Natural Product Synthesis

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# Synthesis of the Sporolide Ring Framework through a Cascade Sequence Involving an Intramolecular [4+2] Cycloaddition Reaction of an *o*-Quinone**

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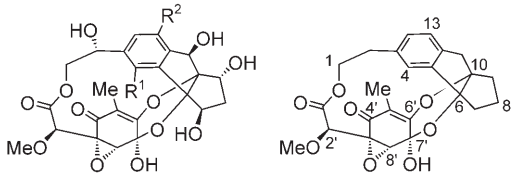
In a recent publication, Fenical and co-workers[1] reported the structural characterization of the two unique molecular frameworks of sporolides A (**1**) and B (**2**; Scheme 1). Isolated from the fermentation broths of a strain of the marine-derived actinomycete *Salinispora tropica*, these compounds feature




***Scheme 1.*** Molecular structures of sporolides A (**1**) and B (**2**) as well as sporolide ring framework **3**.

molecular architectures that contain 24 carbon atoms (among which only two are not oxygenated or $sp^2$ hybridized), 10 stereogenic centers, and no less than seven rings. These marine natural products present an intriguing synthetic challenge in view of their unprecedented molecular structures and the opportunity they present for the development of novel synthetic strategies. Herein we report the construction of model system **3**, which represents the structural skeleton of sporolide A (**1**) and B (**2**) and contains all seven rings of the naturally occurring molecules, through a cascade sequence involving an unprecedented intramolecular [4+2] cycloaddition reaction of an olefinic *o*-quinone.

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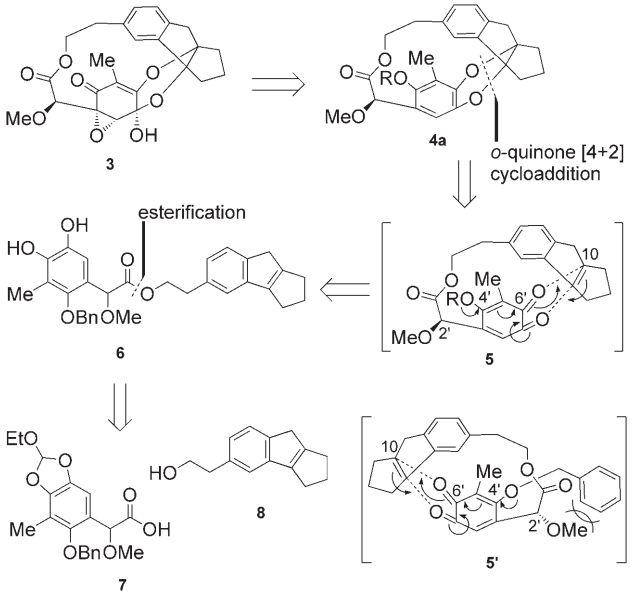
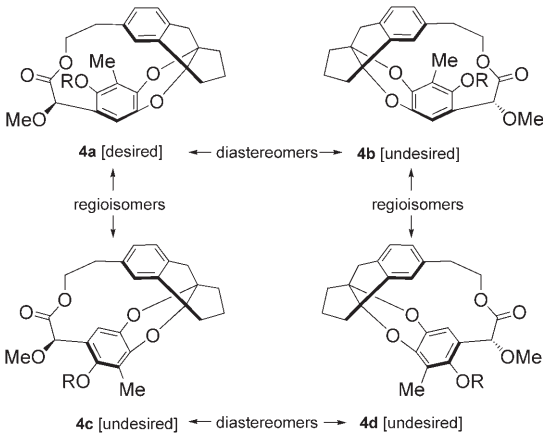
Scheme 2 shows the retrosynthetic analysis of the sporolide model system **3**. Thus, the target molecule was envisioned to arise by selective manipulation of the trioxygenated aromatic nucleus of hexacyclic compound **4a**, whose macrocycle and dioxane moieties were simultaneously dis-




***Scheme 2.*** Retrosynthetic analysis of sporolide ring framework **3**.

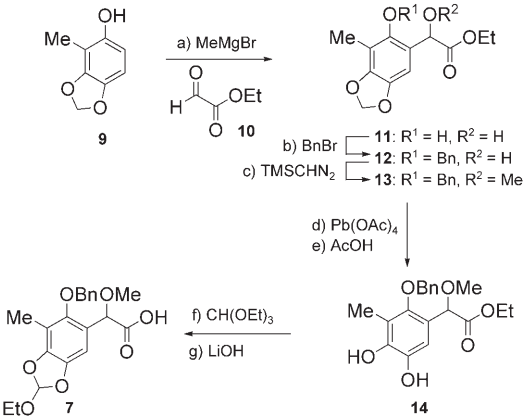
mantled through a retro *o*-quinone [4+2] cycloaddition reaction to reveal *o*-quinone ester **5** as a possible intermediate, whose generation from catechol **6** was considered standard. While the origin of precursor **6** was clear (that is, from building blocks **7** and **8**), the transformation of *o*-quinone **5** to macrocycle **4a** through the intended cycloaddition reaction was based on a rather daring hypothesis since we were aware of no precedent for such an intramolecular reaction of an *o*-quinone.[2,3] Furthermore, should such a scenario be possible, its stereochemical outcome could only be speculated upon at the outset. Encouragingly, both molecular models and molecular mechanics calculations, together with electronic considerations, indicated the desired regio- and diatereoisomer to be favored. Thus, of the four possible isomers of **4a** (**4a**–**4d**, Scheme 3), the desired isomer **4a** was predicted to be the most favored on the basis of electronic (preferential activation of the C6-carbonyl oxygen atom by the C4′-OBn moiety; conjugated addition of the C6-carbonyl oxygen atom onto C10 of the olefinic bond,




***Scheme 3.*** The four possible stereoisomeric products, **4a–4d**, of the intramolecular *o*-quinone indene **5** [4+2] cycloaddition reaction. R = Bn = benzyl.

Scheme 2) and steric grounds (1,3-benzylic strain between the C2′-OMe and the C4′-OBn groups, see **5′**, Scheme 2). The latter effect was reflected in the calculated energy difference of the activation energy of the reactions leading to the four possible isomers, and the strain energy of the final products, **4a–4d** (Scheme 3).[4]

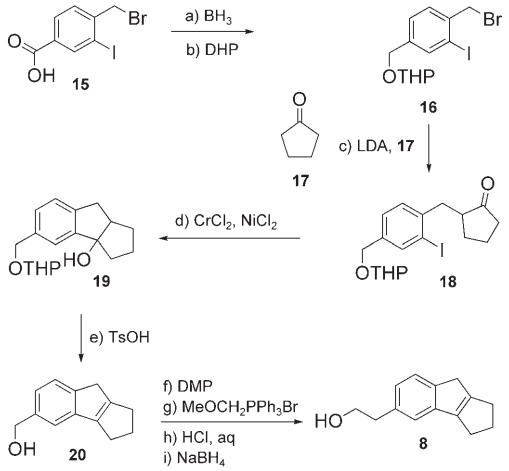
Scheme 4 presents the synthetic approach for the required carboxylic acid building block **7**, starting from the known phenol derivative **9**.[5] Thus, deprotonation of **9** with MeMgBr followed by quenching with ethyl glyoxolate (**10**) resulted in the formation of hydroxy ester **11** in 98% yield. Selective benzylation of the phenol group of **11** ($Cs_2CO_3$, BnBr, NaI, 92% yield) followed by methylation of the resulting secondary alcohol **12** with $TMSCHN_2$ in the presence of $HBF_4$[6]




***Scheme 4.*** Synthesis of building block **7**. Reagents and conditions: a) **9**, MeMgBr (3.0 M in $Et_2O$, 1.2 equiv), THF, 0 °C, 0.5 h; then **10** (50% in toluene, 1.5 equiv), THF, 0 °C, 0.5 h, 98%; b) BnBr (3.0 equiv), $Cs_2CO_3$ (2.0 equiv), NaI (1.0 equiv), DMF, 0→25 °C, 3 h, 92%; c) $TMSCHN_2$ (2.0 M in hexanes, 2.0 equiv), $HBF_4$ (49% in $H_2O$, 1.0 equiv), $CH_2Cl_2$, 0→25 °C, 2 h, 81%; d) $Pb(OAc)_4$ (1.5 equiv), benzene, 80 °C, 16 h; e) AcOH/THF/$H_2O$ (10:5:1), 25 °C, 6 h, 95% over 2 steps; f) $CH(OEt)_3$ (2.0 equiv), TsOH·$H_2O$ (0.2 equiv), 4-Å M.S. (80 mg per mmol **14**), benzene, 80 °C, 16 h, 96%; g) LiOH (20 equiv), dioxane/$H_2O$ (5:1), 80 °C, 3 h, 99%. Ac = acetyl, DMF = *N*,*N*-dimethylformamide, M.S. = molecular sieves, TMS = trimethylsilyl, Ts = *p*-toluenesulfonyl.

furnished intermediate **13** (81% yield). The necessity to remove the catechol protecting group in the presence of the acid-sensitive indene moiety at a subsequent step dictated the exchange of the robust methylene dioxolane with a more labile group at this stage. Thus, **13** was sequentially treated with $Pb(OAc)_4$ (benzene, Δ) and AcOH/THF/$H_2O$ (10:5:1, 25 °C), and the resulting catechol (**14**, 95% overall yield) was converted into the corresponding orthoester by exposure to $CH(OEt)_3$ in the presence of TsOH·$H_2O$[7] (benzene, Δ, 96% yield), from which the desired carboxylic acid **7** was generated by saponification (LiOH, dioxane/$H_2O$ (5:1), 80 °C) in 99% yield.

Scheme 5 summarizes the synthetic approach for the second required building block, indene derivative **8**, starting from the benzoic acid derivative **15**.[8] Reduction of the carboxylic acid moiety of **15** with $BH_3$·THF followed by protection (DHP, TsOH·$H_2O$, 95% yield) of the resulting alcohol furnished THP ether **16**. The latter was then




***Scheme 5.*** Synthesis of building block **8**. Reagents and conditions: a) $BH_3$·THF (1.0 M in THF, 2.0 equiv), THF, 25 °C, 2 h, 80%; b) DHP (1.2 equiv), TsOH·$H_2O$ (0.1 equiv), $CH_2Cl_2$, 0 °C, 0.5 h, 95%; c) **17** (1.3 equiv), LDA (1.3 equiv), THF/HMPA (5:1), −78→0 °C, 1 h; then **16** (1.0 equiv), −78→25 °C, 2 h, 65%; d) $CrCl_2$ (4.0 equiv), $NiCl_2$ (0.02 equiv), DMF, 100 °C, 16 h, 76%; e) TsOH·$H_2O$ (0.1 equiv), benzene, 80 °C, 0.5 h; then $CH_3OH$, 25 °C, 0.5 h, 82%; f) DMP (1.2 equiv), $NaHCO_3$ (3.0 equiv), $CH_2Cl_2$, 25 °C, 0.5 h, 95%; g) $MeOCH_2PPh_3Br$ (1.5 equiv), KHMDS (0.5 M in toluene, 1.5 equiv), THF, 0→25 °C, 2 h, 96%; h) HCl (aq, 2.0 N, 4.0 equiv), THF, 60 °C, 3 h, 88%; i) $NaBH_4$ (1.1 equiv), THF/MeOH (5:1), 0 °C, 0.5 h, 95%. DHP = 3,4-dihydro-2*H*-pyran, DMP = Dess–Martin periodinane, HMPA = hexamethylphosphoramide, KHMDS = potassium hexamethyldisilazane, LDA = lithium diisopropylamide.

employed to alkylate, under basic conditions (LDA, −78→0 °C), cyclopentanone (**17**) to afford cyclopentanone derivative **18**, which was subjected to intramolecular Nozaki–Hiyama–Kishi coupling[9] ($CrCl_2$, cat. $NiCl_2$) to furnish tricyclic tertiary alcohol **19** in 76% yield. Elimination of $H_2O$ from **19** with concomitant removal of the THP group was then achieved by exposure to TsOH·$H_2O$ to afford the hydroxy indene derivative **20** (82% overall yield). The subsequent one-carbon homologation of **20**, as shown in Scheme 5 [DMP oxidation (95% yield); Wittig reaction (96%

yield); HCl aq hydrolysis (88% yield); and $NaBH_4$ reduction (95% yield)], proceeded well to furnish the target fragment **8**.

The required precursor, catechol **6**, was constructed from the newly synthesized building blocks **7** and **8** as shown in Scheme 6. Thus, facilitated by DCC and DMAP, the coupling of carboxylic acid **7** and alcohol **8** led to the formation of ester **21** in 84% yield. Treatment of **21** with $TsOH{\cdot}H_2O$ in MeOH then furnished catechol **6** in 98% yield. Upon heating a toluene solution of **6** (0.005 M) in the presence of $Ag_2O$ (2.0 equiv) at 120°C, we were delighted to observe the formation of a single product whose spectroscopic data were consistent with that of structure **4a**, but did not unambiguously exclude its other three isomers (**4b**–**4d**, Scheme 3).

X-ray crystallographic analysis (Figure 1) of phenol **22**[10] (m.p. 233–234°C, acetone/hexanes, obtained by hydrogenolysis ($H_2$, 20% $Pd(OH)_2$ on carbon (cat.), 85% yield) of **4a**) confirmed its structure, and therefore the structure of **4a**. This additional structural information proves our original hypothesis for both the regio- and stereochemical outcome of the intramolecular [4+2] cycloaddition reaction of *o*-quinone indene **5**. The existence of intermediate *o*-quinone **6** was confirmed by a stepwise sequence in which $Ag_2O$ was used to oxidize catechol **6** at room temperature to give **5** in 99% yield as a stable isolated intermediate. Subsequently, **5** was heated in toluene at 120°C to produce macrocycle **4a** in 50% yield.

Having secured the core skeletal framework of the sporolide natural products through a cascade sequence involving the novel *o*-quinone [4+2] cycloaddition strategy, we then proceeded to demonstrate the applicability of the method by constructing the remaining structural motifs of the molecule. Thus, oxidation of **22** with $PhI(CO_2CF_3)_2$[11] in the presence of PMBOH produced PMB ketal quinone **23**, as a single diastereomer, in 87% yield. Based on steric considerations, the stereochemistry of the PMB ketal **23** was tentatively assigned as having the α configuration as shown in Scheme 6, which was presumed to originate from attack of PMBOH from the bottom face of the cationic intermediate. This assumption was later confirmed by the synthesis of hydroxy epoxide **3**, whose structure was confirmed by NMR spectroscopy and X-ray crystallography (Figure 2). The deprotection of **23** was accomplished by using DDQ to afford hemiketal **24** in 96% yield. Finally, treatment of **24** with five equivalents of *t*BuOOH in the presence of catalytic amounts of DBU[12] furnished the targeted hydroxy epoxide **3** in 60% yield as a single compound. The *syn* relationship between the hydroxy and epoxide moieties was expected from the known directing effect of the hydroxy group on the epoxidation reaction.[12] The $^1H$ and $^{13}C$ NMR spectroscopic data of **3** were consistent with those of the naturally occurring sporolides A and B.[1] The relative configuration of the epoxide moiety was confirmed by the observed NOE interaction between H4 and H8′, and between H8′ and the $CH_3O$ group at position 2′, as shown in **3′** (Scheme 6). Finally, the assigned structure of model system **3** (m.p. 218–219°C, acetone/hexanes) was confirmed by X-ray crystallography (Figure 2).[13]

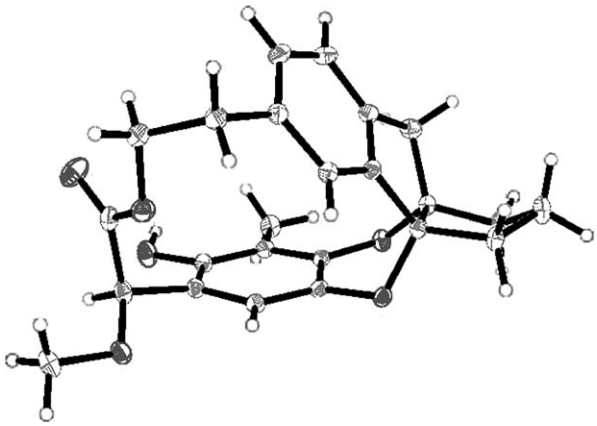
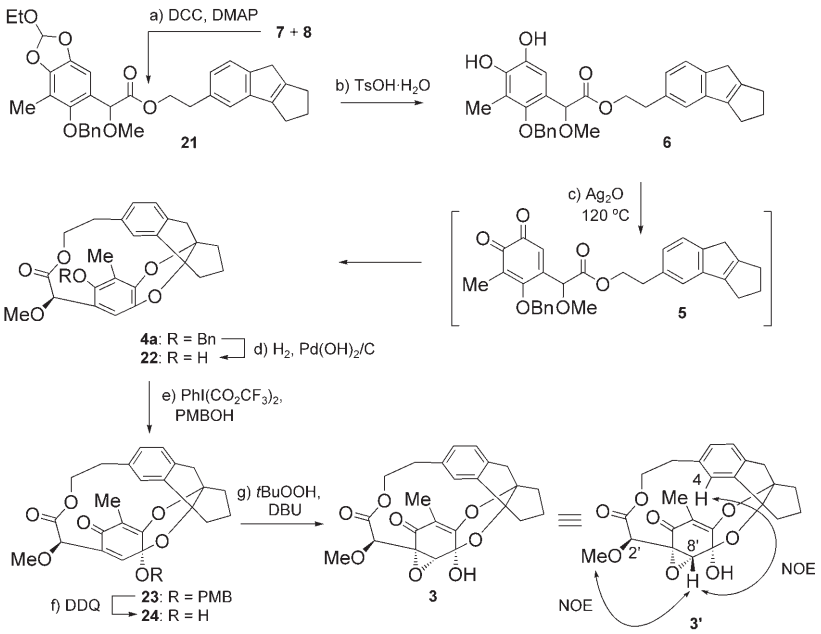


***Figure 1.*** ORTEP plot of **22** with thermal ellipsoids at 30% probability level.




***Scheme 6.*** Synthesis of sporolide ring framework **3**. Reagents and conditions: a) **7** (1.25 equiv), **8** (1.0 equiv), DCC (1.3 equiv), DMAP (0.2 equiv), $CH_2Cl_2$, 25°C, 3 h, 84%; b) $TsOH{\cdot}H_2O$ (0.05 equiv), MeOH, 25°C, 24 h, 98%; c) one-step procedure: $Ag_2O$ (2.0 equiv), toluene (0.005 M solution), 120°C, 1 h, 60%; two-step procedure: 1. $Ag_2O$ (2.0 equiv), $CH_2Cl_2$, 25°C, 99%; 2. toluene (0.005 M solution), 120°C, 3 h, 50%; d) $H_2$ (ca. 1 atm), $Pd(OH)_2$/C (20 wt%), EtOH, 25°C, 14 h, 85%; e) $PhI(CO_2CF_3)_2$ (1.05 equiv), PMBOH (10 equiv), $K_2CO_3$ (5.0 equiv), MeCN, 0→25°C, 5 min, 87%; f) DDQ (1.5 equiv), $CH_2Cl_2/H_2O$ (10:1), 25°C, 15 h, 96%; g) *t*BuOOH (5.0 equiv), DBU (0.2 equiv), $CH_2Cl_2$, 40°C, 24 h, 60%. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DCC = *N*,*N*′-dicyclohexylcarbodiimide, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = dimethylaminopyridine, PMB = *p*-methoxybenzyl, THP = tetrahydropyranyl.

In conclusion, we have demonstrated the feasibility of a cascade sequence involving a novel intramolecular [4+2] cycloaddition reaction as a means to stereoselectively construct the dioxane-containing macrocy-

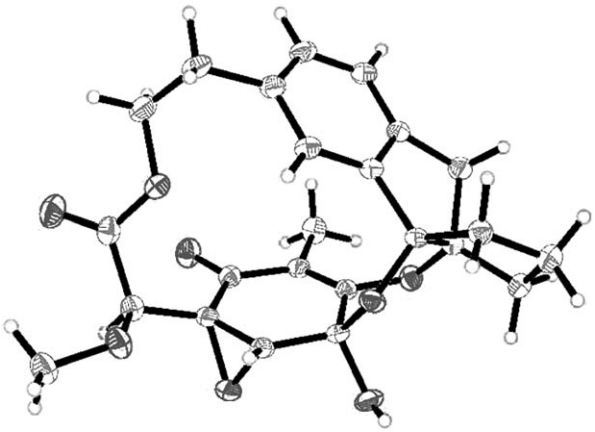


***Figure 2.*** ORTEP plot of model system **3** with thermal ellipsoids at 30% probability level.

cle of sporolides A (**1**) and B (**2**). In addition, we have shown how such an efficient strategy can be employed to form the hydroxy epoxide moiety of these natural products. Furthermore, the reported chemistry raises the possibility of such a [4+2] cycloaddition process being involved in the biogenesis of these structurally intriguing molecules.[14] Given the unprecedented nature and potential of the reported cycloaddition reaction as well as the unusual architectures of the sporolide family of natural products, further applications and studies towards these molecular targets are anticipated.

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[1] G. O. Buchanan, P. G. Williams, R. H. Feling, C. A. Kauffman, P. R. Jensen, W. Fenical, *Org. Lett.* **2005**, *7*, 2731 – 2734.

[2] *o*-Quinones are capable of participating in intermolecular [4+2] reactions with either their 1,2-dicarbonyl moiety or with their endocyclic diene system; for reviews on *o*-quinone chemistry, see a) L. Horner, H. Merz, *Justus Liebigs Ann. Chem.* **1950**, *570*, 89 – 120; b) V. Nair, S. Kumar, *Synlett* **1996**, 1143 – 1147.

[3] For a different type of intramolecular reaction of *o*-quinones, see K. C. Nicolaou, T. Lister, R. M. Denton, C. F. Gelin, *Angew. Chem.* **2007**, *119*, 7645 – 7649; *Angew. Chem. Int. Ed.* **2007**, *46*, 7501 – 7504.

[4] The following values were obtained using the Spartan '06 program (Wavefunction, INC): relative differences of activation energies of reactions leading to products: **4a**: $\Delta E$a = 0 kcal mol$^{-1}$; **4b**: $\Delta E$a = 2.72 kcal mol$^{-1}$; **4c**: $\Delta E$a = 12.8 kcal mol$^{-1}$; **4d**: $\Delta E$a = 9.98 kcal mol$^{-1}$; relative differences in strain energies of products: **4a**: $\Delta E_{Final}$ = 0 kcal mol$^{-1}$; **4b**: $\Delta E_{Final}$ = 3.22 kcal mol$^{-1}$; **4c**: $\Delta E_{Final}$ = 10.4 kcal mol$^{-1}$; **4d**: $\Delta E_{Final}$ = 7.95 kcal mol$^{-1}$.

[5] X. Chen, J. Chen, M. De Paolis, J. Zhu, *J. Org. Chem.* **2005**, *70*, 4397 – 4408.

[6] T. Aoyama, T. Shioiri, *Tetrahedron Lett.* **1990**, *31*, 5507 – 5508.

[7] S. Danishefsky, J. Y. Lee, *J. Am. Chem. Soc.* **1989**, *111*, 4829 – 4837.

[8] S. Shankar, G. Vaidyanathan, D. Affleck, P. C. Welsh, M. R. Zalutsky, *Bioconjugate Chem.* **2003**, *14*, 331 – 341.

[9] A. Fürstner, *Chem. Rev.* **1999**, *99*, 991 – 1046.

[10] CCDC 667552 contains the supplementary crystallographic data for compound **22**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

[11] Y. Tamura, T. Yakura, J. Haruta, Y. Kita, *J. Org. Chem.* **1987**, *52*, 3927 – 3930.

[12] K. Zilbeyaz, E. Sahin, H. Kilic, *Tetrahedron: Asymmetry* **2007**, *18*, 791 – 796.

[13] CCDC 669253 contains the supplementary crystallographic data for model system **3**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

[14] a) W. Fenical, P. R. Jensen, *Nat. Chem. Biol.* **2006**, *2*, 666 – 673; b) D. W. Udwary, L. Zeigler, R. N. Asolkar, V. Singan, A. Lapidus, W. Fenical, P. R. Jensen, B. S. Moore, *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 10376 – 10381; c) C. L. Perrin, B. L. Rodgers, J. M. O'Connor, *J. Am. Chem. Soc.* **2007**, *129*, 4795 – 4799.

  