VOLUME 72, NUMBER 5

JOC Articles

MARCH 2, 2007

© Copyright 2007 by the American Chemical Society

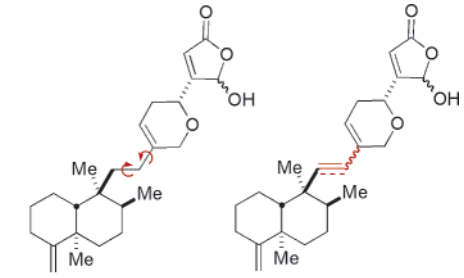
# Conformationally Restricted (+)-Cacospongionolide B Analogues. Influence on Secretory Phospholipase $A_2$ Inhibition

Ryan P. Murelli, Atwood K. Cheung, and Marc L. Snapper*

*Department of Chemistry, Merkert Chemistry Center, Boston College, 2609 Beacon Street, Chestnut Hill, Massachusetts 02467*

*marc.snapper@bc.edu*

*Received July 6, 2006*




A new approach to (+)-cacospongionolide was developed to access conformationally restricted variants of the natural product. The flexible aliphatic region between the decalin and side chain portion of the natural product was replaced with alkenyl and alkynyl linkers to probe the influence of structural rigidity in the inhibition of secretary phospholipase $A_2$ ($sPLA_2$). It was found that when the aliphatic section is replaced with a *Z*-olefin or an alkyne, $sPLA_2$ inhibitory activity suffered relative to the natural product; however, an *E*-olefin-containing analogue led to an enhanced activity. These results suggest that preferred $sPLA_2$ binding conformation of the natural product is similar to the geometry of the *E*-olefin-containing analogue.

## Introduction

The marine sponge metabolite (+)-cacospongionolide B (+)-**1** is a member of a class of compounds bearing a $\gamma$-hydroxybutenolide moiety. This functionality has been suggested to be important in the inhibition of several forms of secretary phospholipase $A_2$ ($sPLA_2$),[1] enzymes involved in events leading to inflammation.[2] Given the role of chronic inflammation in diseases such as asthma, psoriasis, cancer, atherosclerosis, and rheumatoid arthritis, it is becoming increasingly important to discover and develop more effective agents that can mediate these pro-inflammatory signaling events.[3] With a successful route to cacospongionolide B already in hand, efforts have turned toward understanding the structural features of the natural product responsible for inhibiting $sPLA_2$ activity.[4] Our previous findings indicated that furan **2** possessed comparable $sPLA_2$ inhibitory activity to (+)-**1**, while the enantiomer of the natural

(1) Monti, M. C.; Casapullo, A.; Riccio, R.; Gomez-Paloma, L. *Bioorg. Med. Chem.* **2004**, *12*, 1467.

(2) For a recent review on $sPLA_2$, see: Triggiani, M.; Granata, F.; Giannattasio, G.; Marone, G. *J. Allergy Clin. Immunol.* **2005**, *116*, 1000.

(3) Heller, A.; Koch, T.; Schmeck, J.; can Ackern, K. *Drugs* **1998**, *55*, 487.

(4) Cheung, A. K.; Murelli, R. P.; Snapper, M. L. *J. Org. Chem.* **2004,** 69, 5712.

(5) (a) Cheung, A. K.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 11584. For related synthetic studies, see: (b) Demeke, D.; Forsyth, C. J. *Org. Lett.* **2003**, *5*, 991.

10.1021/jo061407a CCC: $37.00 © 2007 American Chemical Society
Published on Web 10/17/2006

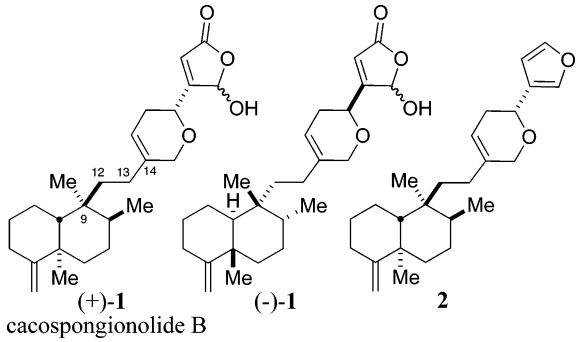



**FIGURE 1.** Cacospongionolide B and structural analogues.

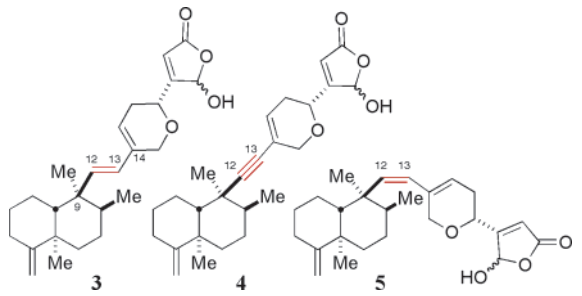



**FIGURE 2.** Conformationally restricted cacospongionolides.

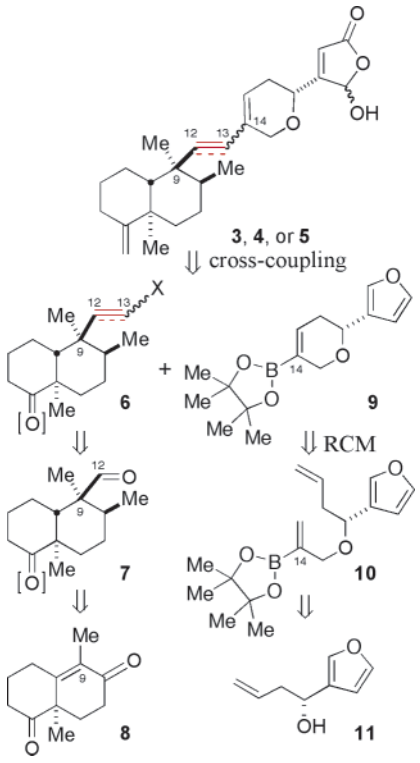
product (−)-**1** was less active. In addition, several unnatural diastereomers of the natural product were identified that displayed improved *s*PLA$_2$ inhibitory activity over (+)-**1**.[5]

A common practice in strengthening small molecule interactions with macromolecular targets is to rigidify flexible portions of the ligand, thus reducing the entropic loss that takes place when the small molecule interacts with its target in a particular conformation.[6] When the redesigned inhibitor's geometry emulates correctly the specific binding conformation of the flexible ligand, appreciable increases in binding efficiency are possible. Accordingly, we envisioned that changes in the flexible aliphatic region (C9−C12−C13−C14) between the dihydropyran and decalin regions of cacospongionolide B could provide more potent *s*PLA$_2$ inhibitors.

Probing several geometries was considered prudent given our lack of knowledge of cacospongionolide B's specific conformation when interacting with *s*PLA$_2$. Three cacospongionolide B analogues (**3**−**5**) that provide complementary geometric constraints in the C9−C12−C13−C14 region of the natural product are illustrated in Figure 2. In each of these examples, the unsaturation introduced at the C12−C13 bond serves to limit significantly the rotational freedom between the decalin and side chain regions of these molecules. Moreover, the conjugated nature of dienes **3** and **5** provides additional constraints for the C13−C14 bond, as well.

Unfortunately, these compounds were not readily accessible through our original synthesis.[4,5] Herein is described a new synthetic route featuring a revised fragment coupling strategy required to access these conformationally rigidified variants of cacospongionolide. In addition, preliminary activity studies of these new cacospongionolide analogues in *s*PLA$_2$ inhibitory assays are reported.

**SCHEME 1. Retrosynthesis to the Conformationally Restricted Analogues 3−5**




## Results and Discussion

**Chemistry.** Scheme 1 illustrates our plan for preparing the rigidified analogues **3**−**5**. We envisioned that if the appropriately functionalized alkenyl or alkynyl halide **6** can be generated in a stereocontrolled manner, a cross-coupling with dihydropyranyl borane **9** should provide the desired conformationally restricted products **3**−**5**. Fragment **9** should be available through a ring closing metathesis (RCM) of the appropriately functionalized vinyl borane **10**,[7] which in turn can be prepared from the known homoallylic alcohol **11**. We anticipated that any of the required alkenyl or alkynyl halides (**6**) needed in the cross-coupling step can be prepared from aldehyde **7**. Intermediate **7** should be available from enone **8**, which was used in our initial route to (+)-**1**.

Starting from commercially available 3-furaldehyde, we accessed the known homoallylic alcohol **11** in 82% yield and 93% ee through Brown's asymmetric allylboration (Scheme 2).[8,9] Alternatively, alcohol **11** could be prepared in 82% ee and 64% yield in a proline oxide-catalyzed asymmetric addition of trichloroallyl silane into 3-furaldehyde.[10] In either case,

(6) (a) Khan, A. R.; Parrish, J. C.; Fraser, M. E.; Smith, W. W.; Bartlett, P. A.; James, M. N. G. *Biochemistry* **1998**, *37*, 16839. (b) Kang, J.-H.; Kim, S. Y.; Lee, J.; Marquez, V. E.; Lewin, N. E.; Pearce, L. V.; Blumberg, P. M. *J. Med. Chem.* **2004**, *47*, 4000. (c) White, M. C.; Burke, M. D.; Peleg, S.; Brem, H.; Posner, G. H. *Bioorg. Med. Chem.* **2001**, *9*, 1691. (d) Vajda, S.; Wheng, Z.; Rosenfeld, R.; DeLisi, C. *Biochemistry* **1994**, *33*, 13977.

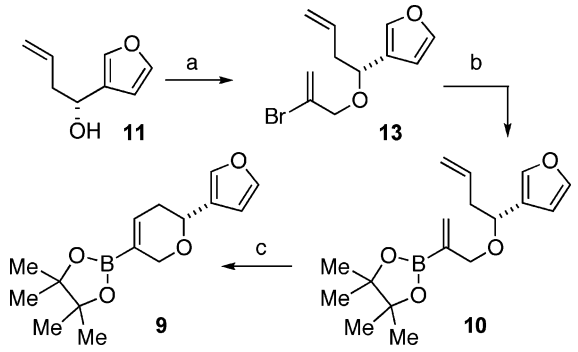
(7) Renaud, J.; Ouellet, S. G. *J. Am. Chem. Soc.* **1998**, *120*, 7995.

(8) Racherla, E. S.; Liao, Y.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 6614.

(9) Purification of the homoallylic alcohol **11** remained troubling, given the similar polarity and boiling points of the desired product and the pineol byproduct. When attempts to purify using Brown's previously described methods failed in our hands, it was found that passing the reaction mixture through a short column of 10% $AgNO_3$ impregnated silica with use of a 50/50 mixture of hexanes and diethyl ether afforded high yields and purity of the desired product.

(10) Traverse, J. T.; Zhao, Y.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2005**, *7*, 3151.

**SCHEME 2. Synthesis of Dihydropyranyl Borane 9**[a]



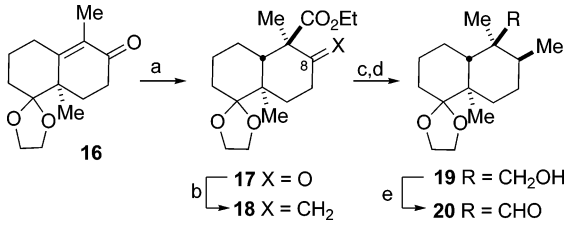
[a] Reagents and conditions: (a) NaH, 15-C-5, benzene, 0 °C to rt; 2,3-dibromopropene (**12**), 0 °C (75%). (b) *t*-BuLi, $Et_2O$, −78 °C; 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**14**), −78 °C to rt. (c) IMes($Cy_3P$)($Cl_2$)Ru=CHPh (**15**, 10 mol %), benzene (45%, 2 steps).

O-alkylation of **11** with 2,3-dibromopropene **12** afforded allylic ether **13** in 75% yield. Lithium−halogen exchange followed by isopropoxy borolane **14** trap provided the pinacol borolane **10**, which was carried on to the borolane fragment **9** through a RCM by using Grubbs' second generation catalyst **15** in 45% overall yield for the two steps.[7] With access to pyran **9**, attention was turned toward generating coupling partner **6**.

Aldehyde **7** presented itself as a versatile target from which all the rigidified analogues could be generated. As shown in Scheme 3, a scalable enantioselective synthesis of the appropriately functionalized aldehyde **20** was, therefore, pursued. With use of a procedure by Crabtree et al.,[11] optically pure enone **16**[12] was subjected to a reductive alkylation with Mander's reagent to access $\beta$-ketoester **17** in 85% yield (14:1 dr). A more streamlined approach could be envisioned by performing the reductive alkylation with formaldehyde; however, this route provided poor yields (≤50%) and unsatisfactory diastereoselectivity (≤5:1). In addition, when the resultant alcohol was subjected to a Wittig olefination, retro-aldol products predominated. The Wittig olefination of $\beta$-keto ethyl ester **17**, on the other hand, provided the desired exocyclic C8 alkene **18** in 83% yield.[13] Interestingly, the olefination of the corresponding $\beta$-keto methyl ester led primarily to decarboxylation byproducts. In any event, subjecting the newly formed olefin to a stereoselective reduction with platinum oxide afforded an inseparable, 8:1 mixture of diastereomers,[14] which after LAH reduction were easily separable through silica gel chromatography to afford diastereomer **19**. Oxidation led to our target aldehyde **20** in quantitative yield.[15]

Given that Wittig olefinations can lead to olefin isomers, it was initially expected that the *E*- and *Z*-vinyl bromides could be accessed in a single reaction from aldehyde **20**.[16] Unfortunately, this olefination was unsuccessful on aldehyde **20**, presumably due to the dense steric environment encompassing the carbonyl group. The use of various bases and solvents with

**SCHEME 3. Synthesis of Aldehyde 20**[a]



[a] Reagents and conditions: (a) Li°/$NH_3$, *t*-BuOH, $Et_2O$, −33 °C; ethyl cyanoformate, $Et_2O$, −78 °C (85%, 14:1 dr). (b) $Ph_3PCH_3Br$, KO*t*-Bu, THF, rt (83%). (c) $PtO_2$, 1 atm of $H_2$, $CH_2Cl_2$, rt. (d) LAH, THF, rt (84%, 2 steps, 7.7:1 dr). (e) TPAP, NMO, $CH_2Cl_2$, 4 Å MS (>98%).

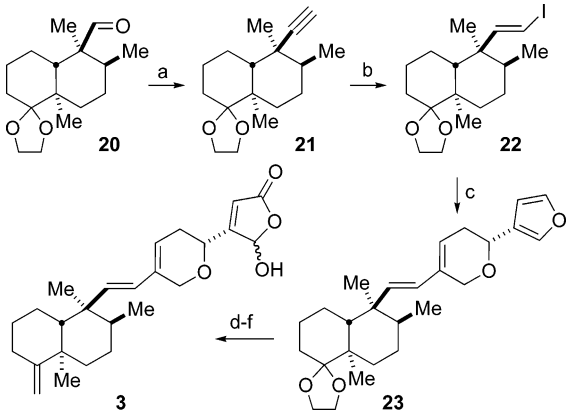
bromomethyl triphenylphosphonium bromide and aldehyde **20** gave inconsistent results ranging from no conversion, which was often the case when temperatures were held below −10 °C, to decomposition of the ylide under conditions approaching room temperature, to full conversion to an unexpected non-halogenated terminal olefin, which was the case when using Ley's one-pot TPAP-NMO/Wittig reaction.[17] Conversion to a *trans*-vinyl iodide through Takai olefination,[18] as well as various alkyne-generating reactions,[19] also was not successful. On the other hand, as illustrated in Scheme 4, conversion of aldehyde **20** to acetylene **21** was possible through a modified Seyferth−Gilbert protocol.[20] With use of an excess of the Ohira−Bestmann reagent[21] and extended reaction times, acetylene **21** was prepared in an 86% yield (based on 93% conversion of starting material).

From the acetylene **21**, all of the conformationally restricted linkers were accessible. As also shown is Scheme 4, hydrozirconation of alkyne **21** with Schwartz's reagent generated in situ, followed by an iodide trap provided the *E*-vinyl iodide **22**, as well as some of the reduced terminal olefin.[22] Subjecting this reaction mixture to cross-coupling conditions with fragment **9** afforded diene **23** with the desired *E*-olefin geometry in 60% overall yield for the two steps.[23] The final three steps of the synthesis followed our original route to the natural product. A mild ketal deprotection of **23** with acetic acid and water, followed by Wittig olefination at room temperature completed the carbon frame in moderate yields. Selective photooxidation of the furan ring with rose bengal under basic conditions then completed the synthesis of analogue **3**.

Access to the other conformationally restricted variants is illustrated in Scheme 5. Bromination of acetylene **21** to generate **24** was achieved quantitatively by using *N*-bromosuccinimide in the presence of catalytic silver nitrate.[24] Suzuki coupling of **24** with borane **9** afforded enyne **25** in 85% yield. As with analogue **3**, ketal deprotection, olefination, and photooxidation provided the alkyne-containing analogue **4**. Alkyne **25** could also be converted to diene **26** with a *Z*-olefin in quantitative yields through careful hydrogenation. As before, diene **26** was

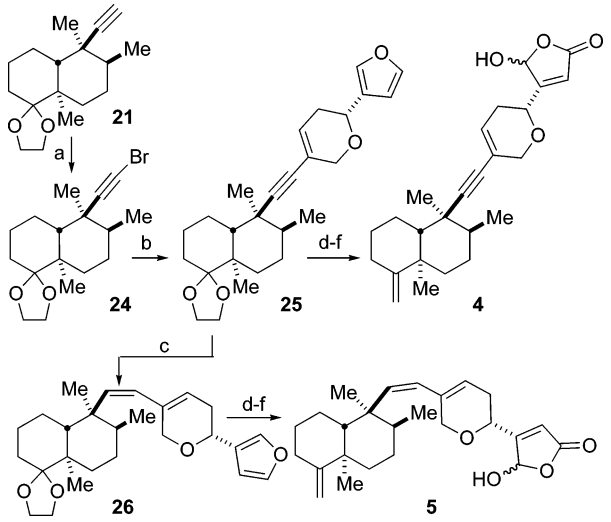
(11) Crabtree, S. R.; Mander, L. N.; Sethi, S. P. *Org. Synth.* **1992**, *70*, 256.
(12) (a) Uma, R.; Swaminathan, S.; Rajagapolan, K. *Tetrahedron Lett.* **1984**, *25*, 5825. (b) Hagiwara, H.; Uda, H. *J. Org. Chem.* **1988**, *53*, 2308.
(13) Ishikazi, M.; Iwahara, K.; Niima, Y.; Satoh, H.; Hoshino, O. *Tetrahedron* **2001**, *57*, 2729.
(14) Bruner, S. D.; Radeke, H. S.; Tallarico, J. A.; Snapper, M. L. *J. Org. Chem.* **1995**, *60*, 1114.
(15) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, *21*, 1625.
(16) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1980**, *21*, 4021.
(17) MacCoss, R. N.; Balskus, E. P.; Ley, S. V. *Tetrahedron Lett.* **2003**, *44*, 7779.
(18) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
(19) (a) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, *2*, 107. (b) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1980**, *21*, 4021. (c) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769.
(20) Kerr, W. J.; McLaughlin, M.; Morrison, A. J.; Pauson, P. L. *Org. Lett.* **2001**, *3*, 2945.
(21) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.
(22) Gallagher, W. P.; Maleczka, R. E., Jr. *J. Org. Chem.* **2003**, *68*, 6775.
(23) Stewert, S. K.; Whiting, A. *Tetrahedron Lett.* **1995**, *36*, 3925.

**SCHEME 4. Synthesis of Rigidified Cacospongionolide Analogue 3**



[a] Reagents and conditions: (a) $CH_3COCN_2PO(OMe)_2$ (Ohira−Bestmann reagent), $K_2CO_3$, MeOH, rt, (86%, 93% conversion). (b) (i) $Cp_2ZrCl_2$, $LiHBEt_3$, THF, rt; (*ii*) $I_2$, THF, 0 °C. (c) **9**, 5 mol % of $Pd(PPh_3)_4$, LiOH(aq), THF, rt (60% over 2 steps). (d) AcOH:$H_2O$ (3:1), 60 °C (75%). (e) $CH_3PPh_3Br$, KO*t*Bu, THF, rt (67%). (f) Rose bengal, $O_2$, $CH_2Cl_2$/MeOH, *i*$Pr_2$NEt, *hν*, −78 °C to rt (56%).

**SCHEME 5. Synthesis of Compounds 4 and 5**



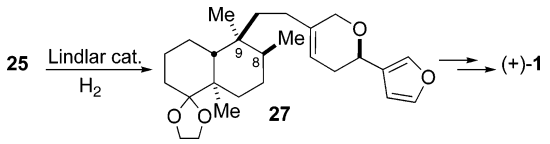
[a] Reagents and conditions: (a) 30 mol % $AgNO_3$, NBS, acetone, rt (>98%). (b) Dihydropyranyl borane **9**, 5 mol % of $Pd(PPh_3)_4$, KOH(aq), THF, rt (85%). (c) Lindlar's catalyst, quinoline, EtOAc, 1 atm of $H_2$, (>98%). (d) AcOH:$H_2O$ (3:1), 60 °C (88−90%). (e) $CH_3PPh_3Br$, KO*t*Bu, THF, rt (65-80%). (f) Rose bengal, $O_2$, $CH_2Cl_2$/MeOH, *i*$Pr_2$NEt, *hν*, −78 °C to rt (42−50%).

then transformed into the desired *Z*-olefin-contain analogue **5** through the same deprotection of the ketal, olefination, and photooxidation sequence.

Alternatively, extended hydrogenation times and increased catalyst loading during the Lindlar reduction of alkyne **25** led to the over-reduced product **27** (Scheme 6). Interestingly, compound **27** is an intermediate in our previous synthesis of (+)-cacospongionolide B. These results provided a formal synthesis of (+)-**1**, and moreover, confirmed the appropriate C8 and C9 stereochemistry of the cacospongionolide analogues generated in this modified reaction sequence. With the desired conformationally restricted analogues **3**−**5** in hand, efforts turned toward their evaluation as *s*$PLA_2$ inhibitors.

**Biology.** The newly synthesized analogues were examined along with the natural product (**1**) in a bee venom *s*$PLA_2$ assay.

**SCHEME 6. Formal Synthesis of (+)-Cacospongionolide**



It was found that *E*-analogue **3** displays increased potency over the natural product, while analogues **4** and **5** showed decreased activity (Figure 3). This result suggests that the binding conformation of cacospongionolide B may more closely resemble the extended geometry of the *E*-analogue **3** (Figure 4).

Pharmacological relevance of bee venom *s*$PLA_2$ is limited when compared to that of human *s*$PLA_2$. In particular, group V phospholipase $A_2$ has been gaining interest over the last several years because of its unique ability to effectively cleave normal mammalian cell membranes, and thus has become a strong target for pharmaceutical study.[25] While cacospongionolide B is a known inhibitor of human type IIa *s*$PLA_2$,[26] to the best of our knowledge the natural product had not been tested as a type V inhibitor. We therefore examined cacospongionolide B in human (type V) *s*$PLA_2$ assays. Unfortunately, cacospongionolide B showed no inhibition of human type V *s*$PLA_2$ at concentrations of up to 180 $\mu$M.

## Conclusions

A revised synthesis of cacospongionolide B provides an effective strategy for preparing conformationally restricted cacospongionolide B analogues. *s*$PLA_2$ inhibition studies with these structural variants indicate that (a) cacospongionolide B's binding conformation is likely to resemble that of the *E*-bridged analogue **4**, (b) compound **4** displayed increased inhibitory potency over cacospongionolide B in a bee venom *s*$PLA_2$, and (c) (+)-cacospongionolide B does not appear to have notable inhibitory activity against human type V *s*$PLA_2$.

## Experimental

**General Information.** Starting materials and reagents were purchased from a commercial supplier and used without further purification with the exception of the following: Diisopropylethylamine was distilled over $CaH_2$ and stored over KOH prior to use; isoprene was freshly distilled from $Na^0$; diethyl ether, tetrahydrofuran, benzene, hexanes, ethyl acetate, and dichloromethane were dried on an alumina column, using a solvent dispensing system;[27] hexanes and diethyl ether used in chromatography were distilled prior to use. All reactions were conducted in over-dried (135 °C) or flame-dried glassware under an inert $N_2$ atmosphere.

**Ethyl 5′,8a′-Dimethyl-6′-oxooctahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalene]-5′-carboxylate (17).** To a stirred solution of $Li^0$ (260 mg, 37.2 mmol) in dried $NH_3$ (75 mL) under a dry ice/acetone condenser was added a solution of enone **16** (4.00 g, 16.9 mmol) and *t*-BuOH (1.10 mL, 11.5 mmol) in $Et_2O$ (30 mL). The mixture was stirred for 1 h at which time isoprene, freshly distilled from $Na^0$, was added dropwise until the solution turned from deep blue to white (or often pink). The $NH_3$ was evaporated, and $Et_2O$ and isoprene were pumped off under vacuum. Once evaporation was

(24) Hofmeister, H; Annen, K; Laurant, H; Weichert, R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 727.
(25) Wilton, D. C. *Eur. J. Lipid Sci. Technol.* **2005**, *107*, 193−205.
(26) De Rosa, S.; Crispino, A.; De Giulio, A.; Iodice, C.; Benrezzouk, R.; Terencio, M. C.; Ferrándiz, M. L.; Alcaraz, M. J.; Payá, M. *J. Nat. Prod.* **1998**, *61*, 931.
(27) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518.

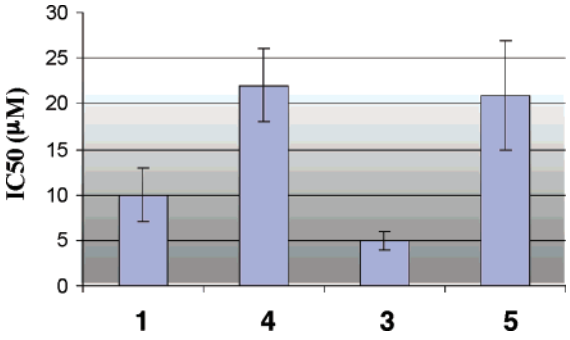



**FIGURE 3.** Inhibition of bee venom *s*PLA$_2$.

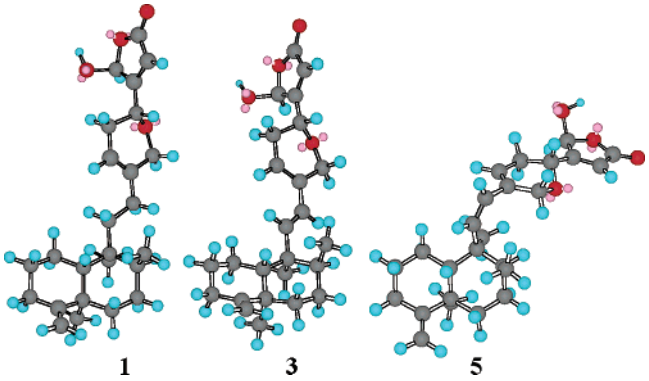



**FIGURE 4.** Structural models of the cacospongionolide B and the *E*- and *Z*-analogues **3** and **5**.

complete, a $N_2$ atmosphere was resubmitted and $Et_2O$ (50 mL) was added. The solution was cooled to −78 °C, ethyl cyanoformate (2.00 g, 20.2 mmol) was added dropwise to the side of the flask, and the reaction mixture was stirred at this temperature for 1 h. The reaction mixture was quenched with water (50 mL) and extracted with $Et_2O$ (3 × 20 mL). The organic layers were washed with brine, dried over $MgSO_4$, and concentrated to a light green oil (14:1 dr). The aqueous layers were treated with $KMnO_4$ prior to disposal. Column chromatography (7:1 hexanes:$Et_2O$) provided desired diastereomer **17** (4.2 g) and undesired product (300 mg) (85% yield). Mp 62−65 °C. FTIR (NaCl, thin film) 3025 (m), 2952 (s), 2881 (m), 1734 (s), 1707 (s), 1249 (m), 1184 (m), 1132 (m), 1054 (m), 950 (w) cm$^{-1}$. $^1$H NMR (100 MHz, $CDCl_3$) $\delta$ 1.10 (m, 1H), 1.25 (m, 6H), 1.33 (s, 3H), 1.61 (m, 6H), 2.07 (dt, $J$ = 13.5, 5.1 Hz, 1H), 2.41 (m, 1H), 2.59, (dt, $J$ = 14.3, 6.2 Hz, 1H), 2.77 (dd, $J$ = 12.0, 2.8 Hz, 1H), 3.92 (m, 4H), 4.19 (m, 2H). $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 210.6, 173.2, 112.7, 65.7, 65.3, 61.5, 61.5, 45.3, 42.3, 35.0, 30.8, 29.4, 23.6, 23.0, 17.4, 16.3, 14.6. $[\alpha]^{20}_D$ +11.1 (*c*, 7.15, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 66.07; H, 8.35.

**Ethyl 5′,8a′-Dimethyl-6′-methyleneoctahydro-2′*H*-spiro[[1,3]-dioxolane-2,1′-naphthalene]-5′-carboxylate (18).** To a mixture of methyltriphenylphosphonium bromide (4.5 g, 40.6 mmol) and KO*t*-Bu (4.55 g, 40.6 mmol) was added THF (80 mL). The bright yellow ylide solution was stirred for an additional 10 min before the $\beta$-ketoester **17** (4.18 g, 13.5 mmol) in THF (20 mL) was added. The solution was stirred for 1 h at which time the reaction was judged complete by TLC, quenched with $H_2O$ (40 mL), and extracted with $Et_2O$ (3 × 20 mL). Aqueous layers were back-extracted with $Et_2O$ (3 × 20 mL), and the combined organics were dried over $MgSO_4$ and concentrated to a bright yellow oil. The mixture was passed through a short pad of silica (4 × 1 cm$^2$ with 1:1 hexanes:$Et_2O$) to provide product **18** (3.5 g, 83% yield) as a clear oil. $R_f$ 0.9 in 2:1 $Et_2O$:hexanes. FTIR (NaCl, thin film) 2984 (m), 2950 (m), 2870 (m), 1724 (m), 1224 (m), 1138 (m), 1060 (m), 414 (m) cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.01 (m, 1H), 1.15 (s, 3H), 1.26 (t, $J$ = 7.1 Hz, 3H), 1.27 (s, 3H), 1.3−1.8 (m, 7H), 2.20 (dt, $J$ = 13.9, 3.8 Hz, 1H), 2.41 (m, 1H), 2.53 (dd, $J$ = 12.1, 2.6 Hz, 1H), 3.89 (m, 4H), 4.20 (m, 2H), 4.39 (s, 1H), 4.72 (s, 1H). $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 176.5, 151.8, 113.1, 107.9, 65.7, 65.2, 60.9, 54.8, 44.8, 43.0, 31.2, 31.1, 28.9, 24.1, 23.2, 19.5, 16.7, 14.7. $[\alpha]^{20}_D$ +6.7 (*c*. 3.1, $CHCl_3$). Anal. Calcd for $C_{18}H_{28}O_4$; C, 70.10; H, 9.15. Found: C, 69.95; H, 9.22.

**(5′,6′,8a′-Trimethyloctahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalene]-5′-yl)methanol (19).** $H_2$ (g) was bubbled through a heterogeneous solution of $PtO_2$ (32 mg, 0.14 mmol) and olefin **18** (445 mg, 1.44 mmol) in $CH_2Cl_2$ (15 mL) for 20 min. The reaction was stirred for 12 h and then passed directly through a short pad of silica (1 × 5 cm$^2$ with $Et_2O$) and concentrated to a clear oil (440 mg) as an inseparable mixture of diastereomers.

To a stirring suspension of LAH (216 mg, 5.67 mmol) in THF (20 mL) was added the diastereomeric esters (440 mg, 1.42 mmol). The reaction mixture was stirred at room temperature for 2 h, was judged complete by TLC, and was quenched by slow addition of ice cold $Na_2SO_{4(aq)}$ (saturated, 40 mL). The organic layer was separated and the aqueous layer extracted with $Et_2O$ (5 × 20 mL). The combined organics were dried over $MgSO_4$ and concentrated to a clear oil. Diastereomers were separated by silica gel chromatography (3:1 hexanes:$Et_2O$) to provide the desired diastereomer **19** (287 mg, 1.07 mmol) as a clear oil and the undesired diastereomer (37 mg, 0.14 mmol) in a 7.6:1 ratio (84% yield over 2 steps). FTIR (NaCl, thin film) 3452 (br), 2949 (s), 2867 (s), 1464 (m), 1382 (m), 1187 (m), 1111 (m), 1029 (m), 948 (m), 904 (m) cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.95 (s, 3H), 1.03 (d, $J$ = 7.2 Hz, 3H), 1.09 (s, 3H), 1.11−1.35 (m, 5H), 1.38−1.53 (m, 2H), 1.57−1.80 (m, 5H), 1.91 (tt, $J$ = 14.0, 4.0 Hz, 1H), 3.38 (dd, $J$ = 16.0, 10.4 Hz, 2H), 3.84 (m, 1H), 3.95 (m, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 113.5, 43.8, 39.7, 39.6, 35.1, 30.7, 25.4, 24.0, 23.3, 21.0, 19.6, 17.5, 15.2. $[\alpha]^{20}_D$ +27 (*c*. 1.0, $CHCl_3$). Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.42; H, 10.40.

**5′,6′,8a′-Trimethyloctahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalene]-5′-carbaldehyde (20).** A $CH_2Cl_2$ (10 mL) solution of alcohol **19** (270 mg, 1.01 mmol), 4-methylmorpholine *N*-oxide (130 mg, 1.10 mmol), and 4 Å MS (300 mg) was stirred for 10 min. At this time, tetra-*n*-propylammonium pyruthenate (17.5 mg, 0.05 mmol) was added in one portion and the reaction was stirred for 1 h. The reaction was found complete by TLC, passed through a pad of silica (1 × 20 cm$^2$ with 1:1 hexanes:$Et_2O$), and concentrated to provide aldehyde **20** (260 mg, 98% yield) as a clear oil. FTIR (NaCl, thin film) 2949 (s), 2880 (s), 2704 (m), 1728 (s), 1464 (s), 1388 (m), 1180 (m), 1130 (m), 1061 (m), 1029 (m), 941 (m) cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.08 (d, $J$ = 7.2 Hz, 3H), 1.10 (s, 6H), 1.16 (dt, $J$ = 12.8, 4.0 Hz, 1H), 1.24−1.40 (m, 3H), 1.50−1.73 (m, 5H), 1.80 (td, $J$ = 13.6, 3.6 Hz, 1H), 1.95 (tt, $J$ = 13.6, 4.0 Hz, 1H), 2.40 (dd, $J$ = 12.4, 3.2 Hz, 1H), 3.87 (m, 1H), 3.97 (m, 3H), 9.42 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 209.5, 113.2, 65.6, 65.2, 51.0, 43.0, 37.2, 36.7, 30.9, 25.4, 23.7, 23.3, 23.1, 17.4, 16.9, 15.4. $[\alpha]^{20}_D$ +42 (*c* 0.99, $CHCl_3$). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 71.97; H, 9.91.

**5′-Ethynyl-5′,6′,8a′-trimethyloctahydro-2′*H*-spiro[[1,3]dioxolane-2,1′-naphthalene] (21).** To aldehyde **20** (260 mg, 0.977 mmol) in MeOH (2 mL) was added the Ohira−Bestmann reagent (243 mg, 1.27 mmol) and $K_2CO_3$ (169 mg, 1.27 mmol).[21] After 12 h an additional 0.5 equiv each of the Ohira−Bestmann reagent (93 mg, 0.49 mmol) and of $K_2CO_3$ (65 mg, 0.49 mmol) were added. An additional 2 equiv of those reagents were added in 0.5 equiv portions periodically over the next 4 d. The reaction mixture was then quenched with water (5 mL), extracted with $Et_2O$ (3 × 10 mL), dried over $MgSO_4$, and concentrated. Column chromatography (8:1 hexanes:$Et_2O$) afforded the desired acetylene **21** (220 mg, 0.83 mmol, 85% yield) as a white solid. Mp 63−65 °C. $R_f$ 0.8 in 4:1 hexanes:$Et_2O$. FTIR (NaCl, thin film) 3303 (br), 3060 (w), 3027 (m), 2921(s), 2878 (m), 2102 (w), 1455 (m), 1186 (m), 1053 (m), 626 (m) cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.01 (s, 3H), 1.28 (m, 6H), 1.36−1.97 (m, 9H), 2.04 (dd, $J$ = 12.5, 2.9, 1H), 2.16 (s,

3H), 3.96 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 113.5, 93.0, 69.6, 65.6, 65.3, 43.8, 41.3, 39.7, 38.2, 31.1, 24.3, 23.9, 23.7, 23.3, 22.8, 17.4, 17.1. $[\alpha]^{20}_D$ +20 (*c* 0.70, $CHCl_3$). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.83; H, 9.89.

**5′-(Bromoethynyl)-5′,6′,8a′-trimethyloctahydro-2′*H*-spiro-[[1,3]dioxolane-2,1′-naphthalene] (24).** A solution of acetylene **21** (100 mg, 0.38 mmol), *N*-bromosuccinimide (81 mg, 0.46 mmol), and $AgNO_3$ (20 mg, 0.12 mmol) in acetone (10 mL) was stirred at room temperature for 1 h at which time the reaction was judged complete by gas chromatography. Acetone was evaporated in vacuo, and the resulting product was passed through a short plug of silica gel (1 × 6 cm$^2$ with $CH_2Cl_2$). Solvent was evaporated in vacuo to leave bromoacetylene **24** (130 mg, 0.38 mmol, >98% yield) as a white solid. Mp 134−136 °C. $R_f$ 0.8 in 4:1 hexanes:$Et_2O$. FTIR (NaCl, thin film) 3059 (m), 3028 (m), 2920 (s), 1492 (w), 1453 (w), 1134 (w), 1051 (w), 759 (m) cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.04 (s, 3H), 1.21 (m, 6H), 1.31−1.92 (m, 11H), 2.00 (dd, $J$ = 12.4, 2.8 Hz, 1H), 3.90 (m, 4H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 113.4, 88.7, 65.6, 65.3, 43.8, 41.4, 41.3, 39.2, 38.5, 31.0, 23.9, 23.9, 23.7, 23.3, 23.0, 17.4, 17.2. $[\alpha]^{20}_D$ −2.3 (*c*. 4.0, $CHCl_3$). Anal. Calcd for $C_{17}H_{25}BrO_2$: C, 59.83; H, 7.38. Found: C, 59.62; H, 7.24.

**3-(1-(2-Bromoallyloxy)but-3-enyl)furan (13).** To a stirring solution of dry NaH (168 mg, 6.99 mmol) in benzene (10 mL) at 0 °C was added alcohol **11** (322 mg, 2.33 mmol). The reaction was allowed to warm to room temperature and stirred for 2 h. At this time the reaction was cooled to 0 °C and 15-Crown-5 (257 mg, 1.17 mmol) was added. The reaction was again allowed to warm to room temperature and stirred for 45 min. At this time, freshly distilled 2,3-dibromopropene **12** (722 mL, 6.99 mmol) was added, and the reaction was warmed to room temperature and stirred for 8 h. The reaction mixture was then quenched with $H_2O$ (20 mL) on an ice bath, and extracted with $Et_2O$ (3 × 10 mL). The organic layers were dried over $MgSO_4$ and concentrated to a red oil. Flash chromatography with pentane:$Et_2O$ (20:1) afforded pure divinyl bromide **13** (450 mg, 1.75 mmol, 75% yield) as a clear liquid. FTIR (NaCl, thin film) 3077 (m), 3026 (m), 2979 (m), 2923 (s), 2856 (m), 1640 (m), 1501 (m), 1160 (m), 1085 (s), 1021 (m), 795 (m), 601 (m), 425 (m). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 2.55 (m, 2H), 3.94 (d, $J$ = 14.2 Hz, 1H), 4.05 (d, $J$ = 14.3 Hz, 1 H), 4.39 (t, $J$ = 6.7 Hz, 1H), 5.07 (m, 2H), 5.60 (s, 1H), 5.80 (m, 1H), 5.92 (m, 1H), 6.40 (m, 1H), 7.37 (s, 1H), 7.41 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 143.7, 140.5, 134.4, 129.8, 125.4, 117.6, 117.6, 108.9, 73.4, 72.3, 41.3. $[\alpha]^{20}_D$ +50 (*c*. 4.4, $CHCl_3$). HRMS (EI+) *m*/*z* calcd for $C_{11}H_{13}BrO_2$ 256.0099 g/mol, found 256.0097 g/mol.

**2-(6-(Furan-3-yl)-5,6-dihydro-2*H*-pyran-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9).** To a stirring solution of divinyl bromide **13** (500 mg, 1.95 mmol) in $Et_2O$ (20 mL) at −78 °C was added dropwise *tert*-butyllithium (1.7 M in pentanes, 2.4 mL, 4.09 mmol). The solution was maintained at −78 °C for 1 h, at which time 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **14** (397 mg, 1.95 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 10 min and then allowed to warm to room temperature and stirred for an additional 1 h. The reaction was then quenched by addition to $Et_2O$:$H_2O$ (1:1, 20 mL) on ice, and neutralized to a pH of 7−8 by dropwise addition of $HCl_{aq}$ (1 M). The organic layers were separated, and the aqueous layers extracted with $Et_2O$ (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated to yield a clear oil, which is immediately subjected to the subsequent reaction.

A solution of divinyl borolane **10** and Grubbs' second generation catalyst **15** (120 mg, 0.14 mmol) in benzene (60 mL) was stirred at room temperature for 3−4 h, whereby the reaction was deemed complete by TLC. The reaction mixture was stirred open to air for 1 h to help facilitate decomposition of catalyst, and was then concentrated to a dark brown oil. Filtering the oil through a short plug of silica gel (4 × 10 cm$^2$ with 1:1 $Et_2O$:hexanes; silica base washed by loading the column with a solution of pyridine in $Et_2O$ (10%) and flushing the column with $Et_2O$ until pyridine is no longer detectable by UV on silica plates) led to the desired product **9** as a white solid (240 mg, 45% yield for two steps). Residual ruthenium will often make the metathesis product light brown in color. This discoloration, however, does not affect the subsequent Suzuki couplings. Mp 75−85 °C. FTIR (NaCl, thin film) 2980 (m), 2931 (w), 2826 (w), 1641 (m), 1388 (m), 1357 (m), 1320 (m), 1301 (m), 1141 (m), 1042 (m), 1005 (m), 851 (m), 795 (m), 666 (m), 604 (m) cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.46 (s, 1H, Ar), 7.43 (t, $J$ = 1.7 Hz, 1H, Ar), 7.20−7.50 (dd, $J$ = 5.0, 2.4 Hz, 1H), 6.48 (s, 1H, Ar), 4.56 (dd, $J$ = 9.7, 3.7 Hz, 1H), 4.39−4.50 (m, 2H), 2.32−2.53 (m, 2H), 1.31 (s, 12 H). $^{13}$C NMR (400 MHz, $CDCl_3$) $\delta$ 147.9, 143.0, 139.1, 138.7, 127.9, 108.8, 83.4, 67.9, 67.5, 32.6, 24.9. $[\alpha]^{20}_D$ +185 (*c* 0.54, $CHCl_3$). HRMS (ESI+) *m*/*z* calcd for $C_{15}H_{21}BO_4Na$ 299.1431, found 299.1432.

**(4a′*R*,5′*S*,6′*S*,8a′*R*)-5′-(((*R*)-6-(Furan-3-yl)-5,6-dihydro-2*H*-pyran-3-yl)ethynyl)-5′,6′,8a′-trimethyloctahydro-2′*H*-spiro[[1,3]-dioxolane-2,1′-naphthalene] (25).** Bromide **24** (131 mg, 0.382 mmol) and borolane **9** (116 mg, 0.420 mmol) were taken up in $KOH_{aq}$ (2.7 M, 4.7 mL, 1.26 mmol) and degassed for 10 min by bubbling $N_2$ through the solution. Tetrakis(triphenylphosphine)-palladium (13 mg, 0.01 mmol) was disolved in distilled/degassed THF (2 mL) and added to the aqueous solution. The miscible solvents were stirred for 8−12 h, then the reaction was deemed complete by TLC. The reaction mixture was diluted in $Et_2O$ (5 mL) and washed with brine (1 × 5 mL). The aqueous layer was back-extracted with $Et_2O$ (3 × 5 mL). The organic layers were combined and dried over $MgSO_4$, filtered, and concentrated to a canary yellow oil. Silica gel flash chromatography (10:1 hexanes:$Et_2O$) gave the desired product **25** as a clear oil (131 mg, 84% yield). FTIR (NaCl, thin film) 3137 (w), 2865 (s), 2209 (w), 1446 (m), 1192 (m), 879 (m), 607 (m) cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 0.92 (s, 3H), 1.09 (m, 6H), 1.15−1.80 (m, 12H), 1.84 (dd, $J$ = 12.3, 2.8 Hz, 1H), 2.21 (m, 2H), 3.77 (m, 4H), 4.11 (d, $J$ = 17.9 Hz, 1H), 4.06 (d, $J$ = 16.8 Hz, 1H), 4.37 (dd, $J$ = 9.7, 3.7 Hz, 1H), 5.93 (m, 1H), 6.27 (s, 1H), 7.24 (s, 1H), 7.26 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 143.4, 139.5, 128.4, 126.6, 121.6, 113.5, 109.1, 99.9, 79.0, 68.5, 68.4, 65.6, 65.3, 43.9, 41.6, 40.2, 38.5, 31.7, 31.1, 24.2, 24.0, 23.7, 23.4, 23.0, 17.4, 17.3. $[\alpha]^{20}_D$ +50 (*c* 0.76, $CHCl_3$). HRMS (TOF MS ES+) calcd for $C_{26}H_{34}O_4Na$ 433.2355, found 433.2357.

**(4a′*R*,5′*R*,6′*S*,8a′*R*)-5′-((*Z*)-2-((*R*)-6-(Furan-3-yl)-5,6-dihydro-2*H*-pyran-3-yl)vinyl)-5′,6′,8a′-trimethyloctahydro-2′*H*-spiro-[[1,3]dioxolane-2,1′-naphthalene] (26).** A solution of acetylene **25** (30 mg, 73 mmol), Lindlar's catalyst (45 mg), and quinoline (5 mL) added to hexanes:ethyl acetate (3 mL of a 1:1). $H_2$ (via balloon) was bubbled through the solution for ∼10 min. The reaction mixture then stirred under $H_2$ atm for 8 h. The reaction was monitored by gas chromatography. More catalyst was added as needed. The reaction mixture was passed through a short column of silica gel (1 × 4 cm$^2$ with $Et_2O$) and washed twice with $HCl_{aq}$ (1 M, 2 × 5 mL). The organic layers were dried over $MgSO_4$ and concentrated to a clear oil **26** (30 mg, >95% yield) with an $R_f$ of 0.45 in 10:1 hexanes:$Et_2O$. FTIR (NaCl, thin film) 3070 (w), 3040 (m), 2952 (s), 2874 (m), 2837 (w), 1383 (w), 1185 (m), 1063 (m), 875 (m), 535 (m) cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.09 (d, $J$ = 7.3 Hz, 3H), 1.12 (s, 3H), 1.22 (s, 3H), 1.24−2.06 (m, 12H), 2.33 (m, 2H), 3.84 (m, 1H), 3.96 (m, 3H), 4.11 (d, $J$ = 16.3 Hz, 1H), 4.19 (d, $J$ = 16.3 Hz, 1H), 4.52 (dd, $J$ = 10.0, 4.0 Hz, 1H), 5.32 (d, $J$ = 13.3 Hz, 1H), 5.59 (m, 2H), 6.43 (s, 1H), 7.39 (s, 1H). 7.42 (s, 1H). $^{13}$C NMR (100 MHz) $\delta$ 146.6, 143.3, 139.4, 136.5, 126.9, 124.7, 120.3, 113.7, 109.1, 68.8, 68.6, 65.7, 65.2, 44.2, 44.0, 43.8, 42.0, 31.7, 31.3, 25.6, 23.9, 23.7, 22.7, 20.8, 17.9, 16.5. $[\alpha]^{20}_D$ +130 (*c* 0.95, $CHCl_3$). HRMS (TOF MS ES+) calcd for $C_{26}H_{37}O_4$ 413.2692, found 413.2701.

**(4a′*R*,5′*R*,6′*S*,8a′*R*)-5′-((*E*)-2-((*R*)-6-(Furan-3-yl)-5,6-dihydro-2*H*-pyran-3-yl)vinyl)-5′,6′,8a′-trimethyloctahydro-2′*H*-spiro-[[1,3]dioxolane-2,1′-naphthalene] (23).** To a heterogeneous mixture of zirconocene dichloride (221 mg, 0.758 mmol) in THF (2

mL) at room temperature was added $LiEt_3BH$ (1 M in THF) (Superhydride) (758 mL, 0.758 mmol). The reaction mixture was stirred for 1 h while being protected from light. At this time acetylene **21** (100 mg, 0.379 mmol) in THF (1 mL) was added dropwise. The reaction mixture was stirred for 2 h, during which time the reaction mixture changed from a heterogeneous white solution to a homogeneous, yellow solution. The reaction mixture was cooled to 0 °C and excess iodine (1 g in 2 mL of THF) was added dropwise until a dark red color persisted. The reaction was allowed to stir for 20 min, diluted with $CH_2Cl_2$ (10 mL), and washed with $Na_2S_2O_{3(aq)}$ (saturated, 10 mL). The organic layer was dried over $MgSO_4$ and concentrated to a yellow oil. Silica gel flash chromatography with hexanes:$Et_2O$ (20:1) afforded the desired *E*-iodide **22** along with a minor inseparable byproduct. The reaction was taken on without further purification.

Vinyl iodide **22** (104 mg, 0.265 mmol) and borolane **9** (80 mg, 0.29 mmol) were dissolved in LiOH (aq) (1.0 M, 2.95 mL, 2.92 mmol) and the solution was degassed for several minutes by bubbling $N_2$ through the solution. Tetrakis(triphenylphosphine)-palladium (15 mg, 5 mol %) was dissolved in degassed THF (1 mL) and added to the heterogeneous aqueous mixture. The reaction was allowed to proceed for 8 h before diluting with $Et_2O$ (5 mL) and washing with brine (1 × 5 mL). The aqueous layer was extracted with $Et_2O$ (3 × 5 mL), and the organics layers were combined, dried over $MgSO_4$, and concentrated to a yellow oil. Silica gel chromatography (15:1 hexanes:$Et_2O$) provided the desired product **22** as a clear oil (94 mg, 60% yield, 2 steps). $R_f$ 0.2 in 15:1 hexanes:$Et_2O$. FTIR (NaCl, thin film) 3099 (m), 3069 (m), 3067 (m), 2928 (s), 2919 (s), 2909 (s), 1185 (m), 1062 (m), 763 (m), 703 (m), 540 (m) $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.97 (d, $J$ = 7.2 Hz, 3H), 1.09 (s, 3H), 1.12 (s, 3H), 1.16−1.36 (m, 3H), 1.34−1.55 (m, 3H), 1.56−1.71 (m, 3H), 1.69−1.86 (m, 2H), 1.81−2.01 (m, 1H), 2.56−2.40 (m, 1H), 2.38−2.51 (m, 1H), 3.80−3.89 (m, 1H), 3.89−4.03 (m, 3H), 4.38 (d, $J$ = 15.8 Hz, 1H), 4.42 (d, $J$ = 15.8 Hz, 1H), 4.51 (dd, $J$ = 9.8, 3.6 Hz, 1H), 5.37 (d, $J$ = 16.8 Hz, 1H), 5.75 (m, 1H), 5.85 (d, $J$ = 16.7, 1H), 6.14 (m, 1H), 7.38 (m, 1H), 7.41 (m, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 143.17, 139.8, 139.3, 134.9, 126.7, 125.4, 122.3, 113.7, 109.0, 69.0, 66.3, 65.6, 65.1, 43.6, 42.1, 41.7, 40.5, 32.1, 31.0, 25.9, 24.1, 23.4, 22.3, 20.3, 17.9, 16.4. $[\alpha]^{20}_D$ +47 (*c*. 0.70, $CHCl_3$). HRMS (TOF MS ES+) calcd for $C_{26}H_{37}O_4$ 413.2692, found 413.2694.

**(A) Representative Procedure for Ketal Hydrolysis: (4a*R*,5*S*,6*S*,-8a*R*)-5-(((*R*)-6-(Furan-3-yl)-5,6-dihydro-2*H*-pyran-3-yl)ethynyl)-5,6,8-trimethyloctahydronaphthalen-1(2*H*)-one (ketone 4a).** A solution of ketal **25** (107 mg, 0.26 mmol) in AcOH:$H_2O$ (4:1, 5 mL) was stirred at 60 °C for 1 h. At this point, the reaction was deemed complete by TLC analysis. The reaction was quenched at 0−4 °C with $NaOH_{aq}$ (1 M, 5 mL) solution and extracted with $Et_2O$ (5 × 5 mL). The organic layers were combined, washed with $NaHCO_{3(aq)}$ (1 × 10 mL) and brine (1 × 10 mL), then dried over $MgSO_4$. Concentration under vacuum yielded **4a** as a white solid (85 mg, 88% yield, $R_f$ 0.3 in 5:1 hexanes:$Et_2O$). Mp 55−60 °C. FTIR (NaCl, thin film) 3145 (w), 2951 (m), 2869 (m), 2833 (w), 1707 (s), 1096 (m), 757 (m), 412 (m) $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.20 (m, 6H), 1.39 (s, 3H), 1.45−2.56 (m, 13H), 2.65 (dt, $J$ = 13.7, 6.8 Hz, 1H), 4.24 (m, 2H), 4.56 (dd, $J$ = 9.6, 3.8 Hz, 1H), 6.14 (m, 1H), 6.46 (s, 1H), 7.44 (s, 1H), 7.46 (s, 1H). $^{13}C$ NMR (100 MHz) $\delta$ 214.8, 143.4, 139.5, 129.1, 126.5, 121.3, 109.0, 98.6, 79.7, 68.4, 68.3, 49.2, 45.7, 40.9, 38.2, 38.0, 31.7, 26.4, 26.3, 24.7, 23.7, 23.1, 19.4, 17.0. $[\alpha]^{20}_D$ +62.7 (*c*. 0.165, $CHCl_3$). HRMS (TOF MS ES+) calcd for $C_{24}H_{30}O_3$ 366.2192, found 366.2195.

**(B) Representative Procedure for Ketone Olefination: (*R*)-2-(Furan-3-yl)-5-(((1*S*,2*S*,4a*R*,8a*S*)-1,2,4a-trimethyl-5-methylenedecahydronaphthalen-1-yl)ethynyl)-3,6-dihydro-2*H*-pyran (olefin 4b).** To a mixture of methyltriphenylphosphonium bromide (400 mg, 1.12 mmol) and KO*t*-Bu (125 mg, 1.12 mmol) was added THF (5 mL). The bright yellow ylide solution was stirred for 10 min before ketone **4a** (85 mg, 0.23 mmol) in THF (1 mL) was added. The solution was stirred for 1 h at which time the reaction was judged complete by TLC. The reaction was quenched with $NH_4Cl_{aq}$ (saturated, 5 mL), extracted with $Et_2O$ (3 × 5 mL), dried over $MgSO_4$, and concentrated to a bright yellow oil. The resulting oil was passed through a plug of silica gel(1 × 4 $cm^2$ with 9:1 hexanes:$Et_2O$, $R_f$ of 0.45), then concentrated to provide a white solid **4b** (55 mg, 65% yield). Mp 78−82 °C. FTIR (NaCl, thin film) 3081 (w), 3059 (m), 3027 (s), 2974 (m), 2931 (s), 2905 (s), 2867 (m), 2360 (w), 1379 (w), 1160 (w), 1098 (w), 875 (m), 788 (w) $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.97 (s, 3H), 1.07 (d, $J$ = 7.2 Hz, 3H), 1.19 (s, 3H), 1.19−1.58 (m, 5H), 1.61−1.96 (m, 5H), 2.03 (m, 1H), 2.13−2.43 (m, 3H), 4.06 (d, $J$ = 15.5 Hz, 1H) 4.18 (d, $J$ = 15.5 Hz, 1H), 4.44 (m, 3H), 5.98 (m, 1H), 6.32 (m, 1H), 7.29 (t, $J$ = 1.6 Hz, 1H), 7.31 (m, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 159.6, 143.2, 139.3, 128.4, 126.4, 121.5, 109.0, 102.8, 99.7, 79.0, 68.3, 68.3, 46.2, 40.7, 40.3, 38.5, 33.4, 31.6, 30.1, 28.8, 24.5, 24.3, 24.2, 20.9, 17.3. $[\alpha]^{20}_D$ +83 (*c*. 0.35, $CHCl_3$). HRMS (TOF MS ES+) calcd for $C_{25}H_{32}O_2$ 365.2481, found 365.2479.

**(C) Representative Procedure for Photooxidation: 5-Hydroxy-4-((*R*)-5-(((1*S*,2*S*,4a*R*,8a*S*)-1,2,4a-trimethyl-5-methylenedecahydronaphthalen-1-yl)ethynyl)-3,6-dihydro-2*H*-pyran-2-yl)furan-2(5*H*)-one (4).** Furan **4b** (15 mg, 0.041 mmol), diisopropylethylamine (21 mL, 0.124 mmol), and Rose Bengal (0.1 mg, 8 mmol) were dissolved in dichloromethane:methanol (1:1, 1 mL). $O_2$ was bubbled through the solution for 10 min, then the solution was cooled to −78 °C. The solution was next irradiated with a 150 W tungsten lamp while $O_2$ continued to bubble. The irradiation continued for an additional 10 min at which time the lamp was turned off, then the reaction mixture was warmed to room temperature and stirred for an additional 2 h while being protected from light. At this time the reaction was found complete by TLC. Concentration and filtration through a silica plug (1 × 4 $cm^2$ with $Et_2O$) afforded compound **4** as a white solid (8 mg, 50% yield) with an $R_f$ of 0.8 in $Et_2O$. Mp 88−92 °C. FTIR (NaCl, thin film) 3370 (br), 2975 (m), 2940 (s), 2864 (m), 1752 (s), 1647 (m), 1461 (m), 1129 (m), 1100 (m), 955 (m), 902 (m), 722 (m). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.92 (s, 3H), 1.03 (d, $J$ = 7.19 Hz, 3H), 1.14 (s, 3H), 1.00−1.53 (m, 6H), 1.60−1.92 (m, 5H), 1.97−2.12 (m, 1H), 2.14−2.26 (m, 2H), 3.64 (br s, 1H), 4.09−4.24 (m, 2H), 4.40 (t, $J$ = 6.2 Hz, 1H), 4.49 (m, 2H), 5.98−6.08 (m, 1H), 6.12 (br s, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.1, 159.6, 126.7, 118.7, 117.9, 102.9, 97.6, 97.1, 78.3, 69.4, 68.6, 68.3, 46.2, 40.7, 40.3, 38.4, 33.4, 30.1, 29.6, 29.2, 28.8, 24.4, 24.3, 24.2, 20.9, 17.2. $[\alpha]^{20}_D$ +107 (*c*. 0.13, $CHCl_3$). HRMS (TOF MS ES+) calcd for $C_{25}H_{33}O_4$ 397.2392, found 397.2379.

**(4a*R*,5*R*,6*S*,8a*R*)-5-((*E*)-2-((*R*)-6-(Furan-3-yl)-5,6-dihydro-2*H*-pyran-3-yl)vinyl)-5,6,8a-trimethyloctahydronaphthalen-1(2*H*)-one (ketone 3a).** See the representative procedure for ketal hydrolysis (A). Ketal **23** (0.073 mmol) provided ketone **3a** in 75% yield as a white solid ($R_f$ 0.4 in 2:1 hexane:$Et_2O$). Mp 128−132 °C. FTIR (NaCl, thin film) 3072 (m), 3046 (s), 2940 (s), 2869 (w), 1704 (s), 1505 (m), 1462 (w), 1159 (w), 1092 (w), 876 (w), 819 (w), 754 (m), 702 (m) $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.84 (d, $J$ = 7.2 Hz, 3H), 0.99 (s, 3H), 1.12 (s, 3H), 1.19−1.60 (m, 8H), 1.85 (m, 2H), 2.14 (m, 1H), 2.29 (m, 1H), 2.38 (m, 1H), 2.49 (td, $J$ = 13.7, 7.1 Hz, 1H), 4.33 (s, 2H), 4.44 (dd, $J$ = 9.8, 3.8 Hz, 1H), 5.19 (d, $J$ = 16.5 Hz, 1H), 5.708 (m, 1H), 5.79 (d, $J$ = 16.7 Hz, 1H), 6.34 (m, 1H), 7.30 (m, 1H), 7.33 (m, 1H). $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 215.2, 143.2, 139.3, 138.1, 134.7, 126.6, 126.0, 123.0, 109.0, 68.9, 66.2, 49.1, 46.3, 42.5, 40.1, 38.0, 32.0, 26.5, 26.5, 25.6, 22.3, 20.8, 19.8, 16.2. $[\alpha]^{20}_D$ +51 (*c* 0.75, $CHCl_3$). HRMS (EI+) *m/z* calcd for $C_{24}H_{32}O_3Na$ 391.2249, found 391.2252.

**(*R*)-2-(Furan-3-yl)-5-((*E*)-2-((1*R*,2*S*,4a*R*,8a*R*)-1,2,4a-trimethyl-5-methylenedecahydronaphthalen-1-yl)vinyl)-3,6-dihydro-2*H*-pyran (olefin 3b).** See the representative procedure for ketone olefination (B). Ketone **3a** (0.054 mmol) provided olefin **3b** in 67% yield as white solid ($R_f$ of 0.8 in 10:1 hexanes:$Et_2O$). Mp 93−97 °C FTIR 3059 (m), 3026 (m), 2924 (s), 2850 (w), 1601 (w), 1492 (w), 1449 (w), 752 (m), 699 (m), 541 (m). $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 0.95 (d, $J$ = 7.2 Hz, 3H), 1.12 (s, 6H), 1.19−1.59 (m,

7H), 1.81 (m, 2H), 2.01−2.19 (m, 2H), 2.22−2.55 (m, 3H), 4.42 (s, 2H), 4.52 (m, 3H), 5.28 (d, $J$ = 16.7 Hz, 1H), 5.76 (m, 1H), 5.85 (d, $J$ = 16.7 Hz, 1H), 6.43 (m, 1H), 7.39 (t, $J$ = 1.7 Hz, 1H), 7.42 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.3, 143.2, 139.7, 139.3, 134.9, 126.7, 125.4, 122.3, 109.0, 102.4, 69.0, 66.3, 47.0, 42.3, 40.7, 40.3, 33.5, 32.0, 30.4, 28.9, 26.5, 23.6, 21.3, 20.5, 16.4. $[\alpha]^{20}_D$ +91 (*c.* 0.30, $CHCl_3$). HRMS (TOF MS ES+) calcd for $C_{25}H_{33}O_2$ 365.2481, found 365.2479.

**5-Hydroxy-4-((*R*)-5-((*E*)-2-((1*R*,2*S*,4a*R*,8a*R*)-1,2,4a-trimethyl-5-methylenedecahydronaphthalen-1-yl)vinyl)-3,6-dihydro-2*H*-pyran-2-yl)furan-2(5*H*)-one (3).** See the representative procedure for photooxidation (C). Olefin **3b** (0.027 mmol) provided a diastereomeric mixture of analogue **3** in 56% yield as white solid ($R_f$ 0.8 in $Et_2O$). Mp 175 °C dec. FTIR (NaCl, thin film) 3402 (br), 2934 (s), 2865 (m), 1745 (s), 1635 (m), 1439 (m), 1381 (m), 1127 (m), 988 (m), 908 (m), 727 (m). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.94 (d, $J$ = 7.2 Hz, 3H), 1.12 (s, 6H), 1.10−1.40 (m, 6H), 1.50 (m, 1H), 1.60 (m, 1H), 1.80 (m, 2H), 1.98−2.20 (m, 2H), 2.22−2.50 (m, 2H), 3.90 (br s, 1H), 4.32−4.56 (m, 5H), 5.28 (d, $J$ = 16.8 Hz, 1H), 5.73 (m, 1H), 5.83 (d, $J$ = 16.8 Hz, 1H), 6.07 (s, 1H), 6.16 (br s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 160.2, 140.5, 125.0, 120.6, 102.5, 66.5, 47.0, 47.0, 42.4, 40.7, 40.3, 33.5, 30.4, 28.9, 26.4, 23.6, 21.3, 20.5, 16.5. $[\alpha]^{20}_D$ +100 (*c* 0.19, $CHCl_3$). HRMS (TOF MS ES+) calcd for $C_{25}H_{35}O_4$ 399.2554, found 399.2535.

**(4a*R*,5*R*,6*S*,8a*R*)-5-((*Z*)-2-((*R*)-6-(Furan-3-yl)-5,6-dihydro-2*H*-pyran-3-yl)vinyl)-5,6,8a-trimethyloctahydronaphthalen-1(2*H*)-one (ketone 5a).** See the representative procedure for ketal hydrolysis (A). Ketal **26** (0.13 mmol) provided ketone **5a** in 90% yield as white solid ($R_f$ 0.3 in 4:1 hexanes:$Et_2O$). Mp 145−150 °C. FTIR (NaCl, thin film) 3071 (w), 2961 (s), 2870 (s), 2834 (m), 1716 (s), 1501(w), 1091(w), 876 (w) cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.08 (d, $J$ = 7.2 Hz, 3H), 1.25 (s, 3H), 1.37 (s, 3H), 1.14−1.38 (m, 9H), 2.19−2.54 (m, 4H), 2.64 (td, $J$ = 14.1, 7.0 Hz, 1H), 4.22 (m, 2H), 4.58 (dd, $J$ = 9.7, 3.7 Hz, 1H), 5.28 (d, $J$ = 12.7 Hz, 1H), 5.67 (m, 2H), 6.48 (s, 1H), 7.44 (m, 1H), 7.37 (s, 1H). $^{13}$C NMR (100 MHz) $\delta$ 215.2, 145.1, 143.4, 139.4, 136.3, 126.8, 125.5, 120.7, 109.1, 68.8, 68.5, 49.4, 48.4, 44.6, 41.7, 38.2, 31.7, 26.8, 26.4, 25.3, 22.8, 21.2, 19.8, 15.3. $[\alpha]^{20}_D$ +126 (*c* 0.85 in $CHCl_3$). HRMS (ESI+) *m*/*z* calcd for $C_{24}H_{33}O_3$ 369.2430, found 369.2430.

**(*R*)-2-(Furan-3-yl)-5-((*Z*)-2-((1*R*,2*S*,4a*R*,8a*R*)-1,2,4a-trimethyl-5-methylenedecahydronaphthalen-1-yl)vinyl)-3,6-dihydro-2*H*-pyran (olefin 5b).** See the representative procedure for olefination (B). Ketone **5a** (0.12 mmol) provided olefin **5b** in 80% yield as white solid ($R_f$ of 0.5 in 20:1 hexanes:$Et_2O$). Mp 68−72 °C. FTIR (NaCl, thin film) 3059 (m), 3026 (s), 2921 (s), 2849 (w), 1601 (w), 1493 (w), 1449 (w), 748 (m), 696 (m), 537 (m). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 1.03 (d, $J$ = 7.3 Hz, 3H), 1.10 (s, 3H), 1.23 (s, 3H), 1.13−1.53 (m, 7H), 1.73−1.90 (m, 3H), 1.93−2.15 (m, 2H), 2.20−2.43 (m, 2H), 3.95−4.13 (m, 2H), 4.37 (m, 3H), 5.21 (d, $J$ = 13.1, 1H), 5.48−5.63 (m, 2H), 6.41 (m, 1H), 7.38 (t, $J$ = 1.7 Hz, 1H), 7.40 (m, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 160.5, 146.5, 143.3, 139.4, 136.5, 126.9, 124.8, 120.4, 109.1, 102.5, 68.9, 68.6, 49.4, 44.3, 42.2, 40.6, 33.7, 31.7, 30.3, 29.2, 26.2, 24.0, 21.5, 20.8, 16.6. $[\alpha]^{20}_D$ +49 (*c.* 0.35, $CHCl_3$). HRMS (TOF MS EI) calcd for $C_{25}H_{34}O_2$ 366.2559, found 366.2557.

**5-Hydroxy-4-((*R*)-5-((*Z*)-2-((1*R*,2*S*,4a*R*,8a*R*)-1,2,4a-trimethyl-5-methylenedecahydronaphthalen-1-yl)vinyl)-3,6-dihydro-2*H*-pyran-2-yl)furan-2(5*H*)-one (5).** See the representative procedure for photooxidation (C). Olefin **5b** (0.098 mmol) provided a diastereomeric mixture of analogue **5** in 42% yield as white solid ($R_f$ 0.5 in $Et_2O$). Mp 120−125 °C. FTIR (NaCl, thin film) 3372 (br), 2967 (m), 2922 (s), 2848 (m), 1764 (s), 16.28 (w), 1451 (m), 1377 (m), 1126 (m), 1115 (m), 955 (m), 887 (m). $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 1.03 (d, $J$ = 7.3 Hz, 3H), 1.10 (s, 3H), 1.21 (s, 3H), 0.9−1.7 (m, 7H), 1.76 (m, 3H), 2.07 (m, 2H), 2.31 (m, 2H), 3.97 (br s, 1H), 4.13 (s, 2H), 4.44 (m, 1H), 4.51 (d, $J$ = 9.8 Hz, 2H), 5.26 (d, $J$ = 13.3 Hz, 1H), 5.55 (m, 2H), 5.93−6.30 (m, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.1, 160.3, 160.2, 147.1, 143.9, 124.1, 124.0, 119.6, 118.9, 102.4, 97.3, 68.8, 68.4, 66.1, 49.2, 44.3, 42.1, 40.5, 33.5, 30.2, 30.0, 29.1, 26.1, 25.8, 23.9, 21.3, 20.8, 16.4. $[\alpha]^{20}_D$ +540 (*c* 0.40, $CHCl_3$). HRMS (TOF MS ES+) calcd for $C_{25}H_{34}O_4$-Na 421.2346, found 421.2355.

**Phospholipase $A_2$ Assays.** The following assays were performed with commercially available *s*$PLA_2$ assay kits. The *s*$PLA_2$ assay buffer consisted of 25 mM Tris-HCl (pH 7.5) containing 10 mM $CaCl_2$, 100 mM KCl, 0.3 mM Triton X-100, and 1 mg/mL BSA. Diheptanoyl thio-PC was provided as substrate, and was diluted with assay buffer to a concentration of 0.42 mM (final well concentration of 0.36 mM). Substrate hydrolysis rates were determined by using a 10 mM solution of 5,5′-dithiobis(2-nitrobenzoic acid) (Ellman's reagent) in 0.4 M tris-HCl (pH 8.0), and UV data were recorded on a microplate reader (410 nm). Inhibitors were diluted with molecular biology grade DMSO.

**Assay of Bee Venom *s*$PLA_2$** A 100 $\mu$g/mL solution of bee venom s$PLA_2$ was diluted by a factor of 200 with assay buffer, stored on ice, and used within 1 h of dilution. Final assay concentrations of (+)-**1**, **3**, **4**, and **5** ranged from 80 to 2.5 $\mu$M. Across a 96-well plate was added *s*$PLA_2$ solutions (10 $\mu$L) and inhibitor solutions (5 $\mu$L). Ellman's reagent (10 $\mu$L) was then added to each well, and the reactions were initiated by addition of substrate solution (200 $\mu$L) at room temperature (22.3 ± 0.1 °C). The plates were carefully shaken, and the absorbance was read every 10 s over a 2 min period, and resultant slopes were calculated as the change in optical density over time (mOD/min). The percent inhibition values were calculated as compared to a control, and were plotted versus log[inhibitor]. The $IC_{50}$ values were extrapolated from the resulting curves and are reported as an average of three measurements with error bars representing plus and minus one standard deviation unit.

**Assay of Human Type V *s*$PLA_2$** A vial of human recombinant (Type V) *s*$PLA_2$ was diluted by a factor of 100 with assay buffer, stored on ice, and used within 1 h of dilution. A known inhibitor, thioetheramide-PC ($IC_{50}$ = 1.3 $\mu$M; final well concentration of diheptanoyl thio PC is 0.42 mM), was used as a control (6.1−0.18 $\mu$M well concentrations). Similar to the previous assay, *s*$PLA_2$ solution (10 $\mu$L) and inhibitor solutions (10 $\mu$L) were mixed in wells. Substrate (200 $\mu$L) was then added to these solutions, and the mixture was carefully shaken and incubated at 25 °C for 15 min. Following incubation, Ellman's reagent (10 $\mu$L) was added and allowed to react for 1 min before measuring absorbance. Percent inhibition was calculated as compared to a control and plotted versus inhibitor concentrations (0.37−1.5 $\mu$M). An $IC_{50}$ value of 0.9 ± 0.1 $\mu$M was calculated from the resultant plots as the average of three experiments. In contrast, no noticeable inhibition was observed when (+)-**1** (193−6.0 $\mu$M well concentrations) was subjected to identical assay conditions.

**Acknowledgment.** The NIH (CAR01-66617) is acknowledged for financial support of this research. Helpful discussions with Rachel N. MacCoss and Emily P. Balskus are also appreciated. We thank Prof. Salvatore De Rosa for providing a photograph of *Fasciospongia cavernosa* used for the journal cover art.

**Note Added after ASAP Publication.** The word "Secretory" was misspelled in the title in the version published ASAP October 17, 2006; the corrected version was published ASAP October 19, 2006.

**Supporting Information Available:** Experimental procedures and $^1$H and $^{13}$C NMR spectral data for all new compounds, as well as data from $PLA_2$ assays. This material is available free of charge via the Internet at http://pubs.acs.org.

JO061407A