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Synthesis of (−)-Hamigeran B

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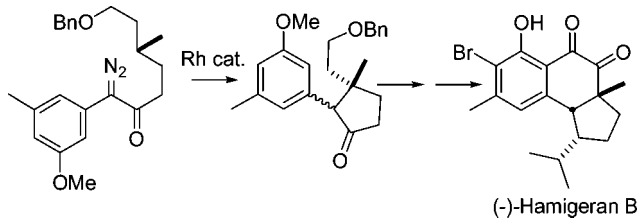
Received May 16, 2008



The synthesis of (−)-hamigeran B has been achieved, based on a new approach to cyclopentane construction, the rhodium-mediated intramolecular C−H insertion of α-aryl−α-diazoketones. The *endo*-isopropyl group was installed by selective hydrogenation of a cyclopropylidene substituent.

Introduction

(−)-Hamigeran B **1** is one of a family of eight hamigerans (Figure 1) isolated[1] in 2000 from the poecilosclerid sponge *Hamigera tarangaensis*, collected from the Hen and Chicken Islands east of New Zealand. Hamigeran B was the only one of the family to show antiviral activity, effecting complete inhibition of both herpes and polio viruses at low concentration and with only slight cytotoxicity.

A central concern in the total synthesis of the hamigerans is the construction of the cyclic quaternary center, from which the other two stereocenters may evolve. Three independent approaches to this problem have been described. Nicolaou[2] first reported an asymmetric synthesis utilizing a [4 + 2] photocycloaddition. This route started from an enantiomerically pure epoxide, obtained via the Jacobsen hydrolytic kinetic resolution. Clive[3] described a synthesis in which the chiral quaternary center was constructed using Meyers' chiral auxiliary. Trost[4] installed the quaternary stereogenic center by Pd-catalyzed asymmetric allylic alkylation of a preformed cyclopentanone.

We envisioned that the key intermediate **12**(Scheme 1) could be assembled by convergent coupling of **9** with the enantiomerically pure citronellol derivative **10**.[5,6] Rh-mediated intramolecular C−H insertion,[7] proceeding with retention of absolute configuration,[8] would then complete the cyclopentane

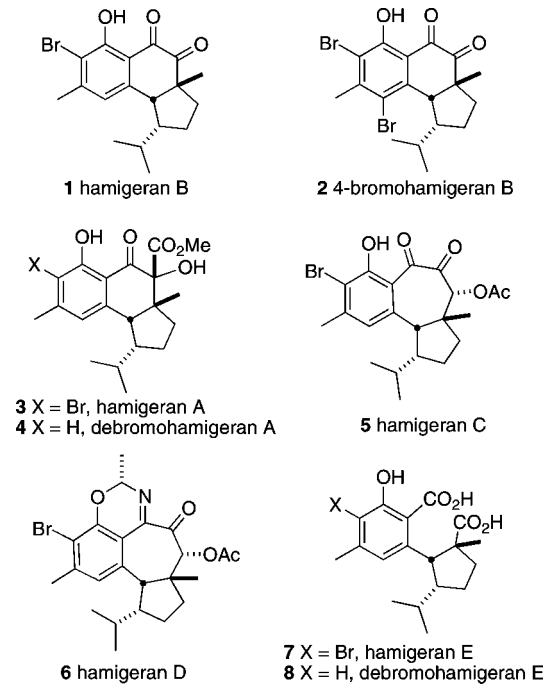


FIGURE 1. Structures of hamigerans.

(1) Wellington, K. D.; Cambie, R. C.; Rutledge, P. S.; Bergquist, P. R. *J. Nat. Prod.* **2000**, *63*, 79.

(2) (a) Nicolaou, K. C.; Gray, D.; Tae, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3675. (b) Nicolaou, K. C.; Gray, D.; Tae, J. *Angew Chem., Int. Ed.* **2001**, *40*, 3679. (c) Nicolaou, K. C.; Gray, D. L. F.; Tae, J. *J. Am. Chem. Soc.* **2004**, *126*, 613.

(3) (a) Clive, D. L. J.; Wang, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 3406. (b) Clive, D. L. J.; Wang, J. *Tetrahedron Lett.* **2003**, *44*, 7731. (c) Clive, D. L. J.; Wang, J. *J. Org. Chem.* **2004**, *69*, 2773.

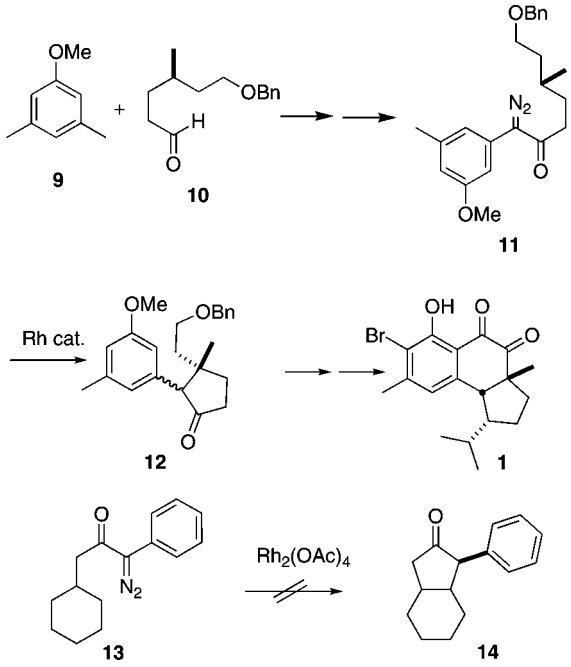
(4) (a) Trost, B. M.; Pissot-Soldermann, C.; Chen, I.; Schroeder, G. M. *J. Am. Chem. Soc.* **2004**, *126*, 4480. (b) Trost, B. M.; Pissot-Soldermann, C.; Chen, I. *Chem.−Eur. J.* **2005**, *11*, 951.

(5) For a review of natural products synthesized from citronellal, see: Lenardao, E. J.; Botteselle, G. V.; Azambuja, F.; Perin, G.; Jacob, R. G. *Tetrahedron* **2007**, *63*, 6671.

(6) Overman, L. E.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1982**, *104*, 7225.

10.1021/jo8010683 CCC: $40.75
Published on Web 09/05/2008

SCHEME 1



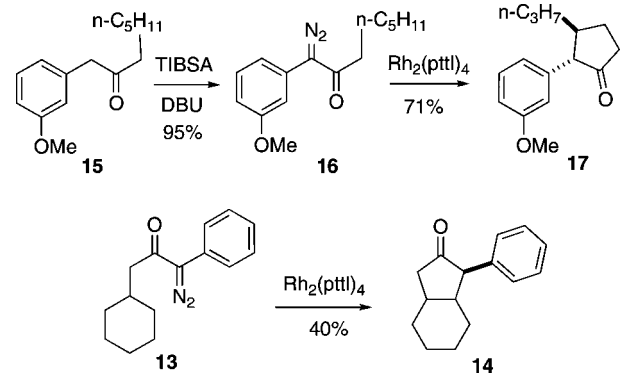
assembly while at the same time securing the enantiomerically pure quaternary center of **12**. Our enthusiasm for this approach was, however, tempered by the earlier report[9] that the α-aryl−α-diazoketone **13** could not be induced to cyclize to **14**.[10]

Results and Discussion

Construction and Cyclization of α-Aryl−α-Diazoketones: In order to develop this approach to cyclopropane construction, two challenges (Scheme 2) had to be overcome.[11] The first challenge was to optimize the base, solvent, and sulfonyl azide for the diazo transfer reaction on an α-arylketone. Overall, we found that 2,4,6-triisopropylbenzenesulfonyl azide (TIBSA) was better than benzenesulfonyl azide, methanesulfonyl azide, 4-acetamidobenzenesulfonyl azide, or *p*-nitrobenzenesulfonyl azide, especially on substrates with an electron-rich aromatic ring. As the solvent, toluene was better than dichloromethane or acetonitrile. In combination with DBU, TIBSA gave consistently high yields of α-aryl−α-diazoketones.

The next challenge was the Rh-mediated intramolecular C−H insertion. Because of the electron-donating aromatic substituent, dimer formation was always the main side reaction competing with C−H insertion. By altering the temperature, the solvent, the addition sequence, and the rhodium catalyst, the yields of the C−H insertion could be improved. Under the optimized

SCHEME 2



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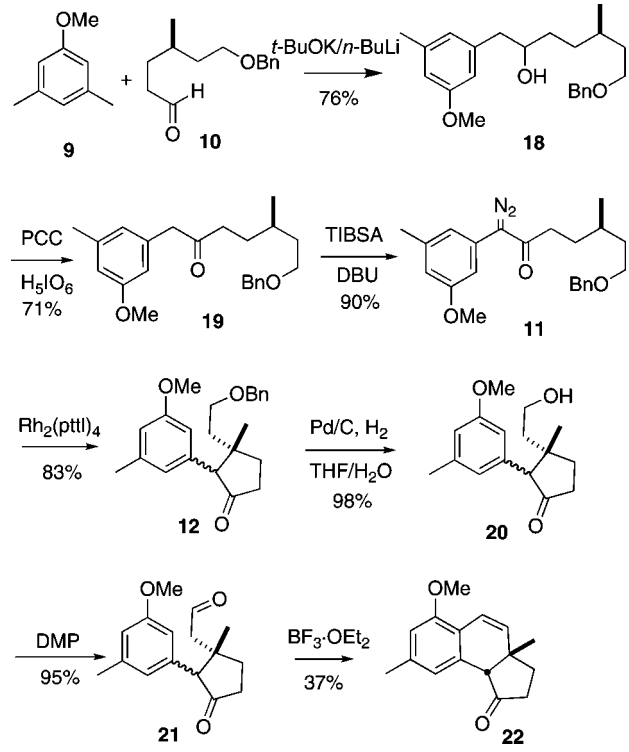


conditions (toluene as the solvent, rapid addition of the diazoketone into rhodium catalyst $Rh_2(pttl)_4$)[12] at room temperature), the diazoketone **16** cyclized efficiently. We were pleased to observe that, under these conditions, even **13** could be induced to cyclize to **14**, albeit in modest yield.

Synthesis of the Tricyclic Ketone 21: The known aldehyde **10**[6] (Scheme 3) was derived from (*R*)-citronellol in two steps. Direct benzylic deprotonation of 3,5-dimethylanisole **9** by 1 equiv of "super base"[13] in THF followed by addition of the aldehyde **10** at low temperature led to the alcohol **18** as a mixture of two diastereomers. Phenethyl alcohols such as **18** are sometimes difficult to oxidize, and several reagents were ineffective. Fortunately, the PCC-catalyzed oxidation with periodic acid[14] worked well.

With the ketone **19** in hand, we could bring to bear our earlier experience developing the cyclization protocol. Diazo transfer

(7) For the first reports of Rh-mediated intramolecular C−H insertion, see: (a) Wenkert, E.; Davis, L. L.; Mylari, B. L.; Solomon, M. F.; da Silva, R. R.; Shulman, S.; Warnet, R. J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. *J. Org. Chem.* **1982**, *47*, 3242. (b) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808. For a review of natural products synthesized by Rh-mediated intramolecular C−H insertion reaction, see: (c) Taber, D. F.; Stiriba, S. E. *Chem.—Eur. J.* **1998**, *4*, 990. For a recent example, see: (d) Taber, D. F.; Frankowski, K. J. *J. Org. Chem.* **2005**, *70*, 6417.

(8) Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196.

(9) Mateos, A. F.; Coca, G. P.; Alonso, J. J. P.; González, R. R.; Hernández, C. T. *Synlett* **1996**, 1134.

(10) For the first report of intermolecular Rh-mediated C−H insertion using α-aryl−α-diazo *esters*, see: (a) Davies, H. M. L.; Hansen, T. *J. Am. Chem. Soc.* **1997**, *119*, 9075. For recent reviews, see: (b) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (c) Davies, H. M. L.; Nikolai, J. *Org. Biomol. Chem.* **2005**, *3*, 4176.

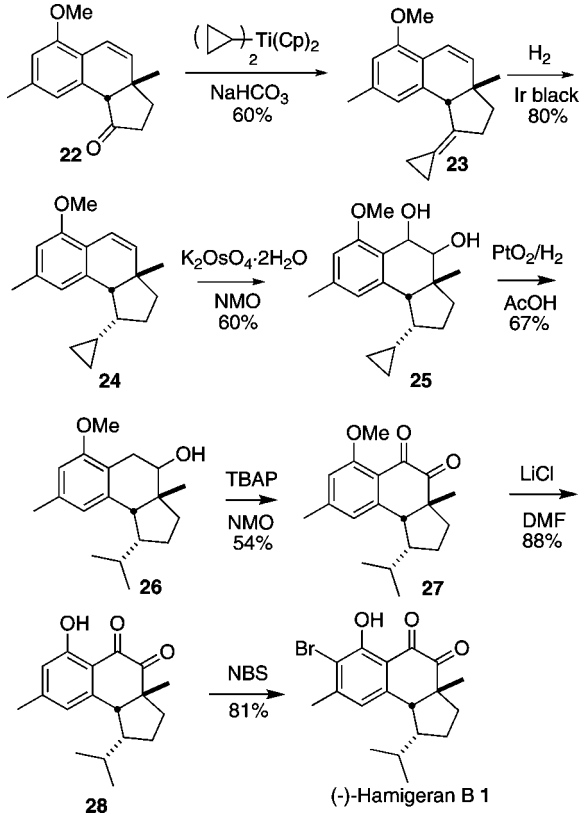
(11) Taber, D. F.; Tian, W. *J. Org. Chem.* **2007**, *72*, 3207.

(12) Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, *39*, 79. $Rh_2(Pttl)_4$ is dirhodium(II) tetrakis [*N*-phthaloyl-(*S*)-*t*-leucinate.

(13) Guggisberg, Y.; Faigl, F.; Schlosser, M. *J. Organomet. Chem.* **1991**, *415*, 1.

(14) Hunsen, M. *Tetrahedron Lett.* **2005**, *46*, 1651.

SCHEME 4



reaction by TIBSA and DBU in toluene was high yielding, delivering **11**. The diazoketone **11** was unusually unstable and light sensitive. A quick chromatography of **11** and immediate processing were required.

We were pleased to find, based on our previous optimization, that Rh-mediated C−H insertion to form the cyclopentane also proceeded efficiently. The product was a mixture of two diastereomers at the α position, as expected. The two diastereomers could be separated by column chromatography, but interconverted on storage, so we carried the mixture on.

Removal of the benzyl protecting group by hydrogenation followed by oxidation with the Dess−Martin reagent gave the aldehyde **21**, still as a mixture of α-diastereomers. Under acid catalysis, the two diastereomers of the aldehyde **21** readily interconverted. The cis isomer of **21** could easily participate in the intramolecular Friedel−Crafts reaction to form the cyclized benzylic alcohol. In situ, the alcohol underwent dehydration to give the alkene **22**.[15]

Synthesis of (−)-Hamigeran B: Wittig reagents did not convert ketone **22** into the corresponding alkene, perhaps because **22** was quite acidic. The Petasis reagent,[16] known to be nonbasic, was successful, delivering alkene **23** in 60% yield (Scheme 4). The strained alkene was unstable under the reaction condition (55 °C), easily isomerizing to the endocyclic cyclopentene during the reaction. We found that inclusion of $NaHCO_3$ in the reaction mixture prevented the isomerization.

With the diene **23** in hand, we were again faced with two challenges, differentiating the two alkenes, and controlling the diastereoselectivity of the hydrogenation of the cyclopropylidene. The propensity of the alkene to move into and around the ring was exacerbated by hydrogenation catalysts. Ir black was finally tried because it was known to minimize such alkene migrations.[4,17] The reduction was successful, delivering essentially a single diastereomer. We were pleased to observe that the strained cyclopropylidene could be hydrogenated without concomitant reduction of the benzylic alkene.

Upjohn dihydroxylation[3,18] of the alkene **24** led to the diol **25** as a mixture of diastereomers. Hydrogenolytic cleavage[7b,19] of the cyclopropane ring at 50 °C by PtO_2/AcOH established the isopropyl group and also removed the benzylic alcohol. Fortunately, oxidation of **26** with TBAP/NMO[20] led directly to the diketone **27**, presumably by the oxidation of the enol form of the initially generated ketone. Demethylation and bromination following the literature precedent[3,4] then led to (−)-hamigeran B **1**, identical (^{1}H NMR, ^{13}C NMR, $[\alpha]_D$) with natural and previously synthesized material.[1−4]

Conclusion

We have developed a general route to the 6,6,5-tricyclic skeleton of (−)-hamigeran B based on C−H insertion of an α-aryl−α-diazoketone followed by Friedel−Crafts cyclization. The installation of the *endo*-isopropyl group was achieved by selective hydrogenation of a cyclopropylidene substituent. We expect that Rh-mediated intramolecular C−H insertion of α-aryl−α-diazoketones will be a powerful tool for the synthesis of natural products of biological interest.

Experimental Section

(5*R*)-7-(Benzyloxy)-1-(3-methoxy-5-methylphenyl)-5-methyl-1-diazoheptan-2-one (11). To 300 mL of toluene were added the ketone **19** (10.0 g, 28.2 mmol), DBU (8.6 g, 56.5 mmol), and 2,4,6-triisopropylbenzenesulfonylazide (10.5 g, 33.9 mmol) sequentially at 0 °C.[11] The reaction mixture was maintained in darkness and stirred at rt for 4 h. The reaction mixture was directly chromatographed to afford the diazoketone **11** as a yellow oil (9.66 g, 25.4 mmol, 90% yield): TLC R_f (PE/MTBE = 8/2) = 0.50; $[\alpha]^{20}_D$ = +3.93 (*c* 2.80, CH_2Cl_2); ^{1}H NMR δ 0.90 (3H, d, J = 6.8 Hz), 1.60 (5H, m), 2.31 (3H, s), 2.55 (2H, m), 3.49 (2H, m), 3.77 (3H, s), 4.47 (2H, s), 6.60 (1H, s), 6.82 (1H, s), 6.97 (1H, s), 7.27 (5H, m); ^{13}C NMR δ u[21] 31.6, 36.5, 36.9, 68.4, 72.1, 73.0, 126.6, 138.6, 140.0, 160.1, 193.0; d 19.4, 21.7, 29.7, 55.2, 108.6, 113.6, 118.6, 127.5, 127.6, 128.3; IR (film, cm^{-1}) 2927, 2073, 1649, 1592, 1240; HRMS calcd for $C_{23}H_{28}O_3$ (M − N_2) 352.2038, obsd 352.2041.

(3*S*)-3-(2-(Benzyloxy)ethyl)-2-(3-methoxy-5-methylphenyl)-3-methylcyclopentanone (12). Rh_2(R-pttl)$_4$[12] (5 mg) was dissolved in 2 mL of toluene. To this solution was added a solution of the diazoketone **11** (140 mg, 0.368 mmol) in 2.0 mL of toluene at rt within 1 min. The reaction was continued for an additional 15 min at rt. Then the reaction mixture was concentrated and chromatographed to afford the ketone **12** as a mixture of two diastereomers (108 mg, 0.305 mmol, 83% yield): TLC R_f (PE/MTBE = 8/2) = 0.22; ^{1}H NMR δ 0.79 (1.2H, s), 1.18 (1.8H, s), 1.50 (1.0H, m), 1.67 (1.0H, m), 1.83 (1.0H, m), 1.94 (1.0H, m), 2.31 (1.0H, m),

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(18) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

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(20) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625.

(21) ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" and for methylene and quaternary carbons as "u".

2.34 (3.0H, s), 2.42 (1.0H, m), 3.11 (0.6H, s), 3.24 (0.4H, s), 3.4−3.6 (2.0H, m), 3.74 (1.2H, s), 3.75 (1.8H, s), 4.41 (1.2H, s), 4.49 (0.8H, s), 6.43 (2.0H, m), 6.62 (1.0H, s), 7.28 (5H, m); ^{13}C NMR δ u 32.3, 33.2, 33.8, 35.9, 36.1, 40.8, 43.2, 43.3, 67.0, 67.2, 73.2, 73.3, 135.9, 136.2, 138.3, 139.0, 139.1, 159.3, 159.4, 217.6, 217.9; d 20.7, 21.7, 21.8, 26.1, 55.2, 67.4, 68.9, 113.2, 113.3, 113.4, 113.6, 123.5, 123.9, 127.7, 128.5; IR (film, cm^{-1}) 2959, 1724, 1173, 1068; HRMS calcd for $C_{23}H_{28}O_3$ (M^+) 352.2038, obsd 352.2023.

(3*S*)-3-(2-Hydroxyethyl)-2-(3-methoxy-5-methylphenyl)-3-methylcyclopentanone (20). The ketone **12** (6.03 g, 17.1 mmol) was dissolved in 50 mL of THF and 1 mL of water; 5% Pd/C (1.0 g) was added at rt. The reaction container was then filled with hydrogen gas (1 atm) and stirred vigorously overnight. The mixture was passed through a pad of Celite then dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed to afford the alcohol **20** as a mixture of two diastereomers (4.41 g, 16.8 mmol, 98% yield): TLC R_f (PE/MTBE = 6/4) = 0.10; ^{1}H NMR δ 0.80 (1.8H, s), 1.19 (1.2H, s), 1.2−1.4 (1H, m), 1.7−1.9 (3H, m), 2.17 (1H, m), 2.30 (3H, s), 2.47 (1H, m), 3.11 (0.4H, s), 3.20 (0.6H, s), 3.6 (1H, m), 3.7 (2H, m), 3.75 (3H, s), 6.42 (2H, m), 6.63 (1H, s); ^{13}C NMR δ u 32.1, 33.3, 35.8, 35.9, 36.8, 43.1, 43.2, 43.7, 59.2, 59.4, 135.9, 136.1, 139.0, 139.1, 159.3, 159.4, 217.6, 217.9; d 20.4, 21.7, 26.0, 55.2, 67.5, 68.8, 113.2, 113.2, 113.4, 113.6, 123.4, 123.8; IR (film, cm^{-1}) 3428, 2952, 1733, 1595, 1459; HRMS calcd for $C_{16}H_{22}O_3$ (M^+) 262.1569, obsd 262.1557.

(1*S*)-2-(2-(3-Methoxy-5-methylphenyl)-1-methyl-3-oxocyclopentyl)acetaldehyde (21). Dess−Martin periodinane (7.42 g, 17.5 mmol) was added into the solution of the alcohol **20** (3.06 g, 11.7 mmol) in 100 mL of DCM at rt. The reaction continued for 30 min. The mixture was diluted with 300 mL of ether and passed through a pad of silica gel. The eluant was concentrated in vacuo. The residue was chromatographed to afford the ketone **21** as a mixture of two diastereomers (2.90 g, 11.1 mmol, 95% yield): TLC R_f (PE/MTBE = 6/4) = 0.29; ^{1}H NMR δ 0.94 (0.6H, s), 1.40 (2.4H, s), 1.90 (1H, m), 2.14 (2H, m), 2.23 (1.0H, m), 2.32 (3H, s), 2.50 (2H, m), 3.19 (0.8H, s), 3.41 (0.2H, s), 3.77 (3H, s), 6.39 (1H, s), 6.43 (1H, s), 6.65 (1H, s), 9.59 (0.8H, t, J = 2.4 Hz), 9.83 (0.2H, t, J = 2.4 Hz); ^{13}C NMR δ u 33.0, 33.1, 35.8, 36.2, 43.3, 43.7, 48.9, 54.4, 135.6, 135.9, 139.7, 140.1, 159.9, 160.1, 216.4, 217.4; d 21.6, 22.1, 26.7, 55.6, 66.7, 68.3, 113.7, 113.9, 114.0, 123.5, 124.0, 202.3, 202.4; IR (film, cm^{-1}) 2958, 2739, 1735, 1597, 1287; HRMS calcd for $C_{16}H_{20}O_3$ (M^+) 260.1412, obsd 260.1408.

(3a*S*,9b*S*)-6-Methoxy-3a,8-dimethyl-3,3a-dihydro-2*H*-cyclopenta[α]naphthalen-1(9*βH*)-one (22). The aldehyde **21** (0.407 g, 1.56 mmol) was dissolved in 15 mL of diethyl ether at rt. BF_3•OEt_2 (5 mL) was added at once. The reaction mixture turned blue right after the addition. The mixture was stirred for 1 h before quenching by water. The mixture was partitioned between MTBE and, sequentially, water, saturated aqueous $NaHCO_3$, and brine. The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to afford the alkene **22** as a colorless oil (0.138 g, 0.570 mmol, 37% yield): TLC R_f (PE/MTBE = 8/2) = 0.33; $[\alpha]^{20}_D$ = −109.8 (c 1.90, CH_2Cl_2); ^{1}H NMR δ 1.12 (3H, s), 1.81 (1H, m), 2.02 (2H, m), 2.29 (3H, s), 2.47 (1H, m), 2.83 (1H, s), 3.72 (3H, s), 5.48 (1H, dd, J = 1.2, 9.6 Hz), 6.52 (1H, s), 6.57 (1H, s), 6.70 (1H, d, J = 10 Hz); ^{13}C NMR δ u 35.5, 38.8, 41.8, 117.4, 131.1, 138.3, 154.9, 217.6; d 21.9, 25.7, 55.5, 60.1, 110.8, 121.8, 123.5, 132.4; IR (film, cm^{-1}) 2951, 1742, 1460, 1270, 1104; HRMS calcd for $C_{16}H_{18}O_2$ (M^+) 242.1307, obsd 242.1296.

(3a*S*,9b*R*)-1-Cyclopropylidene-6-methoxy-3a,8-dimethyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[α]naphthalene (23). The ketone **22** (0.185 g, 0.763 mmol) and $NaHCO_3$ (12 mg) were added to 5 mL of toluene. Petasis reagent[16] (6.5 mL, 0.7 M in toluene, 4.58 mmol) was added at rt. The reaction mixture was maintained at 55−60 °C for 2 days, then chromatographed directly. The alkene **23** was isolated as yellow oil (0.120 g, 0.45 mmol, 60% yield): TLC R_f (PE/MTBE = 8/2) = 0.80; $[\alpha]^{20}_D$ = +103.8 (c 6.26, CH_2Cl_2); ^{1}H NMR δ 0.49 (1H, m), 0.69 (1H, m), 0.76 (1H, m), 0.87 (1H, m), 1.10 (3H, s), 1.75 (1H, m), 1.90 (1H, m), 2.30 (1H, m), 2.33 (3H, s), 2.50 (1H, m), 3.29 (1H, br s), 3.78 (3H, s), 5.51 (1H, d, J = 9.6 Hz), 6.52 (1H, s), 6.69 (1H, s), 6.70 (1H, d, J = 10 Hz); ^{13}C NMR δ u 1.0, 2.7, 32.4, 39.8, 44.1, 113.0, 117.4, 136.6, 136.7, 154.6; d 21.8, 24.8, 54.1, 55.3, 109.3, 119.9, 124.0, 134.4; IR (film, cm^{-1}) 2919, 2837, 1571, 1459, 1324, 1095; HRMS calcd for $C_{19}H_{22}O$ (M^+) 266.1671, obsd 266.1660.

(1*R*,3a*S*,9b*S*)-1-Cyclopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,9b-tetrahydro-1*H*-cyclopenta[α]naphthalene (24). The alkene **23** (0.36 g, 1.35 mmol) and Ir black[4] (50 mg) were mixed with 10 mL of EtOH at rt. The mixture was then placed in a Parr reactor filled with H_2 (1100 psi). The reaction was monitored by GC−MS. After about 4−8 h, the reaction mixture was diluted with diethyl ether (100 mL) and passed through a pad of Celite. The eluant was concentrated and chromatographed to afford **24** as a colorless oil (0.201 g, 0.749 mmol, 55% yield, 80% yield based on starting material not recovered). Starting material was recovered (0.11 g, 31% yield, TLC R_f (PE/DCM = 8.5/1.5) = 0.29): TLC R_f (PE/DCM = 8.5/1.5) = 0.43; $[\alpha]^{20}_D$ = +10.1 (c 6.22, CH_2Cl_2); ^{1}H NMR δ −0.39 (1H, m), −0.21 (1H, m), −0.14 (1H, m), 0.06 (1H, m), 0.23 (1H, m), 1.04 (3H, s), 1.36 (1H, m), 1.49 (1H, m), 1.58 (1H, m), 1.85 (2H, m), 2.31 (3H, s), 2.85 (1H, d, J = 10 Hz), 3.80 (3H, s), 5.56 (1H, d, J = 10 Hz), 6.50 (1H, s), 6.54 (1H, s), 6.66 (1H, d, J = 10 Hz); ^{13}C NMR δ u 2.4, 5.4, 32.6, 41.1, 43.0, 119.3, 136.5, 136.9, 154.4; ^{13}C NMR δ 13.6, 21.7, 26.9, 52.2, 52.5, 55.4, 109.0, 118.8, 124.0, 135.9; IR (film, cm^{-1}) 2942, 2861, 1575, 1458, 1100; HRMS calcd for $C_{19}H_{24}O$ (M^+) 268.1827, obsd 268.1824.

(1*R*,3a*R*,9b*R*)-1-Cyclopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[α]naphthalene-4,5-diol (25). The alkene **24** (200 mg, 0.745 mmol) was combined with CCl_4 (4 mL), water (1 mL), acetone (8 mL), and *t*-BuOH (4 mL) at rt. Potassium osmium(VI) oxide dihydrate (14 mg, 5% mol) and *N*-methylmorpholine-*N*-oxide (0.41 g, 3.50 mmol) were added at once.[3,18] The reaction mixture was stirred vigorously at rt for 2 days, then partitioned between MTBE and, sequentially, saturated aqueous NH_4Cl and brine. The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to afford the diol **25** as a mixture of diastereomers (96 mg, 0.317 mmol, 43% yield, 60% yield based on starting material not recovered). Starting material was recovered (55 mg, 28% yield, TLC R_f (PE/MTBE = 6/4) = 0.80): TLC R_f (PE/MTBE = 6/4) = 0.29; ^{1}H NMR δ −0.20−0.40 (4H, m), 0.54 (1H, m), 1.17 (1.5H, s), 1.19 (1.5H, s), 1.25 (3H, s), 1.53 (6 H, m), 1.88 (1 H, m), 2.09 (1 H, m), 2.18 (1 H, s), 2.32 (3 H, s), 2.40 (1 H, m), 2.63 (1H, s), 2.96 (1 H, d, J = 8.0 Hz), 3.05 (1 H, d, J = 9.2 Hz), 3.60 (1 H, d, J = 4.0 Hz), 3.85 (1.5 H, s), 3.87 (1.5 H, s), 3.93 (1 H, m), 5.06 (1 H, dd, J = 4.4, 8.0 Hz), 6.54 (1 H, s), 6.68 (0.5H, s), 6.82 (0.5 H, s); ^{13}C NMR δ u 2.99, 3.76, 5.67, 6.09, 29.9, 31.3, 33.7, 36.9, 43.6, 44.4, 121.6, 122.0, 137.0, 137.1, 137.3, 138.0, 157.1, 157.3; d 12.2, 14.0, 21.2, 21.3, 28.8, 29.8, 49.2, 51.5, 53.1, 53.7, 54.8, 54.9, 65.0, 65.9, 71.4, 74.4, 107.8, 108.0, 123.7, 124.1; IR (film, cm^{-1}) 2955, 1709, 1677, 1459, 1107; HRMS calcd for $C_{19}H_{26}O_3Na$ (M + Na) 325.1780, obsd 325.1772.

(1*R*,3a*R*,9b*R*)-1-Isopropyl-6-methoxy-3a,8-dimethyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[α]naphthalen-4-ol (26). The diol **25** (36 mg, 0.12 mmol) and PtO_2 (10 mg) were mixed in AcOH (2.5 mL) at rt. H_2 (1 atm) was bubbled through the mixture as it was maintained in an oil bath (50 °C).[7b,19] The reaction was monitored by TLC. When the reaction completed (about 1 h), it was diluted with 20 mL of Et_2O and passed through a pad of Celite. The eluant was concentrated and chromatographed to afford the alcohol **26** as a colorless oil (23 mg, 0.079 mmol, 67% yield): TLC R_f (PE/MTBE = 8/2) = 0.25; ^{1}H NMR (360 MHz) δ 0.66 (3H, d, J = 6.5 Hz), 0.96 (1H, m), 1.09 (3H, d, J = 6.5 Hz), 1.13 (1H, m), 1.30 (3H, s), 1.48 (1H, m), 1.61 (1H, m), 1.86 (1H, m), 2.11 (1H, m), 2.30 (3H, s), 2.38 (1H, m), 3.01 (2H, m), 3.55 (1H, dd, J = 4.3, 11.5 Hz), 3.79 (3H, s), 6.51 (1H, s), 6.60 (1H, s); ^{13}C NMR (90 MHz) δ u 28.3, 29.7, 31.9, 45.7, 122.5, 135.0, 138.2, 156.3; d 21.5, 21.7, 23.9, 26.4, 29.6, 53.3, 53.9, 55.3,75.7, 108.2, 122.7; IR (film, cm^{-1})

2924, 2855, 1458, 1264; HRMS calcd for $C_{19}H_{28}O_2$ (M^+) 288.2089, obsd 288.2088.

(1*R*,3a*R*,9b*R*)-1-Isopropyl-6-methoxy-3a,8-dimethyl-1,2,3,3a-tetrahydro-9b*H*-cyclopenta[α]naphthalene-4,5-dione (27). The alcohol **26** (68 mg, 0.236 mmol), powdered 4 Å molecular sieve (0.65 g), *N*-methylmorpholine-*N*-oxide (272 mg, 2.32 mmol), and TBAP (tetra-*n*-butylammonium perruthenate)[20] (10 mg) were mixed in DCM (3 mL) at rt. The reaction was monitored by TLC. After about 3 h, it was chromatographed directly to afford the known[3] diketone **27** as a yellow oil (38 mg, 0.127 mmol, 54% yield): TLC R_f (PE/MTBE = 8/2) = 0.08; $[\alpha]^{20}_D = -345.9$ (*c* 0.74, CH_2Cl_2); ^{1}H NMR (360 MHz) δ 0.44 (3H, d, J = 6.5 Hz), 0.57 (3H, d, J = 6.5 Hz), 1.20 (1H, m), 1.28 (3H, s), 1.55 (2H, m), 1.79 (1H, m), 2.25 (1H, m), 2.43 (3H, s), 2.50 (1H, m), 3.35 (1H, d, J = 9.7 Hz), 3.95 (3H, s), 6.71 (1H, s), 6.78 (1H, s); ^{13}C NMR (90 MHz) δ u 28.2, 35.6, 55.3, 120.8, 146.1, 147.4, 161.6, 181.0, 201.9; d 20.5, 22.6, 23.3, 24.3, 28.7, 52.0, 56.2, 56.2, 111.1, 124.5.

(1*R*,3a*R*,9b*R*)-6-Hydroxy-1-isopropyl-3a,8-dimethyl-1,2,3,3a-tetrahydro-9b*H*-cyclopenta[α]naphthalene-4,5-dione (28). Following Clive's procedure,[3] the phenol **28** was isolated as a yellow solid (88% yield): TLC R_f (PE/MTBE = 8/2) = 0.46; $[\alpha]^{20}_D = -225.8$ (*c* 0.62, CH_2Cl_2); ^{1}H NMR δ 0.43 (3H, d, J = 6.8 Hz), 0.54 (3H, d, J = 6.8 Hz), 1.22 (1H, m), 1.30 (3H, s), 1.55 (1H, m), 1.67 (1H, m), 1.79 (1H, m), 2.26 (1H, m), 2.39 (3H, s), 2.64 (1H, m), 3.40 (1H, d, J = 9.2 Hz), 6.70 (1H, s), 6.73 (1H, s), 11.90 (1H, s); ^{13}C NMR δ u 27.1, 34.0, 57.0, 116.9, 144.3, 150.9, 164.8, 184.5, 200.2; d 20.0, 22.7, 23.3, 24.6, 28.3, 51.6, 56.7, 116.4, 123.5.

(−)-Hamigeran B (1). Following Trost's procedure,[4] **1** was isolated as a yellow solid (81% yield). The product was recrystallized from hexanes before it was characterized: mp = 155 − 160 °C (lit.[1−4] mp 154−167 °C); TLC R_f (PE/MTBE/MeOH = 90/10/1) = 0.47; $[\alpha]^{20}_D = -200$ (*c* 0.14, CH_2Cl_2) (lit.[1−4] $[\alpha]_D = -151.1$ to −211); ^{1}H NMR δ 0.45 (3H, d, J = 6.4 Hz), 0.54 (3H, d, J = 6.8 Hz), 1.20 (1H, m), 1.30 (3H, s), 1.54 (1H, m), 1.68 (1H, m), 1.80 (1H, m), 2.30 (1H, m), 2.51 (3H, s), 2.64 (1H, m), 3.38 (1H, d, J = 9.2 Hz), 6.83 (1H, s), 12.63 (s, 1 H); ^{13}C NMR δ u 26.9, 34.0, 57.1, 111.8, 116.4, 142.9, 150.4, 161.0, 184.6, 199.2; d 19.9, 23.5, 24.5, 24.6, 28.3, 51.5, 56.4, 124.4.

Acknowledgment. We thank John Dykins for high-resolution mass spectra under the financial support by NSF 0541775. This work was supported by the National Institutes of Health (GM 060287).

Supporting Information Available: Experimental generals and spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8010683