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Pyranophane Transannular Diels−Alder Approach to (+)-Chatancin: A Biomimetic Asymmetric Total Synthesis

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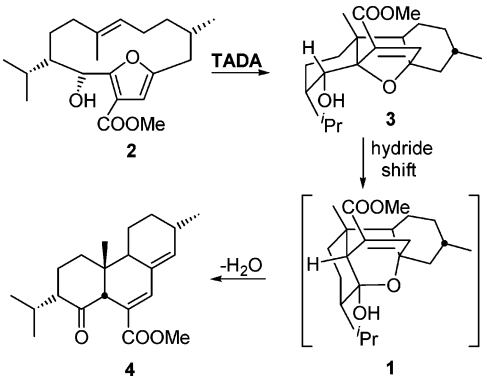
Received August 14, 2003

An asymmetric total synthesis of (+)-chatancin was achieved via a transannular Diels−Alder (TADA) reaction of an in situ generated macrocyclic pyranophane pseudobase. The presented route constitutes the second of two proposed biosynthetic pathways that involves a TADA reaction. It links this diterpene biogenetically to the cembranoids. A set of TADA selection rules that rationalize the formation of (+)-chatancin from a dynamic equilibrium of four 2-hydroxy-*2H*-pyrane bicycles and their 16 potential TADA transition states are also outlined. Beyond the TADA reaction, highlights of the synthetic work include the assembly of a chiral acyclic macrocyclization substrate from (*S*)-citronellol and an efficient macrocyclization via a *β*-ketosulfoxyde/enone Michael addition.

(+)-Chatancin (**1**) was isolated from soft coral *Sarcophyton sp*. in a screening program conducted to identify novel platelet activating factor (PAF) antagonists from marine organisms.[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, inflammation, and respiratory and cardiovascular diseases. The appealing bioactivity of diterpene **1** and its seven stereogenic centers dispersed on a unique, cis-anti-cis (CAC) dodecahydrophenanthrene framework, locked by an internal hemiketal ring, has already inspired a racemic total synthesis.[2] Beyond the challenging structure, we were further intrigued by its distinctive carbon functional pattern similar to that of cembranoids isolated also from *Sarcophytons* as well as from other soft corals.[3] Cembranoids, diterpenes with a 14-membered macrocycle, are known to be common intermediates in the biogenesis of a divers array of polycyclic diterpenes. However, no transannular Diels−Alder (TADA) reaction was ever found to be the method of internal cyclization with cembranoids. In fact, to date, only two biomimetic TADA syntheses are known in natural product synthesis.[4] As we have long been interested in the TADA reaction and its applications in natural product synthesis,[5] it was implicit to investigate this type of cyclization as a biosynthetic route to **1**.

SCHEME 1. Furanophane TADA Approach



In principle, two distinct biosynthetic TADA routes may be envisaged to reach **1** from a cembranoid. The first route, which involves artificial furanocembranoid **2**, was investigated recently by a nonenzymatic synthetic method (Scheme 1).[6] In that furanophane approach, we found that, although **2** selectively generates TADA adduct **3** in a reversible reaction, the extreme acid sensitivity of **1** and the strongly acidic condition required for the conclusive hydride shift-mediated oxygen transposition allowed only for the isolation of anhydrochatancin **4**.

In the alternative, pyranophane biosynthetic proposal, the cembranoid is oxidized differently, to bicyclic 2-hydroxy-*2H*-pyrane **5a**, which can cyclize to **1** directly under very mild conditions.[7] However, in an aqueous media, pyrilium pseudobases 2-hydroxy-*2H*-pyranes are known to be in a delicate, pH-dependent equilibrium with their pyrylium ion and their open enedione forms.[8] Application of this equilibrium to the asymmetric case of **5a** suggests

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(3) Rodriguez, A. D. *Tetrahedron* **1995**, *51*, 4571−4618.
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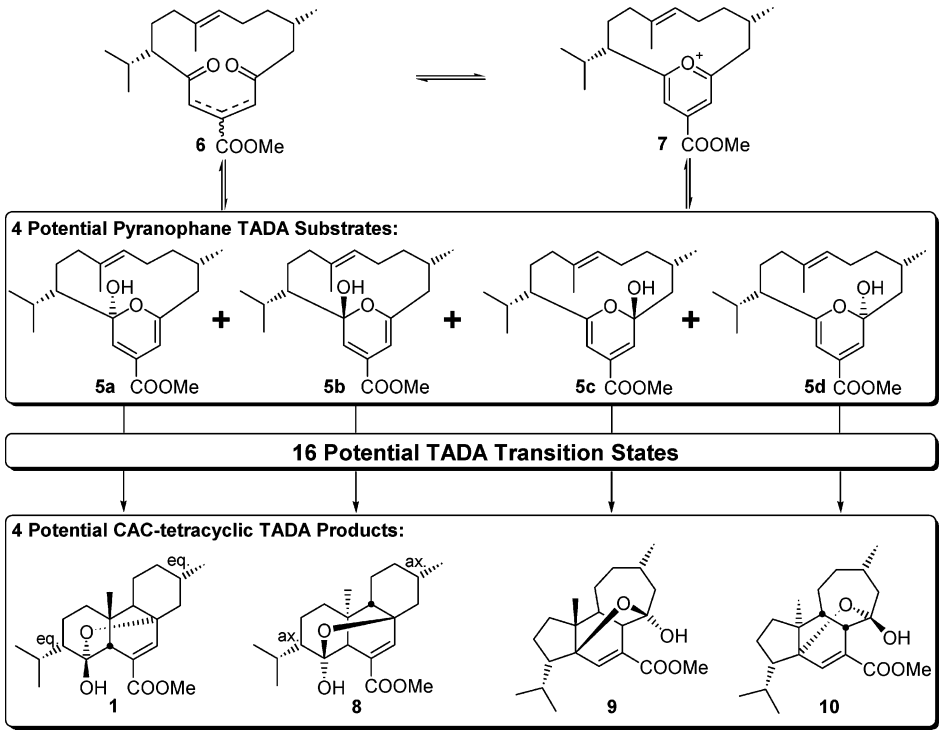
10.1021/jo035193y CCC: $25.00
Published on Web 11/22/2003

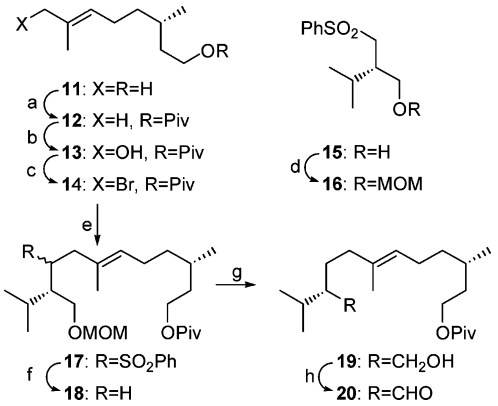
SCHEME 2. Pyranophane TADA Approach



a complex mixture of four macrocyclic diketones **6**, pyrylium ion **7**, and four pseudobases **5a**−**d** of the latter (Scheme 2). Consequently, to test a plausible participation of a TADA reaction in the biosynthesis, all four pseudobases **5** must be taken into account.[9] Since, in principle, every macrocyclic TADA substrate can have four operative conformations, arising from the approach of the diene and the dienophile via each of their respective π-faces, the four pseudobases of **5** can generate 16 potential transition states (TS). However, TSs in which the hydroxyl group is sandwiched between the diene and the dienophile can safely be eliminated to reduce the number to eight. Furthermore, cis-trans-trans (CTT) macrocycles **5a** and **5b** as well as TCT macrocycles **5c** and **5d** can generate only the four CAC tetracycles (**1** and **8**−**10**, respectively), as in the TSs leading to the alternative four TAT tetracycles, the overlap of the diene and the dienophile can only be perpendicular, therefore unproductive.[5] What is left behind is one quadrant of the initial 4 × 4 TS table. To further narrow this short list of potential TSs, their potential products should be reviewed as the TADA reaction is presumed to have a late TS. Thus, in these CAC tetracycles, the A.B.C[6.6.6] ring system of **1** and **8** is expected to be favored over the crowded A.B.C[5.6.7] ring system of **9** and **10**. Finally, inspection of the remaining two A.B.C[6.6.6] CAC tetracycles shows that both peripheral alkyl groups of **1** are equatorial, while those of **8** are axial. These selection rules should lend a clear preference to the formation of **1** under near neutral aqueous conditions and minimal thermal activation upon acquiring any of **5**, **6**, or **7**. Now we report our results on the synthetic investigation of this hypothesis.

(9) Although pyrylium **7** could also be considered as a TADA substrate, it was excluded based on steric arguments beyond its aromaticity.

SCHEME 3 [a]



[a] Reagents and conditions: (a) *t*-BuCOCl, pyridine (100%). (b) SeO_2, salicylic acid, *t*-BuOOH, CH_2Cl_2, 30 h (43%). (c) MsCl, Et_3N, THF, 0 °C then LiBr, 0 °C → rt (84%). (d) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, 0 °C → rt (98%). (e) **16**, n-BuLi, THF, −78 °C → −25 °C then **14** (92%). (f) Na/Hg, Na_2HPO_4, MeOH/THF 1:2, 2 h then (a) (70%). (g) HCl, *i*-PrOH, 55 °C, 8 h (81%). (h) TPAP, NMO, CH_2Cl_2 (86%).

Synthesis of the chiral pyranophane substrate started with (*S*)-citronellol (**11**) (Scheme 3). After a quantitative protection as pivalate **12**, applying Sharpless' selenium dioxide-mediated allylic oxidation protocol functionalized the other terminus and set the configuration of the dienophile to afford alcohol **13** in 43% yield.[10] A standard mesylation and nucleophile bromination turned this alcohol into allylic bromide **14** in 84% combined yield. A typical methoxymethyl protection of alcohol **15**[11] generated the reagent for the introduction of the stereogenic

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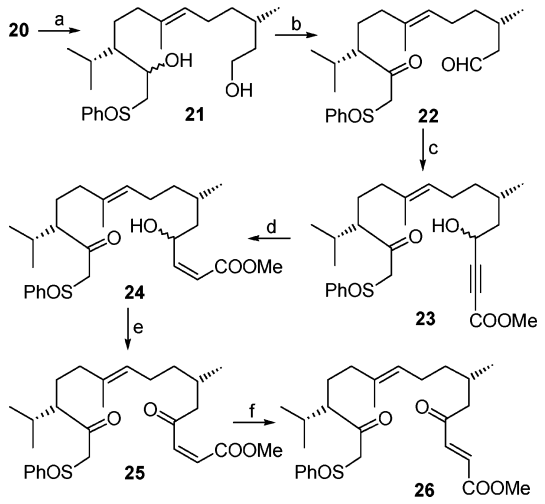
isopropyl group. This was accomplished with an alkylation of the lithium salt of sulfone **16** with **14**, followed by a reductive desulfonylation of intermediate **17** with sodium amalgam under buffered condition to afford **18** in a 64% combined yield.[11] Preparation for further extension on this side included a MOM deprotection to alcohol **19** and its tetrapropylammonium perruthenate (TPAP)-mediated oxidation to aldehyde **20** with *N*-methylmorpholine *N*-oxide (NMO) in 71% combined yield.[12]

Aldehyde **20** then served as an electrophile in the condensation with an in situ generated lithium salt of methylphenyl sulfoxide.[13] A subsequent basic hydrolysis completed the partial deprotection of the pivalate group observed after condensation to isolate ultimately epimeric diol **21** in quantitative yield. A double oxidation of this diol to keto aldehyde **22** with Dess−Martin periodinane,[14] in 83% yield, arranged one side for the macrocyclization and prepared the other for further extension.[15] Accordingly, selective condensation on the aldehyde side was achieved with 2.5 equiv of lithium salt of methyl propiolate to afford acetylene **23** in 84% yield.[16] A catalytic partial hydrogenation with Lindlar catalyst afforded *cis*-enol **24** quantitatively,[17] then a second, pyridine-buffered Dess−Martin periodinane oxidation delivered *cis*-enone **25** in 83% yield.[14] Finally, an iodine-catalyzed isomerization of the enone system concluded the assembly of acyclic, macrocyclization substrate *trans*-enone **26** by setting the right configuration for an intramolecular Michael reaction.

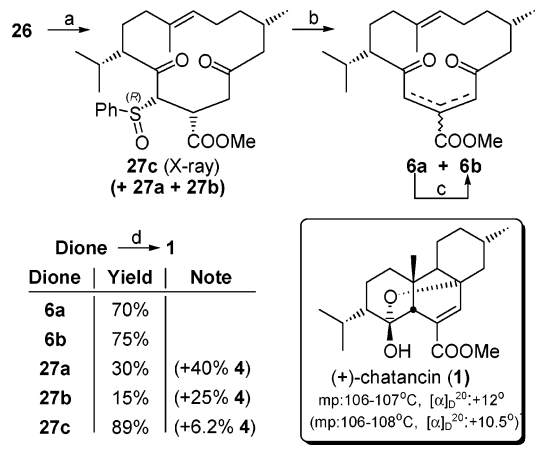
Macrocyclizations are frequently the bottlenecks of TADA syntheses. However, in this case, applying a terminal β-keto sulfoxide as a Michael donor, a smooth macrocyclization was observed even without slow addition and under medium dilution despite the unstable nature of the product. Separation and purification of these sulfoxide macrocycles **27** afforded three out of the eight possible diastereomers in an excellent 80% combined yield (Scheme 5).[18] Moreover, one of them, **27c**, was crystalline and offered an easy determination of its all-α stereochemistry by X-ray crystallography. The exact stereochemistry of **27a** and **27b** was not determined due to their instability. Pyrolysis of **27c** in toluene at 115 °C afforded a separable mixture of two diones, **6a** and **6b**, out of the four possible isomers in 80% combined yield to reach two of the targeted pyranophane substrates in Scheme 2. Again, their exact stereochemistry was not determined but their structure was unambiguously verified by NMR and MS. Interestingly, the major, kinetic product **6a** could be slowly isomerized to the thermodynamic product **6b** under buffered, acid-catalyzed conditions at room temperature. Heating **6a** and **6b** just over 110 °C in an aqueous medium gave (+)-chatancin in 70% and 75% yield, respectively.[19] The presence of water in the medium is essential as under the aprotic pyrolysis conditions a step before, no TADA product was observed. Indeed, heating any of **27** in the same aqueous medium applied for the TADA reaction also gave **1**. In fact, the highest yield that could be achieved was with **27c**. Appearance of anhydrochatancin **4** underlines the instability of **1** and makes this tandem sequence even more remarkable. It produces a complex polycyclic ring system with five new stereogenic centers under exceptionally

SCHEME 4[a]



[a] Reagents and conditions: (a) LDA, MeSOPh, THF then NaOMe, MeOH (100%). (b) Dess−Martin [O], CH_2Cl_2 (83%). (c) HC≡CCOOMe, LDA, THF, −80 °C (84%). (d) H_2, Lindlar cat., *c*-hex, CH_2Cl_2 (100%). (e) Dess−Martin [O], pyridine, CH_2Cl_2, 0 °C → rt (83%). (f) I_2, Et_2O, 0 °C → rt (85%).

SCHEME 5[a]



[a] Reagents and conditions: (a) Cs_2CO_3, acetone, [**26**] = 6.4 mM, 15 °C, 7 h (80%, **27a**/**27b**/**27c** ~ 12:59:29). (b) PhMe, 110−115 °C, 15 min (80%, **6a**/**6b** ~ 5:3). (c) HBF_4, NaOAc, acetone, 48 h (80%). (d) DMSO/H_2O 1:1, 105−110 °C, 3−18 h, (up to 89%).

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mild conditions. Consequently, to generate (+)-chatancin, dione **6a** or **6b** must enter and remain in the equilibrium shown in Scheme 2. Furthermore, the critical role of water suggests pyrylium ion **7** as a central intermediate in the equilibrium. These experiments verify our initial hypothesis about a possible pyranophane TADA reaction in the biogenesis.[20]

In summary, a short, asymmetric total synthesis of (+)-chatancin was developed to investigate the biogenetic relationship between the cembranoids and the target. The synthesis required bicyclic 2-hydroxy-*2H*-pyrane **5a**, thus the name "pyranophane approach", as a substrate for the conclusive TADA reaction. As **5a** is a member of a tentative multicomponent equilibrium, its open form, **6**, was targeted. Assembly of **6** started with successive extensions of both termini of (*S*)-citronellol to reach acyclic macrocyclization substrate **26** intramolecular Michael reaction, which delivered sulfoxide macrocycle **27** with high yield. Heating **27** or its pyrolysis product **6** in an aqueous media indeed produced (+)-chatancin in up to 89% yield to verify the feasibility of this proposal.

Experimental Section

(4*S*,11*S*,7*E*)-2-Benzenesulfinyl-4-isopropyl-7,11-dimethyl-3,13-dioxo-cyclotetradeca-7-enecarboxylic Acid Methyl Ester (27). Cesium carbonate (1.442 g, 4.43 mmol) was added to a solution of ketone **26** (1.28 g, 2.7 mmol) in acetone (420 mL) at 15 °C. After being stirred for 7 h at this temperature, the mixture was filtered on a pad of Celite and evaporated. The crude product was a mixture of macrocycles. Three of them were separated and purified by FC (15% acetone in toluene) to give 123.7 mg (9.7%) of less polar macrocycle **27a** as a clear oil, 605.4 mg (47.3%) of more polar macrocycle **27b** as a clear oil, and 289.5 g (23%) of macrocycle **27c** as white crystals; mp 132−134 °C; $[\alpha]^{20}_D$ +217.3 (*c* 1.05, $CHCl_3$); ^{1}H NMR δ 7.85−7.69 (m, 2H), 7.55−7.38 (m, 3H), 5.04 (t, J = 5.0 Hz, 1H), 4.44 (m, 1H), 3.96 (dd, J = 10.8 and 2.2 Hz, 1H), 3.76 (s, 3H), 3.59−3.49 (dd, J = 13.0 and 10.7 Hz), 2.50−1.0 (m, 14H), 1.44 (s, 3H), 0.95 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz), 0.10 (d, J = 6.7 Hz, 3H); ^{13}C NMR δ 208.0, 205.8, 171.2, 134.5, 131.7, 129.2, 129.1, 127.8, 126.1, 78.4, 53.8, 52.2, 50.1, 40.9, 37.8, 35.8, 35.4, 28.5, 28.4, 24.8, 21.8, 21.4, 19.1, 16.4, 14.7; IR 3047, 2874, 1741, 1714, 1697, 1444, 1380, 1225 cm^{-1}; HRMS 475.2527 ± 0.0014 (475.2518 for MH^+: $C_{27}H_{39}O_5S$).

(4*S*,11*S*)-4-Isopropyl-7,11-dimethyl-3,13-dioxo-cyclotetradeca-1,7-dienecarboxylic Acid Methyl Ester or (5*S*,-12*S*)-12-Isopropyl-5,9-dimethyl-3,13-dioxo-cyclotetradeca-1,8-dienecarboxylic Acid Methyl Ester (macrocycles 6a and 6b). A solution of macrocycle **27c** (73 mg, 0.154 mmol) in toluene (2.0 mL) was heated at 110−115 °C for 15 min. After evaporation of the mixture, a crystallization from ether/hexane gave 26 mg (50.6%) of macrocycle **6a** as white crystals: mp 95−97 °C; $[\alpha]^{20}_D$ −132.1 (*c* 1.355, $CHCl_3$); ^{1}H NMR δ 6.24 (s, 1H), 5.01 (t, J = 5.0 Hz, 1H), 3.81 (1s, 3H), 3.23 (s, 2H), 3.02 (dd, J = 13.6 and 4.9 Hz, 1H), 2.35−1.20 (m, 12H), 1.40 (s, 3H), 0.93, 0.91 and 0.88 (3 × d, J = 6.2 and 7.2 Hz, 3 × 3H); ^{13}C NMR δ 206.2, 199.9, 169.1, 138.5, 136.6, 132.7, 127.1, 58.2, 52.4, 48.7, 48.3, 40.0, 36.0, 31.4, 28.3, 26.1, 23.5, 20.6, 20.4, 19.8, 15.0; IR 2959, 2929, 1732, 1710, 1692, 1620, 1436, 1371, 1246 cm^{-1}; HRMS 348.2303 ± 0.0010 (348.2300 for M^+: $C_{21}H_{32}O_4$). The supernatant of the crystallization was purified by FC (10, 20, 30% ether in hexane) to give 15.8 mg (29.5%) of macrocycle **6b** as a colorless oil. $[\alpha]_D^{23}$ −57.3 (*c* 0.79, $CHCl_3$); ^{1}H NMR δ 7.22 (s, 1H), 4.93 (t, J = 5.0 Hz, 1H), 4.07 and 3.52 (2 × d, J = 6.2 Hz, 2H), 3.80 (s, 3H), 3.84−3.70 (m, 1H), 2.48−0.8 (m, 12H), 1.56 (s, 3H), 0.89, 0.88, 0.87 (3 × d, J = 6.1 and 6.8 Hz, 3 × 3H); ^{13}C NMR δ 206.5, 204.7, 167.3, 135.4, 134.6, 134.1, 127.4, 61.1, 52.8, 48.9, 41.9, 38.0, 35.6, 29.6, 27.7, 24.0, 23.1, 21.1, 20.8, 19.1, 15.2; IR 2960, 2931, 2873, 1722, 1688, 1616, 1437, 1372, 1274, 1251 cm^{-1}; HRMS 348.2303 ± 0.0010 (348.2300 for M^+: $C_{21}H_{32}O_4$).

Isomerization of Macrocycle 6a to Macrocycle 6b. Sodium acetate (0.7 mg, 8.6 μmol) and fluoroboric acid (0.6 μL, 7.1 μmol, 48−60% purified) were added to a solution of macrocycle **6a** (2.5 mg, 7.1 μmol) in acetone (0.7 mL) at room temperature. After 48 h of stirring, a solution of NH_4Cl (saturated) was added and the mixture was extracted with CH_2Cl_2. The residue was purified by FC (15% ether in hexane) to yield 2.0 mg (80%) of macrocycle **6b**.

(+)-Chatancin 1. (a) From macrocycle 6a: A solution of macrocycle **6a** (11 mg, 31.5 μmol) in a mixture of DMSO (1.0 mL) and water (1.0 mL) was heated at 105−110 °C for 6.5 h. Upon cooling, water (15 mL) was added then the mixture was extracted with a mixture of ether/hexane (50:50, 6 × 15 mL). The crude product was purified by FC (20 to 30% ether in hexane) to give 7.0 mg (70%) of (+)-chatancin **1**: mp 106−107 °C; $[\alpha]^{23}_D$ +12.0 (*c* 0.980, $CHCl_3$); ^{1}H NMR (C_6D_6) δ 7.24 (d, J = 3.9 Hz, 1H), 3.55 (1s, 3H), 3.04 (d, J = 1.8 Hz, 1H), 2.61 (7 × d, J = 6.9 and 2.2 Hz, 1H), 1.98 (ddd, J = 10.4, 3.5, and 2.0 Hz, 2H), 1.70−0.43 (m, H), 1.21 and 1.09 (2 × d, J = 6.9 Hz, 2 × 3H), 0.90 (d, J = 6.0 Hz, 3H), 0.79 (s, 3H); ^{13}C NMR δ 165.1, 143.7, 135.9, 98.8, 75.6, 53.0, 51.2, 48.8, 47.6, 42.3, 37.7, 36.0, 34.5, 29.4, 27.2, 25.5, 24.3, 23.0, 22.2, 18.5, 18.4; IR 3597, 3011, 2956, 2930, 2873, 1714, 1631, 1456, 1436, 1272, 1214 cm^{-1}; HRMS 348.2296 ± 0.0010 (348.2300 for M^+: $C_{21}H_{32}O_4$). ^{1}H NMR, ^{13}C NMR, and IR spectra are identical with those of an authentic sample of (+)-chatancin.[1]

(b) From macrocycle 6b: A solution of macrocycle **6b** (1.6 mg, 4.59 μmol) in a mixture of DMSO (0.4 mL) and water (0.4 mL) was heated at 105−110 °C for 18 h. After cooling, water (10 mL) was added then the mixture was extracted with a mixture of ether/hexane (50:50, 6 × 10 mL). The crude product was purified by FC (20 to 30% ether in hexane) to give 1.2 mg (75%) of (+)-chatancin **1**.

(c) From macrocycle 27c (crystal): A solution of macrocycle **27c** (272 mg, 0.574 mmol) in the mixture of DMSO (12.8 mL) and water (12.8 mL) was heated at 105−110 °C for 2.5 h. Upon cooling, water (50 mL) was added and the mixture was extracted with a mixture of hexanes−ether (50:50, 6 × 30 mL). The crude product was purified by FC (7% acetone in toluene) to afford 177 mg (89%) of (+)-chatancin and 11.7 mg (6.2%) of anhydrochatancin **4**: $[\alpha]^{20}_D$ 110 (*c* 1.05, CH_2Cl_2); ^{1}H NMR δ 7.18 (s, 1H), 5.87 (s, 1H), 3.73 (s, 3H), 3.34 (s, 1H), 2.3−1.10 (m, 12H), 1.00 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H), 0.83 (s, 3H); ^{13}C NMR δ 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, 21.2, 18.6; IR 2931, 1721, 1631, 1256 cm^{-1}; HRMS 330.2188 ± 0.0010 (330.2195 for M^+: $C_{21}H_{30}O_3$). ^{1}H NMR, ^{13}C NMR, and IR spectra are identical with those of anhydrochatancin **4**, kindly supplied by E. Gössinger.

(d) From macrocycle 27a: A solution of macrocycle **27a** (120 mg, 0.253 mmol) in a mixture of DMSO (2.0 mL) and water (0.5 mL) was heated at 105−110 °C for 3 h. Upon cooling, water (20 mL) was added then the mixture was extracted with a mixture of ether/hexane (50:50, 6 × 30 mL). The crude product was purified by FC (20 to 30% ether in hexane) to afford 26 mg (30%) of (+)-chatancin **1** and 37 mg (40%) of anhydrochatancin **4**.

(e) From macrocycle 27b: A solution of macrocycle **27b** (605 mg, 1.276 mmol) in a mixture of DMSO (7.0 mL) and water (4.0 mL) was heated at 105−110 °C for 3 h. Similar workup as for **27a** afforded 82 mg (15%) of (+)-chatancin **1** and 139.4 mg (25%) of anhydrochatancin **4**.

(20) Further, categorical evidence could be obtained by incubation of isotopically labeled **6** with a cell culture of soft coral *Sarcophyton sp.* The nonphysiological temperature of the chemosynthetic TADA reaction may also suggest an enzymatic assistance from a TADA-ase in the biosynthesis.

Acknowledgment. We wish to thank Dr. Aiya Sato for an authentic sample of (+)-chatancin and Prof. Edda Gössinger for thoughtful discussions and for supplying analytical and spectroscopic data for (±)-**4**.

Supporting Information Available: Experimental procedures and characterization data for all new compounds, ^{1}H NMR spectra for all compounds, and X-ray crystal structure data for compound **27c** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org. The crystal structure for **27c** has been deposited at the Cambridge Crystallographic Data Centre (CCDC 217495).

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