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Transannular Diels–Alder Studies on the Asymmetric Total Synthesis of Chatancin: The Pyranophane Approach

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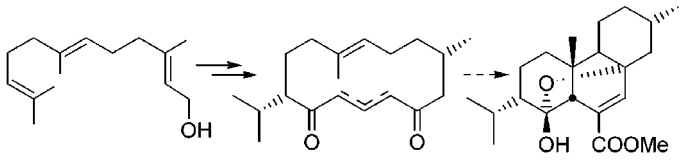
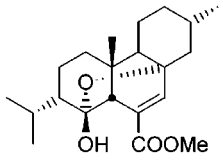
ABSTRACT



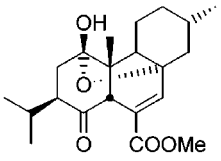
trans-trans-farnesol **28** (+)-chatancin

A pathway is proposed for the biosynthesis of (+)-chatancin and (+)-sarcophytin linking these tetracycles to cembranoids by a pyranophane transannular Diels–Alder reaction. Preliminary synthetic results in this direction to reach macrocyclic dienedione 28 from farnesol are reported. Major synthetic steps include a Prins reaction, two enantioselective hydrogenations, and a macrocyclization via a β-ketosulfoxide Michael-addition on an enone.

PAF antagonist (+)-chatancin[1] (**1**) and (+)-sarcophytin[2] (**2**) were isolated from two different soft coral species of the *Sarcophyton* genus growing thousands of miles apart. Both diterpenes have seven stereogenic centers on a *cis-anti-cis* (CAC) dodecahydrophenantrene skeleton possessing an almost identical functional pattern; they even share a hemiketal bridge although with a dissimilar bridgehead and size, a consequence of an additional carbonyl group in **2**. Moreover, this resemblance extends to their ring-A *iso*-propyl groups; although epimeric both are equatorial. These similarities hint that both **1** and **2** belong to a novel tetracyclic diterpene family. It is possible that their biosynthesis may involve a transannular Diels−Alder (TADA) reaction, which



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



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

coincides with our interest in this reaction.[3] Recently, we have put forward a possible biomimetic synthesis of **1**,[4a] involving a hydride shift mediated oxygen transposition on the TADA product of a furanocembranoid and reported the results of our model studies in that direction.[4b] Now, we propose an alternative biosynthetic pathway involving also a TADA reaction, however, not with a furan but rather a 2*H*-pyran diene.

Performing a retro-TADA transformation on **1** generates pyranophane pseudobase **3a**, which can be traced back to

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

(2) For isolation, 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 shown is the opposite of that reported in ref 2a.

(3) Deslongchamps, P. *Pure Appl. Chem.* **1992**, *64*, 1831−1847.

(4) (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.

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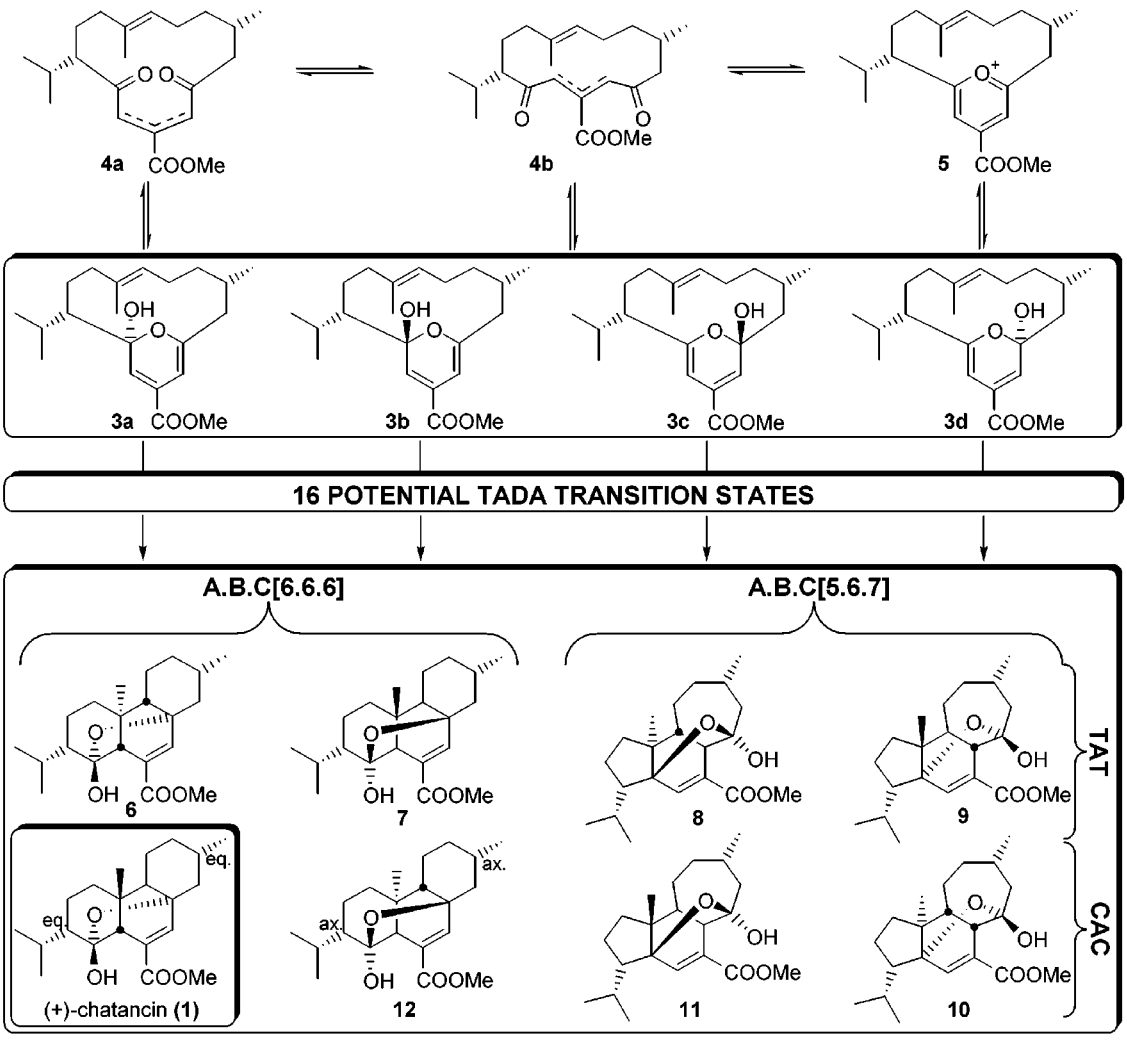
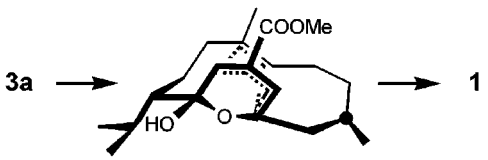
Scheme 1



macrocyclic diketone **4a** (Scheme 1). Examination of the branching of **4a**, omitting the results of skeletal oxidations, reveals its relation to the cembranoid diterpenes.

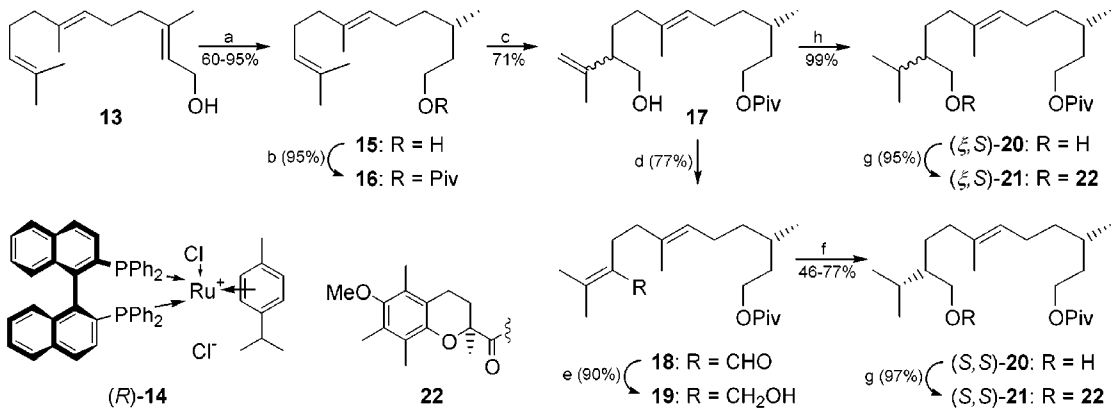
However, from a (bio)synthetic sense, the dynamic equilibrium of **3a** and **4a** should also be considered.[5] Accordingly, in aqueous media these structures are expected to be in a delicate, pH-dependent equilibrium of pseudobases **3**, diketones **4**, and even pyrylium ion **5**. Consequently, to test a plausible involvement of a TADA reaction in this respect, all four pseudobases **3** and their potential TADA products must also be taken into account. Since, in principle, every macrocyclic TADA substrate can have four operative conformations, arising from approach of the diene and dienophile via each of their respective π-faces, the four pseudobases **3** can generate 16 potential transition states (TS). However, the TS in which the hydroxyl group is sandwiched between the diene and the dienophile can safely be eliminated to reduce their number to eight. Moreover, this number can further be halved by excluding TSs leading to hypothetical TAT tetracycles **6**−**9** since, here, the approach of the diene and the dienophile can only be perpendicular and thus unproductive.[3] From the remaining four TS, leading to CAC tetracycles, two would give the A.B.C[5.6.7] ring system of **10** and **11**, which are expected to be disfavored over the alternative A.B.C[6.6.6] system of **1** and **12**. Finally, inspection of these A.B.C[6.6.6] CAC tetracycles, the TADA products of the remaining two TS, shows that **12** has axial peripheral alkyl groups, which again are disfavored over the equatorial ones (Scheme 2). This assumption shows a clear preference for the formation of natural product **1** when a late TS is presumed, and thus, under minimal activation

Scheme 2. Anticipated Operative Transition State



(5) Williams, A. *J. Am. Chem. Soc.* **1971**, *93*, 2733.

Scheme 3[a]



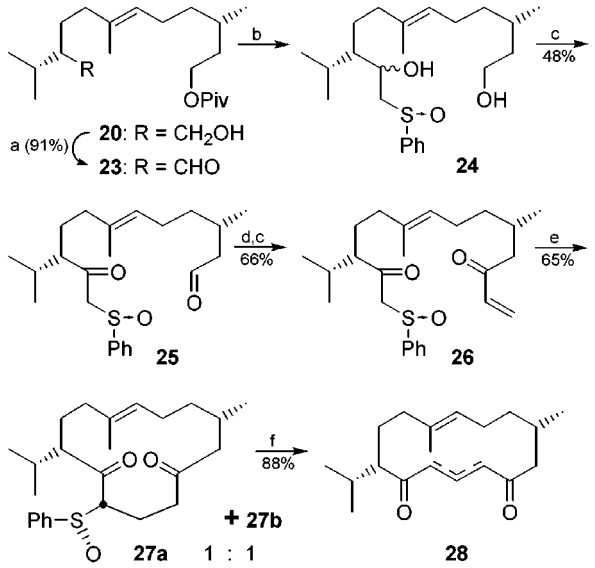
[a] Reagents and conditions: (a) 0.15% (*R*)-**14**, H_2, 1400 psi, 1 day. (b) Piv-Cl, pyridine/CH_2Cl_2. (c) $(CH_2O)_n$, 2 equiv Me_2AlCl, CH_2Cl_2, −80 to 15 °C in 15 min. (d) Swern [O] then Et_3N, 5 h. (e) $NaBH_4$, $CeCl_3$, MeOH, −20 °C. (f) 1.5% (*S*)-**14**, H_2, 1700 psi, 5 days, (97% ee). (g) **22**-OH, DCC, 4-Me_2N-pyridine, CH_2Cl_2. (h) $(PPh_3)_3RhCl$, H_2, PhH.

(heat), these selection rules should prevail.[6] This proposal also implies that acquiring either of compounds **3**, **4**, or **5** can offer an easy access to target **1**. To test our proposal, we initiated a synthetic investigation, preliminary results of which are reported herein.

Our synthesis started with commercial *trans-trans* farnesol (**13**), containing 15 of the 20 carbons of the target skeleton (Scheme 3). Following the precedents,[7] enantioselective catalytic hydrogenation, with (*R*)-**14** catalyst,[8] gave dienol **15**.[9,10] After alcohol protection, Prins reaction[11] on pivalate **16** afforded alcohol **17**.[10] Swern oxidation[12] and a subsequent in situ isomerization of the terminal double bond into conjugation gave aldehyde **18**.[10] Reduction[13] provided allyl alcohol **19**,[10] the substrate for another enantioselective catalytic hydrogenation.[7,9] Since we had found no precedent for the analogous hydrogenation of a tetrasubstituted allylic alcohol, we selected (*S*)-**14**[8] on the basis of the only example of a corresponding reduction of a tetrasubstituted carboxylic acid.[14] The excellent ee of alcohol (*S*,*S*)-**20** was determined by comparing the *iso*-propyl signals in the ^1H NMR spectra of (*S*,*S*)-**21**, an ester with (*S*)-Trolox methyl ether[15] (**22**-OH), to the corresponding epimeric mixture (ξ,*S*)-**21**, made from **17** by a selective catalytic hydrogenation over Wilkinson catalyst to (ξ,*S*)-**20** and a subsequent esterification.[10]

After much experimentation, we selected a Michael addition with a β-keto-sulfoxide for the macrocyclization step (Scheme 4). Thus, tetrapropylammonium perruthenate (TPAP),

Scheme 4[a]



[a] Reagents and conditions: (a) TPAP/NMO, CH_2Cl_2, 0 to 23 °C, 0.5 h. (b) $PhSOCH_2Li$, THF, −80 to 0 °C, 15 h. (c) Dess−Martin periodinane, CH_2Cl_2, $NaHCO_3$, 23 °C. (d) CH_2=CHLi, THF, −80 °C, 1 h. (e) MeCN, Cs_2CO_3, 23 °C, 4 h, 1.7 mM. (f) PhMe, $CaCO_3$, reflux, 1.5 h.

N-methylmorpholine *N*-oxide (NMO) oxidation[16] of alcohol (*S*,*S*)-**20** to aldehyde **23** afforded the electrophile for functionalization at this terminus. During condensation with $PhSOCH_2Li$, deprotection of the other terminus also occurred

(6) Biosynthesis of **2** may involve further oxidation in ring A, followed by transketalization and an epimerization of the *iso*-propyl group.

(7) (a) Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.; Kasahara, I.; Noyori, *J. Am. Chem. Soc.* **1987**, *109*, 1596−1597. (b) R. Mashima, K.; Kusano, K.; Ohta, T.; Noyori, R.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1989**, 1208−1210. (c) Imperiali, B.; Zimmerman, J. W. *Tetrahedron Lett.* **1988**, *29*, 5343−5344.

(8) Used to be available from Aldrich then, now from Fluka (cat. no.): (*R*)-**14**, 37,765-1; 14800 and (*S*)-**14**, 37,767-8; 14801, respectively.

(9) Reproduction of this reaction became difficult. Early experiments, conducted with catalyst from Aldrich, gave pure **15** and **20** (<4% overhydrogenation) with excellent conversions. Later, after switching to Fluka, these results deteriorated to necessitate an extra purification step on a $AgNO_3$-impregnated silica column. See also refs 8 and 10.

(10) See Supporting Information for experimental details.

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(12) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.

(13) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(14) Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3176−3178.

(15) Walther, W.; Vetter, W.; Vecchi, M.; Schneider, H.; Müller, R. K.; Netscher, T. *Chimia* **1991**, *45*, 121−123.

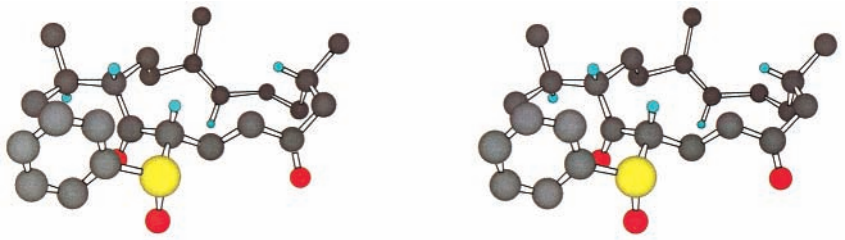

Figure 1. X-ray structure of macrocyclic sulfoxide **27a** in stereoview (hydrogens are partially hidden for clarity).

to provide diol **24**.[10] Parallel, double oxidation[17] with Dess−Martin periodinane produced aldehyde **25** in an acceptable yield. Alkylation with excess vinyllithium gave an allylic alcohol, which after a subsequent periodinane oxidation[17] afforded acyclic substrate **26**.[10] The strategic macrocyclization was carried out under high dilution to afford a 1:1 mixture of only two macrocycles of **27**, the less polar of which, **27a**, gave suitable crystals for X-ray analysis (Figure 1).[10] To our delight, not only the macrocyclic structure was confirmed but also the absolute configuration of the *iso*-propyl group through its relative position to the vis-à-vis methyl group, absolute configuration of which had been well established in respect to catalyst (*R*)-**14**.[7b]

When sulfoxide mixture **27** was thermolyzed under buffered conditions, an inseparable 3:2 mixture of *trans*[18]-dienediones **28** was produced.[10] Exploratory investigations indicated that the ene-1,5-dione systems of **28** are feasible Michael acceptors, e.g., with cyanide.

Further studies are underway to introduce the last carbon of the skeleton and to induce the requisite pyran cyclization and TADA reaction.

Acknowledgment. We thank Marc Drouin for the X-ray analysis. Financial support from BioChem Pharma and NSERC-Canada are highly appreciated.

Supporting Information Available: Experimental procedures and full characterization data for compounds **15**−**21** and **23**−**28**, ^{1}H NMR spectra of (*S*,*S*)-**21** and (ξ,*S*)-**21**, and X-ray data for **27a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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

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

(18) Double bond stereochemistry follows from coupling constants in the ^{1}H NMR spectra of the mixture.