) Sugano, M.; Shindo, T.; Sato, A.; Iijima, Y.; Oshima, T.; Kuwano, H.; Hata, T. *J. Org. Chem.* **1990**, *55*, 5803−5805. For an exciting racemic total synthesis of chatancin, see: (b) Aigner, J.; Gössinger, E.; Kählig, H.; Menz, T.; Pflugseder, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 2226−2228.

(2) For isolation studies, see: (a) Anjaneyulu, A. S. R.; Venugopal, M. J. R. V.; Sarada, P.; Rao, G. V.; Clardy, J.; Lobkovsky, E. *Tetrahedron Lett.* **1998**, *39*, 135−138. (b) The absolute configuration of **2** has not been established. The enantiomer depicted is the opposite of that reported in ref 2a.

(3) (a) Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243−4260. (b) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773−775. (c) Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552−4553.

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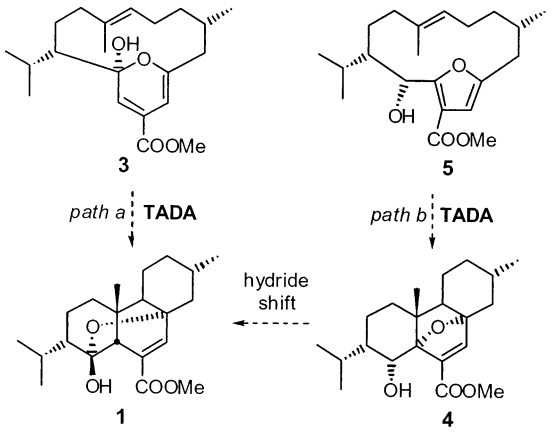
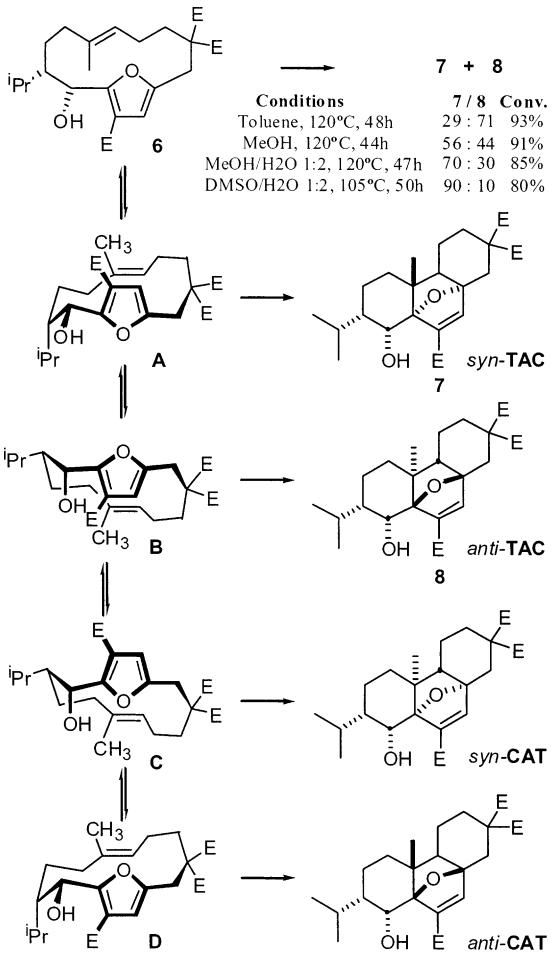
SCHEME 1



the unusual CAC ring systems of **1** and **2**, it is reasonable to raise the possibility of a transannular Diels−Alder (TADA) reaction in the biogenesis of such species. In principle, two distinct biosynthetic TADA routes to chatancin may be envisaged. The first route would be directly from pyranophane **3**, a component of a pH dependent equilibrium mixture of macrocyclic diketones, pyrylium ions, and pseudobases (Scheme 1, path a).[5] Alternatively, in a hydride shift mediated oxygen transposition on tetracycle **4**, a TADA product of furanophane **5** would constitute the second possible route (Scheme 1, path b).[6] Earlier, during the course of the asymmetric total synthesis of diterpene (+)-maritimol, we demonstrated the use of a TADA substrate to effect stereofacial and diastereocontrol, which was induced by a remote nitrile moiety.[7] In this article, we present the results of our investigation of path b, wherein a densely functionalized furan (diene) is employed in a reverse electron demand reaction to further illustrate the synthetic potentials of TADA chemistry.

Applications of furans in intramolecular Diels−Alder chemistry are well documented.[8] Albeit with discordant results, a few examples of TADA reaction has been reported in the literature. In such reported cases, either a quantitative formation of a [5.6.5] tricycle,[9a] or a complete cycloreversion of a [7.6.7] tricycle has been observed. (The latter product was obtained only when forcing conditions, i.e., high pressure, had been employed.[9b]) Our earlier model studies had also revealed that TADA reactions should be reversible at higher elevated temperatures.[6b] More importantly, these studies also indicated that high levels of stereofacial control could be achieved with model furanophane **6** (Scheme 2). Thus, of the four theoretical TADA products of a *trans-trans-trans* (TTT) triene,[2] only one pair of TAC [6.6.6] tricycles, i.e., **7** and

SCHEME 2[a]



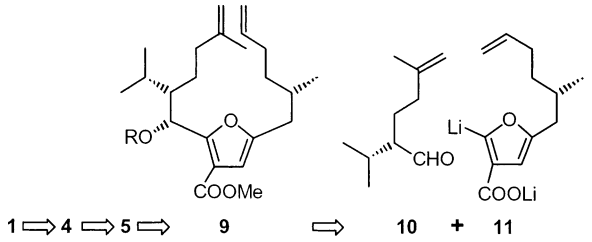
[a] Syn and anti denote the relative stereochemistry of the bridge and the hydroxy oxygens. E = COOMe.

8, were formed in relative proportions which was highly dependent on the H-bonding character of the solvent system used. These observations can be rationalized by examining the four conformers (**A**−**D**) that lead to the transition states (TS) in the TADA reaction. Accordingly, the absence of the CAT products can be attributed to the steric repulsion between the furan oxygen and the dienophile methyl group. On the other hand, the origin of solvent dependence can be justified as being a result of an internal H-bond between the hydroxy and the carbomethoxy moiety. It either stabilizes the conformer leading to the *anti*-TAC product **8** in an aprotic medium or, upon its breakdown in water, the expected kinetic *syn*-TAC product **7** is formed.[6b] Additional examination also suggests that substitution of the geminal diester in **6** with an α-methyl group in **5** ought to favor the TADA reaction toward the formation of the desired *syn*-TAC product (**4**) due to the quasi-equatorial position of the α-methyl in conformer **A** over its quasi-axial position in conformer **B**.

As with almost every transannular process, the synthesis of the requisite macrocycle is a genuine challenge, a fact that was further adumbrated, in the case at hand, by model studies.[6b] We initially chose to address this problem by invoking Marshall's strategy.[10] In one of his pseudopterane syntheses, he had suggested that the

(4) Uchio, Y.; Nitta, M.; Nozaki, H.; Iwagawa, T.; Hase, T. *Chem. Lett.* **1983**, 1719−1720.
(5) Toró, A.; L'Heureux, A.; Deslongchamps, P. *Organic Lett.* **2000**, *2*, 2737−2740.
(6) (a) Toró, A.; Wang, Y.; Deslongchamps, P. *Tetrahedron Lett.* **1999**, *40*, 2765−2768. (b) Toró, A.; Wang, Y.; Drouin, M.; Deslongchamps, P. *Tetrahedron Lett.* **1999**, *40*, 2769−2772.
(7) Toró, A.; Nowak, P.; Deslongchamps, P. *J. Am. Chem. Soc.* **2000**, *122*, 4526−4527.
(8) For a recent review on furan Diels−Alder chemistry, see: Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, *53*, 14179−14233.
(9) (a) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1992**, *57*, 3387−3396. (b) Cattalini, M.; Cossu, S.; Fabris, F.; De Lucchi, O. *Synth. Commun.* **1996**, *26*, 637−647.

SCHEME 3

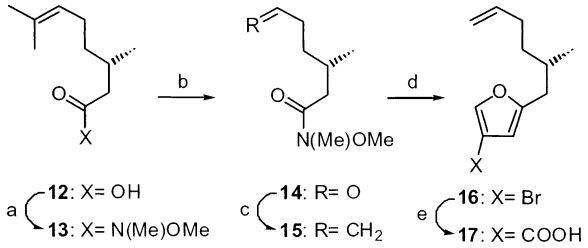


macrocyclization should precede furan formation so that the initial cyclization can proceed without undue ring strain and the aromatic resonance energy of the furan can help to overcome the inherent ring strain imposed during formation of the bridged furanocycle. Despite our concerted efforts, this macrocyclization strategy proved futile in the foregoing case.[11]

Ring-closing metathesis[12] (RCM) has been increasingly used to effect macrocyclizations, and we sought to explore this alternative method. We reasoned that the ease of assembly of the substrate diene for the RCM macrocyclization outweighs the potential problems associated with the lack of control over the (*E* vs *Z*) olefin stereochemistry. Accordingly, a retrosynthetic analysis of the furanophane approach leads to chiral diene **9** (Scheme 3), which in turn should be available as a coupling product of aldehyde **10** and dilithiofuroate **11**.[13] Actual synthesis of the furan synthon started with (*S*)-citronellic acid (**12**)[14] (Scheme 4). After formation of its Weinreb amide **13**, an ozonolysis followed by a Wittig olefination on intermediate aldehyde **14** replaced the terminal isopropenyl group to the desired methylene to afford enamide **15** (57%). Coupling with dilithio propargylate followed by HBr cyclization[15] afforded bromofuran **16** (63%). This was then converted into the furoic acid **17** (86%) by a typical lithiation–CO_2 quench sequence.

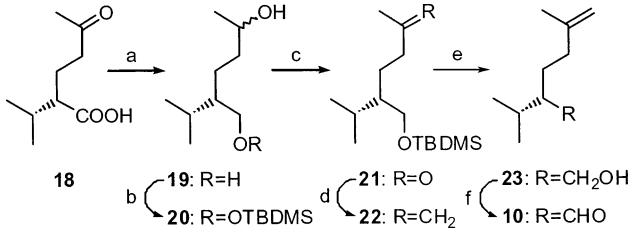
Synthesis of aldehyde **10** started with exhaustive borane reduction of ketoacid **18**[16] followed by selective monosilylation of diol **19** at the primary position (54%) (Scheme 5). Swern oxidation[17] of alcohol **20** (84%), Wittig olefination of ketone **21** (97%), terminal deprotection of

SCHEME 4[a]



[a] Reagents and conditions: (a) ^{i}BuOCOCl, Et_3N, CH_2Cl_2, 0 °C then MeNHOMe·HCl; (b) O_3, CH_2Cl_2, −80 °C then Me_2S; (c) $CH_2{=}PPh_3$, THF (57%); (d) LiC≡CCH_2OLi, THF/HMPA, −50 to +15 °C then HBr, PhH, 55 °C (63%); (e) BuLi, THF, −80 °C then CO_2 (86%).

SCHEME 5[a]



[a] Reagents and conditions: (a) BH_3, THF, −80 to +20 °C; (b) TBDMS-Cl, imidazole, CH_2Cl_2 (54%); (c) Swern [O] (84%); (d) $CH_2{=}PPh_3$, THF (97%); (e) Bu_4NF, THF, 0 °C (94%); (f) TPAP/NMO (83%).

silyl ether **22** (94%) and oxidation of alcohol **23** using tetrapropylammonium perruthenate (TPAP),[18] *N*-methylmorpholine *N*-oxide (NMO) concluded the synthesis (83%).

Coupling of aldehyde **10** with dilithiofuroate **11**,[13] generated in situ from furoic acid **17** was carried out as precedented[6a] (Scheme 6). The product was isolated again as a 2:1 isomeric mixture of methyl esters (96%) from which the major α-isomer[19] **24a** (61%) was separated by chromatography. Since our model studies showed that 11-*tert*-butyldimethylsilyloxy group inhibits TADA reaction even at 250 °C, this group was selected as hydroxy protection for the RCM studies. Use of the first generation Grubbs' catalyst **25a**[20a,21] merely resulted in an isomeric mixture of dimerized products even under high dilution. In contrast, second generation Grubbs' catalyst **25b**[20b,21] cyclized acyclic diene **9** (R = TBDMS) in an almost quantitative yield.[20,22] However, this compound was assigned the furanophane structure **27** having an olefin with the cis stereochemistry.[23]

(10) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1991**, *56*, 6264–6266.

(11) These attempts included Feist–Benary, Pall–Knorr, and radical cyclizations on terminal β-ketoesters, as well as McMurry or Nozaki–Kishi couplings on substrates derived from compound **20** in ref 5.

(12) For reviews on metathesis, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446–452. (b) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1833–1836. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036–2056. (d) Fürstner, A. *Top. Catal.* **1997**, *4*, 285–299. (e) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–188. (f) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (g) Ivin, K. J. *J. Mol. Catal. A.: Chem.* **1998**, *133*, 1–16. (h) Randall, M. L.; Snapper, M. L. *J. Mol. Catal A.: Chem.* **1998**, *133*, 29–40. (i) Phillips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75–89. (j) Truka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29. (k) Hoveyda, A. H.; Schrock, R. H. *Chem. Eur. J.* **2001**, *7*, 945–950. (l) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043.

(13) Knight, D. W.; Nott, A. P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1125–1131.

(14) Obtained from the commercially available (*l*)-citronellal: Rigby, J. H.; McGuire, T.; Senanayake, C.; Khemani, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3449–3457.

(15) Ley, S. V.; Norman, J.; Griffith, W. P.; Marshden, S. P. *Synthesis* **1994**, 639–666.

(16) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.

(17) Obrecht, D. *Helv. Chim. Acta* **1989**, *72*, 447–456.

(18) Obtained from (*S*)-(+)-piperitone, which is in turn derived from the commercially available (*l*)-menthone: (a) Dauben, W. G.; Thiessen, W. E.; Resnick, P. R. *J. Org. Chem.* **1965**, *35*, 1693–1698. (b) Hiroi, K.; Umemura, M. *Tetrahedron* **1993**, *49*, 1831–1840.

(19) ^{1}H NMR coupling constants and X-ray structural analysis data of our previously reported compounds (ref 6b) were used to identify the isomers.

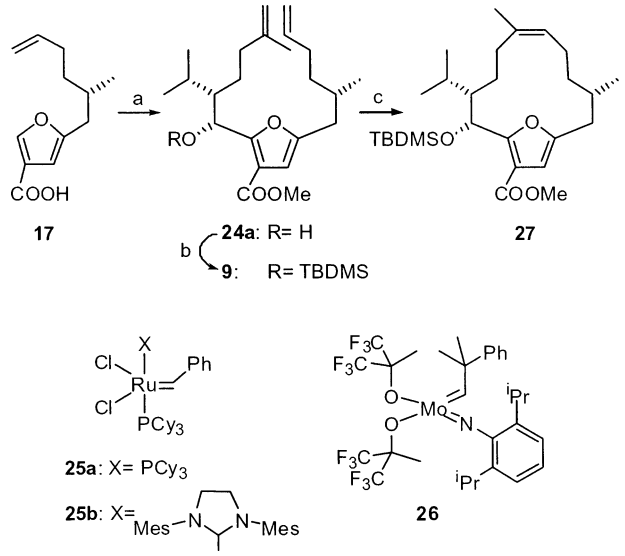
(20) (a) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **1995**, *34*, 2039–2041. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, 953–956.

(21) Purchased from Strem Chemicals, Inc., Newburyport, MA.

(22) Schrock's catalyst **26** (Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. J. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886) gave the same compound.

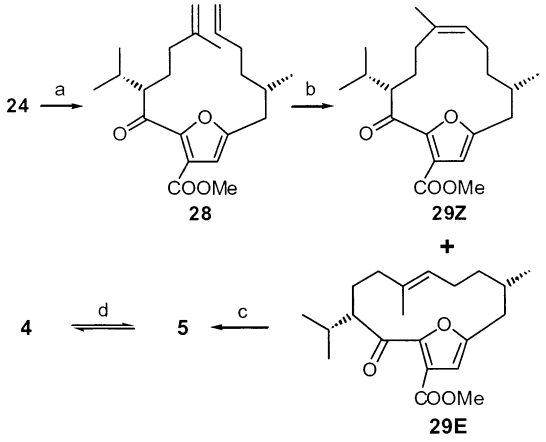
(23) This TTC triene, after desilylation, did not produce any TADA product due to the cis dienophile. It only underwent slow thermal decomposition in full accordance with our earlier observation (ref 6).

SCHEME 6[a]



[a] Reagents and conditions: (a) 2 equiv of LDA, THF, −80 °C then **10**, isolate acid then CH_2N_2 (96%, $\alpha/\beta \approx 2{:}1$); (b) TBDMS-OTf, 2,6-lutidine, CH_2Cl_2 (96%); (c) **25b**, CH_2Cl_2, E, 21 h, high dilution (93%).

SCHEME 7[a]

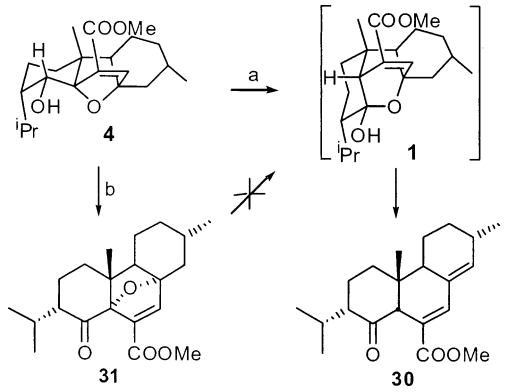


[a] Reagents and conditions: (a) Dess−Martin [O] (91%); (b) **25b**, CH_2Cl_2, E, 3 h, high dilution (70%, **29Z**/**29E** ≈ 44:26); (c) $NaBH_4$, MeOH, 10 °C, 5 h (91%); (d) 115 °C, DMSO/H_2O 2:1, 3d (70% conversion).

On the other hand, dienone **28**, obtained from the epimeric mixture of alcohol **24** via Dess−Martin periodinane oxidation[24] did produce the desired macrocycle **29E** though as a minor component in addition to the TTC macrocycle **29Z** in an easily separable, 2:1 isomeric mixture (Scheme 7). Apart from the steric effects, the different chelation characteristics of the substrate diene might be responsible for the formation of **29E**.[25] To our further delight, we were able to selectively reduce the latter product to obtain the much sought after furanophane substrate **5** (91%).

Having had thus procured the desired furanophane, the stage was set for the TADA investigations. Heating of furanophane **5** in 66% aqueous DMSO at 115 °C

SCHEME 8[a]



[a] Reagents and conditions: (a) $SnCl_4$, CH_2Cl_2, −80 to +20 °C, 1day (90%); (b) Dess−Martin [O] (94%).

cleanly afforded tetracycle **4** although in 70% yield even after protracted reaction times (3 days; cf. Scheme 8). The improvement in stereofacial control over that anticipated based on the model studies is most likely due to the influence of the remote methyl group, which renders conformation **A** completely predominant. This observation is a reflection upon the significance of the judicious choice of substituents that will govern the conformation of the macrocycle at the transition-state level. In a related experiment, heating of tetracycle **4** at the same temperature in toluene-d_8 produced a far less clean (65:35) mixture of furanophane **5** and tetracycle **4** after 6 days. It is evident that this TADA reaction not only proceeds with stereofacial control and diastereospecificity in an aqueous media, but that it is also reversible. Consequently, if the product is consumed by the consecutive reaction in the biosynthesis, this equilibrium may be pushed toward a full conversion.

At this stage of the synthesis, it remained for us to explore the feasibility of the final step, i.e., the hydride shift mediated oxygen transposition step. Structural architecture of tetracycle **4** for this step seems favorable: the hydrogen to be shifted is antiperiplanar to the ring oxygen while the hydrogens on the other side of the bicyclic ring are not (Scheme 8). The adjacent axial methyl group is also out of reach. Semiempirical calculations indicated a staggering 12 kcal/mol energy gain during the transformation **4** to **1**. This can be explained by two factors: release of the bicyclooxaheptene ring strain, and flipping of the isopropyl group from axial to equatorial position while the hydroxyl group remains equatorial. Accordingly, Lewis acids such as $SnCl_4$ or trimethylsilyltriflate (TMSOTf) could trigger the opening of the bicyclooxaheptene ring and the anticipated hydride shift. Unfortunately, however, the extreme acid sensitivity of chatancin (**1**) stymied the favorable conclusion of this event; the only product that could be isolated was anhydrochatancin **30**[26,27]

While within the confines of traditional chemical means chatancin seems to elude a "biomimetic" approach,

(24) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

(25) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792−803.

(26) ^1H NMR, ^{13}C NM and IR spectra of **30** was identical to that of anhydrochatancin observed during the isolation and the previous total synthesis (ref 1).

(27) Less acidic or basic (Oppenauer or Tishchenko) conditions left tetracycle **4** unchanged or led to decomposition. Attempted single electron reduction of ketone **31** with SmI_2 was not productive either.

a nearly neutral but locally Lewis acidic microenvironment of a Sarcophyton enzyme might be capable of inducing this ultimate step. In the meantime, the alternative pyranophane route (path a in Scheme 1) is also under investigation.

In summary, as one of the two routes that was proposed earlier to involve a TADA reaction in the biosynthesis of **1**, the furanophane TADA strategy was tested in a biomimetic approach. Following a short synthesis of requisite furanophane **5**, the strategic TADA reaction proved to be highly selective to give tetracycle **4** as expected. Even the anticipated hydride shift of this latter could be induced, although with a water elimination instead of the hemiketal ring formation due to the forbidding acid sensitivity of the natural product. Despite this setback, this route still cannot be ruled out if an enzymatic assistance is invoked for the final step in the biogenesis.

Experimental Section

General Methods. All air-sensitive reactions were carried out under argon. Solvents were distilled under nitrogen, tetrahydrofuran (THF), and ethyl ether (Et_2O) from sodium benzophenoneketyl and dichloromethane, diisopropylamine, triethylamine, dimethyl sulfoxide (DMSO), hexamethylphosphoramide (HMPA), and acetonitrile from calcium hydride. Flash chromatography (FC) was carried out using 230−400 mesh silica gel. Thin-layer chromatography (TLC) was performed on precoated glass plates silica. Spots were visualized by UV light (254 nm) and/or with dipping in a cerium sulfate−ammonium molybdate developing solution and charring on a hot plate. All concentrations are given in g/100 mL for the optical rotations measurements (1 dm, 1 mL cell). Proton magnetic resonance (^{1}H NMR) and carbon magnetic resonance (^{13}C NMR) spectra were recorded at 300 and 62.5 MHz, respectively, in chloroform-*d* (7.26 and 77.0 ppm, respectively) as solvent. Chemical shifts are reported in ppm on δ scale. Coupling constants are reported to the nearest 0.1 Hz. Infrared (IR) spectra were recorded neat on KBr pastille. Only diagnostic bands are reported on cm^{-1} scale.

(3*S*,10*S*,11*R*,6*Z*)-Methyl 11-*tert*-Butyldimethylsilyloxy-10-isopropyl-3,7-dimethyl-15-oxabicyclo[10.2.1]pentadeca-1(14),6,12-triene-13-carboxylate (27). A CH_2Cl_2 (5 mL) solution of diene **9** (49.1 mg, 100 μmol) was added with a syringe pump over 1 h to a refluxing stirred CH_2Cl_2 (20 mL) solution of catalyst tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene]benzylideneruthenium(IV) dichloride **25b** (8.5 mg, 10 μmol). Following 20 h reflux, the mixture was evaporated. FC (5% ether in hexane) afforded 43.2 mg (93%) title macrocycle **27** as a colorless oil. $[\alpha]^{20}_D$: +40.2 (*c* = 5.0, hexane). ^{1}H NMR: 6.29 (s, 1H), 5.65 (d, *J* = 2.9 Hz, 1H), 5.14 (t, *J* = 7.4 Hz, 1H), 3.81 (s, 3H), 2.67 (dd, *J* = 14.6, 4.6 Hz, 1H), 2.45 (dd, *J* = 14.6, 11.7 Hz, 1H), 2.75−2.60, 2.40−2.35, 2.10−1.95, 1.95−1.80, 1.80−1.60 and 1.40−1.25 (6m, 1H + 1H + 1H + 1H + 2H + 4H, respectively), 1.67 (s, 3H), 1.14 (tt, *J* = 13.3, 4.2 Hz, 1H), 1.07 (d, *J* = 6.5 Hz, 3H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.90 (s, 9H), 0.00 and −0.25 (2s, 2 × 3H). ^{13}C NMR: 164.1, 161.8, 154.7, 137.6, 124.5, 112.7, 106.0, 68.8, 51.3, 50.7, 35.2, 34.9, 33.2, 29.5, 28.1, 26.7, 25.7, 23.7, 22.0, 21.0, 20.9, 20.6, 18.1, −5.2, −5.4. IR: 2956, 1721, 1610, 1567, 1074. HR-MS: 405.2466 ± 0.0012 (405.2461 for $(M - C_4H_9)^+$ $C_{23}H_{37}O_4Si$).

(2*S*,2′*S*)-Methyl 2-(1-Oxo-2-isopropyl-5-methylhex-5-enyl)-5-(2′-methylhex-5′-enyl)furan-3-carboxylate (28). Dess−Martin periodinane (551 mg, 1.3 mmol) was added to a CH_2Cl_2 (10 mL) solution of epimeric alcohol **24** (376 mg, 1 mmol) at 0 °C. After the mixture was stirred for 1 h at 0 °C, it was diluted with hexane (30 mL) and stirred with a solution of Na_2SO_3 (5 mL, satd) for 10 min at 23 °C to destroy the excess reagent. Following an aqueous workup, FC (10% to 20% ether in hexane) afforded 342 mg (91%) title ketone **28** as a colorless oil. ^{1}H NMR: 6.42 (s,1H), 5.78 (dddd, *J* = 17.0, 10.2, 6.6, 6.6 Hz, 1H), 5.01 (ddd, *J* = 17.2, 3.3, 1.6 Hz, 1H), 4.96 (dd, *J* = 10.2, 1.4 Hz, 1H), 4.64 and 4.59 (2s, 2 × 1H), 3.87 (s, 3H), 3.25−3.15 (m, 1H), 2.68 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.55 (dd, *J* = 15.0, 7.6 Hz, 1H), 1.67 (s, 3H), 2.2−1.2 (m, 10H), 0.93 (d, *J* = 6.7 Hz, 6H), 0.91 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR: 193.1, 163.6, 157.7, 150.6, 145.3, 138.2, 122.8, 114.6, 110.2, 110.1, 53.1, 52.2, 35.6, 35.4, 35.1, 31.8, 31.1, 30.6, 26.0, 22.1, 20.7, 19.4, 19.2. IR: 2960, 1732, 1680, 1646, 1530, 1230. HR-MS: 374.2450 ± 0.0011 (374.2457 for M^+ $C_{23}H_{34}O_4$).

(3*S*,10*S*)-(6*Z* and 6*E*)-Methyl 11-Oxo-10-isopropyl-3,7-dimethyl-15-oxabicyclo[10.2.1]pentadeca-1(14),6,12-triene-13-carboxylate (29*Z* and 29*E*). A CH_2Cl_2 (5 mL) solution of diene **28** (290 mg, 774 μmol) was added with a syringe pump over 1 h to a refluxing stirred CH_2Cl_2 (190 mL) solution of catalyst tricyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene]benzylideneruthenium(IV) dichloride 25b (65 mg, 77 μmol). Following 2 h reflux, the mixture was evaporated to ∼20 mL, filtered through silica, and eluted with CH_2Cl_2 (200 mL) and a mix of 20% ether and hexane (100 mL). Crude ^{1}H NMR showed a 29*Z*/29*E* ratio of 63:37. FC (60% to 100% CH_2Cl_2 in hexane, then 10% ether in hexane) of this mixture afforded 118 mg (44%) 6*Z*-macrocycle **29Z** as a colorless oil. ^{1}H NMR: 6.42 (s, 1H), 5.11 (t, *J* = 6.8 Hz, 1H), 3.89 (s, 3H), 2.94 (dd, *J* = 14.7, 4.1 Hz, 1H), 2.84 (ddd, *J* = 8.8, 7.4, 4.2 Hz, 1H), 2.43 (dd, *J* = 14.7, 8.0 Hz, 1H), 2.2−1.2 (m, 10H), 1.68 (d, *J* = 1.0 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H). It was followed by 6*E*-macrocycle **29*E*** (71 mg, 26%) evaporated to a colorless oil. $[\alpha]^{20}_D$: +19.8 (*c* 4.0, hexane). ^{1}H NMR: 6.47 (d, *J* = 1.1 Hz, 1H), 4.33 (ddd, *J* = 10.3, 2.6, 1.4 Hz, 1H), 3.89 (s, 3H), 3.22 (t, *J* = 9.0 Hz, 1H), 2.67 (ddd, *J* = 14.8, 3.1, 1.1 Hz, 1H), 2.32 (dd, *J* = 14.8, 12.5 Hz, 1H), 2.1−1.2 (m, 10H), 1.54 (s, 3H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR: 195.0, 163.6, 157.6, 150.5, 133.4, 128.1, 122.1, 111.3, 52.3, 50.6, 37.6, 36.4, 34.9, 31.9, 31.4, 27.3, 26.6, 22.0, 21.1, 20.6, 14.2. IR: 2955, 1742, 1680, 1529, 1216. HR-MS: 346.2146 ± 0.0010 (346.2144 for M^+ $C_{21}H_{30}O_4$).

(3*S*,10*S*,11*R*)-Methyl 11-Hydroxy-10-isopropyl-3,7-dimethyl-15-oxabicyclo[10.2.1]pentadeca-1(14),6,12-triene-13-carboxylate (5). Sodium borohydride (80 mg) was added to a methanol (2 mL) solution of ketone **29*E*** (40.1 mg, 114 μmol) at 0 °C. After the mixture was stirred for 5 h at 10 °C, hexane (10 mL) and HCl (1 mL) were added. Following an aqueous workup, FC (5% to 10% ether in hexane) afforded 33.2 mg (91%) title alcohol **5** as a colorless oil. $[\alpha]^{20}_D$: −82.7 (*c* 3.3, hexane). ^{1}H NMR: 6.21 (d, *J* = 7.7 Hz, 1H), 6.16 (d, *J* = 1.3 Hz, 1H), 5.05 (d, *J* = 7.7 Hz, 1H), 4.75 (dd, *J* = 6.9, 6.1 Hz, 1H), 3.85 (s, 3H), 2.58 (ddd, *J* = 14.4, 1.7, 1.7 Hz, 1H), 2.15 (dd, *J* = 14.4, 11.8 Hz, 1H), 2.1−1.1 (m, 11H), 1.30 (s, 3H), 1.08 (d, *J* = 6.7 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 1.04 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR: 167.0, 163.7, 153.4, 135.8, 124.4, 114.7, 106.8, 71.5, 52.3, 49.0, 38.1, 35.9, 35.3, 30.8, 29.9, 25.0, 23.5, 22.1, 21.6, 20.4, 16.4. IR: 3373 (br), 2953, 1693, 1571, 1088. HR-MS: 348.2289 ± 0.0010 (348.2300 for M^+ $C_{21}H_{32}O_4$).

(1*R*,2*S*,4a*R*,4b*R*,7*S*,8a*S*,10a*R*)-4a,7-Dimethyl-8a,10a-epoxy-1-hydroxy-2-isopropyl-10-methoxycarbonyl-1,2,3,4,-4a,4b,5,6,7,8,8a,10a-dodecahydrophenanthrene (4). Furanophane **5** (122 mg, 350 μmol) was heated in a mixture of DMSO (15 mL) and water (10 mL) for 3 days at 115 °C. Upon cooling, water (100 mL) and CH_2Cl_2 (20 mL) were added then the mixture was extracted with hexane (3 × 100 mL). After drying and evaporation, ^{1}H NMR spectra of the crude product indicated a clean TADA reaction with a ratio of **4**/**5** ≈ 4:1. FC (10% to 20% ether in hexane) afforded 32 mg (26%) recovered furanophane **5** and 82 mg (67%, 91% corrected) of the title tetracycle: $[\alpha]^{20}_D$: +14.0 (*c* 8.2, hexane). ^{1}H NMR: 7.12 (s, 1H), 4.79 (d, *J* = 4.0 Hz, 1H), 3.75 (s, 3H), 2.21 (ddd, *J* = 14.3, 3.4, 1.1 Hz, 1H), 2.1−0.7 (m, 13H), 1.09 (d, *J* = 6.5 Hz, 3H), 1.04 (d, *J* = 6.4 Hz, 3H), 090 (d, *J* = 6.7 Hz, 3H) 0.77 (s, 3H).

^{13}C NMR: 164.2, 147.7, 143.8, 94.3, 87.8, 68.7, 57.3, 51.7, 43.7, 43.2, 39.2, 35.3, 34.6, 31.0, 27.4, 26.4, 23.5, 23.1, 22.4, 22.0, 18.6. IR: 3570 (br), 2927, 1719, 1608, 1454. HR-MS: 348.2289 ± 0.0010 (348.2300 for M^+ $C_{21}H_{32}O_4$).

(2*S*,4a*R*,4b*R*,7*S*,10a*R*)-4a,7-Dimethyl-1-oxo-2-isopropyl-10-methoxycarbonyl-1,2,3,4,4a,4b,5,6,7,10a-decahydrophenanthrene (30) (Anhydrochatancin). $SnCl_4$ (770 μL, 770 μmol, 1 M in CH_2Cl_2) was added to a CH_2Cl_2 (3 mL) solution of tetracycle **4** (27 mg, 77 μmol) at −78 °C. The mixture was stirred at 23 °C for 19 h, diluted with hexane, and quenched with a saturated $NaHCO_3$ solution. Aqueous workup and FC (5% to 20% ether in hexane) afforded 23 mg (90%) anhydrochatancin. $[\alpha]^{20}_D$: +110 (*c* 2.3, CH_2Cl_2). ^{1}H NMR: 7.18 (s, 1H), 5.87 (s, 1H), 3.73 (s, 3H), 3.34 (s, 1H), 2.3−1.1 (m, 12H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 084 (d, *J* = 6.7 Hz, 3H), 0.83 (s, 3H). ^{13}C NMR: 209.9, 167.8, 142.7, 139.6, 134.2, 124.1, 59.2, 56.2, 51.7, 41.8, 36.6, 34.6, 31.9, 31.2, 25.9, 23.9, 22.8, 22.1, 21.3, 21.3, 18.6. IR: 2931, 1712, 1631, 1256. HR-MS: 330.2198 ± 0.0010 (330.2195 for M^+ $C_{21}H_{30}O_3$). ^{1}H NMR, ^{13}C NMR, and IR spectra are identical to that of Goessinger's anhydrochatancin[1,26] (which was identical to Sato's, according to personal communication).

(2*S*,4a*R*,4b*R*,7*S*,8a*S*,10a*R*)-4a,7-Dimethyl-8a,10a-epoxy-1-oxo-2-isopropyl-10-methoxycarbonyl-1,2,3,4,4a,4b,5,6,7,8,-8a,10a-dodecahydrophenanthrene (31). Dess−Martin periodinane (4.2 mg, 10 μmol) was added to a $CDCl_3$ (0.8 mL) solution of alcohol **4** (3.5 mg, 1 mmol) at 0 °C. After 30 min at 0 °C, it was diluted with hexane (10 mL) and stirred with a solution of Na_2SO_3 (5 mL, sat.) for 10 min at 23 °C to destroy the excess reagent. The product (3.3 mg, 94%) was pure enough for the further investigation. $[\alpha]^{20}_D$: −53 (*c* 0.3, hexane). ^{1}H NMR: 7.10 (s, 1H), 3.73 (s, 3H), 2.72 (ddd, *J* = 9.4, 7.3, 7.3 Hz, 1H), 2.3−1.5 (m, 8H), 1.49 (d, *J* = 13.7 Hz, 1H), 1.48 (d, *J* = 12.9 Hz, 1H), 1.40 (d, *J* = 12.0 Hz, 1H), 1.15−1.10 (m, 1H), 1.04 (d, *J* = 6.5 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.98 (s, 3H), 092 (d, *J* = 6.7 Hz, 3H), 0.74 (qd, *J* = 13.3, 3.5 Hz, 1H). ^{13}C NMR: 207.7, 163.4, 146.5, 143.7, 93.6, 88.9, 56.8, 51.8, 46.9, 39.0, 35.1, 34.8, 31.0, 29.7, 27.0, 26.4, 23.0, 22.3, 21.2, 19.0 18.2. IR: 2927, 1724, 1608, 1453, 1200. HR-MS: 346.2144 ± 0.0010 (346.2144 for M^+ $C_{21}H_{30}O_4$).

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Supporting Information Available: Procedures for the preparation of compounds **9**−**24** and their ^{1}H NMR, ^{13}C NMR, MS, IR, and $[\alpha]_D$ data. Copies of ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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